

# **Cigar Smoking and the Risk of Head and Neck Cancer**

**Pooled Analysis in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium**

**Mia Hashibe, PhD**

*Professor, & Director of Research & Practice, Division of Public Health,  
Department of Family and Preventive Medicine*

*Investigator, Cancer Control & Population Sciences, Huntsman Cancer Institute*

*Director of Research Facilitation & Implementation, Utah Cancer Registry*

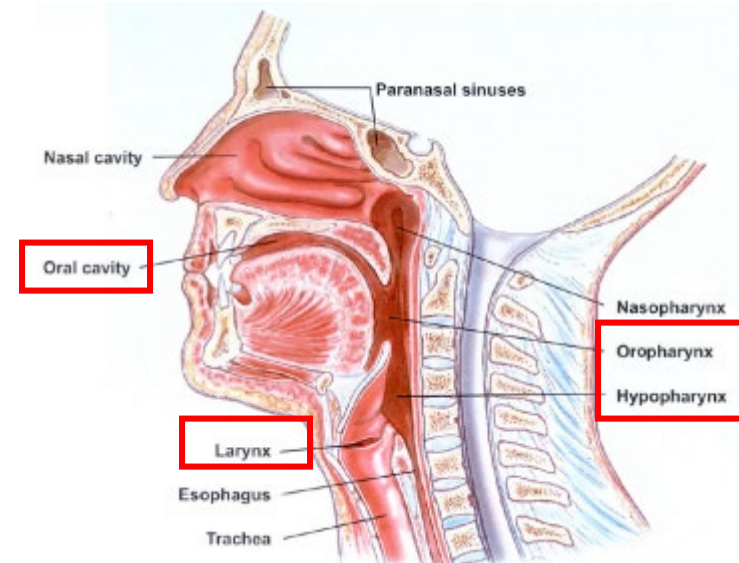
# Disclosures

- **The individual studies in INHANCE were funded by the following grants:**
- Milan and Rome studies: Italian Association for Research on Cancer (Associazione Italiana per la ricerca sul Cancro, AIRC);
- Aviano and Italy Multicenter studies: Italian Association for Research on Cancer (AIRC), Italian League Against Cancer and Italian Ministry of Research;
- Swiss study: Swiss League against Cancer and the Swiss Research against Cancer/Oncosuisse [KFS-700, OCS-1633];
- Central Europe study: World Cancer Research Fund and the European Commission's INCO-COPERNICUS Program [Contract No. IC15- 75 CT98-0332];
- New York study: National Institutes of Health (NIH) US [P01CA068384 K07CA104231];
- Seattle study: National Institutes of Health (NIH) US [R01CA048896, R01DE012609];
- Iowa study: National Institutes of Health (NIH) US [NIDCR R01DE11979, NIDCR R01DE13110, NIH FIRCA TW01500] and Veterans Affairs Merit Review Funds;
- North Carolina study: National Institutes of Health (NIH) US 85 [R01CA61188], and in part by a grant from the National Institute of Environmental Health Sciences [P30ES010126];
- Tampa study: National Institutes of Health (NIH) US [P01CA068384, K07CA104231, R01DE13158];
- Los Angeles study: National Institute of Health (NIH) US [P50CA90388, R01DA11386, R03CA77954, T32CA09142, U01CA96134, R21ES011667] and the Alper Research Program for Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center;
- Houston study: National Institutes of Health (NIH) US [R01ES11740, R01CA131274];
- Puerto Rico study: jointly funded by National Institutes of Health (NIH) US and NIDCR intramural programs;
- Latin America study: Fondo para la Investigacion Cientifica y Tecnologica (FONCYT) Argentina, IMIM (Barcelona), Fundação de Amparo à Pesquisa no Estado de São Paulo (FAPESP) [No 01/01768-2], and European Commission [IC18-CT97-0222];
- IARC Multicenter study: Fondo de Investigaciones Sanitarias (FIS) of the Spanish Government [FIS 97/0024, FIS 97/0662, BAE 01/5013], International Union Against Cancer (UICC), and Yamagiwa-Yoshida Memorial International Cancer Study Grant.
- US multicenter: The Intramural Program of the National Cancer Institute, National Institutes of Health, USA
- São Paulo: São Paulo study (Gencapo): Fundação de Amparo à Pesquisa no Estado de São Paulo (FAPESP) [No 10/51168-0]
- MSKCC: NIH [R01CA51845]
  
- **Current and recent employer(s) and any other affiliation(s):** University of Utah, Huntsman Cancer Institute, Utah Cancer Registry, International Agency for Research on Cancer (IARC), Board Member for NCI PDQ Prevention and Screening

# Head and neck cancer

Number of estimated head and neck cancer cases in the world, Globocan, 2020

	Cases
Oral	377,713
Oropharynx	98,412
Hypopharynx	84,254
Larynx	184,615
<b>TOTAL</b>	<b>744,994</b>



**Head and neck cancer = oral cavity, oropharynx, hypopharynx, larynx**  
**Upper aerodigestive tract cancer (UADT) = oral cavity, pharynx, larynx + esophagus**

**For epidemiologic studies, we combine these sites since they have shared etiology of tobacco and alcohol**

# Previous Literature

- Epidemiologic studies generally support an association between cigar smoking and HNC risk, but studies may be limited by
  - ▣ Small sample sizes, imprecise estimates
  - ▣ Difficulty considering exclusive cigar smokers
- We used the INHANCE pooled data to analyze the association between cigar smoking and HNC
  - ▣ stratified by cigarette smoking,
  - ▣ and among exclusive and predominant cigar smokers.

# Methods

- **INHANCE:** The **I**nternational **H**ead and **N**eck **C**ancer **E**pidemiology (INHANCE) Consortium is a collaboration of research groups leading large scale epidemiology studies of head and neck cancer.
- <https://inhance.utah.edu/>
- Pooled data
- 19 case-control studies
  - 13,935 HNC cases
  - 18,691 controls
- A few centers in the multicenter studies were excluded from analyses of cigar smoking since no cases or controls reported using cigars (811 cases and 1095 controls)

Study Location	N Cases	N Controls
Aviano, Italy	482	855
Central Europe (multicenter)	762	907
Houston, Texas	829	865
IARC (international multicenter)	881	992
Iowa	546	759
Italy (multicenter)	1261	2716
Latin America (multicenter)	2191	1706
Los Angeles, California	417	1004
Milan, Italy	416	1531
New York State (multicenter)	1118	906
New York, New York (MSKCC)	133	168
North Carolina	180	202
Puerto Rico	350	521
Rome, Italy	361	396
Sao Paulo, Brazil	1764	1508
Seattle, Washington	407	607
Switzerland	516	883
Tampa, Florida	207	897
United States (multicenter)	1114	1268



# Statistical Methods I

---

- Hierarchical logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs)
  - Study center included as a random effect to account for heterogeneity across centers
  - Adjusted for age, sex, race/ethnicity, education, alcohol use (mL of ethanol per day), cigarette smoking (years), and pipe smoking (years)

# Statistical methods II

- Cigar Smoking
  - Ever
  - Frequency (times/day)
  - Duration (years)
  - Cumulative (frequency \* duration \* 4g tobacco/cigar )
  
- Analyses of ever, frequency, duration and cumulative cigar smoking were stratified by cigarette smoking

# Statistical methods III

- Exclusive Use
  - Exclusive cigar smoking defined as ever smoking cigars and never smoking cigarettes or pipes
  
- Dominant and Predominant Use
  - Calculated total lifetime tobacco grams from cigarettes, cigars, and pipes consumed based on IARC equivalence estimates
    - Frequency multiplied by duration
    - 1 cigarette = 1 gram
    - 1 cigar = 4 grams
    - 1 pipe = 3.5 grams
  - Dominant cigar use defined as 100% lifetime use of only cigars
  - Predominant cigar use defined as 66.6% to 99.9% of lifetime use of only cigars



# Characteristics of Head and Neck Cancer Cases and Controls in the INHANCE Consortium, 1981–2007

	Cases		Controls	
	n	%	N	%
<b>Race/ethnicity</b>				
Asian/Pacific Islander	49	0.4	84	0.4
Black	581	4.2	674	3.6
Hispanic/Latino	213	1.5	429	2.3
Latin American	3,955	28.4	3,214	17.2
Non-Hispanic white	9,014	64.7	14,124	75.6
Other	123	0.9	166	0.9
<b>Sex</b>				
Male	11,108	79.7	13,025	69.7
Female	2,827	20.3	5,666	30.3

## Cigar Smoking and HNC among Never Cigarette Smokers

	N Cases	N Controls	OR	95% CI
<b>Cigar Smoking</b>				
Never	1,567	6,824	1	Referent
Ever	171	155	2.54	1.93, 3.34
Missing	1	4		
<b>Frequency (cigars/day)</b>				
Never	1,567	6,824	1	Referent
1–10	130	136	1.99	1.47, 2.71
>10	39	14	10.13	4.96, 20.67
Missing	3	9		
P for trend	<0.0001			

Odds ratios adjusted for age, sex, race/ethnicity, education, frequency of alcohol use, duration of pipe smoking.

- ❑ Ever smoking cigars was associated with increased HNC risk
- ❑ HNC risk appeared to increase with increasing frequency

# Cigar Smoking and HNC among Never Cigarette Smokers

Cigar Smoking	N Cases	N Controls	OR	95% CI
<b>Duration (years)</b>				
Never	1,567	6,824	1	Referent
1–10	19	52	0.91	0.51, 1.62
11–20	18	19	2.42	1.18, 4.95
21–30	18	24	1.92	0.95, 3.85
31–40	43	29	3.78	2.18, 6.55
>40	68	27	5.62	3.29, 9.60
Missing	6	8		
P for trend	<0.0001			
<b>Cumulative (cigar-years)</b>				
Never	1,567	6,824	1	Referent
1–10	18	44	0.96	0.52, 1.77
11–20	20	41	1.15	0.63, 2.11
>20	127	64	4.87	3.36, 7.06
Missing	7	10		
P for trend	<0.0001			

Odds ratios adjusted for age, sex, race/ethnicity, education, frequency of alcohol use, duration of pipe smoking.

- HNC risk increased with increasing duration and cumulative use of cigar smoking

# Cigar Smoking and HNC risk among Ever Cigarette Smokers

	N Cases	N Controls	OR	95% CI
<b>Cigar Smoking</b>				
Never	10,525	9,759	1.00	Referent
Ever	779	814	0.90	0.78, 1.02
Missing	15	14		
<b>Frequency (cigars/day)</b>				
Never	10,525	9,759	1.00	Referent
1–10	550	618	0.89	0.77, 1.03
>10	184	155	0.99	0.74, 1.32
Missing	60	55		
P for trend	0.62			

Odds ratios adjusted for age, sex, race/ethnicity, education, frequency of alcohol use, duration of cigarette smoking, duration of pipe smoking.

- Never cigar smokers include cigarette smokers, so the OR is estimating the \*added\* risk of cigar use, but cigar use is fairly infrequent relative to cigarette use

# Cigar Smoking and HNC among Ever Cigarette Smokers

	N Cases	N Controls	OR	95% CI
<b>Duration (years)</b>				
Never	10,525	9,759	1	Referent
1–10	331	391	0.77	0.64, 0.92
11–20	114	130	1.04	0.77, 1.42
21–30	99	113	0.98	0.70, 1.36
31–40	91	78	1.20	0.83, 1.72
>40	123	87	1.04	0.73, 1.48
Missing	36	29		
P for trend	0.63			
<b>Cumulative (cigar-years)</b>				
Never	10,525	9,759	1	Referent
1–10	162	245	0.71	0.56, 0.90
11–20	226	228	0.99	0.79, 1.23
>20	337	296	1.01	0.82, 1.25
Missing	69	59		
P for trend	0.05			

Odds ratios adjusted for age, sex, race/ethnicity, education, frequency of alcohol use, duration of cigarette smoking, duration of pipe smoking.

# Exclusive and Joint Use, and HNC risk

<b>Exclusive/Joint Tobacco Smoking</b>	<b>N Cases</b>	<b>N Controls</b>	<b>OR</b>	<b>95% CI</b>
Never smoker	1,567	7,154	1	Referent
Cigarette, cigar, and pipe	211	277	2.42	1.96, 2.99
Cigarette and cigar	566	541	3.05	2.61, 3.56
Cigarette and pipe	371	445	2.94	2.49, 3.48
Cigar and pipe	61	52	3.44	2.29, 5.17
Cigarette only	10,880	9,996	3.93	3.67, 4.22
Cigar only	110	103	3.49	2.58, 4.73
Pipe only	77	71	3.71	2.59, 5.33
Missing	92	52		

# Dominant and Predominant Use

<b>Dominant/Predominant Tobacco Smoking</b>	<b>N Cases</b>	<b>N Controls</b>	<b>OR</b>	<b>95% CI</b>
Never smoker	1,567	7,154	1	Referent
Predominantly cigarette	659	736	2.88	2.51, 3.30
Only cigarette	10,755	9,895	3.94	3.67, 4.23
Predominantly cigar	131	111	3.22	2.38, 4.35
Only cigar	107	97	3.56	2.62, 4.86
Predominantly pipe	48	50	2.93	1.89, 4.55
Only pipe	75	70	3.67	2.55, 5.28
Less 66.0% for any smoking product	237	261	2.72	2.20, 3.35
Missing	356	317		

# Summary

- Cigar smoking was associated with increased HNC risk
  - Among never cigarette smokers
    - Including dose response trends for frequency, duration and cumulative cigar use
  - Increased HNC risk is observed among exclusive cigar users
    - and among dominant/predominant cigar users
  
- Increased risk of HNC among cigar smokers had magnitude of associations similar to that for cigarette smoking



# Acknowledgements

- Core Analysis and Writing Group
  - Dr. Annah Wyss (NIEHS), Dr. Andrew Olshan (UNC)
  - Dr. Mia Hashibe (Univ of Utah), Dr. Amy Lee (Univ of Utah),
  - Dr. Shu-Chun Chuang (National Health Research Institutes Taiwan), Dr. Paolo Boffetta (Mount Sinai)
- All INHANCE Consortium members
- UICC International Cancer Technology Transfer Fellowship
- INHANCE and study-specific grants
- Reference: Wyss et al, American Journal of Epidemiology, 2013, 178(5):679-90

**Table 1.** Characteristics of Head and Neck Cancer Cases and Controls in the International Head and Neck Cancer Epidemiology Consortium, 1981–2007<sup>a</sup>

<b>Characteristic</b>	<b>No. of Cases</b>	<b>%</b>	<b>No. of Controls</b>	<b>%</b>
Total	13,935		18,691	
Race/ethnicity <sup>b</sup>				
Asian/Pacific Islander	49	0.4	84	0.4
Black	581	4.2	674	3.6
Hispanic/Latino	213	1.5	429	2.3
Latin American	3,955	28.4	3,214	17.2
Non-Hispanic white	9,014	64.7	14,124	75.6
Other	123	0.9	166	0.9
Age, years				
17–39	502	3.6	1,356	7.3
40–44	766	5.5	1,345	7.2
45–49	1,508	10.8	2,042	10.9
50–54	2,169	15.6	2,808	15.0
55–59	2,537	18.2	3,108	16.6
60–64	2,340	16.8	2,827	15.1
65–69	1,936	13.9	2,408	12.9
70–74	1,341	9.6	1,774	9.5
75–96	836	6.0	1,023	5.5

**Table 1.** Continued

Characteristic	No. of Cases	%	No. of Controls	%
Sex				
Male	11,108	79.7	13,025	69.7
Female	2,827	20.3	5,666	30.3
Educational level <sup>c</sup>				
No formal education	280	2.0	190	1.0
Less than junior high school	5,656	40.6	7,081	37.9
Some high school	2,077	14.9	2,267	12.1
High school graduate	1,849	13.3	2,280	12.2
Vocational school, some college	2,068	14.8	3,456	18.5
College graduate/postgraduate	1,278	9.2	2,768	14.8
Missing	730	5.2	651	3.5
Tumor site				
Head and neck (not otherwise specified)	314	2.3		
Hypopharynx	1,026	7.4		
Larynx	3,461	24.8		
Oral cavity	4,110	29.5		
Oral/pharynx (not otherwise specified)	1,190	8.5		
Oropharynx	3,834	27.5		

**Web Table 1. Odds Ratios for Cigar Smoking and Head and Neck Cancer Stratified by Tumor Site, Region, Sex, and Age in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium**

	Never Cigarette Smoking				Ever Cigarette Smoking				
Tumor Site <sup>g</sup>	Cases	Controls	OR <sup>b</sup>	95% CI	Cases	Controls	OR <sup>c</sup>	95% CI	
<b>Oral Cavity</b>									
Never Smoker <sup>f</sup>	600	6824	1.0	Referent	2,931	9,759	1.0	Referent	
Ever Smoker	61	155	<b>2.83</b>	<b>1.91, 4.17</b>	240	814	0.90	0.74, 1.09	
<b>Pharynx</b>									
Never Smoker	541	6,824	1.0	Referent	3,753	9,759	1.0	Referent	
Ever Smoker	71	155	<b>2.34</b>	<b>1.59, 3.42</b>	305	814	0.96	0.80, 1.15	
<b>Hypopharynx</b>									
Never Smoker	58	6,394	1.0	Referent	855	9,076	1.0	Referent	
Ever Smoker	11	139	2.51	0.90, 6.97	52	675	0.83	0.57, 1.22	
<b>Oropharynx</b>									
Never Smoker	483	6,824	1.0	Referent	2,898	9,759	1.0	Referent	
Ever Smoker	60	155	<b>2.31</b>	<b>1.54, 3.45</b>	253	814	0.97	0.80, 1.17	
<b>NOS</b>									
Never Smoker	205	6,824	1.0	Referent	859	9,759	1.0	Referent	
Ever Smoker	21	155	<b>2.52</b>	<b>1.34, 4.74</b>	64	814	0.84	0.60, 1.17	
<b>Larynx</b>									
Never Smoker	178	5,501	1.0	Referent	2,737	7,557	1.0	Referent	
Ever Smoker	17	63	<b>6.31</b>	<b>3.09, 12.92</b>	153	471	0.77	0.59, 1.01	
<b>SCC All Sites</b>									
Never Smoker	1142	5696	1.0	Referent	7,490	8,214	1.0	Referent	
Ever Smoker	146	155	<b>2.77</b>	<b>2.08, 3.71</b>	678	782	0.89	0.77, 1.02	

**Web Table 1. Odds Ratios for Cigar Smoking and Head and Neck Cancer Stratified by Region in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium**

	Never Cigarette Smoking				Ever Cigarette Smoking				
	Cases	Controls	OR <sup>b</sup>	95% CI	Cases	Controls	OR <sup>c</sup>	95% CI	
<b>Europe</b>									
Never Smoker	336	2873	1.0	Referent	3,182	4,010	1.0	Referent	
Ever Smoker	16	16	<b>5.54</b>	<b>2.16, 14.21</b>	282	266	0.99	0.75, 1.29	
Missing	0	1			3	10			
<b>North America</b>									
Never Smoker	854	2,565	1.0	Referent	3,660	3,591	1.0	Referent	
Ever Smoker	117	128	<b>1.50</b>	<b>1.05, 2.15</b>	338	414	0.90	0.74, 1.11	
Missing	1	3			10	4			
<b>South America</b>									
Never Smoker	377	1,386	1.0	Referent	3,683	2,158	1.0	Referent	
Ever Smoker	38	11	-- <sup>i</sup>	-- <sup>i</sup>	159	134	0.69	0.49, 0.98	
Missing	0	0			2	0			

**Web Table 1. Odds Ratios for Cigar Smoking and Head and Neck Cancer Stratified by Sex, and Age in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium**

	Never Cigarette Smoking				Ever Cigarette Smoking				
	Cases	Controls	OR <sup>b</sup>	95% CI	Cases	Controls	OR <sup>c</sup>	95% CI	
<b>Sex</b>									
<b>Female</b>									
<b>Never Smoker</b>	732	3,236	1.0	Referent	1,876	2,091	1.0	Referent	
<b>Ever Smoker</b>	11	2	<b>21.98</b>	<b>4.11, 117.52</b>	29	10	<b>2.56</b>	<b>1.02, 6.42</b>	
<b>Missing</b>	1	2			3	3			
<b>Male</b>									
<b>Never Smoker</b>	835	3,588	1.0	Referent	8,649	7,668	1.0	Referent	
<b>Ever Smoker</b>	160	153	<b>2.44</b>	<b>1.82, 3.26</b>	750	804	0.92	0.80, 1.05	
<b>Missing</b>	0	2			12	11			
<b>Age</b>									
<b>&lt;45 years</b>									
<b>Never Smoker</b>	279	1,157	1.0	Referent	855	1,358	1.0	Referent	
<b>Ever Smoker</b>	5	10	1.78	0.51, 6.20	33	46	1.02	0.57, 1.83	
<b>Missing</b>	0	2			2	3			
<b>≥45 years</b>									
<b>Never Smoker</b>	1,288	5,667	1.0	Referent	9,670	8,401	1.0	Referent	
<b>Ever Smoker</b>	166	145	<b>2.90</b>	<b>2.18, 3.86</b>	746	768	0.87	0.76, 0.99	
<b>Missing</b>	1	2			13	11			