

***Supplementary Material***

**Opium Use and the Risk of Head and Neck Squamous Cell Carcinoma**

Elham Mohebbi\*, Maryam Hadji\*, Hamideh Rashidian, Abass Rezaianzadeh, Maryam Marzban, Ali Akbar Haghdoost, Ahmad Naghibzadeh Tahami, Abdolvahab Moradi, Mahin Gholipour, Farid Najafi, Roya Safari-Faramani, Reza Alizadeh-Navaei, Alireza Ansari-Moghaddam, Mahdieh Bakhshi, Azim Nejatizadeh, Masumeh Mahmoudi, Soodabeh Shahidsales, Saeideh Ahmadi-Simab, Ali Asghar Arabi Mianroodi, Monireh Sadat Seyyedsalehi, Bayan Hosseini, Vahideh Peyghambari, Mohammad Shirkhoda, Reza Shirkoohi, Elmira Ebrahimi, Soheila Manifar, Mohammad Ali Mohagheghi, Laura Rozek, Paul Brennan, Hossein Poustchi, Arash Etemadi, Eero Pukkala, Joachim Schüz, Reza Malekzadeh, Elisabete Weiderpass, Afarin Rahimi-Movaghar, Paolo Boffetta, Farin Kamanagar, Kazem Zendehei\*\*

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Supplementary Table 1- The association of opium use with laryngeal squamous cell carcinoma by larynx anatomy.

	Controls N (%)	Supraglottis (76 cases)		Glottis (102 cases)		Larynx, NOS (85 cases)		Other sub-sites of Larynx * (64 cases)	
		Cases N (%)	Adjusted OR <sup>†</sup> (95%CI)	Cases N (%)	Adjusted OR (95%CI)	Cases N (%)	Adjusted OR (95%CI)	Cases N (%)	Adjusted OR (95%CI)
<b>Regular Opium Use ‡</b>									
<b>Non- user §</b>	2664 (86.92)	10 (13.16)	Referent	38 (37.25)	Referent	26 (30.59)	Referent	22 (34.38)	Referent
<b>Regular user   </b>	401 (13.08)	66 (86.84)	18.27 (8.23 to 40.53)	64 (62.75)	6.20 (3.61 to 10.63)	59 (69.41)	4.38 (2.49 to 7.70)	42 (65.62)	7.89 (4.21 to 14.77)
<b>P for heterogeneity</b>			<0.0001		<0.0001		<0.0001		<0.0001
<b>Duration of opium use (Year)</b>									
<b>1<sup>st</sup> Tertile (≤11)</b>	143 (35.66)	11(16.67)	Referent	10 (15.63)	Referent	8 (13.56)	Referent	6 (14.29)	Referent
<b>2<sup>nd</sup> Tertile (12-23)</b>	127 (31.67)	20 (30.30)	1.31 (0.53 to 3.23)	28 (43.75)	2.45 (0.95 to 6.29)	20 (33.90)	2.11 (0.84 to 5.29)	12 (28.57)	1.67 (0.51 to 5.44)
<b>3<sup>rd</sup> Tertile (≥24)</b>	131 (32.67)	35 (53.03)	2.16 (0.92 to 5.08)	26 (40.72)	2.02 (0.75 to 5.39)	31 (52.54)	4.11 (1.64 to 10.30)	24 (57.14)	4.59 (1.46 to 14.40)
<b>P trend ¶</b>			0.06		0.21		0.002		0.006
<b>P for heterogeneity</b>			<0.0001		<0.0001		<0.0001		<0.0001
<b>Cumulative use # (Gram-Year)</b>									
<b>1<sup>st</sup> Tertile (≤3.6)</b>	134 (33.42)	9 (13.64)	Referent	6 (9.38)	Referent	7 (11.86)	Referent	4 (9.52)	Referent
<b>2<sup>nd</sup> Tertile (3.7- 24.4)</b>	134 (33.42)	22 (33.33)	1.68 (0.66 to 4.22)	19 (29.69)	3.35 (1.04 to 10.79)	22 (37.29)	2.68 (1.04 to 6.91)	14 (33.33)	2.60 (0.73 to 9.30)
<b>3<sup>rd</sup> Tertile (≥24.5)</b>	133 (33.16)	35 (35.03)	1.58 (0.62 to 3.99)	39 (60.94)	3.57 (1.14 to 11.20)	30 (50.85)	2.67 (1.01 to 7.10)	24 (57.14)	3.68 (1.04 to 13.01)
<b>P trend</b>			0.42		0.05		0.07		0.04
<b>P for heterogeneity</b>			<0.0001		<0.0001		<0.0001		<0.0001
<b>Frequency-Year**</b>									
<b>1<sup>st</sup> Tertile (≤8)</b>	138 (34.41)	4 (6.06)	Referent	6 (9.38)	Referent	2 (3.39)	Referent	2 (4.76)	Referent
<b>2<sup>nd</sup> Tertile (8.1-22)</b>	130 (32.43)	14 (21.21)	3.20 (0.96 to 10.59)	10 (15.62)	1.85 (0.54 to 6.34)	10 (16.95)	4.75 (0.99 to 22.69)	9 (21.43)	4.89 (0.92 to 25.91)
<b>3<sup>rd</sup> Tertile(≥23)</b>	133 (33.16)	48 (72.73)	6.64 (2.18 to 20.19)	48 (75.00)	6.47 (2.20 to 19.00)	47 (79.66)	19.63 (4.50 to 85.59)	31 (73.81)	11.63 (2.47 to 54.69)
<b>P trend</b>			<0.0001		<0.0001		<0.0001		<0.0001
<b>P for heterogeneity</b>			<0.0001		<0.0001		<0.0001		<0.0001

**Cont. Supplementary Table 1- The association of opium use with laryngeal squamous cell carcinoma by parts of larynx.**

	Controls N (%)	Supraglottis (76 cases)		Glottis (102 cases)		Larynx, NOS (85 cases)		Other sub-sites of Larynx * (64 cases)	
		Cases N (%)	Adjusted OR † (95%CI)	Cases N (%)	Adjusted OR(95%CI)	Cases N (%)	Adjusted OR (95%CI)	Cases N (%)	Adjusted OR (95%CI)
<b>Average intensity (gram/day)</b>									
<b>1<sup>st</sup> Tertile (≤0.4)</b>	150 (37.41)	12 (18.18)	Referent	10 (15.62)	Referent	16 (27.12)	Referent	6 (14.29)	Referent
<b>2<sup>nd</sup> Tertile (0.5-2)</b>	118 (29.43)	26 (39.40)	1.93 (0.80 to 4.69)	21 (32.81)	1.55 (0.57 to 4.16)	20 (33.90)	0.96 (0.43 to 2.12)	16 (38.10)	2.59 (0.85 to 7.86)
<b>3<sup>rd</sup> Tertile (≥2)</b>	133 (33.16)	28 (42.42)	1.13 (0.45 to 2.82)	33 (51.57)	1.45 (0.54 to 3.85)	23 (38.98)	0.78 (0.33 to 1.80)	20 (47.62)	2.04 (0.64 to 6.53)
<b>P trend</b>			0.94		0.53		0.54		0.31
<b>P for heterogeneity</b>			<0.0001		<0.0001		<0.0001		<0.0001
<b>Type of opium used</b>									
<b>Non-user</b>	2664 (86.92)	10 (13.16)	Referent	38 (37.25)	Referent	26 (30.59)	Referent	22 (34.38)	Referent
<b>Crude opium (Teriak)</b>	360 (11.75)	56 (73.68)	16.97 (7.56 to 38.12)	49 (48.04)	5.31 (3.03 to 9.31)	48 (56.47)	3.92 (2.19 to 7.02)	29 (45.31)	5.88 (3.00 to 11.51)
<b>Opium juice (Shireh)</b>	41 (1.33)	10 (13.16)	30.09 (10.03 to 90.27)	15 (14.71)	14.55 (5.96 to 35.54)	11 (12.94)	8.47 (3.45 to 20.78)	13 (20.31)	24.99 (10.07 to 62.00)
<b>P for heterogeneity</b>			<0.0001		<0.0001		<0.0001		<0.0001
<b>Route of opium use</b>									
<b>Non-user</b>	2664 (86.92)	10 (13.16)	Referent	38 (37.25)	Referent	26 (30.59)	Referent	22 (34.38)	Referent
<b>Only smoking</b>	337 (11.00)	33 (43.42)	10.37 (4.48 to 24.00)	40 (39.22)	4.65 (2.61 to 8.26)	28 (32.94)	2.53 (1.34 to 4.78)	24 (37.50)	5.49 (2.76 to 10.1)
<b>Only oral ingestion</b>	28 (0.91)	12 (15.79)	72.34 (24.09 to 217.25)	4 (3.92)	13.12 (3.39 to 50.78)	8 (9.41)	11.17 (4.01 to 31.09)	1 (1.56)	4.92 (0.54 to 44.56)
<b>Both routes</b>	36 (1.17)	21 (27.63)	52.92 (19.48 to 143.73)	20 (19.61)	27.05 (10.99 to 66.55)	23 (27.06)	17.42 (7.93 to 38.26)	17 (26.56)	40.12 (15.57 to 103.41)
<b>P for heterogeneity</b>			<0.0001		<0.0001		<0.0001		<0.0001

\* Other sub-sites included sub-glottis, laryngeal cartilage, and overlapping lesions of larynx.

† Random-effect odds ratio. adjusted for age(categorical), gender (categorical), place of residence (categorical), pack-years of cigarette smoking (continuous), head-years of water-pipe smoking (continuous), regular alcohol drinking (categorical), socioeconomic status (categorical), and oral health (DMF index: continuous). Likelihood heterogeneity test by center.

‡ Regular opium use: using opium at least once a week for at least a six-month consecutive period during the lifetime.

§ Non-user included non-regular users.

|| After reclassifying opium users who started opium use within three- year prior cancer diagnosis.

¶ P trend: P-values for trend were obtained from adjusted models by assigning values of 1, 2, and 3 to low use (T1), moderate use (T2), and high use (T3), respectively.

# Cumulative use: Total frequency of opium use (per day) multiplied amount (gram) of opium, then multiplied total duration (year).

\*\* Frequency-Year: Total frequency of opium use (per day) multiplied total duration (year)

**Supplementary Table 2- The association of opium use with head and neck squamous cell carcinoma among never tobacco smokers including cigarette and water-pipe smoking.**

	HNSCC Case * N (%)	Controls N (%)	Adjusted OR <sup>†</sup> (95%CI <sup>‡</sup> )
Total	246	1964	
Regular Opium Use <sup>§</sup>			
Non user <sup>  </sup>	207 (84.15)	1859 (94.65)	Referent
Regular user <sup>¶</sup>	39 (15.85)	105 (5.35)	5.17 (3.26 to 8.21)
P for heterogeneity			<0.0001
Duration of opium use (year)			
1 <sup>st</sup> Tertile (≤11)	15 (38.46)	49 (46.67)	Referent
2 <sup>nd</sup> Tertile (12-23)	11 (28.21)	24 (22.86)	2.11 (0.68 to 6.49)
3 <sup>rd</sup> Tertile (≥24)	13 (33.33)	32 (30.47)	2.70 (0.95 to 7.65)
P trend <sup>#</sup>			0.05
P for heterogeneity			<0.0001
Cumulative use <sup>**</sup> (Gram-Year)			
1 <sup>st</sup> Tertile (≤3.6)	11 (28.21)	41 (39.05)	Referent
2 <sup>nd</sup> Tertile (3.7- 24.4)	17 (43.58)	38 (36.19)	2.08 (0.77 to 5.59)
3 <sup>rd</sup> Tertile (≥24.5)	11 (28.21)	26 (24.76)	2.42 (0.80 to 7.35)
P trend			0.10
P for heterogeneity			<0.0001
Frequency-Year <sup>††</sup>			
1 <sup>st</sup> Tertile (≤8)	8 (20.51)	40 (38.10)	Referent
2 <sup>nd</sup> Tertile (8.1-22)	11 (28.21)	39 (37.14)	1.91 (0.61 to 6.02)
3 <sup>rd</sup> Tertile (≥23)	20 (51.28)	26 (24.76)	6.27 (2.03 to 19.39)
P trend			0.001
P for heterogeneity			<0.0001
Average intensity (gram/day)			
1 <sup>st</sup> Tertile (≤0.4)	17 (43.59)	50 (47.62)	Referent
2 <sup>nd</sup> Tertile (0.5-2)	9 (23.08)	32 (30.48)	0.57 (0.16 to 2.01)
3 <sup>rd</sup> Tertile (≥2)	13 (33.33)	23 (21.90)	1.71 (0.50 to 5.80)
P trend			0.26
P for heterogeneity			<0.0001
Type of opium used			
Non-user	207 (84.15)	1859 (94.65)	Referent
Crude opium (Teriak)	35 (14.23)	94 (4.79)	5.11 (3.16 to 8.26)
Opium juice (Shireh)	4 (1.62)	11 (0.56)	5.79 (1.71 to 19.57)
P for heterogeneity			<0.0001
Route of opium use			
Non-user	207 (84.15)	1859 (94.65)	Referent
Smoking only	20 (8.13)	86 (4.38)	3.39 (1.93 to 5.95)
Only oral ingestion	6 (2.44)	12 (0.61)	6.45 (2.21 to 18.82)
Both routes	13 (5.28)	7 (0.36)	24.78 (9.18 to 66.89)
P for heterogeneity			<0.0001

\* HNSCC: head and neck squamous cell carcinoma. Cases and controls were frequently matched on age, gender, and place of residence.

<sup>†</sup> Random-effect odds ratio. adjusted for age(categorical), gender (categorical), place of residence (categorical), pack-years of cigarette smoking (continuous), head-years of water-pipe smoking (continuous), regular alcohol drinking (categorical), socioeconomic status (categorical), and oral health (DMF index: continuous). Likelihood heterogeneity test by center.

<sup>‡</sup> 95% CI:95% confidence interval.

<sup>§</sup>Regular opium use: using opium at least once a week for at least a six-month consecutive period during the lifetime.

<sup>||</sup> Non-user included non-regular users.

<sup>¶</sup> After reclassifying opium users who started opium use within three-year prior cancer diagnosis.

<sup>#</sup> P trend: P-values for trend were obtained from adjusted models by assigning values of 1, 2, and 3 to low use (T1), moderate use (T2), and high use (T3), respectively.

<sup>\*\*</sup> Cumulative use: Total frequency of opium use (per day) multiplied amount (gram) of opium and total duration (year).

<sup>††</sup> Frequency-Year: Total frequency of opium use (per day) multiplied total duration (year).