Effects of smoking and drinking on oropharyngeal cancer outcome by HPV serostatus

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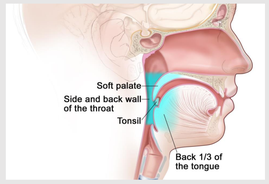
Background

Oropharyngeal Cancer (OPC)



- Worldwide in 2018[1]:
  92,887 Cases
  51,005 Deaths

Risk Factors

Human Papillomavirus (HPV) Infection

- Most common STI in the US and Worldwide[2]
- Latent infections with high-risk HPV strain has been associated with multiple cancers[2]

HPV and OPCs

- HPV DNA isolated from >70% of new OPC cases[3]
- HPV16 has been causally associated with OPCs[3]
- HPV positive [HPV(+)] OPCs tend to have better outcomes than HPV negative [HPV(-)] OPCs[2]
- De-escalation strategies are being evaluated to reduce morbidity[4]
- Smoking and alcohol use may modify survival in HPV(+) OPC[4]
  - A 10 pack-years smoking cutoff for risk stratification has previously been proposed[5]

Aims

- **Describe the epidemiologic differences between HPV(+) and HPV(-) OPC patients**
- **Investigate the relationships between smoking and alcohol history at diagnosis and survival related to HPV status of OPCs**

Methods

Prospective Cohort Study

371 OPC-diagnosed participants recruited from UPMC otolaryngology clinics from 2005 – 2014

↓

Data at diagnosis collected by face-to-face interview

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Antibodies against HPV 16 and 18 E1, E2, E6, and E7 detected by multiplex serology method[6]

↓

HPV(+) defined as high HPV16 E6 (MFI>1000) positivity or type-specific 3 out of 4 HPV16/18 E1, E2, E6, or E7 positivity

↓

Follow-up data abstracted from medical records and other primary resources by certified cancer registrar

Results

Table 1: Participant Characteristics

	HPV SEROSTATUS				
	Positive (n=243)		Negative (n=128)		
	n	%	n	%	P-val[a]
Sex					**<0.0001**
Male	209	86.0	79	61.7	
Female	34	14.0	49	38.3	
Age, years					**0.005**
Median	56.1		59.4		
IQR	50.4 – 61.8		52.2 – 66.3		
Range	36.5 – 76.2		21.1 – 79.5		
Smoking Status					**<0.0001**
Never	95	39.1	28	21.9	
Former	84	34.6	30	23.4	
Current	64	26.3	70	54.7	
Pack-years Smoked					**<0.0001**
Median	4.3		34.1		
IQR	0 – 33		5.4 – 52.1		
Range	0 – 110.4		0 – 102		
Drinking Status					0.332
Never	48	19.8	18	14.1	
Former	63	25.9	32	25	
Current	132	54.3	78	60.9	
Drinking Intensity (Drinks/Day)					0.114
Median	0.86		1.43		
IQR	0.29 – 2.86		0.86 – 4		
Range	0 – 25		0 – 24		
Follow-up Time (years)					**0.011**
Median	4.43		3.59		
Range	0.12 – 14.30		0.12-11.94		

[a] t-test for continuous variables, and Chi-square test for categorical variables.

Table 2: Univariate Cox Regression Survival Analysis

	HPV SEROSTATUS			
	Positive (n=243)		Negative (n=128)	
	HR	95% CI	HR	95% CI
Overall Mortality Hazard	Ref		**3.03**	**2.10 – 4.37**
Age, years	**1.042**	**1.008 – 1.078**	**1.034**	**1.009 – 1.060**
Sex				
Male	Ref		Ref	
Female	0.878	0.39 – 1.97	0.716	0.43 – 1.19
Pack-years Smoked	1.009	0.999 – 1.018	1.007	0.999 – 1.015
Pack-years Categorized				
< 10	Ref		Ref	
≥ 10	**1.88**	**1.07-3.31**	**3.32**	**1.69-6.54**
< 2	Ref		Ref	
≥ 2	**2.78**	**1.45 – 5.34**	**4.86**	**2.08 – 11.36**
Drinking Intensity (Drinks/Day)	**1.062**	**1.007 – 1.120**	**1.093**	**1.020 – 1.170**
Drink Intensity Categorized				
< 1	Ref		Ref	
≥ 1	1.27	0.73 – 2.22	**1.99**	**1.16 – 3.39**

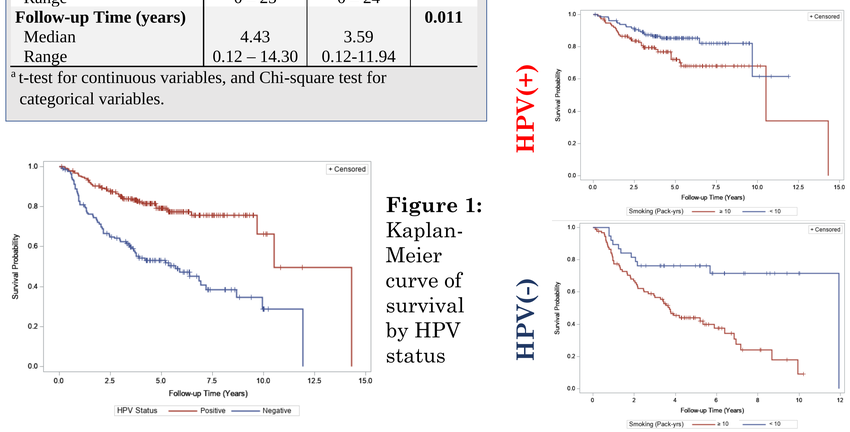

Figure 1: Kaplan-Meier curve of survival by HPV status

Figure 2: Kaplan-Meier curves showing the association between survival and smoking categorized by 10 pack-years

Table 3: Age and Sex Adjusted Cox Regression

	HPV SEROSTATUS			
	Positive (n=243)		Negative (n=128)	
	HR	95% CI	HR	95% CI
Overall Mortality Hazard	Ref		**2.92**	**2.00 – 4.27**
Pack-years Smoked	1.006	0.997 – 1.016	1.004	0.996 – 1.012
Pack-years Categorized				
< 10	Ref		Ref	
≥ 10	1.70	0.96 – 3.01	**2.89**	**1.44 – 5.82**
< 2	Ref		Ref	
≥ 2	**2.57**	**1.33 – 4.95**	**4.38**	**1.84 – 10.41**
Drinking Intensity (Drinks/Day)	**1.065**	**1.01 – 1.122**	**1.109**	**1.028 – 1.196**
Drink Intensity Categorized				
< 1	Ref		Ref	
≥ 1	1.338	0.748 – 2.392	**1.879**	**1.055 – 3.346**

Table 4: Age, Sex, and TNM Cancer Stage Adjusted Cox Regression

	HPV SEROSTATUS			
	Positive (n=243)		Negative (n=128)	
	HR	95% CI	HR	95% CI
Overall Mortality Hazard	Ref		**2.94**	**1.94 – 4.46**
Pack-years Smoked	1.007	0.997 – 1.017	0.998	0.989-1.008
Pack-years Categorized				
< 10	Ref		Ref	
≥ 10	1.54	0.85 – 2.80	1.91	0.90 – 4.07
< 2	Ref		Ref	
≥ 2	**2.27**	**1.14 – 4.51**	**2.85**	**1.16 – 7.04**
Drinking Intensity (Drinks/Day)	**1.074**	**1.017 – 1.135**	**1.111**	**1.021 – 1.209**
Drink Intensity Categorized				
< 1	Ref		Ref	
≥ 1	1.29	0.70 – 2.39	1.81	0.97 – 3.36

Results

- Compared to HPV(-) OPC patients, HPV(+) patients were **(Table 1)**:
  - Younger
  - More likely to be male
  - Less likely to be current smokers
  - Less intense smokers (fewer pack-years smoked)
  - Similar in drinking status and intensity
- HPV positivity was predictive of better survival **(Figure 1)**
- By univariate Cox proportional hazards regression **(Table 2):**
  - Pack-years smoked was not a significant predictor of OPC survival in either group
  - Cutoff values of 2 or 10 pack-years were significant predictors in both groups
  - Drinking intensity was a significant predictor of OPC survival in both groups
- After adjustment, the 10 pack-years cutoff was no longer predictive of survival, but the 2 pack-years cutoff remained predictive for both HPV(+) and HPV(-) OPCs **(Tables 3 and 4)**
- In Age and Sex adjusted analyses, smoking had a greater influence on survival for HPV(-) OPCs than for HPV(+) OPCs, but this effect was reduced when adjustment was made for TNM Stage **(Tables 3 and 4)**
- The association of drinking intensity with OPC survival holds after adjusting for Age, Sex, and TNM Stage (**Table 4)**
- A drinking intensity cutoff value of 1 was not predictive of survival after Age, Sex, and TNM Stage adjustment **(Table 4)**

Conclusions

- A 2 pack-years cutoff is more predictive of OPC survival than a 10 pack-years cutoff or continuous pack-years variable
  - This may indicate that the currently-used cutoff is set too high
- A continuous drinking intensity variable may represent changes in OPC survival better than a cutoff value
- These results can help inform the development of methods to identify candidates for treatment de-escalation

Strengths

- Survival data available on patients over a long period of follow-up
- High level of data completeness from study participants due to interview-based acquisition method

Limitations

- Self-reported pack-years and drinking intensity may suffer from recall bias
- Drinking intensity (drinks/day) does not represent cumulative lifetime alcohol exposure or variations in drinking habit

References / Acknowledgements

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