

UCLA

UCLA Electronic Theses and Dissertations

Title

Dark-Colored Alcohol Drink and Lung and Head and Neck Cancers: A Case-Control Study in Los Angeles County

Permalink

<https://escholarship.org/uc/item/0hn66641>

Author

Pan, Yancen

Publication Date

2021

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Dark-Colored Alcohol Drink and Lung and Head and Neck Cancers:

A Case-Control Study in Los Angeles County

A thesis submitted in partial satisfaction

of the requirement for the degree Master of Science in Epidemiology

by

Yancen Pan

2021

ABSTRACT OF THE THESIS

Dark-Colored Alcohol Drink and Lung and Head and Neck Cancers: A Case-Control Study in Los Angeles County

by

Yancen Pan

Master of Science in Epidemiology

University of California, Los Angeles, 2021

Professor Zuo-Feng Zhang, Chair

Background: Alcohol beverage has been defined as group 1 carcinogen by IARC, along with cumulated epidemiological data indicating that head and neck cancer is an alcohol-related cancer. There is a weak relationship between alcohol consumption and lung cancer. However, there are few studies on the carcinogenic effect of different-colored alcohol, and little is known about the mechanism of carcinogenicity for different ingredients in alcohols, especially the color contents produced in the fermentation or brewing processing.

Methods: From 1999 to 2004, newly diagnosed lung cancer and head and neck cancer cases, as well as population controls, were recruited from Los Angeles County. A total of 611 lung cancer cases, 601 head and neck cancers and 1,040 healthy controls were interviewed by a structured questionnaire, including detailed alcohol consumption information. After adjusting potential

confounders, adjusted odds ratios (ORs) and 95% confidence intervals (95% CL) were estimated by unconditional logistic regression. Results: After adjusted for age, education, ethnicity, gender, smoking status and tobacco consumption, dark-colored alcohol drinking was negatively associated with lung cancer (OR for always and most drinking dark-colored alcohol = 0.613; 95% CL: 0.438, 0.858). For specific alcohol type, along with the increasing frequency of drinking dark-colored wine, the inverse associations become stronger for dark-colored wine (ORs = 0.771, 0.719, 0.484 in never, half or less, and always and most group V.S. non-drinkers). For head and neck cancer, the patterns of observed associations were similar between dark-colored wine and beer/liquor and also consistent with associations between all types of alcohols and head and neck cancers.

Conclusion: the overall dark-colored alcohols and specifically in wine are inversely associated with lung cancer, indicating “anti-cancer” properties of dark-colored alcohol beverages. More research is needed to conduct in-depth studies on potential mechanisms of different types of dark-colored alcohol for potential preventive measures

The thesis of Yancen Pan is approved.

Roch Arnaud Kibsa Nianogo

Jian Yu Rao

Zuo-Feng Zhang, Committee Chair

University of California, Los Angeles

2021

CONTENTS

I. Introduction	1
II. Methods	3
1 . Study population	3
2 . Data collection and Specific Variables	4
3 . Statistical Analysis.....	5
III. Results	6
IV. Discussion	16

LIST OF TABLES

Table 1. Distribution of demographic and consumption variables for cancer cases and controls.....	10
Table 2. Association (estimated as adjusted OR and 95% CLs) between frequency of dark-colored alcohols consumption and cancer incidence.....	12
Table 3. Association (estimated as adjusted OR and 95% CLs) between frequency of dark-colored beer/liquor consumption and cancer incidence	13
Table 4. Association (estimated as adjusted OR and 95% CLs) between frequency of dark-colored wine consumption and cancer incidence	14
Table 5. Association (estimated as adjusted OR and 95% CLs) between the amount of alcohol consumption and cancer incidence	15

I. Introduction

Alcohol beverage is defined as group 1 carcinogen by IARC [1-2], along with cumulated epidemiological data indicating that it is an established risk factor for head and neck cancer [3]. According to WHO data, beer is the most widely consumed in the United States in 2016, followed by distilled alcohol, such as liquors [4]. However, although there were studies indicated the independent associations between head and neck cancer and the consumption of beer, wine or liquor [5], most studies only focus on the carcinogenic effect of alcohol, and there has been a few studies indicating the carcinogenic effect of different-colored alcohol [6], and little is known about the mechanism of carcinogenicity for different ingredients in alcohols, especially the color contents produced in the fermentation or brewing processing.

The dark color comes from deeply roasted malt of beer and liquor or from natural pigment of wine. For beer or liquor, the process of roasting is called Maillard Reaction, which produces carcinogenic products, such as acrylamide, a group 2A carcinogen [7-10]. So, those dark-colored alcohol may contain some carcinogens, which might be an independent of the carcinogenic effect of alcohol. And other color-producing processes, such as burned in peat or aged in charred oak barrels, may be possibly generate some carcinogens [6]. However, some evidence also shows that some of the Maillard

Reaction Products (MRPs) may have antioxidation, which help to stabilize beer in the process of brewing, and MRPs with higher antioxidative capacity exhibit superior antimutagenic activity [11-12].

On the other hand, red wine, consisting complex compounds such as resveratrol, exhibits chemopreventive and therapeutic effects against cancer, because resveratrol is a kind of natural polyphenols derived from grapes [13]. An experimental study also indicated that a natural polyphenol compound ellagic acid (EA) inhibited lung cancer cell proliferation [14]. However, besides lung cancer, more population-based studies are needed to test and confirm the potential protective effect of other cancer types.

There have been few studies focusing on the potential effect of colored alcohol beverages. A study found that the risk of hypopharyngeal cancer was much stronger for individuals with high consumption of dark alcohol [6]. However, it would be worthwhile to examine other types of cancer sites such as lung cancer.

Therefore, the objective of this study is to determine the association between the consumption frequency of dark-colored alcohol and cancers, specifically, lung cancer and head and neck cancer.

II. Methods

1. Study population

From 1999 to 2004, newly diagnosed lung cancer and head and neck cancer cases were recruited from Los Angeles County, as well as the population-based controls without histories of lung cancer or head and neck cancer. There are previous studies and publications describing details about the process of recruitment and data collection [15]. Specifically, all the participants were living in LA County at the time of cancer diagnosis, and those participants were 18-65 years old during the enrollment. Participants should be able to speak English or Spanish, or should have available translators. The cases of lung cancer and head and neck cancer were histologically confirmed and recruited by the rapid ascertainment system of University of Southern California (USC) Cancer Surveillance Program. Controls were LA residents and were originally matched to the cases by three characteristics: age (10-year intervals), sex and neighborhood. The original study identified 1556 lung cancer cases, 1301 head and neck cancer cases and 1321 population controls. Among all eligible subjects, the participation rates were 39 % (611 of 1556) for lung cancer, 46% for head and neck cancer (601 of 1301), and 79 % (1040 of 1321) for controls. In order to increase the power, the matches were broken and the controls for both cancers were included in the analysis. The study were approved by the Institutional Review Boards (IRBs) of the University of California, Los Angeles (UCLA) and UCS; all the participants provided written informed consent [16].

2. Data collection and Specific Variables

Face-to-face in-person interviews were conducted by trained interviewers using a standard questionnaire. Demographic factors, details about overall alcohol consumption, and about dark-colored beer, liquor and wine consumption were collected. Other information, including tobacco smoking histories (cigarette, cigar, and pipe), occupational and environmental exposures and medical histories, were also collected. The amount of smoking was transformed into pack-year, which is defined as the number of packs of cigarette consumed per day multiplying the corresponding smoking year. The amount of alcohol consumption was transformed into drink-year, which is defined as the number of drinks of alcohol consumed per day multiplying the corresponding drinking years.

We categorized liquors into light-colored and dark-colored. For example, whiskeys, dark rum, and cognac are dark-colored liquors, while vodka, gin, and light rum are light-colored liquors; We also classified beers as dark and light, and classified wines into dark/red wines and light/white wines.

Participants were asked if they have ever been a time when they have had at least one alcoholic drink (including beer, wine, or liquor) per month for a period of at least six months, and those who answered “No” in this question would be defined as Non-drinkers. Then, those who answered “Yes” in this question (those who were drinkers) were asked details about their alcohol consumptions,

including what types of alcohol they drank (beer, liquor or wine), and the ages of starting, changing or quitting the specific type of alcohol. And the drinkers were also asked the number, unit and frequency of the relevant alcohol consumption specifically. For beer, wine or liquor drinkers, the questionnaire also asked how often they had used to drink dark-colored beer/wine/liquor. Participants should choose the frequency of dark-colored alcohol consumption within choices of “Don’t drink”, “Never”, “Less than half”, “About half”, and “Most of the time or always”. Then, we combined beer, wine and liquor as overall dark-colored alcohol. Those who never drank any types of alcohol were defined as “Never” drinkers, and those who always or mostly drank at least one of three dark-colored alcohols (dark-colored beer, liquor or wine) were defined as “Always and Mostly” drinkers. Then the subjects who were in between of “Never” and “Always and Mostly”, were defined as “Half or Less” drinkers.

3. Statistical Analysis

The association between the frequency of drinking dark-colored alcohol and cancers was tested by adjusted odds ratios (ORs) and 95% confidence intervals (95% CL), which were estimated by unconditional logistic regression to increase the power, compared to standard matched analysis. As potential confounders, these were the covariates included into the model: age, gender, race/ethnicity,

educational level, and cigarette smoking. Age and gender (categorical) were the matching variables, and to minimize the age confounding and to account for the age-matching, it was stratified into 15 fine categories (<34, 35-36, 37-38, 39-40, 41-42, 43-44, 45-46, 47-48, 49-50, 51-52, 53-54, 55-56, 57-58, and 59-62). [15] Race/ethnicity (Non-Hispanic White, Mexican, African American, Asian, Other) and education level (Less than High School, High School, College, Graduate and More) were both categorical. Smoking included tobacco smoking status (categorical as ever/never), and tobacco consumptions (continuous as pack-years). For exposure variables, including DarkBeerFreq/RedWineFreq/ DarkLiquorFreq (how often did participants drink dark-colored beers/wine/liquor), P_{trend} was estimated for a dose-response association. All the reported P values were based on two-sided tests, and all analysis was performed by the SAS (version 9.4) .

III. Results

The distribution of the selected demographic factors and the consumption variables (alcohol and cigarette), as well as the consumption frequency of dark-colored alcohols are showed for both types of cancer cases and controls in Table 1. Most subjects were more than or equal to 47 years old, and cases were older than controls. Most subjects were non-Hispanic Whites, followed by African Americans or Mexicans. Almost half of lung cancer cases (49.59%) were males, while about three

quarters (75.54%) of head and neck cancer cases and more than half (59.9%) of the controls were males. In terms of education, most subjects completed college, and controls had higher education level than both cancer cases. As expectation that smoking is a risk factor for many cancer types, the cases of both cancers were more likely to smoke heavily than controls, and lung cancer cases were more likely to consume more cigarette than head and neck cases. For alcohol drinking, the cases of both cancers were likely to drink more alcohol than controls, and head and neck cancer cases drank more alcohol than lung cancer cases. For the frequency of drinking dark-colored alcohol, subjects drank dark-colored alcohol in different ranges of frequency, and more than one third subjects drank dark-colored alcohol “more than half” or “always and mostly” in their daily alcohol drinking.

Adjusted associations (estimated as adjusted odd ratios and 95% CLs) between each type of cancer and dark-colored alcohol are shown in Table 2. When adjusted for age, education, ethnicity, gender, smoking status and tobacco consumption, the ORs of all non-reference lung cancer groups were less than 1, while the ORs of all non-reference head and neck cancer groups were larger than 1. Compared with non-drinkers, those always and mostly drank dark-colored alcohol were negatively associated with lung cancer, with the estimated ORs 0.613 (95% CL: 0.438, 0.858), but the associations of head and neck cancer are not significant. However, for both lung cancer and head and

neck cancer, there were dose-response relationships with the increasing frequency of drinking dark-colored alcohol.

Since the dark-colored products and corresponding mechanisms are different in wine and beer/liquor, the same model was used separately for beer/liquor and wine in each type of cancer, and the outcomes are shown in Table 3 and Table 4. For head and neck cancer, the associations were in the same patterns in wine and beer/liquor as that in combining three types of alcohols. However, for lung cancer, along with the increasing frequency of drinking dark-colored wine, the negative associations increased (ORs = 0.771, 0.719, 0.484 in never, half or less, and always and mostly group V.S. non-drinkers); but with the increasing frequency of drinking dark-colored beer/liquor, the negative associations were in opposite direction (ORs = 0.494, 0.667, 0.706 in never, half or less, and always and most group V.S. non-drinkers).

In order to test the consistency of the associations between alcohol consumption and lung cancer or head and neck cancer, the total amount of alcohol consumption was included in the same model as an exposure, adjusted associations (estimated as adjusted Odd Ratios and 95% CIs) for each type of cancer were showed in Table 5. For lung cancer, the odds of light alcohol consumption (less than 50 drink-year) was 0.643 times of those non-drinkers (OR=0.643, 95% CI: 0.471, 0.876). Although this

inversed association existed, the ORs were closer to 1 with the amount of alcohol consumption increasing. On the contrary, in head and neck cancer, ORs were more than 1 and increased with the amount of alcohol consumption increasing. When consuming alcohol heavily (more than 100 drink per-day), there was a positive association, compared with non-drinkers (OR=2.138, 95%CL: 1.466, 3.119). In addition, with increasing consumption of alcohol, there were dose-response relationships in both types of cancers.

**Table 1. Distribution of demographic and consumption variables
for cancer cases and controls**

	Number of Cases (%)		Number of Controls (%)
	Lung Cancer	Head and Neck Cancer	
Total No. of Subjects	611	601	1040
Age (year)			
≤36	7 (1.14)	40 (6.65)	62 (5.97)
≥37 and ≤46	91 (14.89)	107 (17.8)	219 (21.07)
≥47 and ≤56	356 (58.27)	309 (51.41)	575 (55.34)
≥57	157 (25.70)	145 (24.13)	183 (17.61)
Ethnicity			
Non-Hispanic White	359 (58.85)	341 (56.93)	634 (61.02)
Mexican	53 (8.69)	70 (11.69)	150 (14.44)
African American	96 (15.74)	69 (11.52)	102 (9.82)
Asian	70 (11.48)	64 (10.68)	62 (5.97)
Other	32 (5.25)	55 (9.18)	91 (8.76)
Gender			
Female	308 (50.41)	147 (24.46)	417 (40.10)
Male	303 (49.59)	454 (75.54)	623 (59.90)
Education			
Less than High School	46 (7.53)	63 (10.48)	70 (6.73)
High School	219 (35.84)	210 (34.94)	231 (22.21)
College	275 (45.01)	259 (43.09)	481 (46.25)
Graduate and More	71 (11.62)	69 (11.48)	258 (24.81)
Tobacco Consume (pack-year)			
0	110 (18.00)	182 (30.28)	492 (47.35)
>0-20	102 (16.69)	147 (24.46)	353 (33.97)
>20-40	202 (33.06)	146 (24.29)	136 (13.09)

	>40	197 (32.24)	126 (20.97)	58 (5.58)
Alcohol Consume				
(drink-year)				
	0	170 (27.87)	117 (19.53)	264 (25.48)
	>0-50	265 (43.44)	236 (39.40)	579 (55.89)
	>50-100	45 (7.38)	49 (8.18)	62 (5.98)
	>100	130 (21.31)	197 (32.89)	131 (12.64)
Dark-colored alcohol¹				
	Non-drinker ²	170 (27.82)	117 (19.47)	264 (25.38)
	Never ³	5 (0.82)	6 (1.00)	6 (0.58)
	Half or less	219 (35.84)	252 (41.93)	363 (34.90)
	Always and Mostly ⁴	217 (35.52)	226(37.60)	407 (39.13)

1. Include dark-colored beer, liquor and wine.

2. Participants who never drank alcohol for more than 6 months in their life.

3. Include those who never drank any dark-colored alcohols (never drink dark-colored beer, liquor and wine).

4. Include those who always and mostly drank at least one of dark-colored alcohols (dark-colored beer, liquor or wine).

Table 2. Association (estimated as adjusted OR and 95% CLs) between frequency of dark-colored alcohol consumption and cancer incidence

Frequency of Dark-colored alcohol consumption	Control s (N)	Lung Cancer		Head and Neck Cancer		
		Cases	Adjusted OR	Cases(	Adjusted OR	
		(N)	(95% CLs) *	N)	(95% CLs) *	
Dark-colored alcohol*						
Non-drinker ¹	264	170	1	117	1	
Never ²	6	5	0.844 (0.198, 3.602)	6	1.446 (0.382, 5.472)	
Half or less	363	219	0.726 (0.521, 1.012)	252	1.390 (1.014,1.904)	
Always and Mostly ³	407	217	0.613 (0.438, 0.858)	226	1.015 (0.735, 1.402)	
P-trend			0.01		0.01	

*Adjust for: age, education, ethnicity, gender, smoking status, tobacco consumption.

1. Include those who never drank alcohol for more than 6 months in their life.
2. Include those who never drank any dark-colored alcohols (never drink dark-colored beer, liquor and wine).
3. Include those who always and mostly drank at least one of dark-colored alcohols (dark-colored beer, liquor and wine).

Table 3. Association (estimated as adjusted OR and 95% CLs) between frequency of dark-colored beer/liquor consumption and cancer incidence

Frequency of Dark-colored alcohol consumption	Controls (N)	Lung Cancer		Head and Neck Cancer		
		Cases	Adjusted OR	Cases	Adjusted OR	
		(N)	(95% CLs) *	(N)	(95% CLs) *	
Dark-colored beer/liquor*						
Non-drinker ¹	264	170	1	117	1	
Never ²	43	26	0.494 (0.258, 0.949)	36	1.409 (0.801, 2.481)	
Half or less	468	242	0.667 (0.483, 0.922)	282	1.275 (0.938, 1.733)	
Always and Mostly ³	256	273	0.706 (0.493, 1.011)	166	1.035 (0.732, 1.462)	
P-trend			0.01		0.01	

* Adjust for: age, education, ethnicity, gender, smoking status, tobacco consumption.

1. Include those who never drank alcohol for more than 6 months in their life.
2. Include those who never drank any dark-colored beer and liquor.
3. Include those who always drank one of dark-colored beer or liquor.

Table 4. Association (estimated as adjusted OR and 95% CLs) between frequency of dark-colored wine consumption and cancer incidence

Frequency of Dark-colored alcohol consumption	Control s (N)	Lung Cancer		Head and Neck Cancer		
		Cases	Adjusted OR	Cases	Adjusted OR	
		(N)	(95% CLs) *	(N)	(95% CLs) *	
Dark-colored wine*						
Non-drinker ¹	264	170	1	117	1	
Never ²	66	44	0.771 (0.459, 1.295)	36	1.250 (0.738, 2.116)	
Half or less	601	360	0.719 (0.523, 0.988)	282	1.229 (0.905, 1.669)	
Always and Mostly ³	109	37	0.484 (0.318, 0.739)	166	1.109 (0.766, 1.608)	
P-trend			0.01		0.01	

* Adjust for: age, education, ethnicity, gender, smoking status, tobacco consumption.

1. Include those who never drank alcohol for more than 6 months in their life.
2. Include those who never drank dark-colored wine (red wine).
3. Include those who always and mostly drank dark-colored wine (red wine).

Table 5. Association (estimated as adjusted OR and 95% CLs) between the amount of alcohol consumption and cancer incidence

Frequency of Dark- colored alcohol consumption	Controls (N)	Lung Cancer		Head and Neck Cancer		
		Cases	Adjusted OR	Cases	Adjusted OR	
		(N)	(95% CLs) *	(N)	(95% CLs) *	
Alcohol consumption*						
0	264	170	1	117	1	
>0-50	579	265	0.643 (0.471, 0.876)	236	1.007 (0.744, 1.362)	
>50-100	62	45	0.727 (0.418, 1.263)	49	1.475 (0.902,2.410)	
>100	131	130	0.791 (0.514, 1.218)	179	2.138 (1.466, 3.119)	
P-trend			0.01		0.01	

* Adjust for: age, education, ethnicity, gender, smoking status, tobacco consumption

IV. Discussion

Overall, for three types of dark-colored alcohols, it seemed that high frequency (always and mostly) of dark-colored alcohol consumption may decrease the risk in lung cancer, but not in head and neck cancer. When comparing those who never drank dark-colored alcohols with non-drinkers, the directions of association were different between lung cancer and head and neck cancer, indicating there may be different effects of alcohol in different types of cancer. Along with the increasing frequency of dark-colored alcohol consumption, the ORs were much further from 1 in lung cancer, and much closer to 1 in head and neck cancer, and the dose-response relationships were generally linear for both cancers. These indicated the protective effect of dark-colored products in overall types of alcohol.

The protection of dark-colored products may result from antioxidation, which are the products of Maillard Reaction or storage process in beer/liquor, or from natural pigments in wine. Some mechanisms may explain the protection: MRPs with higher antioxidative capacity exhibit superior antimutagenic activity [11], and there are natural polyphenols in grape pigment [13]. The associations of dark-colored products in this study were partially consistent with a population-based case-control study of oral and pharyngeal cancer in the United States, which indicated that dark liquors were not carcinogenic than light liquors, and non-ethanolic ingredients of alcoholic beverages were not the

major contributors to the excess risk of oral and pharyngeal cancer. [12]

In order to separately observe the outcomes of different types of alcohol, and focus on different mechanisms of brewing and formation in the process of producing dark-colors, the same model was used for beer/liquor and wine respectively. For wine, the dark color/red color comes from anthocyanins in *vitis vinifera* red berries [17], but for beer/liquor, the dark color is from Maillard Reaction or from aged in charred oak barrels. [6-11] Furtherly, a meta-analysis, which included 15 case-control studies of head and neck cancer for the independent associations of these three alcohols, pointed out that the relative risk of head and neck cancer for beer and liquor were comparable, but there are weaker association with moderate wine consumption. [5] All these evidences supported the combination of beer and liquor, and leaving wine alone in the same model.

Similar to the outcomes of combining three types of alcohols, the associations in beer/liquor were not significant for head and neck cancer. For lung cancer, those who drank dark-colored beer/liquor at “Never” and “Half or Less” frequency were significantly less likely to have lung cancer. And judging from that the odds ratios were closer to 1 for both cancers in dark-colored beer/liquor, there may exist different metabolic mechanisms of dark-colored products for lung cancer and head and neck cancer. For wine alone, the associations were similar to overall types of alcohol. For lung cancer, the protective

association was significant when drinking dark-colored wine “Half or Less” and “Always and Mostly”.

And with the increasing frequency of drinking dark-colored wine, the potential protective effects increased in lung cancer, indicating “anti-cancer” effects of the dark-colored products.

When testing the association between alcohol consumption and cancers, the results of the inversed association of light consumption for lung cancer and the results of the positive association of heavy consumption for head neck cancer were consistent with former studies. For lung cancer, a pooled analysis from the international lung cancer consortium and the SYNERGY Study indicated alcohol consumption was inversely associated with lung cancer risk, and the evidence supported that a lower risk of lung cancer for light and moderate drinkers, compared to non-drinkers ($>0-4.9$ g per day: OR=0.80, 95% CI=0.70–0.90; 5–9.9g per day: OR=0.82, 95% CI=0.69–0.99; 10–19.9g per day: OR=0.79, 95% CI=0.65–0.96) [18]. For head and neck cancer, a pooled analysis in the International Head and Neck Cancer Epidemiology Consortium also indicated that alcohol consumption was associated with an increased risk of head and neck cancer, only when alcohol was consumed at high frequency among those never users of tobacco. [19]

The strength of this study was the detailed questionnaire with a comprehensive collection of the lifestyle data, as well as the demographic and socioeconomic data. It allowed us to adjust for as

many as potential confounders as needed, such as cigarette consumption. It also helped us to test the association between overall alcohol consumption and cancers. [15]

One of the limitations of this study design is recall bias, which may result in more dark-colored alcohol consumption in cases than controls, especially when participants were educated and informed the association between alcohols and cancers before the interviews. Another limitation is that there may be unmeasured or uncontrolled confounders, such as nutrients and physical activities, and more models may be needed to adjust other potential confounders.

In conclusion, the results of this population-based case-control study indicated the overall dark-colored alcohols and specifically in wine are inversely associated with lung cancer. However, more research is needed to conduct in-depth studies on potential mechanisms of different types of dark-colored products in each alcohol for potential preventive measures.

Reference

- [1] Alcohol drinking. IARC Working Group, Lyon, 13-20 October 1987. IARC Monogr Eval Carcinog Risks Hum. 1988;44:1-378. PMID: 3236394; PMCID: PMC6421508.
- [2] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol consumption and ethyl carbamate. IARC Monogr Eval Carcinog Risks Hum. 2010;96:3-1383. PMID: 21735939; PMCID: PMC4781168.
- [3] Galbiatti AL, Padovani-Junior JA, Maníglia JV, Rodrigues CD, Pavarino ÉC, Goloni-Bertollo EM. Head and neck cancer: causes, prevention and treatment. Braz J Otorhinolaryngol. 2013 Mar-Apr;79(2):239-47. English, Portuguese. doi: 10.5935/1808-8694.20130041. PMID: 23670332.
- [4] WHO Global Information System on Alcohol and Health.
https://www.who.int/substance_abuse/publications/global_alcohol_report/profiles/usa.pdf?ua=1
- [5] Purdue MP, Hashibe M, Berthiller J, La Vecchia C, Dal Maso L, Herrero R, Franceschi S, Castellsague X, Wei Q, Sturgis EM, Morgenstern H, Zhang ZF, Levi F, Talamini R, Smith E, Muscat J, Lazarus P, Schwartz SM, Chen C, Neto JE, Wünsch-Filho V, Zaridze D, Koifman S, Curado MP, Benhamou S, Matos E, Szeszenia-Dabrowska N, Olshan AF, Lence J, Menezes A, Daudt AW, Mates IN, Pilarska A, Fabianova E, Rudnai P, Winn D, Ferro G, Brennan P, Boffetta P, Hayes RB. Type of alcoholic beverage and risk of head and neck cancer--a pooled analysis within the INHANCE Consortium. Am J Epidemiol. 2009 Jan 15;169(2):132-42. doi: 10.1093/aje/kwn306. Epub 2008 Dec 8. PMID: 19064644; PMCID: PMC2727255.
- [6] Rothman KJ, Cann CI, Fried MP. Carcinogenicity of dark liquor. Am J Public Health. 1989 Nov;79(11):1516-20. doi: 10.2105/ajph.79.11.1516. PMID: 2817164; PMCID: PMC1349805.
- [7] Hellwig M, Henle T. Maillard Reaction Products in Different Types of Brewing Malt. J Agric Food Chem. 2020 Nov 18. doi: 10.1021/acs.jafc.0c06193. Epub ahead of print. PMID: 33205653.
- [8] Marko D, Habermeyer M, Kemény M, Weyand U, Niederberger E, Frank O, Hofmann T. Maillard reaction products modulating the growth of human tumor cells in vitro. Chem Res Toxicol. 2003 Jan;16(1):48-55. doi: 10.1021/tx025531a. PMID: 12693030.
- [9] Virk-Baker MK, Nagy TR, Barnes S, Groopman J. Dietary acrylamide and human cancer: a systematic review of literature. Nutr Cancer. 2014;66(5):774-90. doi: 10.1080/01635581.2014.916323. Epub 2014 May 29. PMID: 24875401; PMCID: PMC4164905.

- [10] Schouten LJ, Hogervorst JG, Konings EJ, Goldbohm RA, van den Brandt PA. Dietary acrylamide intake and the risk of head-neck and thyroid cancers: results from the Netherlands Cohort Study. *Am J Epidemiol*. 2009 Oct 1;170(7):873-84. doi: 10.1093/aje/kwp213. Epub 2009 Aug 31. PMID: 19720866.
- [11] Ko CY, Chen XY, Chang WC, Zeng YM, Lin RH, Zhang XB, Wu JS, Shen SC. Effects of Maillard reaction products in a glucose-glycine alcoholic solution on antioxidative and antimutagenic activities. *J Sci Food Agric*. 2018 Nov;98(14):5242-5247. doi: 10.1002/jsfa.9062. Epub 2018 Jun 1. PMID: 29645274.
- [12] Day GL, Blot WJ, McLaughlin JK, Fraumeni JF Jr. Carcinogenic risk of dark vs. light liquor. *Int J Cancer*. 1994 Nov 1;59(3):319-21. doi: 10.1002/ijc.2910590305. PMID: 7927935.
- [13] Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*. 1997 Jan 10;275(5297):218-20. doi: 10.1126/science.275.5297.218. PMID: 8985016.
- [14] Duan J, Zhan JC, Wang GZ, Zhao XC, Huang WD, Zhou GB. The red wine component ellagic acid induces autophagy and exhibits anti-lung cancer activity in vitro and in vivo. *J Cell Mol Med*. 2019 Jan;23(1):143-154. doi: 10.1111/jcmm.13899. Epub 2018 Oct 24. PMID: 30353639; PMCID: PMC6307804.
- [15] Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, Mack TM, Greenland S. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2006 Oct;15(10):1829-34. doi: 10.1158/1055-9965.EPI-06-0330. PMID: 17035389.
- [16] Chang CP, Meyers TJ, Fu A, Zhang MY, Tashkin DP, Rao JY, Cozen W, Mack TM, Hashibe M, Morgenstern H, Zhang ZF. Dietary glycemic index, glycemic load, and lung cancer risk: A case-control study in Los Angeles County. *Cancer Epidemiol*. 2020 Dec;69:101824. doi: 10.1016/j.canep.2020.101824. Epub 2020 Oct 8. PMID: 33039726; PMCID: PMC7734880.
- [17] Brouillard R, Chassaing S, Fougereousse A. Why are grape/fresh wine anthocyanins so simple and why is it that red wine color lasts so long? *Phytochemistry*. 2003 Dec;64(7):1179-86. doi: 10.1016/s0031-9422(03)00518-1. PMID: 14599515.

[18] Fehring G, Brenner DR, Zhang ZF, Lee YA, Matsuo K, Ito H, Lan Q, Vineis P, Johansson M, Overvad K, Riboli E, Trichopoulou A, Sacerdote C, Stucker I, Boffetta P, Brennan P, Christiani DC, Hong YC, Landi MT, Morgenstern H, Schwartz AG, Wenzlaff AS, Rennert G, McLaughlin JR, Harris CC, Olivo-Marston S, Orlov I, Park BJ, Zauderer M, Barros Dios JM, Ruano Raviña A, Siemiatycki J, Koushik A, Lazarus P, Fernández-Somoano A, Tardon A, Le Marchand L, Brenner H, Saum KU, Duell EJ, Andrew AS, Szeszenia-Dabrowska N, Lissowska J, Zaridze D, Rudnai P, Fabianova E, Mates D, Foretova L, Janout V, Bencko V, Holcatova I, Pesatori AC, Consonni D, Olsson A, Straif K, Hung RJ. Alcohol and lung cancer risk among never smokers: A pooled analysis from the international lung cancer consortium and the SYNERGY study. *Int J Cancer*. 2017 May 1;140(9):1976-1984. doi: 10.1002/ijc.30618. Epub 2017 Feb 27. PMID: 28120396; PMCID: PMC5356930.

[19] Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wünsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, La Vecchia C, Lazarus P, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Zatonski W, Zhang ZF, Berthiller J, Boffetta P. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst*. 2007 May 16;99(10):777-89. doi: 10.1093/jnci/djk179. Erratum in: *J Natl Cancer Inst*. 2008 Feb 6;100(3):225. Fernandez, Leticia [added]. PMID: 17505073.