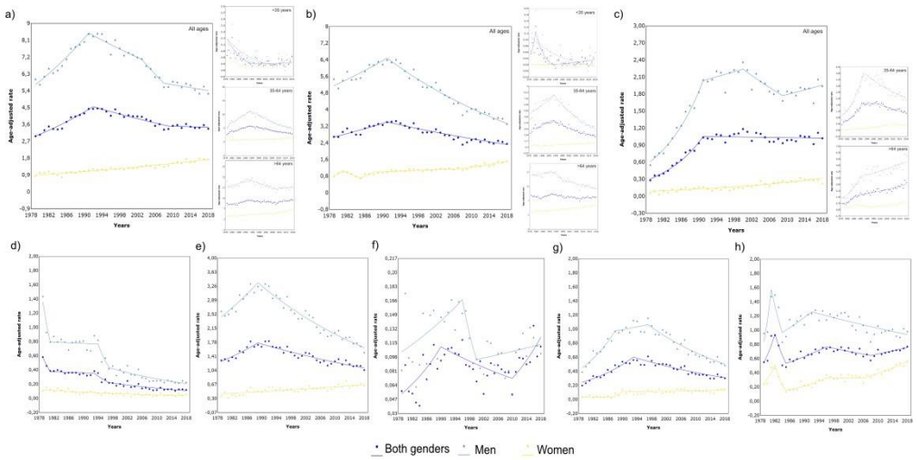

a)
b)
c)
d)
e)
f)
g)
h)
All ages
Age-adjusted rate
Years
Both genders
Men
Women

Figure 1

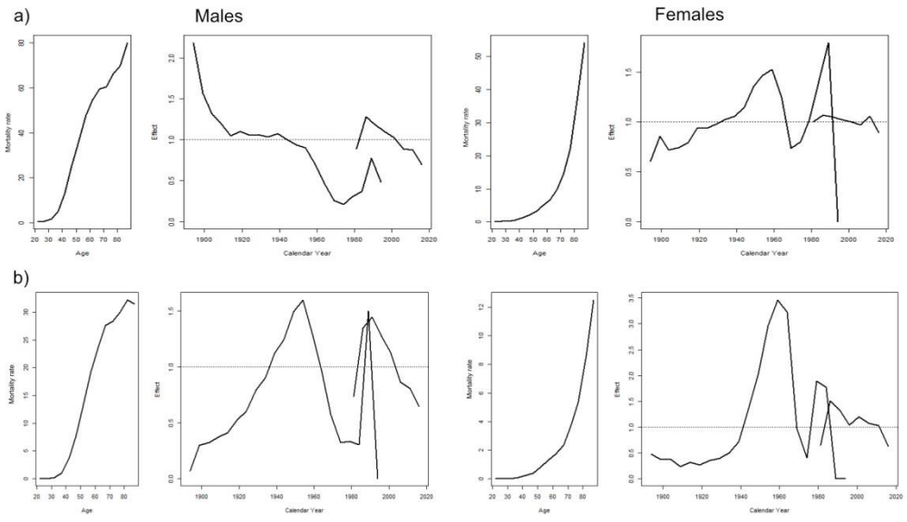


Figure 2

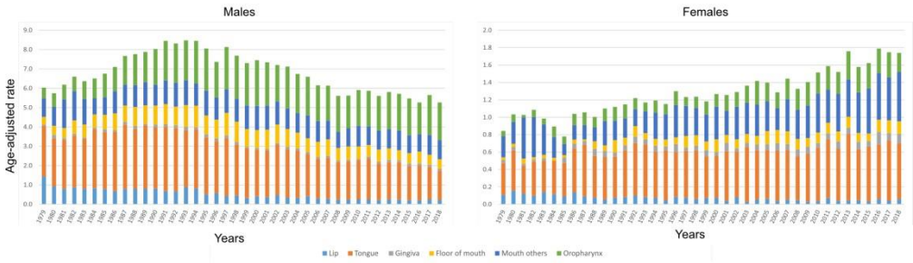

Males
Females
Age-adjusted rate
Years
Years
Lip
Tongue
Gingiva
Floor of mouth
Mouth others
Oropharynx

Figure 3

APPENDIX

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Duran-Romero A.J., Infante-Cossio P., & Pereyra-Rodriguez J.J. Trends in mortality rates for oral and oropharyngeal cancer in Spain, 1979-2018

APPENDIX LEGENDS

Supplementary Table S1. OCOPC mortality in Spain between 1979-2018: deaths by genders and locations.

Supplementary Table S2. Goodness-of-fit test for different APC models for OCC and OPC in Spain between 1979-2018.

Supplementary Figure S1. Sex ratio (male/female) for all ages: a) OCC; b) OPC.

Supplementary Table S1. OCOPC mortality in Spain between 1979-2018: deaths by genders and locations.

a) Male

Year	Lip	Oral cavity sub-site			Other sites of the mouth	Oropharynx	Total oral cavity	Total oropharynx
		Tongue	Gingiva	Floor of mouth				
1979	85	263	10	50	102	66	510	66
1980	72	273	13	58	111	87	527	87
1981	66	295	12	62	170	100	605	100
1982	65	311	11	92	184	102	663	102
1983	67	324	8	83	158	117	640	117
1984	66	372	11	83	103	136	635	136
1985	65	369	19	91	116	155	660	155
1986	67	398	11	118	138	164	732	164
1987	75	423	19	115	136	208	768	208
1988	77	419	17	130	143	228	786	228
1989	77	425	14	137	159	219	812	219
1990	78	419	19	142	145	260	803	260
1991	72	466	19	149	156	297	862	297
1992	73	448	21	138	169	304	849	304
1993	91	415	23	168	185	306	882	306
1994	83	426	21	166	160	329	856	329
1995	59	423	24	147	186	328	839	328
1996	61	398	20	148	169	288	796	288
1997	53	451	23	179	183	337	889	337
1998	53	407	18	161	172	346	811	346
1999	43	395	13	147	182	352	780	352
2000	51	379	15	147	183	386	775	386
2001	50	380	11	161	191	366	793	366
2002	66	433	11	158	186	314	854	314
2003	50	413	19	154	173	366	809	366
2004	46	406	18	143	168	354	781	354
2005	61	371	14	130	203	348	779	348
2006	44	352	14	139	181	332	730	332
2007	47	380	18	156	172	330	773	330
2008	40	350	15	119	149	352	673	352
2009	39	361	14	131	171	319	716	319
2010	41	385	10	122	191	359	749	359
2011	43	404	18	115	186	356	766	356
2012	40	364	22	121	188	357	735	357
2013	46	380	24	117	193	386	760	386
2014	45	388	19	107	198	396	757	396
2015	40	356	25	111	185	398	717	398
2016	42	372	24	126	190	350	754	350
2017	48	356	24	111	219	441	758	441
2018	42	324	22	105	211	420	704	420
TOTAL	2,329	15,274	683	5,037	6,765	11,659	30,088	11,659

b) Female

Year	Oral cavity sub-site				Other sites of the mouth	Oropharynx	Total oral cavity	Total oropharynx
	Lip	Tongue	Gingiva	Floor of mouth				
1979	11	47	5	4	32	6	99	6
1980	15	57	6	5	32	12	115	12
1981	12	41	3	6	61	4	123	4
1982	10	53	3	4	64	10	134	10
1983	14	49	4	5	47	9	119	9
1984	12	55	0	5	34	15	106	15
1985	10	58	9	3	17	14	97	14
1986	15	75	7	7	25	17	129	17
1987	11	89	5	3	24	23	132	23
1988	10	75	10	12	22	19	129	19
1989	8	74	11	10	43	21	146	21
1990	12	75	7	21	36	24	151	24
1991	11	87	8	15	37	26	158	26
1992	13	100	13	17	31	21	174	21
1993	14	101	11	12	42	17	180	17
1994	9	91	12	13	51	25	176	25
1995	8	101	8	14	49	20	180	20
1996	14	94	17	13	65	29	203	29
1997	14	96	7	22	61	18	200	18
1998	10	105	10	21	59	23	205	23
1999	13	89	14	19	58	28	193	28
2000	15	92	9	27	70	28	213	28
2001	7	113	20	17	55	35	212	35
2002	16	104	8	21	76	33	225	33
2003	6	129	9	21	75	40	240	40
2004	12	117	15	20	77	55	241	55
2005	14	119	14	32	74	44	253	44
2006	9	127	20	33	57	38	246	38
2007	13	132	17	33	85	51	280	51
2008	13	121	18	27	79	52	258	52
2009	8	129	19	24	90	60	270	60
2010	10	150	13	29	110	55	312	55
2011	20	168	17	30	99	62	334	62
2012	13	153	21	28	111	62	326	62
2013	14	193	19	31	118	76	375	76
2014	14	151	22	23	123	70	333	70
2015	11	171	17	23	143	70	365	70
2016	19	173	40	36	151	68	419	68
2017	15	194	25	40	141	74	415	74
2018	20	182	33	37	162	56	434	56
TOTAL	495	4,330	526	763	2,786	1,410	8,900	1,410

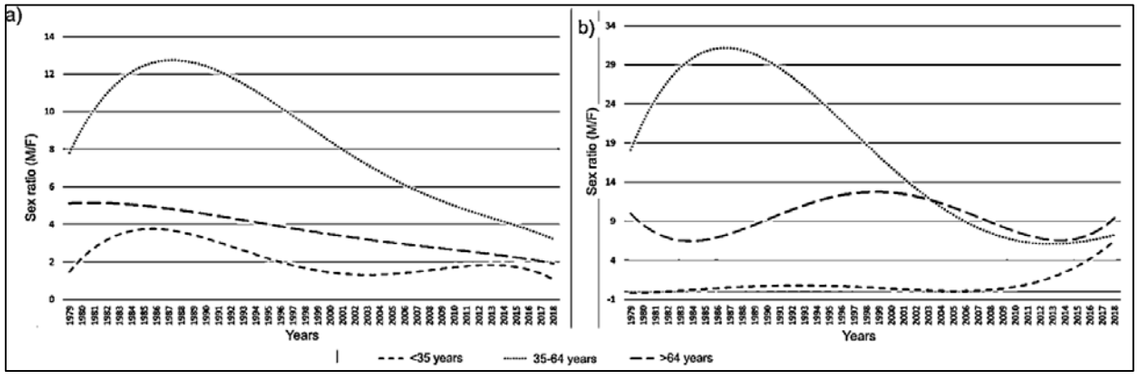
Note: OCOPC: Oral cavity and oropharyngeal cancer.

Supplementary Table S2. Goodness-of-fit test for different APC models for OCC and OPC in Spain between 1979-2018.

Model	Df	Deviance	p	AIC	df	Deviance	p	AIC
	Males				*Females*			
OPC								
Age-model	98	1391.32	<**0.001**	2003.17	98	456.00	<**0.001**	864.04
Age-drift model	97	1370.21	<**0.001**	1984.06	97	325.50	<**0.001**	735.53
Age-period model	91	683.46	<**0.001**	1309.31	91	271.17	<**0.001**	693.21
Age-period-cohort model	72	77.33	**0.312**	741.17	72	77.04	**0.320**	537.07
Age-cohort model	78	478.18	<**0.001**	1130.03	78	135.03	<**0.001**	538.07
OCC								
Age-model	98	3227.37	<**0.001**	3988.34	98	233.32	<**0.001**	855.32
Age-drift model	97	1371.82	<**0.001**	2134.78	97	183.19	<**0.001**	807.20
Age-period model	91	724.26	<**0.001**	1499.23	91	160.94	<**0.001**	796.93
Age-period-cohort model	72	101.52	**0.013**	914.49	72	81.55	**0.207**	755.55
Age-cohort model	78	577.09	<**0.001**	1378.06	78	100.67	**0.043**	762.67

Note: Df: degrees of freedom; AIC: Akaike information criteria; OCC: Oral cavity cancer; OPC: Oropharyngeal cancer.

Supplementary Figure S1. Sex ratio (male/female) for all ages: a) OCC; b) OPC.



The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title page (pag. 1) and Summary (pag 2)	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Summary (pag 2) Summary (pag 2) Summary (pag 2)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction (pag 3)		
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction (pag 3)		
Methods					
Study Design	4	Present key elements of study design early in the paper	M&Methods (pag 4)		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	M&Methods (pag 4)		

Participants	6	*(a)Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b)Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	N/A	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	N/A N/A M&Methods (pag 4)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	M&Methods (pag 4)	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	M&Methods (pag 4)
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	N/A		

Bias	9	Describe any efforts to address potential sources of bias	N/A		
Study size	10	Explain how the study size was arrived at	N/A		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	M&Methods (pag 4)		
Statistical methods	12	(a)Describe all statistical methods, including those used to control for confounding (b)Describe any methods used to examine subgroups and interactions (c)Explain how missing data were addressed *(d)Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e)Describe any sensitivity analyses	M&Methods (pag 4)		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	M&Methods (pag 4) M&Methods (pag 4)

Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods (pag 4)
Results					
Participants	13	(a)Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b)Give reasons for non-participation at each stage. (c)Consider use of a flow diagram	Results (pag 5)	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results (pag 5)
Descriptive data	14	(a)Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b)Indicate the number of participants with missing data for each variable of interest *(c)Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Results (pag 5)		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure	N/A		

		Cross-sectional study - Report numbers of outcome events or summary measures			
Main results	16	(a)Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b)Report category boundaries when continuous variables were categorized (c)If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results (pag 5)		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results (pag 5)		
Key results	18	Summarise key results with reference to study objectives	Dicussion (pag. 7)		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Dicussion (pag. 7)	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Dicussion (pag. 7)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar	Dicussion (pag. 7)		

		studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Dicussion (pag. 7)		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Pag 11		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Results (pag 5)

TITLE:

Trends in mortality rates for oral and oropharyngeal cancer in Spain, 1979-2018

RUNNING HEAD:

Mortality trends for oral and oropharyngeal cancer

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Abstract

Objective: To analyse mortality rate trends in Spain for oral cavity and oropharyngeal cancer (OCOPC) from 1979 to 2018, evaluating differences between oral cavity cancer (OCC) and oropharyngeal cancer (OPC).

Materials and Methods: Death certificates and mid-year population data were collected from the Spanish National Statistics Institute. Age-standardized mortality rates were calculated using the direct method. Joinpoint regressions were used to identify significant changes in mortality trends. Independent effects of age, period, and cohort (APC) were estimated.

Results: 52,057 deaths were registered from OCOPC, 38,988 from OCC and 13,069 from OPC between 1979-2018. While OCC mortality rates declined, OCOPC rates increased slightly and OPC significantly. OCC and OPC mortality reached their highest values between 1979-1992, when OCC rates began to decrease in males and OPC levelled off until 2018. Lip cancer suffered the highest drop. APC models showed a mortality increase in males and females from 40-45 and 50-55 years of age, respectively.

Conclusions: Favourable OCC mortality trends was plausibly influenced by decreased tobacco/alcohol consumption, while OPC rise was probably associated with increased human papillomavirus infection. The importance of closely monitoring these cancers by age group, sex and location, and continuing with preventive measures against known risk factors, is highlighted.

Keywords

Mortality rates, oral cavity cancer, oropharyngeal cancer, age-period-cohort analysis, Spain

INTRODUCTION

Oral cavity cancer (OCC) and oropharyngeal cancer (OPC) are two closely related malignancies traditionally combined under the term oral cavity and oropharyngeal cancer (OCOPC). They represent a worrying health problem as, in 2018, OCC and OPC were estimated to have caused 177,400 (119,700 males, 7,700 females) and 51,000 deaths (42,100 males, 8,900 females) worldwide, respectively (Ferlay et al., 2019).

Although the incidence and mortality from OCOPC had been gradually increasing over the past decades, a decrease in the rate of male deaths from OCC has been reported in Southern European countries over the past 30 years (Bosetti et al., 2020), plausibly associated with a drop in cigarette and alcohol consumption (Chaturvedi et al., 2013). In contrast, OCC rates in males reached high values in recent decades in several Central and Eastern European countries, as well as rates of OPC in the US and most European countries (Chaturvedi et al., 2011; Wang & Palefsky, 2016). These divergent patterns hypothesized different exposure in diverse geographical areas to risk factors such as tobacco and alcohol and, probably, human papillomavirus (HPV) (Prue, Lawler, Bakerm & Warnakulasuriya, 2016; Tachezy et al., 2005; Valls-Ontañón et al., 2019). The association of HPV with OCOPC is variable since it represents a well-established causal factor for OPC, while its role is unclear in OCC (Lai et al., 2017). HPV DNA has been detected in up to 80% of OPC (Gillison, Chaturvedi, Anderson & Fakhry, 2015), particularly genotype 16 (Weatherspoon, Chattopadhyay, Boroumand & Garcia, 2015). A meta-analysis from 2015 estimated that 45.8% of OPC and 24.2% of OCC were attributable to HPV infection based on detection of HPV DNA by PCR (Gillison et al., 2015). In Spain, the HPV positive population is relatively low, with an estimated prevalence at the late 1990s of 2.2% of the population for high-risk genotypes (De Vuyst, Clifford, Li & Franceschi, 2009), but it seems to have increased over time (Rodrigo et al. al., 2014).

Information on mortality rates from OCOPC in Spain is scarce (Bonifazi et al., 2011; Garavello et al., 2010). Nieto and Ramos (Nieto & Ramos, 2002) reported trend mortality rates similar to the rest of Southern/Mediterranean European countries, showing a gradually increase in death rates from the 1950s to the mid-1990s, when they began to decline until the beginning of 21st century, particularly in males. With the aim of providing an update on recent trends in mortality from OCOPC in Spain, the present study analysed the death rates between 1979 and 2018, considering gender, age and anatomical cancer sub-site, using data from the official Spanish death records. We compared the general patterns and mortality trends between OCC and OPC combined and separately over a 40-year

period and discussed the possible influence on mortality of different risk factors involved in these tumours.

MATERIALS AND METHODS

Data collection

Death records and mid-year population data were collected from the Spanish National Statistics Institute (http://www.ine.es) for the period 1979-2018. Death certificates containing any of the following locations with their respective codes from the 9th or 10th edition of the International Classification of Diseases (ICD-9, ICD-10) as cause of death were considered for the present study. The codes included for OCC were: lip (140, C00), tongue (141, C01-02), gingiva (143, C03), floor of the mouth (144, C04), and other sites of the mouth (145, C05-06); and for OPC: oropharynx (146, C09-10). Malignant neoplasms of the nasopharynx, hypopharynx, and major salivary glands were excluded.

Statistical analysis

Age-adjusted mortality rates were calculated by the direct method using the 2013 European standard population (European Commission Revision of the European Standard Population-Report of Eurostat's Task Force, 2013) as reference for each year, for combined OCOPC, separately for OCC and OPC, and for each cancer sub-site. These calculations were made for the entire country and stratified by gender and three age groups (<35, 35-64 and >64 years). Mortality rates were expressed as deaths per 100,000, and the software used to obtain them included: Epidat3.1®, Microsoft® Excel and SPSS Statistics 25®. In addition, sex ratio was calculated to assess mortality differences between genders, defined as the ratio of male to female mortality rate.

Joinpoint regression models were used to identify significant trend changes in mortality rates during the studied period and to estimate the average annual percent change (AAPC). For this purpose, the Joinpoint software developed by the Surveillance Research Program of the US National Cancer Institute was employed (National Cancer Institute. Joinpoint Regression Program, 2020). The maximum Joinpoints allowed in the analysis were 5.

Age-period-cohort (APC) models were fitted to assess independent effects of those items on

mortality. To address the problem of "non-identifiability", penalty functions proposed by Decarli et al. (Decarli, Vecchia, Malvezzi & Micciolo, 2014), based on the Osmond and Garner model (Osmond & Gardner, 1982), were used. APC models were estimated using Poisson regression and generalized linear interactive modelling macros for R® software provided by the authors to complete the calculations. We divided data into 5-year periods and age quinquenniums to carry out these estimates. Additionally, goodness-of-fit of APC models was compared.

RESULTS

Between 1979 and 2018, 52,057 deaths from OCOPC were registered in Spain, of which 38,988 were separately attributed to OCC (30,088 males, 8,900 females) and 13,069 to OPC (11,659 males, 1,410 females). In 2018, there were 1,614 deaths from OCOPC (OCC=1,138, OPC=476), with an OCC/OPC ratio=2.39 (Supporting Information Table S1).

Regarding age-standardized mortality rates from 1979-83 to 2014-18 (Table 1), the main findings to be highlighted were: 1) The overall mortality rates for OCOPC grew slightly from 3.24 to 3.45/100,000 between 1979-1983 and 2014-2018; 2) Interestingly, while mortality rates for OPC rose significantly from 0.37 to 1.03/100,000, OCC rates showed a reduction from 2.86 to 2.42 /100,000 in the last 4 decades; 3) Joinpoint analysis showed two trend changes in OCOPC mortality rates during three periods: a) from 1979 to 1992, mortality rates grew with its highest AAPC=3.3 (95% CI 2.7-3.9); b) from 1992 to 2009, they experienced a sustained decrease; and c) from 2009 to 2018, they levelled off; 4) Joinpoint analysis for OOC and OPC revealed that, after increasing from 1979 to 1991, mortality from OCC showed a dropping phase while mortality from OPC levelled off until 2018.

Relating to sex-stratified analysis (Table 2), male mortality rates for OCOPC and OCC declined from 1979-1983 to 2014-2018, while mortality for OPC increased. By contrast, female mortality rates rose for OCOPC, OCC and OPC, with OPC showing the most important increase in relative terms, having rates 5 times higher at the end of the period. The Joinpoint analysis for OCOPC in males defined two different trend periods: from 1979 to 1991, in which mortality rates grew to their peak and, from 1991 to 2018, when they decreased significantly. Similar trends were found for OCC. However, for OPC mortality rates, after an initial ascent from 1979 to 1991 and a subsequent fall in the period 1991-2009, a progressive increase was observed until 2018. In females, mortality rates rose steadily from 1979 to 2018, more sharply in OPC.

Age group analysis (Table 3) showed a widespread decline of mortality rates in the group <35 year of age, while rates rose in those over 35 years for OPC, more markedly in the group over 64 years. Trend analysis reflected: 1) A sustained reduction for the <35 year group,; 2) A high OPC mortality rate value for the 35-64 year group in the period 1979-1991; 3) An increase for OCOPC and OPC for the >64 year group, particularly the last one that consistently grew since the 1990s.

Joinpoints and mortality trends in relation to the general population by gender and cancer location (previously described with Table 1) are depicted in Figure 1. Interestingly, lip cancer declined from 1979 to 2018, with two marked drops in the early 1980s and mid-1990s. In males, lip, tongue, and other locations showed decreasing mortality rate trends, while gingiva and floor of the mouth rose slightly. In females, mortality trends had a sustained increase from 1979 to 2018, except for lip cancer, which showed a steady decrease.

With regard to the sex-ratio (Supporting Information Figure S1), the gap between males and females showed an increase in OCC rates until the late 1980s, when a progressive reduction of this gap began, more pronounced for the >64 year group. A similar reduction in the sex ratio was also observed in OPC rates throughout the period, although a growing trend in the gap was detected from 2013.

In the analysis of the independent effects of APC on mortality, a constant rise in male mortality was found from 40-45 years of age, and a strong increase in female mortality from 50-55 years of age (Figure 2). Estimates of the age-specific mortality rate reached values close to 35 and 80/100,000 in males, and 15 and 55/100,000 in females, respectively, for OPC and OCC. Focusing on birth cohort effect, death rates rose gradually in females from those born in the 1940s, particularly for OPC. By contrast, males born from the 1940s showed lower mortality rates for OCC, which could also be interpreted as a cohort effect. However, cohort analysis showed two peaks in the 1950s and 1990s for OPC rates in males. Moreover, a dropping mortality trend is seen in males in the 1990s for OCC and OPC, which could be interpreted as a period effect. The degree of goodness for each possible regression model has been calculated for the evaluation of the APC independent effects. The age-cohort model is the best fitting two-factor model for males and females, as it has a lower Akaike information criterion (AIC) and a narrower deviation for OCC and OPC (Supporting Information Table S2). The contribution of OCC and OPC to the total mortality by year and gender may be seen in Figure 3.

DISCUSSION

This study represents the longest mortality series of OCOPC reported to date in Spain. The most relevant finding confirmed a significant reduction mortality from OCC during the last 40 years in contrast to mortality from OPC which exhibited a clear increase. OCOPC showed a slight rise in the global mortality rates, more markedly until the 1990s, when they began a downward trend that has levelled off to the present day. While OCC mortality rates decreased in males, OCOPC mortality increased in females, and OPC in both genders.

To interpret and compare our findings with other studies, it is necessary to consider that the classification of OCC and OPC is not the same worldwide. They are two different sites which can lead to misclassification. While OCC arises from the structures comprising the lips, the anterior two-third of mobile tongue, the buccal mucosa, the gingiva, the hard palate, the retromolar trigone, and the floor of the mouth (Montero & Patel, 2015); OPC develops from the posterior area to the mouth including the base of tongue (posterior one-third), the soft palate, the tonsillar complex (tonsil, tonsillar fossa and pillars), and the posterior and lateral pharyngeal walls (Cohan et al., 2009). However, other studies have considered only a few locations in the oral cavity or the oropharynx; others have included the soft palate as part of the mouth, the entire pharynx, or the salivary glands; and others have excluded the lip, and the hypo, naso and oropharynx (Seoane-Mato et al., 2014; van Dijk, Brands, Geurts, Merkx & Roodenburg, 2016; Zheng, Kirita, Kurumatani, Sugimura & Yonemasu, 1999). This controversy can be explained by the close topographical continuity between the oral cavity and the oropharynx mucosal lining tissue in a highly focused area. Therefore, an agreement is needed to clarify and standardize the terms of OCC and OPC to identify the rate of each neoplasm in epidemiological reports, given the growing evidence of changing trends in cancer registries and risk factors between both cancers (Conway, Purkayastha & Chestnutt, 2018).

Incidence and mortality of OCOPC have experienced a paradigm shift in recent years. Currently, two groups of malignancies are generally accepted, those influenced by tobacco and alcohol exposure, and those associated with HPV infection (Chaturvedi et al., 2011; Gillison et al., 2015; Lai et al., 2017). In Spain, legislative and cultural changes in the late 1980s favoured a decrease in the population's exposure to smoking and alcohol consumption which resulted in a decline in the incidence and mortality rates of those cancers associated with these etiological factors, in

particular OCC. This change has been more pronounced in males since the 1990s, as mortality has not declined in females throughout the period analysed, probably linked to their incorporation into the tobacco habit that occurred in Spain during the last decades of the 20th century (Conway et al., 2018; Nieto & Ramos, 2002). In addition, the prevalence of alcohol drinking in males has decreased considerably since then, leading to a more favourable incidence and mortality trend (Bosetti et al., 2020).

With regard to oral HPV infection, a prevalence of 4.5% has been reported for the general adult population worldwide, higher in developing countries (7.3%) than in developed ones (3.6%) (Kreimer et al., 2010). In Spain, the prevalence of genital HPV infection is estimated to be among the lowest in Europe (de Sanjose et al., 2003; Rodrigo et al., 2014). However, changes in sexual behaviour in our country are inducing a greater expansion of HPV infection in the population (Seoane-Mato et al., 2014), rising from 1.3% in 1990 to 6.1% in 2009 (Rodrigo et al., 2014). The first coordinated vaccination campaigns against HPV began in 2007 in 14-year-old girls and are currently being expanded to men who report having sex with men. It seems reasonable to consider that the mortality rate increase observed in OPC from 2009 to 2018 could coincide with a rise in the HPV incidence. Nevertheless, the potential benefit effect of HPV vaccination on OCOPC incidence and mortality are still unknown in Spain, since barely a decade has elapsed from the start of institutional vaccination campaigns to detect its influence as a protective factor. Recently, a study in the US has reported a significant lower prevalence of OPC in patients vaccinated against HPV (Katz, 2020).

Our findings support the theory of the end of OCC epidemic behaviour described some decades ago in some European countries due to the reduction of tobacco and alcohol consumption in males (Bonifazi et al., 2011). In Spain, OCC mortality rates increased worryingly from the 1970s to the early 1990s substantially in males (Nieto & Ramos, 2002), when they tended to level off. Seoane-Mato et al. (Seoane-Mato et al., 2014) examined oral cavity, pharyngeal, oesophageal and gastric cancer mortality rates up to 2006, finding a decrease in mortality since the 1990s. Our data, updated to 2018, confirm these trends. This same pattern has been perceived in the first decade of the 21st century in Southern and most Central countries of Europe (Bonifazi et al., 2011; Garavello et al., 2010). Moreover, mortality in some Northern and Eastern Europe countries has shown an increase between 1990 and 2004 and even, in one country, this trend has been reported until 2012 (van Dijk et al., 2016). The US, China, Japan and Australia also showed a decline in mortality (Bosetti et al., 2020).

In Spain, early cancer diagnosis campaigns, lifestyle changes, and high fruit and vegetable consumption may also have influenced the favourable patterns from the 1990s (Nieto & Ramos, 2002; Seoane-Mato et al., 2014). Nonetheless, it should be noted that only moderate improvements in survival have been reported in the past three decades despite progress in the management of these neoplasms (Infante-Cossio, Torres-Carranza, Cayuela, Gutierrez-Perez & Gili-Miner, 2009). Consequently, it is unlikely that advances in therapeutic modalities and care for patient quality of life have played a key role in mortality rate trends. On the other hand, the proportion of advanced stages at diagnosis has remained stable in recent decades (McGurk.,Chan, Jones, O'regan & Sherriff, 2005; Warnakulasuriya, 2009), so that changes in incidence exhibit a fairly faithful reflection of mortality. In addition, the Spanish public health system offers universal and free assistance and has not undergone substantial changes in recent decades. Therefore, the influence of access to health care on mortality trends may be small compared to other countries.

We have found significant differences in the mortality trends analysis by sub-sites. Lip cancer has shown a dramatic decrease since the beginning of the period, more marked in males. Lip cancer mortality trends has recently been analysed in 185 countries, finding a reduction in most of them (Miranda-Filho & Bray, 2020), probably due to sun exposure prevention campaigns (Greinert et al., 2015), since ultraviolet radiation is an important risk factor for lip cancer. We have also found reductions in mortality from cancer of the tongue, floor of the mouth and other sites of the mouth. Gingiva cancer has shown a variable pattern, although the low number of annual deaths produces large variations in its rates.

Joinpoint analysis showed similarities between OCC and OPC, with a coincidence of change points. The similarity of cohort effects suggested exposure to shared risk factors. Analysing the effects of age, period and cohort, an interval of several decades is observed between the first exposure to risk factors and death. In males, OCC mortality rates have decreased in those generations born after the 1950s, indicating that mortality is likely to continue descending in the near future, as the same generations advance in age. In contrast, OCC mortality rates in females have remained high throughout the period. For OPC, mortality rates grew in cohorts born between the 1940s and 1960s for both genders and, therefore high death rates are expected to continue to be recorded in coming years.

Regarding the APC models, although the age cohort model is the most suitable two-factor model

for males and females, we believe that the period effect also plays an important role in males, with a mortality drop in the 1990s for all age groups simultaneously. The best fit for the male age cohort model with a lower AIC and a narrower deviation could be explained by the method used to solve the problem of "non-identifiability", since penalty function models tend to overestimate the effect cohort (González, Llorca & Moreno, 2002).

This study poses some limitations. One limitation is that data collected are subject to omissions at the time of completing death certificates. However, there were no major changes to the classification and coding in subsequent revisions of the ICD. Hence, it is unlikely that mortality trends were influenced by changes in disease diagnosis and certification since these cancers are relatively easy to detect. It would have been desirable to carry out the analysis considering histopathological diagnosis, tobacco/alcohol consumption, HPV exposure, tumour staging, and treatment performed, but death certificates do not include such information in Spain. Another limitation is correlated to the intrinsic problem of APC analysis models, which may overvalue the cohort or period effect depending on the model. This study monitored the total Spanish population over a 40-year period, comprising generations born approximately between 1900 and 2000 and, consequently, it constitutes an important time series with a large data package that allowed the characterization of epidemiological trends. The standardization of rates has been carried out with the standard European population of 2013, so our data are sufficiently reliable and comparable to permit an inference of mortality trends in most of the population of Europe, at least in the Southern/Mediterranean countries. Mortality data are the only ones that allow assessing such a long series of population, and in the case of cancer, previous studies have shown the quality of these data (Seoane-Mato et al., 2014).

CONCLUSIONS

In conclusion, our study provided a comprehensive analysis of OCOPC mortality trends in the last 40 years in Spain. The similarities and differences shown by OCC and OPC mortality trends in this period could explain the variable influence on exposure to risk factors and the efficacy of available therapeutic tools. Some risk factors involved can be prevented through anti-smoking and alcohol consumption campaigns. As OCC death rates have decreased in males in the past three decades, there is still room for improvement in females and OPC mortality, which have become an increasing health problem. Vaccination campaigns for the prevention of HPV-associated malignancies from 2007 onwards could have a preventive effect that should be

evaluated through mortality trends in coming studies. Nevertheless, while the protective role of the HPV vaccine in preventing OCOPC is still unknown, the rise in OPC mortality advises at least conducting educational campaigns on the routes of HPV transmission and its role in OCOPC. Our findings highlight the importance of closely monitoring these cancers by age group, sex and location, and the necessity of continuing with preventive measures against known risk factors.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

All authors were responsible for the study conception and design; analysis and interpretation of the data; and drafting the manuscript. Antonio Jose Duran-Romero was involved in data acquisition and quality control of data and algorithms. Antonio Jose Duran-Romero and Jose Juan Pereyra-Rodriguez performed the statistical analysis. Pedro Infante-Cossio and Jose Juan Pereyra-Rodriguez contributed to the review and editing of the manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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TABLE LEGENDS

Table 1. Age standardized mortality rates and AAPC for all ages.

Table 2. Age standardized mortality rates and AAPC by sex.

Table 3. Age standardized mortality rates and AAPC by age group.

FIGURE LEGENDS

Figure 1. Joinpoints and mortality trends by genders and location: a) OCOPC; b) OCC; c) OPC; d) Lip; e) Tongue; f) Gingiva; g) Floor of the mouth; h) Other sites of the mouth.

Figure 2. APC models for males and females. Age estimates are expressed as age-specific mortality rates per 100,000. Cohort and period estimates are expressed as multiplicative effects in relation to age estimates: a) OCC; b) OPC.

Figure 3. Mortality rates in males and females per year (deaths per 100,000).

ADDITIONAL SUPPORTING INFORMATION LEGENDS

Supplementary Table S1. OCOPC mortality in Spain between 1979-2018: deaths by genders and locations.

Supplementary Table S2. Goodness-of-fit test for different APC models for OCC and OPC in Spain between 1979-2018.

Supplementary Figure S1. Sex ratio (male/female) for all ages: a) OCC; b) OPC.

Table 1. Age standardized mortality rates and AAPC for all ages.

	1979-1983 ASMR (95% CI)	2014-2018 ASMR (95% CI)	Period of years: AAPC (95% CI)	Join point
OCOPC (all ages)	3.24 (2.97;3.49)	3.45 (3.30;3.64)	1979-1992: 3.3 (2.7;3.9)*	2
			1992-2009: -1.5 (-1.9;-1.2)*	
			2009-2018: -0.2 (-0.9;0.5)	
OCC (all ages)	2.86 (2.62;3.11)	2.42 (2.28;2.59)	1979-1991: 2 (0.7;3.3)*	1
			1991-2018: -1.4 (-1.6;-1.2)*	
OPC (all ages)	0.37 (0.29;0.49)	1.03 (0.92;1.16)	1979-1991: 10.8 (9.2;12.5)*	1
			1991-2018: -0.1 (-0.4;0.2)	

Note. ASMR: age standardized mortality rate per 100,000; AAPC: annual average percentage change; 95% CI: 95% confidence interval.
* $p<0.05$.

Table 2. Age standardized mortality rates and AAPC by sex.

	1979-1983 ASMR (95% CI)	2014-2018 ASMR (95% CI)	Period of years: AAPC (95% CI)	Join point	1979-1983 ASMR (95% CI)	2014-2018 ASMR (95% CI)	Period of years: AAPC (95% CI)	Join point
	Men				**Women**			
OCOPC (all ages)	6.18 (5.67;6.77)	5.47 (5.15;5.82)	1979-1991: 3.3 (2.7;4)*	3	0.99 (0.81;1.21)	1.70 (1.54;1.86)	1979-2018: 1.7 (1.5;1.9)*	0
			1991-2003: -1.5 (-2;-0.9)*					
			2003-2008: -3.9 (-6.4;-1.3)*					
			2008-2018: -0.7 (-1.3;0)*					
OCC (all ages)	5.45 (4.95;6.01)	3.58 (3.30;3.87)	1979-1991: 1.9 (0.9;2.9)*	1	0.93 (0.75;1.17)	1.42 (1.28;1.57)	1979-1981: 16.9 (-5.9;45.3)	4
			1991-2018: -2.4 (-2.6;-2.2)*				1981-1985: -9.9 (-19.6;1)	
							1985-1988: 11.7 (-11.1;40.4)	
							1988-2008: 0.8 (0.2;1.4)*	
							2008-2018: 2.6 (1.6;3.7)*	
OPC (all ages)	0.74 (0.59;0.98)	1.89 (1.70;2.10)	1979-1991: 10.6 (9;12.2)*	3	0.06 (0;0.16)	0.27 (0.21; 0.36)	1979-2018: 3.3 (2.7;3.9)*	0
			1991-2000: 1 (-0.7;2.8)					
			2000-2009: -2.6 (-4.1;-1)*					
			2009-2018: 1.1 (-0.2;2.4)					

Note. ASMR: age standardized mortality rate per 100,000; AAPC: annual average percentage change; 95% CI: 95% confidence interval.
* $p<0.05$.

Table 3. Age standardized mortality rates and AAPC by age group.

	1979-1983 ASMR (95% CI)	2014-2018 ASMR (95% CI)	Period of years: AAPC (95% CI)	Join point
<35 years				
OCOPC	0.09 (0.02;0.17)	0.04 (0;0.11)	1979-1994: -10.1 (-14.1;-5.9)*	1
			1994-2018: 0.7 (-1.9;3.3)	
OCC	0.08 (0.01;0.17)	0.04 (0;0.11)	1979-1982: 32 (-24;129.3)	2
			1982-1992: -16.5 (-24.5;-7.6)*	
			1992-2018: 2.1 (0.1;4.3)*	
OPC	0.01 (0;0.07)	0.00 (0;0.02)	**	-
35-64 years				
OCOPC	3.44 (3.12;3.80)	3.21 (2.94;3.48)	1979-1981: 18.3 (-0.9;41)	2
			1981-1993: 4.1 (3.1;5)*	
			1993-2018: -2.6 (-2.9;-2.4)*	
OCC	2.87 (2.57;3.19)	2.02 (1.82;2.22)	1979-1992: 3.4 (2.3;4.4)*	1
			1992-2018: -3.1 (-3.4;-2.7)*	
OPC	0.57 (0.43;0.73)	1.20 (1.06;1.39)	1979-1991: 11.6 (9.7; 13.5)*	2
			1991-2000: 0.3 (-1.5; 2.1)	
			2000-2018: -2.3 (-2.8; -1.8)*	
>64 years				
OCOPC	9.28 (8.28;10.38)	10.95 (10.27;11.67)	1979-1992: 1.7 (1.1;2.4)*	2
			1992-2008: -0.6 (-1;-0.2)*	
			2008-2018: 1.4 (0.7;2)*	
OCC	8.55 (7.60;9.64)	8.16 (7.57;8.77)	1979-1985: -1.7 (-4.3;0.9)	3
			1985-1991: 2.6 (-0.1;5.5)	
			1991-2008: -1 (-1.4;-0.6)*	
			2008-2018: 0.7 (0.2;1.3)*	
OPC	0.72 (0.49;1.11)	2.80 (2.44;3.18)	1979-1987: 13.1 (7.1;19.3)*	1
			1987-2018: 1.9 (1.5;2.3)*	

Note. ASMR: age standardized mortality rate per 100,000; AAPC: annual average percentage change; 95% CI: 95% confidence interval.
* $p<0.05$.
**Because in several years the age-adjusted rate is "0", Joinpoint regression analysis cannot be performed.