Alcohol and head and neck cancer risk in a prospective study

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We investigated the relation between head and neck cancer risk and alcohol consumption in the NIH-AARP Diet and Health Study. During 2 203 500 person-years of follow-up, 611 men and 183 women developed head and neck cancer. With moderate drinking (up to one alcoholic drink per day) as the referent group, non-drinkers showed an increased risk of head and neck cancer (men: hazard ratio (HR) 1.68, 95% confidence interval (95% CI) 1.37–2.06; women: 1.46, 1.02–2.08). Among male and female alcohol drinkers, we observed a significant dose–response relationship between alcohol consumption and risk. The HR for consuming >3 drinks per day was significantly higher in women (2.52, 1.46–4.35) than in men (1.48, 1.15–1.90; P for interaction = 0.0036). The incidence rates per 100 000 person-years for those who consumed >3 drinks per day were similar in men (77.6) and women (75.3). The higher HRs observed in women resulted from lower incidence rates in the referent group: women (14.7), men (34.4). In summary, drinking >3 alcoholic beverages per day was associated with increased risk in men and women, but consumption of up to one drink per day may be associated with reduced risk relative to non-drinking.

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Each year, more than 600 000 individuals are diagnosed with squamous cancers of the head and neck worldwide (Parkin et al., 2005). Head and neck cancer has multiple anatomic sub-sites, including the oral cavity, pharynx, and larynx, which may have distinct aetiologies.

Alcohol use has consistently been indicated as a risk factor for head and neck cancer (Sturgis et al., 2004). However, owing to small case numbers, previous prospective studies have typically collapsed cancers of the head and neck and the esophagus into a single broad category of upper-gastrointestinal tract sites (Gronbaek et al., 1998; Kjaerheim et al., 1998; Boeing, 2002). Few prospective studies have examined the association between alcohol and individual head and neck cancer sub-sites, such as the larynx, oral cavity, or pharynx (Schottenfeld et al., 1974; Boffetta and Garfinkel, 1990; Adami et al., 1992; Tomnnesen et al., 1994; Sigvardsen et al., 1996; Boffetta et al., 2001). Most of these studies have not adjusted for tobacco use, an important potential confounder of the relation between alcohol and head and neck cancer (Boffetta and Garfinkel, 1990). Also, few studies (Franceschi et al., 1994; Gronbaek et al., 1998; Hayes et al., 1999; Castellsague et al., 2004; Polesel et al., 2005) have examined non-drinkers and those that drink less than two drinks per day separately, an important comparison as consumption of less than two drinks per day may reduce cardiovascular disease risk (Maclure, 1993).

Although men are 2–7 times more likely to develop these cancers than women (depending on sub-site) (Parkin et al., 2005), few epidemiological studies have compared the association of alcohol and head and neck cancer in men to that in women (Blot et al., 1988; Franceschi et al., 1994; Hayes et al., 1999; Boffetta et al., 2001). These studies generally indicate higher relative risks in women than in men, although many had small case numbers and all but one were case–control studies precluding the examination of incidence rates.

Alcohol consumption is increasing in many countries worldwide, particularly among women (Boffetta and Hashibe, 2006), and this highlights the need to better understand the association between alcohol consumption and head and neck cancer. We prospectively investigated this association in 492 960 participants of the NIH-AARP diet and health study.

MATERIALS AND METHODS

The establishment and recruitment procedures of the NIH-AARP Diet and Health Study have been described (Schatzkin et al., 2001). Between 1995 and 1996, a dietary questionnaire was mailed to 3.5 million members of AARP, formerly known as the American Association of Retired Persons, a large US organisation whose membership is open to those 50 years of age or older. These members resided in one of eight US states (California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, Georgia, or Michigan). A total of 566 407 respondents (308 692 men and 211 702 women) sufficiently completed the survey and consented to participate in the study. We excluded proxy respondents (n = 15 760) and subjects with cancer at baseline (n = 51 219), calorie intake more than two interquartile ranges from the mean (n = 4419), who died or were diagnosed with cancer on the first
day of follow-up \((n = 10)\), and who failed to provide information on alcohol use \((n = 2039)\). The resulting analytical cohort comprised 492 960 participants.

Cohort follow-up

Addresses for members of the NIH-AARP cohort were updated annually by matching the cohort database to that of the USA Postal Service change of address database (Michaud et al, 2005). Vital status was ascertained by annual linkage to the USA Social Security Administration death master file and responses to mailings. Follow-up time extended from study baseline (between 1995 and 1996) until diagnosis of a head and neck, asepsophageal, or gastric cancer (as diagnosis of one of these cancers is associated with increased surveillance of the other sites), date of death, end of study (31 December 2000), or the date moved out of registry ascertainment area.

Incident cases of cancer were identified by probabilistic linkage between the NIH-AARP cohort membership and eight state cancer registry databases. We estimate that 90% of cancer cases are detected in the cohort by this approach (Michaud et al, 2005). Cancer sites were identified by anatomic site and histologic code of the International Classification of Disease for Oncology, third edition (Fritz, 2000). All cases of head and neck cancer with squamous histology were considered for this analysis. We classified tumours with site codes C32.0 – C32.9 as laryngeal cancer. Oral cavity cancers included tumours with codes C00.1 – C00.9. Cancers of the oropharynx and hypopharynx included tumours of the tonsil (C09.0 – C09.9), oropharynx (C10.0 – C10.9), pyriform sinus (C12.9), hypopharynx (C13.0 – C13.9), and pharynx not otherwise specified (NOS) (C14.0). The overarching head and neck cancer category included those diagnosed with a cancer of the oral cavity, oropharynx and hypopharynx, larynx, and those with other squamous tumours in the head or neck or overlapping region of the lip, oral cavity, and pharynx.

Exposure assessment

The baseline questionnaire contained questions about demographics, daily alcohol, cigarette use, physical activity, and a 124-item food frequency questionnaire (Schatzkin et al, 2001). Usual daily alcohol (wine, beer, and liquor), fruit, and vegetable intakes were calculated from the questionnaire as pyramid servings as the USDA food guide pyramid: one 12 fluid ounce beer, one 5 fluid ounce glass of wine, or one 1.5 ounce shot of liquor (each approximately 13g of alcohol). We used categorical variables of alcohol intake: none, up to 1 drink per day, 1 – 3 drinks per day, and >3 drinks per day. Self-administered questionnaires for alcohol use within the AARP cohort, 24.1% (119 007) non-drinkers, 53.1% (261 889) moderate drinkers of 0 – 1 alcoholic beverages per day, 15.2% (74 834) drinkers of 1 – 3 alcoholic beverages per day, and 7.5% (37 210) drinkers of >3 drinks per day, was similar to that in the United States overall, as data from the 1999 – 2000 NHANES survey indicated 35.5% non-drinkers, 42.7% moderate drinkers of 0 – 1 alcoholic beverages per day, 17.9% drinkers of 1 – 3 alcoholic beverages per day, and 4.0% drinkers of >3 alcoholic beverages per day (Breslow et al, 2006). After 2 203 500 person-years of follow-up, 794 participants were diagnosed with head and neck cancer. We found that gender significantly modified the relation between alcohol and head and neck cancers \((P = 0.0036, 3 \text{ df})\) and present gender stratified estimates throughout. The age-standardised incidence rate per 100 000 person-years among moderate drinking women (up to one drink per day) 

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(14.7, 95\% \text{ CI } 11.3 – 18.0) \text{ was lower than moderate drinking (34.4, 30.0 – 39.0)) men. Among drinkers, increasing alcohol consumption was significantly associated with increased risk. The incidence rates in those who drank 3 alcoholic drinks per day were similar in men and women (women: 75.3, 40.5 – 110.1; men: 77.6, 63.1 – 92.1) (Table 2). In age-adjusted models (Table 2), men and women who drank > 3 alcoholic beverages per day were at increased risk relative to moderate drinkers (men: 2.25, 1.79 – 2.82; women: 5.16, 3.08 – 8.63). The association between increased alcohol consumption and risk among drinkers of alcohol was attenuated but remained statistically significant in multivariate adjusted models. Men (1.48, 1.15 – 1.90) and women (2.52, 1.46 – 4.35) who drank > 3 drinks per day were at increased risk relative to moderate drinkers (Table 3).

When examined by alcohol type, consuming more than three drinks of liquor or beer per day was associated with increased risk.
relative to moderate consumption of these beverages in both men and women (Table 3).

We also investigated the association between alcohol intake and head and neck cancer sub-sites. Women who drank more than three alcoholic drinks per day were at significantly increased risk of oral cavity cancer (2.81, 1.29–6.11) and nonsignificantly increased risk of oropharyngeal and hypopharyngeal cancer (1.97, 0.42–9.31) and laryngeal cancer (2.15, 0.82–5.65) relative to moderate alcohol drinkers. Men who drank more than three alcoholic drinks per day were at significantly increased risk for cancers of the oral cavity (1.52, 1.01–2.27), oropharynx and hypopharynx (2.32, 1.29–4.18), but not the larynx compared to moderate drinkers (1.37, 0.91–2.05) (Table 4).

In both age-adjusted models (Table 2; men: 1.77, 1.45–2.16; women: 1.39, 0.98–1.98) and multivariate adjusted models (Table 3; men: 1.68, 1.37–2.06; women: 1.46, 1.02–2.08), non-drinkers were at increased risk of head and neck cancer relative to moderate alcohol drinkers. When examined by alcohol type (Table 3), non-drinking men were at increased risk relative to moderate drinkers of wine (1.34, 1.10–1.63), beer (1.18, 0.96–1.45), and liquor (1.28, 1.03–1.58), whereas non-drinking women were at increased risk relative to moderate drinkers of wine (1.58, 1.12–2.25) and liquor (1.16, 0.80–1.66).

Table 1  Study characteristics by alcohol intake

| Alcohol intake (drinks per day)* | Zero | <1 | 1–3 | >3 |
|----------------------------------|------|----|-----|----|
| Number                           | %    |    |     |    |
| Entire cohort                    | 119 007 | 24.1 | 261 889 | 53.1 |
| Gender                           |      |    |     |    |
| Male                             | 60 761 | 20.7 | 147 104 | 50.0 |
| Female                           | 58 246 | 29.3 | 114 785 | 57.8 |
| Age (years)b                     | 63.0  | 58.2–66.8 | 62.3 | 57.4–66.4 |
| Body mass index (kg m⁻²)b        | 26.7  | 24.1–30.4 | 26.5 | 23.9–29.4 |
| Total daily caloriesb            | 161.6 | 1206.8–2155.1 | 1606.8 | 1223.9–2092.8 |
| Vegetable consumption (servings per day)b | 3.3 | 2.1–4.9 | 3.4 | 2.3–4.9 |
| Fruit consumption (servings per day)b | 2.5 | 1.4–4.1 | 2.5 | 1.5–3.8 |

**Education (%)**
- Less than high school: 52 199 (29.8) vs 97 856 (55.8)
- 12 years (completed high school): 34 055 (31.2) vs 45 582 (51.5)
- Some post-high school training: 10 232 (23.4) vs 88 837 (54.5)
- Completed college: 17 308 (18.0) vs 53 672 (55.0)

**Daily cigarette use (current or former) (%)**
- Never: 52 199 (29.8) vs 97 856 (55.8)
- Former: 49 726 (20.6) vs 125 703 (52.1)
- Current: 14 821 (21.7) vs 33 980 (49.8)

**Usual daily physical activity**
- Sit during the day/little walking: 10 151 (26.1) vs 20 956 (53.8)
- Sit during the day/walk a fair amount: 36 178 (22.8) vs 87 295 (55.0)
- Stand/walk a lot – no lifting: 44 768 (24.1) vs 97 928 (52.7)
- Lift/carry light loads, stairs, hills: 20 080 (23.8) vs 43 627 (51.6)
- Do heavy work/carry loads: 41 288 (29.1) vs 6600 (47.0)

**Physical activity (leisure) frequency**
- Never: 8771 (40.1) vs 9454 (43.3)
- Rarely: 19 302 (28.9) vs 34 540 (51.7)
- 1–3 times per month: 15 299 (22.9) vs 37 126 (55.5)
- 1–2 times per week: 23 055 (21.7) vs 58 530 (55.2)
- 3–4 times per week: 28 304 (21.5) vs 71 987 (54.6)
- 5 or more times per week: 22 600 (23.9) vs 47 856 (50.6)

**Incidence rates**
- Men (1.77, 1.45–2.16) vs 61.3 (51.9–70.7)
- Women (1.39, 0.98–1.98) vs 20.4 (14.9–25.8)

*Categories may not add up to 492 960 persons owing to missing data. bMedian (interquartile range).
In a large prospective study, we investigated the association between alcohol and head and neck cancer in men and women separately. Consistent with previous studies (Blot et al., 1988; Boffetta and Garfinkel, 1990; Adami et al., 1992; Franceschi et al., 1994; Gronbaek et al., 1998; Kjaerheim et al., 1998; Hayes et al., 1999; Boffetta et al., 2001; Boeing, 2002; Castellague et al., 2004; Sturgis et al., 2004; Polesel et al., 2005; Boffetta and Hashibe, 2006), predominantly of men, we observed a significant dose–response association between increasing alcohol consumption and head and neck cancer in both male and female alcohol drinkers. Results were generally similar for beer, liquor, and wine, although only 0.3% (1528) of the cohort (1064 men and 464 women) drank >3 glasses of wine per day limiting power. Hazard ratios for head and neck cancer sub-sites were also generally similar.

In this study, although the absolute age-standardised incidence rates among those who drank 1–3 alcoholic drinks per day and those who drank >3 alcoholic drinks per day were similar in men and women, the HR for the association between alcohol intake and head and neck cancer risk were significantly higher for women than for men. Similar increased risks among women were observed in most previous studies of this association (Blot et al., 1988; Franceschi et al., 1994; Hayes et al., 1999; Boffetta et al., 2001). In our study, the higher HR observed in women compared to men result from lower incidence rates in the referent group. These differences in baseline incidence suggest the presence of additional gender-specific risk or protective factors. These factors might include occupational carcinogens (Boffetta et al., 2003) or reproductive hormones (Yang et al., 1989; Olsson et al., 2003).

Compared to not-drinking, drinking up to one alcoholic drink per day was associated with reduced head and neck cancer risk. Although some previous epidemiological studies have observed a protective association between moderate alcohol consumption and cancers of the head and neck and the aero- phagus, results overall have been inconsistent (Franceschi et al., 1994; Gronbaek et al., 1998; Hayes et al., 1999; Boffetta et al., 2005). Most previous studies were conducted in populations that drink larger amounts of alcohol (Altieri et al., 2005) than that of the current study.

The observed inverse association could reflect exposure misclassification if former heavy drinkers had stopped drinking at the time of the questionnaire. Excluding either those subjects who reported poor health or the first 2 years of follow-up did not appreciably alter risk estimates and alcohol consumption was assessed before cancer diagnosis. However, some studies suggest that former drinkers remain at elevated risk for head and neck cancer, even 10 years after use (Hayes et al., 1999; Castellague et al., 2004; Polesel et al., 2005). Because we lacked information on past alcohol use, misclassification of non-drinkers may have affected our risk estimates.

It is also possible that moderate alcohol drinking is a proxy for a healthy or privileged lifestyle or an associated exposure. We did adjust models for head and neck cancer risk factors as well as markers of lifestyle, including age, education, body mass index, smoking, physical activity, fruit intake, vegetable intake, and total energy intake. However, the observed protective association could still be due to an unmeasured or poorly measured confounder in our analysis, such as socioeconomic status (SES). Years of education, as with the other covariates used for adjustment, did not attenuate the protective association. We additionally explored SES as a confounder using median income of the census tract in which the participant lived. Inclusion of this variable in the multivariate analysis did not alter risk estimates (data shown). We also examined possible effect modification by smoking status, as health conscious individuals may be more likely to drink moderate quantities of alcohol and less likely to smoke. Although the risk estimates for moderate alcohol consumption were similar among current, former, and never smokers, few cases with head and neck cancer were non-smokers (95 men and 20 women), limiting the power to investigate this stratum.

### Table 3

| Head and neck cancera | Men | Women |
|-----------------------|-----|-------|
| CasesHR 95% CI CasesHR 95% CI |
| Total alcohol 0 drinks per day 165 1.68 1.37–2.06 54 1.46 1.02–2.08 | | |
| < 1 drink per day 226 1.00 (ref) 75 1.00 (ref) | | |
| 1–3 drinks per day 110 1.23 0.98–1.55 36 1.99 1.33–2.99 | | |
| > 3 drinks per day 110 1.48 1.15–1.90 18 2.52 1.46–4.35 | | |
| P-value for trend0.001 & 0.0002 | | |
| Wineb 0 drinks per day 318 1.34 1.10–1.63 91 1.58 1.12–2.25 | | |
| < 1 drink per day 252 1.00 (ref) 74 1.00 (ref) | | |
| 1–3 drinks per day 40 1.16 0.83–1.62 18 1.97 1.17–3.31 | | |
| > 3 drinks per day 1 0.43 0.06–3.05 0 | | |
| P-value for trend0.872 & 0.332 | | |
| Beerb 0 drinks per day 230 1.18 0.96–1.45 107 0.85 0.60–1.19 | | |
| < 1 drink per day 286 1.00 (ref) 67 1.00 (ref) | | |
| 1–3 drinks per day 41 1.24 0.89–1.72 3 0.85 0.27–2.73 | | |
| > 3 drinks per day 54 1.61 1.16–2.22 6 3.40 1.40–8.24 | | |
| P-value for trend0.002 & 0.084 | | |
| Liquorb 0 drinks per day 294 1.28 1.03–1.58 92 1.16 0.80–1.66 | | |
| < 1 drink per day 195 1.00 (ref) 62 1.00 (ref) | | |
| 1–3 drinks per day 61 1.53 1.14–2.04 17 1.86 1.08–3.19 | | |
| > 3 drinks per day 61 1.85 1.37–2.50 12 2.25 1.19–4.26 | | |
| P-value for trend0.001 & 0.003 | | |

95% CI = 95% confidence interval; HR = hazard ratio.

*aAdjusted for gender, age at entry into cohort, body mass index, education, smoke-quit-dose, vigorous physical activity, usual activity throughout the day, fruit, vegetable intake, and total energy.

bThe test for trend was restricted to alcohol drinkers and used a linear variable where each subject was assigned the median intake value for their category.

cAdditionally adjusted for categories of beer and liquor. dAdditionally adjusted for categories of liquor and wine. eAdditionally adjusted for categories of wine and beer.

We performed several sensitivity analyses. Years of education and alcohol intake were positively correlated (Pearson correlation of 0.12); so we stratified our analysis on years of education. The stratified estimates for non-drinkers relative to moderate drinkers were 1.70 (1.21–2.37) for men and 2.57 (1.20–5.53) for women who had a college education or greater and 1.76 (1.35–2.27) for men and 1.35 (0.89–2.03) for women without a college education. We also stratified by smoking status (current, former, and never). Non-drinking men and women were at elevated risk relative to moderate drinkers among current (men: 2.00, 1.39–2.88; women: 1.28, 0.77–2.13), former (men: 1.58, 1.17–2.13; women: 1.77, 0.94–3.34), and never smokers (men: 1.35, 0.85–2.15; women: 1.53, 0.59–3.94). We also excluded those who reported poor health on the questionnaire. After excluding 34,580 men and 25,013 women who reported poor health at baseline, non-drinking men (1.73, 1.32–2.17) and non-drinking women (1.67, 1.12–2.51) were at increased risk relative to moderate drinkers. Similarly, after excluding the first 2 years of follow-up, non-drinking participants remained at increased risk (men: 1.59, 1.21–2.09; women: 1.35, 0.94–4.25).

### DISCUSSION

In a large prospective study, we investigated the association between alcohol and head and neck cancer in men and women.
This study has a number of strengths. It is a large prospective analysis with exposure information collected before cancer diagnosis. We present models separately for men and women and we examined the associations for both total head and neck cancer and by sub-sites. To limit confounding, we adjusted our models for most of the major risk factors for head and neck cancer, including cigarette smoking, a strong risk factor that is associated with alcohol use. Furthermore, the large number of participants who consumed less than one alcoholic drink per day allowed us to investigate the association between moderate drinking and risk. This study also had several limitations. We lacked information on past alcohol consumption and smoking duration. In conclusion, among alcohol drinkers, increasing consumption of alcoholic beverages per day should be interpreted cautiously and must be investigated further, particularly in prospective studies that collect information on lifetime use of alcohol.

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#### Table 4

Adjusted HR and 95% CI for head and neck cancer subtypes by gender

| Cancer Sub-site | Oral cavity | Oropharynx and hypopharynx | Larynx |
|-----------------|-------------|-----------------------------|--------|
|                 | Men         | Women                       | Men    | Women                       | Men    | Women                       |
| Gender          | Cases HR    | 95% CI                      | Cases HR | 95% CI                      | Cases HR    | 95% CI                      |
| Total alcohol   |             |                             |          |                             |          |                             |
| 0 drinks per day| 57 1.43     | 1.03–2.00                   | 24 1.24  | 0.74–2.10                   | 37 2.83     | 1.74–4.61                   |
| <1 drink per day| 92 1.00     | (ref)                       | 38 1.00  | (ref)                       | 30 1.00     | (ref)                       |
| 1–3 drinks per day| 44 1.22  | 0.85–1.76  | 15 1.74  | 0.95–3.20                   | 18 1.53     | 0.85–2.76                   |
| >3 drinks per day| 43 1.52     | 1.01–2.27                   | 9 2.81  | 1.29–6.11                   | 24 2.32     | 1.29–4.18                   |
| P-value for trend | 0.062   | 0.013                       |          | 0.003                       | 0.132       | 0.095                       |
| Wine            |             |                             |          |                             |          |                             |
| 0 drinks per day| 120 1.46    | 1.07–1.99                   | 40 1.43  | 0.86–2.39                   | 60 1.39     | 0.87–2.24                   |
| <1 drink per day| 102 1.00    | (ref)                       | 37 1.00  | (ref)                       | 38 1.00     | (ref)                       |
| 1–3 drinks per day| 14 0.97    | 0.55–1.70                   | 9 2.07  | 0.99–4.34                   | 10 1.98     | 0.98–4.00                   |
| >3 drinks per day| 0 0         | 0                           | 1 2.59  | 0.35–19.05                  | 0 0         | 0                           |
| P-value for trend | 0.401   | 0.451                       |          | 0.093                       | 0.400       | 0.530                       |
| Beer            |             |                             |          |                             |          |                             |
| 0 drinks per day| 79 0.95     | 0.68–1.34                   | 49 0.83  | 0.50–1.35                   | 52 2.52     | 1.53–4.17                   |
| <1 drink per day| 117 1.00    | (ref)                       | 32 1.00  | (ref)                       | 36 1.00     | (ref)                       |
| 1–3 drinks per day| 17 1.30    | 0.78–2.18                   | 1 0.67  | 0.09–4.97                   | 8 1.83      | 0.85–3.97                   |
| >3 drinks per day| 23 1.78     | 1.08–2.94                   | 4 5.96  | 1.94–18.30                  | 13 3.12     | 1.54–6.31                   |
| P-value for trend | 0.016   | 0.092                       |          | 0.003                       | 0.517       | 0.772                       |
| Liquor          |             |                             |          |                             |          |                             |
| 0 drinks per day| 109 1.20    | 0.86–1.68                   | 42 1.04  | 0.62–1.75                   | 53 1.16     | 0.68–1.96                   |
| <1 drink per day| 81 1.00     | (ref)                       | 32 1.00  | (ref)                       | 29 1.00     | (ref)                       |
| 1–3 drinks per day| 25 1.56    | 0.99–2.45                   | 6 1.35  | 0.56–3.26                   | 14 2.36     | 1.24–4.49                   |
| >3 drinks per day| 21 1.65     | 1.00–2.72                   | 6 2.45  | 0.99–6.05                   | 13 2.52     | 1.28–4.99                   |
| P-value for trend | 0.068   | 0.072                       |          | 0.009                       | 0.135       | 0.001                       |

95% CI = 95% confidence interval; HR = hazard ratio. aAdjusted for gender, age at entry into cohort, body mass index, education, smoke-quit-dose, vigorous physical activity, activity throughout the day, fruit intake, vegetable intake, and total energy. bThe test for trend was restricted to alcohol drinkers and used a linear variable where each subject was assigned the median intake value for their category. cAdditionally adjusted for categories of beer and liquor. dAdditionally adjusted for categories of liquor and wine. eAdditionally adjusted for categories of wine and beer.
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