



Alcohol consumption and the risk of cancer in Brazil: A study involving 203,506 cancer patients



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ABSTRACT

This study aims to analyze the association between alcohol consumption and the risk of developing the most common types of cancer in the Brazilian population. It is a case-control study in which the most common types of cancer were considered as cases and non-melanoma skin cancers as controls. Data were routinely obtained by hospital-based cancer registrars. Individuals between 18 and 100 years old, diagnosed between January 1, 2000 and December 31, 2009, with information regarding alcohol consumption, were included. The odds ratio (OR) for each type of cancer was calculated, adjusting for confounding variables. The etiologic fraction (EF) was calculated in cases with statistically significant results. The study included 203,506 individuals (110,550 women and 92,956 men), with an average age of 59 years. A statistically significant association was found between alcohol consumption and increased risk of cancers of the respiratory and digestive systems, prostate, and female breast. The association between alcohol consumption and cancers of the urinary tract, male genital organs, and other neoplasias was not statistically significant. Consumption of alcoholic beverages increased the risk of developing cancer of the nasal cavity, pyriform sinus, oral cavity, oropharynx, nasopharynx, larynx, hypopharynx, lung, esophagus, stomach, liver, pancreas, breast, prostate, colon and rectum, and anus and anal canal.

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Introduction

Cancer is considered an important public health problem, both in developing and developed countries. By the year 2030, 20.3 million new cancer cases and 13.2 million deaths related to the disease are expected (Bray, Jemal, Grey, Ferlay, & Forman, 2012). According to the World Health Organization (WHO, 2005), 40% of all deaths caused by cancer could be avoided.

About a third of the deaths from cancer are due to behavioral and nutritional risk factors such as lack of physical activity, high body mass index, low intake of fruits and vegetables, smoking, and alcohol consumption (WHO, 2015). Exposure to more than one factor increases the risk of developing cancer. An example is the action of alcohol and tobacco together, which increases the risk of oral, pharynx, and larynx cancers (WCRF/AICR, 2007).

In terms of mortality related to alcohol consumption, almost half of the global burden is associated with acute alcoholic intoxication, followed by malignant neoplasms (Rehm et al., 2004). According to

the International Agency for Research on Cancer (IARC, 2010, 2012), there is sufficient evidence that the consumption of alcohol is a potential carcinogen, as it has a causal relationship with oral cavity cancer and cancer of the pharynx, larynx, esophagus, liver, colon and rectum, and breast. Bagnardi, Blangiardo, La Vecchia, and Corrao (2001) reported that drinking alcohol increases the risk of cancer of the oral cavity, pharynx, larynx, esophagus, stomach, colon, rectum, liver, breast, and ovaries. They also showed that there was minimal risk related to lung cancer and prostate cancer. Boffetta and Hashibe (2006) reviewed multiple studies that provided evidence of consistent positive associations between alcohol and multiple cancers such as mouth, pharynx, esophagus, liver, colon, rectum, and breast.

In Brazil, studies confirming the association between alcohol consumption and the development of cancer are scarce; most of the available data refer to studies conducted in North America, Europe, and Asia (Gupta, Wang, Holly, & Bracci, 2010; Kawai et al., 2011; Park et al., 2010). In addition, results obtained in other countries cannot always be applied to the Brazilian population, which has its own ethnic, behavioral, and genetic characteristics. Furthermore, Lachenmeier et al. (2010) stated that there are differences in the behavior of Brazilian and European populations related to alcoholic

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beverage preferences as well as the concentration of the beverage components, such as ethyl carbamate. Similarly, Nóbrega et al. (2013) reported that when compared to other countries, Brazilian spirits have lower concentrations of methanol, ethyl acetate, n-propanol, and isobutanol. At the same time, we are unaware of the existence of robust studies in Brazil.

The aim of this study was to analyze the association between alcohol consumption and the risk of developing the main types of cancer in the Brazilian population.

Method

This was a case-control study. Data collection was performed using the Integrator System of Cancer Hospital Registries (CHR), a web-based system that enables the consolidation and dissemination of data available from the CHR. The CHR covers about 90% of the Brazilian public health system, comprising hospitals providing oncological assistance located in the Federal District and 25 of Brazil's 27 states. The CHR is being gradually implemented over time in the country and it is difficult to estimate the completeness of data coverage (INCA, 2010).

Individuals with information gathered regarding the consumption of alcoholic beverages, diagnosed between January 1, 2000 and December 31, 2009, and aged between 18 and 100 years, were included. The most frequent types of cancer and those with a possible association with alcohol, shown in a recent systematic literature review (Menezes, Bergmann, & Thuler, 2013), were investigated: oral cavity (C00–C08), oropharynx (C10), nasopharynx (C11), pyriform sinus (C12), hypopharynx (C13), esophagus (C15), stomach (C16), colon and rectum (C18–C20), anus and anal canal (C21), liver (C22), gall bladder (C23), other parts of the biliary system (C24), pancreas (C25), nasal cavity, middle ear, and sinuses (C30–C31), larynx (C32), bronchus and lungs (C33–C34), kidney (C64), bladder (C67), central nervous system (C70–C72), thyroid (C73), female breast (C50), vulva (C51), vagina (C52), cervix (C53), endometrium (C54.1), ovary (C56), penis (C60), prostate (C61), testis (C62), and myeloid leukemia (C42), comprising the morphologies 9840, 9860, 9861, 9863, 9871–9874, 9876, 9895–9897, 9910, and 9930 (WHO, 2000). Cases registered as non-melanoma skin cancer (C44) were used as the control group. This group was selected for comparison due to the lack of association between alcoholic beverage consumption and this type of cancer (IARC, 2010). Patients with erroneous data on alcohol consumption ($n = 213$) and with no gender information ($n = 30$) were excluded.

The main exposure variable was alcohol consumption, collected by the cancer registrars from written comments in the medical charts and categorized as current alcohol consumption (more than 3 times per week, independent of amount consumed) and non-consumer. We also analyzed the following variables: age (≤ 24 , 25–39, 40–49, 60–74, and ≥ 75 years), gender (male and female), race [(white, black, mulatto, indigenous, and Asian Brazilians), as adopted for classification by the Instituto Brasileiro de Geografia e Estatística – IBGE (INCA, 2010)], education (illiterate, ≤ 8 years education, and > 8 years education), marital status (with partner, without partner), smoking (smokers and non-smokers), region of residence (North, North-East, Midwest, South-East and South) and year of diagnosis (2000–2004 and 2005–2009).

A descriptive analysis was performed by means of absolute and relative frequency. The odds ratio (OR) for each type of cancer, stratified for males and females, was calculated, assuming a confidence interval of 95%. In order to control for potential confounding variables, adjusted ORs (aORs) by age, sex, race, education, marital status, smoking, region of residence, and year of diagnosis were calculated. The OR values that do not include the null value (1.0) were classified as reduced risk (OR lower than 1.0), low risk (OR

Table 1

Topography of cancers by gender.

Location of tumor	ICD-O-3	Male	Female	Total
Organs of the respiratory system				
Nasal cavity, middle ear, and sinuses	C30–C31	474	286	760
Pyriform sinus	C12	609	45	654
Larynx	C32	5865	839	6704
Bronchi and lungs	C33–C34	8012	3647	11,659
Organs of the digestive system				
Oral cavity	C00–C08	8318	2714	11,032
Oropharynx	C10	2319	400	2719
Nasopharynx	C11	701	292	993
Hypopharynx	C13	1332	149	1481
Esophagus	C15	6341	1838	8179
Stomach	C16	6061	3116	9177
Pancreas	C25	811	700	1511
Liver	C22	701	388	1089
Gall bladder	C23	109	374	483
Other parts of the biliary system	C24	179	173	352
Colon and rectum	C18–C20	7005	7265	14,270
Anus and anal canal	C21	333	964	1297
Organs of the urinary system				
Kidney	C64	1150	814	1964
Bladder	C67	2670	862	3532
Other neoplasms				
Central nervous system	C70–C72	1222	968	2190
Thyroid	C73	706	3317	4023
Myeloid leukemia	C42	1209	987	2196
Male genital organs				
Penis	C60	897	0	897
Prostate	C61	21,228	0	21,228
Testis	C62	1041	0	1041
Breast and female genital organs				
Breast	C50	0	39,472	39,472
Vulva	C51	0	907	907
Vagina	C52	0	254	254
Cervix uteri	C53	0	22,711	22,711
Endometrium	C54.1	0	2551	2551
Ovary	C56	0	3340	3340
Controls: skin	C44	13,663	11,177	24,840
Total	–	92,956	110,550	203,506

1.1–1.5), moderate risk (OR higher than 1.5–2.5), high risk (OR higher than 2.5–3.9), and very high risk (OR higher than or equal to 4) (Rosenthal, 1996). Statistically significant differences were defined as $p < 0.05$.

The etiologic fraction (EF) was calculated for results where the aOR was statistically significant. Assuming that the risk of disease in the population is low and that the OR is similar to the relative risk (RR), the following equation was used: $P_c = (aOR - 1)/aOR$, where P_c is the proportion of exposed cases and aOR is the adjusted odds ratio (Nurminen & Karjalainen, 2001). PASW Statistics software, version 18.0 was used for data analysis.

For better presentation, the results were grouped into organs of the respiratory system, organs of the digestive system, organs of the urinary system, male genital organs, female genital organs, and other organs. This study was performed in accordance with the ethical principles for human investigations and was approved by the Brazilian National Cancer Institute Ethics Committee (128/11).

Results

The study included 203,506 cases of cancer in the period between 2000 and 2009. The three most frequent types of cancer in men were prostate (21,228), oral cavity (8318), and bronchi and lungs (8012), while for women they were breast cancer (39,472), cervical cancer (22,711), and colon and rectum (7265) (Table 1).

The sociodemographic characteristics of the studied population are presented in Table 2. The frequency of individuals who

Table 2
Socio-demographic characteristics (n = 203,506).

Variables	Cases						Controls					
	Total		Male		Female		Total		Male		Female	
	N	%	N	%	N	%	N	%	N	%	N	%
Age (years)												
18–24	1995	1.1	711	0.9	1284	1.3	147	0.6	82	0.6	65	0.6
25–39	17,322	9.7	3512	4.4	13,810	13.9	1437	5.8	795	5.8	642	5.7
40–59	74,253	41.6	27,997	35.3	46,256	46.5	7379	29.7	4136	30.3	3243	29.0
60–74	62,670	35.1	34,753	43.8	27,917	28.1	9029	36.3	5233	38.3	3796	34.0
≥75	22,426	12.6	12,320	15.5	10,106	10.2	6848	27.6	3417	25.0	3431	30.7
Race/skin color												
White	96,060	57.9	44,234	60.6	51,826	55.8	18,406	79.7	10,131	79.8	8275	79.6
Black/Mulatto	69,040	41.6	28,373	38.9	40,667	43.8	4615	20.0	2520	19.9	2095	20.1
Indigenous/Asian Brazilians	795	0.5	363	0.5	432	0.5	70	0.3	42	0.3	28	0.3
Education												
Illiterate	18,957	14.7	7847	14.2	11,110	15.0	2974	15.9	1312	12.5	1662	20.3
≤8 years education	86,926	66.4	38,527	69.6	47,399	64.1	12,471	66.9	7150	68.2	5321	65.1
>8 years education	24,454	18.9	8989	16.2	15,465	20.9	3210	17.2	2022	19.3	1188	14.5
Marital status												
With partner	102,802	59.3	53,711	70.1	49,091	50.8	14,402	59.6	9280	69.9	5122	47.1
Without partner	70,513	40.7	29,908	29.9	47,605	49.2	9757	40.4	4004	30.1	5753	52.9
Smoking												
Smokers	78,343	45.1	48,389	62.6	29,954	31.1	6881	28.5	4970	37.4	1911	17.6
Non-smokers	95,378	54.9	28,970	37.4	66,408	68.9	17,286	71.5	8321	62.6	8965	82.4
Alcohol consumption												
Current alcohol consumption	51,685	28.9	38,193	48.2	13,492	13.6	4277	17.2	3645	26.7	632	5.7
Non-consumer	126,981	71.1	41,100	521.8	85,881	86.4	20,563	82.8	10,018	73.3	10,545	94.3
Region of residence												
North	6916	3.9	2817	3.6	4099	4.1	600	2.4	340	2.5	260	2.3
North-East	33,193	18.6	11,788	14.9	21,405	21.6	5147	20.8	2901	21.3	2246	20.2
Midwest	3306	1.9	1326	1.7	1980	2.0	245	1.0	134	1.0	111	1.0
South-East	88,279	49.6	39,748	50.3	48,531	49.0	11,724	47.4	6510	47.8	5214	46.9
South	46,452	26.1	23,363	29.6	23,089	23.3	7027	28.4	3732	27.4	3295	29.6
Year of diagnosis												
2000–2004	80,396	45.0	32,125	40.5	48,271	48.6	11,262	45.3	6215	45.5	5047	45.2
2005–2009	98,270	55.0	47,168	59.5	51,102	51.4	13,578	54.7	7448	54.5	6130	54.8
Total	178,666	100.0	79,293	44.4	99,373	55.6	24,840	100.0	13,663	55.0	11,177	45.0

Numbers vary due to missing data.

consumed alcohol was higher among case subjects (28.9%) than among control subjects (17.2%), as well as among smokers (45.1% and 28.5%, respectively).

After adjustment of the confounding variables, individuals who consumed alcoholic beverages showed a high risk of developing tumors of the pyriform sinus, oral cavity, oropharynx, hypopharynx, esophagus, and liver; a moderate risk for laryngeal, nasal cavity, nasopharyngeal, stomach, and breast cancers; and a low risk for cancers of the lung and bronchus, pancreas, colon and rectum, anus and anal canal, prostate, penis, and testicle. Risk was not observed for cancers of the gall bladder, other parts of the biliary system, kidney, bladder, vulva, vagina, cervix, thyroid, or myeloid leukemia. Conversely, values suggesting decreased risk of endometrial, ovarian, and central nervous system (CNS) cancers were found. When analyzing men and women separately, the risk classification remained virtually the same, with unimportant changes in the strength of association in most cases (Table 3, Supplementary Table 1, and Supplementary Table 2).

Discussion

This study examined the association between alcohol consumption and the main types of cancer in Brazil. These results provide better knowledge of the local situation and may be useful for planning and evaluating prevention strategies and interventions nationwide.

According to the IARC, there is sufficient evidence to indicate a causal and dose-dependent relationship between alcohol

consumption and cancers of the oral cavity and pharynx (IARC, 2010, 2012). Our results, after adjustment of the confounding variables, also showed an increased risk between alcohol consumption and nasopharynx, oropharynx, hypopharynx, and oral cavity cancer. Etiologic fractions observed in the present study were generally similar to those described by other investigators for the oral cavity and pharynx (Boffetta, Hashibe, La Vecchia, Zatonski, & Rehm, 2006; Parkin, 2011).

With regard to larynx cancer, corroborating previous results (IARC, 2010, 2012; Schütze et al., 2011) we found a higher risk of cancer for alcohol consumption, with an etiologic fraction attributable to alcohol of 37%. In addition, a meta-analysis including 40 publications (38 case-control studies and two cohort studies), after adjustment for sex, age, and smoking habits, confirmed a positive association between moderate (2–3 drinks) and intense (≥4 drinks) alcohol consumption and the risk of laryngeal cancer (RR 1.50, 95% CI: 1.23–1.83 and RR 2.46, 95% CI: 1.88–3.22, respectively) (Islami et al., 2010).

With regard to lung cancer, this study found a low risk related to the consumption of alcohol after adjustment (etiologic fraction of 7%). According to the IARC, there are insufficient data to determine a causal association between alcohol consumption and lung cancer, emphasizing that residual confounding cannot be overlooked even after adjustment for tobacco, which may be the case in this study (IARC, 2010, 2012). In a meta-analysis with the inclusion of seven studies, the association between high alcohol consumption and lung cancer was not statistically significant, after adjustment for smoking (OR 1.00, 95% CI: 0.73–1.26) (Uehara & Kiyohara, 2010).

Table 3
Association between alcohol consumption and the development of different types of cancer in men and women.

Location of tumor	Crude OR			Adjusted OR ^a			Etiologic fraction (%)
	OR	95% CI	p value	OR	95% CI	p value	
Organs of the respiratory system							
Nasal cavity, middle ear, and sinuses	2.9	2.5–3.3	<0.001	1.7	1.4–2.1	<0.001	15.3
Pyriform sinus	15.5	12.9–18.6	<0.001	3.6	2.9–4.7	<0.001	55.1
Larynx	8.4	7.9–8.9	<0.001	2.4	2.2–2.6	<0.001	37.1
Bronchi and lungs	3.1	3.0–3.3	<0.001	1.2	1.1–1.3	<0.001	6.6
Organs of the digestive system							
Oral cavity	7.5	7.1–7.9	<0.001	2.8	2.6–3.1	<0.001	39.1
Oropharynx	12.9	11.8–14.1	<0.001	3.6	3.1–4.1	<0.001	52.7
Nasopharynx	3.0	2.7–3.4	<0.001	1.6	1.3–1.9	<0.001	14.5
Hypopharynx	13.1	11.7–14.8	<0.001	3.9	3.3–4.6	<0.001	54.4
Esophagus	8.9	8.4–9.4	<0.001	3.6	3.3–3.9	<0.001	46.9
Stomach	2.9	2.7–3.0	<0.001	1.6	1.5–1.8	<0.001	14.0
Pancreas	1.9	1.7–2.1	<0.001	1.4	1.2–1.7	<0.001	8.1
Liver	3.5	3.1–4.0	<0.001	2.6	2.1–3.1	<0.001	26.0
Gall bladder	1.0	0.8–1.2	0.376	1.1	0.7–1.6	0.789	^b
Other parts of the biliary system	1.9	1.5–2.4	<0.001	1.4	1.0–2.0	0.091	^b
Colon and rectum	1.5	1.4–1.5	<0.001	1.2	1.2–1.3	<0.001	3.9
Anus and anal canal	1.5	1.4–1.8	<0.001	1.4	1.1–1.7	0.003	7.0
Organs of the urinary system							
Kidney	1.3	1.2–1.5	<0.001	0.9	0.8–1.1	0.332	^b
Bladder	2.0	1.8–2.1	<0.001	1.0	0.9–1.1	0.715	^b
Other neoplasms							
Central nervous system	1.0	0.9–1.2	0.365	0.8	0.7–0.9	0.008	–4.4
Thyroid	0.6	0.6–0.7	<0.001	1.1	1.0–1.3	0.200	^b
Myeloid leukemia	1.3	1.1–1.4	<0.001	0.9	0.8–1.1	0.192	^b

^a Adjusted by gender, age, race, education, marital status, smoking habits, region of residence, and year of diagnosis.

^b FRAP not performed due to lack of statistical significance in the adjusted OR.

For esophageal cancer, our results showed increased risk with an etiologic fraction attributable to consumers of alcoholic drinks of 47%. These results are consistent with those of the IARC (IARC, 2010, 2012) and Schütze et al. (2011). However, this causal relationship can only be attributed to squamous cell carcinoma, because there is evidence that consumption of alcohol is not associated with esophageal adenocarcinoma (IARC, 2012). This effect was also observed in the study of Lubin et al. (2012), who found a risk of squamous cell carcinoma of the esophagus (CCE) when consumption exceeded 3 drinks/day (OR 2.15, 95% CI: 1.3–3.6), but this was not observed for adenocarcinoma. Unfortunately, risk stratification by histological subtypes was not possible in our study.

Although there is not enough evidence of an association between the consumption of alcohol and stomach cancer (IARC, 2010), our results point to an increased risk after adjustment for possible confounders. Similar results were described in a meta-analysis conducted by Tramacere et al. (2012) and in a huge cohort study containing 478,459 participants (Duell et al., 2011), in which the relation between alcohol consumption and the risk of developing stomach cancer was statistically significant (RR 1.12, 95% CI: 1.01–1.24 and HR 1.65, 95% CI: 1.06–2.58, respectively). These discrepancies between the studies may have been found because of the difficulty of adjusting for possible confounders such as nutritional deficiencies.

With regard to pancreatic cancer, Gupta et al. (2010), in a study including 532 subjects and 1701 controls, showed increased risk in men (OR 2.20, 95% CI: 1.1–4.6) who drank 35 doses of alcohol or more per week. Although our results showed a similar risk, with 8% of etiologic fraction due to alcohol consumption, it is possible that the association between alcohol and pancreatic cancer may be caused, at least in part, by residual confounding by smoking (IARC, 2012).

As the IARC (2012) noted, consumption of alcohol has a causal relationship with hepatocellular carcinoma. This study demonstrated a positive association with alcohol consumption, and these results are consistent with a pooled analysis of four cohort studies

conducted in the Japanese population (Schimazu et al., 2012), which found a risk for heavy alcohol consumption in men (HR 1.76, 95% CI: 1.08–2.87) and moderate consumption in women (HR 3.60, 95% CI: 1.22–10.66).

Alcoholic drink consumption has been observed as a risk factor for cancer of the colon and rectum (Fedirko et al., 2011; IARC, 2010, 2012). In our results, 4% of the etiologic fraction was due to alcohol consumption. However, the association between alcohol and colorectal cancer was not confirmed in a study in the United Kingdom that included 579 subjects and 1996 controls (Park et al., 2010).

There is insufficient evidence showing an association between alcohol consumption and prostate cancer (IARC, 2012). However, we found a low risk with an etiologic fraction attributable to alcohol of 3%. Similar results were shown by Rota et al. (2012).

In women, studies have consistently found an increased risk of breast cancer associated with alcohol intake (Boffetta et al., 2006; IARC, 2010, 2012), which was confirmed by this study, where 5% of the etiologic fraction can be attributed to alcohol intake.

We found no recent papers on the association between alcohol and cancer of other parts of the biliary system, gall bladder, anus and anal canal, penis, testicle, vulva, vagina, and cervix. Of these locations, the present study showed a statistically significant association only for other parts of the biliary system in men and the anus and anal canal in women, which should be more fully investigated in etiological studies.

We did not find an association between alcohol consumption and myeloid leukemia, or bladder, central nervous system, thyroid, endometrial, and renal cancer. Similar results were reported in other studies (Fedirko et al., 2013; Galeone et al., 2012; Heinen et al., 2013; IARC, 2010, 2012; Mao et al., 2010).

This study has some limitations that may have affected the results. First, as the survey was based on secondary data, possible information bias and recall bias need to be considered. However, there was no evidence of differential information or recall bias. Second, as it was a hospital-based study, the use of skin cancer as the control rather than healthy individuals representative of the

population from which the cases came may also have influenced the results. No information was available on the types and doses of alcoholic drinks consumed, which may have compromised comparison with other authors who evaluated these data. In addition, there is the possibility that subjects and controls did not correctly declare their consumption of alcohol due to guilt, social stigma, blame related to voluntary exposure to a cancer-risk factor, fear of social disapproval, or due to attitudes and individual beliefs.

A strength of the study is the large sample size that provided precise estimates. As no other comprehensive studies analyzing the relationship between alcohol consumption and various types of cancer in Brazil were identified, and given that the majority of the research in this field has been performed in North America, Europe, and Asia, this study brings important contributions to the development of specific policies for cancer control, given the differences in lifestyle, cultural aspects, and habits of the population according to age, race, education level, marital status, smoking status, region of residence, and year of diagnosis.

Consumption of alcoholic beverages was associated with a risk of developing several types of cancer in Brazil. An elevated risk was found for cancer of the pyriform sinus, oral cavity, oropharynx, hypopharynx, esophagus, and liver; a moderate risk for cancer of the larynx, nasal cavity, nasopharynx, and stomach; and a low risk for cancer of the lung, pancreas, colon and rectum, and anus and anal canal. Among men, an elevated risk was found for cancers of the pyriform sinus, hypopharynx, oropharynx, esophagus, oral cavity, and liver; a moderate risk for cancer of the larynx, nasal cavity, nasopharynx, stomach, pancreas, gall bladder, and other parts of the biliary system; and a low risk for cancer of the lung, colon, and rectum and prostate. Women showed a high risk for developing cancer of the pyriform sinus, hypopharynx, oropharynx, and esophagus; a moderate risk for cancers of the larynx, nasal cavity, oral cavity, liver, anus and anal canal, stomach, and breast; and a low risk for cancers of the lung and colorectum. No association was found between the consumption of alcoholic beverages and the development of myeloid leukemia and cancers of the thyroid, gall bladder, other parts of the biliary system, bladder, and kidney. Among men, no association was observed for cancers of the gall bladder, anus and anal canal, testis, and penis, and among women there was no association with cancers of the nasopharynx, gall bladder, other parts of the biliary system, vulva, vagina, and cervix. Results suggesting a decreased risk of cancer of the CNS were found among men and a decreased risk of cancers of the ovary and endometrium among women.

Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alcohol.2015.07.001>.

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