DOI 10.1002/mnfr.200800122 Mol. Nutr. Food Res. 2009, *53*, 240 – 255

Review

Alcohol use and prostate cancer: A meta-analysis

Kaye Middleton Fillmore[1, 2], Tanya Chikritzhs[1], Tim Stockwell[1, 3], Alan Bostrom[2] and Richard Pascal[1]

[1] National Drug Research Institute, Curtin University, Perth, Australia
[2] Department of Social and Behavioral Sciences, University of California, San Francisco, CA, USA
[3] Centre for Addictions Research of British Columbia, University of Victoria, Victoria BC, Canada

Past reviews have concluded that there is no association between alcohol use and prostate cancer incidence. We performed a meta-analysis of existing epidemiological studies finding, in contrast, evidence to suggest that prostate incidence is positively linearly associated with heavier alcohol use. This finding was largely due to the contribution of population case-control studies and those measuring men recruited before age 60. No relationship between alcohol consumption and prostate cancer was found for cohort and hospital case-control studies. Analyses of design effects modestly suggests that population case-control studies were probably better suited to identify potential alcohol-prostate cancer relationships due to the close temporal proximity of the measurement of level of alcohol consumption to diagnosis. Future efforts should be made to exclude all ill subjects from control groups/baseline samples in addition to accounting for changes in consumption with advancing age and the onset of illness. The alcohol-prostate cancer association remained significant despite controlling for the degree to which studies endeavored to eliminate false negatives from their control groups.

Keywords: Alcohol / Epidemiology / Heavy drinking / Meta-analysis / Prostate cancer

Received: March 22, 2008; revised: May 19, 2008; accepted: May 20, 2008

1 Introduction

The incidence of prostate cancer presents a scientific challenge. Ecological studies report major differences in prostate cancer disease rates across national and racial boundaries [1–2] and men migrating to other countries tend to take on the same incidence rates as those of their adoptive country [1, 3, 4]. While age, race, and family history of prostate cancer (and to a lesser degree, dietary factors although the evidence is not consistent [5–7]) apparently contribute to prostate cancer incidence, they do not sufficiently explain these ecological differences. It has thus been reasoned that environmental factors must play a role.

Valid candidate hypotheses have evaluated why some groups of men display a higher incidence for the disease. Aspects of diet, smoking status, body weight, exercise, social class, and other factors have been examined in multiple studies but the cross-study conclusions are often inconsistent [5]. To date, no major environmental factors have been established that isolate the factor or groups of factors contributing to this serious form of cancer apart from those stated above.

One such series of investigations concerns the role of alcohol. The development of some cancers have been attributed in part to level of alcohol consumption [8, 9] but the association between alcohol and prostate cancer is much less clear, with highly mixed findings from the various studies in this domain. Past efforts to resolve this [2, 10, 11] have affirmed inconsistent findings among cross-study results and the most recent global cancer summary suggests that the evidence between alcohol and prostate cancer incidence is too limited and/or inconsistent to warrant a causative link [8]. Bagnardi *et al.* [12] have provided the only exception, having drawn the conclusion – based on their meta-analysis of a small number of comparative studies – that alcohol consumption is weakly associate with prostate cancer [12].

The current study tested several hypotheses concerning design and methodological characteristics of epidemiological studies that may potentially explain apparent inconsistencies in the alcohol-prostate research literature. The rationale underpinning these hypotheses have been described below.

Correspondence: Dr. Tanya Chikritzhs, National Drug Research Institute, Curtin University, G.P.O. Box U1987, Perth WA 6845, Australia
E-mail: t.n.chikritzhs@curtin.edu.au
Fax: +61-8-9266-1611

2 Study rationale

2.1 Rationale 1

Study designs vary in their ability to reliably capture past and current drinking levels of individuals. Prospective cohort studies have the advantage of obtaining participant information prior to an event or diagnosis occurring. However, these studies rarely enquire about: (i) life-long drinking levels/patterns of subjects prior to entry into the study or (ii) changes in levels/patterns of alcohol use in the interim between first measurement and diagnosis. The latter is an important consideration because the great majority of prospective studies entail only the baseline measurement and both drinking patterns and health can change thereby compromising any implications regarding causality. The time interval between the most recent measure of drinking and diagnosis can be exceedingly long, sometimes approaching a quarter of a century. It is possible that these design characteristics may in fact predispose prospective cohort studies to systematic errors which arise from a failure to take fully into account participant's past drinking practices and changes in their drinking over time. It has also been suggested that study design characteristics may at least partly explain why cohort studies tend to show J-shape associations while case-control studies tend to show positive linear associations when evaluation of a particular disease is dominated by one or the other design [13]. On the other hand, many case-control studies specifically evaluate past exposure and duration of exposure because the event of interest has already occurred. The epidemiological literature typically views case-control designs as inferior to prospective cohort studies due to the absence of before and after comparisons and the suffering from recall bias.

Some analysts have suggested that a critical component for assessing the alcohol-prostate association is the *duration* of specific drinking patterns because, more than likely, it would take many years for *heavier* drinking to affect prostate cancer incidence [10]. Toward this end, some studies – typically case-control studies – ask participants to predate their recollections about drinking to a period well before diagnosis, hospitalization, or first measurement. Other studies enquire about lifetime consumption. The latter group has produced mixed results, most probably due to cross-study differences in these measurements.

2.2 Rationale 2

Individual levels of alcohol consumption vary considerably over time and most drinkers, but not all, will reduce consumption as they age. Some epidemiologists claim that the validity of reported level of alcohol consumption over time is high among nonalcoholic populations [14]. This claim is in marked contrast to that observed by Shaper *et al.* [15] in addition to a substantial body of evidence demonstrating that level of alcohol consumption decreases with increasing age, particularly in the 60s and thereafter (*e.g.*, from prospective mortality studies [16–20]; from longitudinal studies [21–26]; from multiple measurement longitudinal studies [27, 28]). In fact, analysts studying the association of alcohol use with the incidence of any disease among older people are hard pressed to locate sufficient numbers of relatively heavy drinkers once the subjects are in their 70s and beyond.

2.3 Rationale 3

Reduction or termination of level of alcohol consumption during the older years of the life course is closely associated with the onset of ill health, frailty, dementia, and/or use of medications [15, 29–33] and initial diagnosis of prostate cancer is most commonly made among older men. These considerations make critical the proximity of the drinking measure to diagnosis (thereby reducing one type of measurement error) and the degree to which studies exclude from baseline or control samples those subjects already showing signs of illness (thereby reducing the probability of changes in drinking patterns associated with illness).

Given the associations between illness/ageing and reduced alcohol consumption, it is reasonable to assume that most men diagnosed with prostate cancer would have already reduced or discontinued their drinking. However, there is some evidence to suggest that while most one-time heavy drinkers will eventually reduce their consumption to a moderate level, those who are frequent heavy drinkers may persist with high levels of consumption throughout life [27]. It is possible that men who are ill with prostate cancer but who continue to consume a relatively higher amount of alcohol on a weekly basis (14 or more drinks) may constitute such a group. Although the analyses presented here cannot evaluate this directly, they include and differentiate between studies based on samples of alcoholics and studies based on samples from the general population.

Furthermore, given that older men are more likely to reduce their consumption, it is reasonable to expect that samples evaluating younger men would show a stronger association between alcohol use and prostate cancer risk because, relatively speaking, the (shorter) life-time drinking patterns of these subjects would be less subject to the influences of diminishing health and thereby more stable.

2.4 Rationale 4

A large proportion of older men who die from other causes may have also had unidentified prostate cancer. Autopsy studies suggest that a relatively high proportion of elderly men (an estimated 50%) have undiagnosed or latent prostate tumors at the time of death [34, 35]. These findings have implications for epidemiological studies evaluating

prostate cancer incidence. Should Herculean efforts not be made to eliminate false negatives from the control groups of these studies, the control or comparison group is likely to be "contaminated" with men who have the disease and study results would be questionable.

3 Study hypotheses

On the basis of observations drawn from the epidemiological literature the following hypotheses have been proposed.

3.1 Hypothesis 1

Taken overall, epidemiological studies which have examined prostate-cancer incidence/prevalence and compared outcomes for (a) nondrinkers versus current drinkers or (b) nondrinkers versus former drinkers versus current drinkers, will find no significant differences between these groups [36].

3.2 Hypothesis 2

Levels of alcohol consumption among population case-control studies will be more likely to demonstrate positive linear associations between alcohol use and prostate cancer compared to hospital case-control or prospective cohort studies. Should this hypothesis be supported, it may illustrate that design factors common to population case-control samples are the key to understanding the alcohol-prostate cancer association. This hypothesis is advanced on the basis of two additional hypotheses that will be analyzed both independently and jointly in an effort to better understand the mechanisms that might contribute to the overall mixed findings from the relevant studies.

3.3 Hypothesis 3

Efforts to create disease-free control groups (for case-control studies) and baseline samples (for cohort studies) will contribute to apparent differences in outcomes between case-control and prospective cohort designs. Specifically, prostate cancer incidence/prevalence will be more strongly associated with alcohol consumption among studies which made some attempt to exclude those in ill health.

3.4 Hypothesis 4

Measurement error is implicated in studies when the proximity of the measurement for alcohol consumption to diagnosis of prostate cancer is distant in time [36]. Specifically, prostate-cancer incidence/prevalence will be positively associated among studies when measurements of drinking are made closer to time of diagnosis.

3.5 Hypothesis 5

When compared to studies which make no or minimal effort to exclude false negatives for prostate cancer from control groups, studies which make rigorous efforts to eliminate false negatives from control groups will: (a) better predict the incidence of prostate cancer than those which do not; and (b) be more likely to show associations between alcohol consumption and prostate cancer.

4 Methods

4.1 General

Meta-analysis was used to examine apparent relationships between alcohol use and prostate cancer from population case-control, hospital case-control, and cohort studies.

4.2 Types of studies and criteria for selection

A medline search was performed using key words "prostate cancer" and "alcohol" (and variations *e.g.*, carcinoma of prostate, ethyl alcohol) to identify all potential studies published up to and including December 2006. Five studies were not included due to incomplete or insufficient information (efforts were made to contact authors) [37–40]. Brief descriptions of included studies may be found as Supporting Information.

Three design types were evaluated: population case-control studies (20 results for no *vs.* any drinking, five results for no *vs.* former *vs.* any drinking, 63 results for levels of alcohol consumption); hospital case-control studies (14 results for no v*s.* any drinking, six results for no *vs.* former *vs.* any drinking, 34 results for levels of alcohol consumption); and cohort/prospective studies (six results for no *vs.* any drinking, eight results for no *vs.* former *vs.* any drinking, 59 results for levels of alcohol consumption). Some of the latter included both morbidity and mortality outcomes that were tested for differences with no differences found. When multiple papers were published from one study, the most recent publication was included in the analysis, taking into consideration the completeness of results and relevance to our analysis. One study [41] was followed an additional four years [42]; the former was included in our analysis because it was within our sampling frame time period although the results for the later are noted in the Supporting Information. It is important to note that, because comparison groups differ among studies (*e.g.*, some may compare drinkers *vs.* nondrinkers whereas others may compare drinkers *vs.* nondrinkers *vs*. former drinkers) the number of studies available for each set of analyses presented here are not necessarily the same.

Design characteristics of some studies deserve comment. A study by Gronberg *et al.* [43] consisted of a population case-control study in which the sample was drawn from a

prospective twin study with baseline questions in 1967. Cancer diagnoses were drawn from a registry between 1959 and 1989, age matched to controls. Therefore, the diagnosis of cancer preceded the questioning in a minority of cases. Hiatt *et al.* [44] conducted a nested case-control study within a large US health care network. It was difficult to determine if the study should be a population or hospital case-control study; we elected to categorize it as a population case-control study because the men receiving a health examination were not necessarily ill.

Results from individual studies were presented as relative risks, odds ratios, and percents. Frequencies and percents were converted to odds ratios. For some studies (primarily case-control) alcohol use was not necessarily the primary focus but outcomes for alcohol were presented as percentage differences between cases and controls without adjusting for other factors. As they enabled an expanded total sample, results from such studies were included. Importantly; however, all studies were analyzed to determine whether those with and without specific adjustments produced significantly different outcomes.

An additional meta-analysis assessed the subgroup of five studies that had retrospectively measured the duration of years drinking [45–49]. This analysis treated duration of drinking as a continuous measure. One study in this group [48] measured the duration of drinking only for participants who drank on a daily basis.

4.2.1 Variables

Three dependent variables were assessed: (a) no drinking *versus* any drinking; (b) no drinking *versus* former drinking *versus* current drinking; (c) continuous models of drinking levels. For the latter (c), midpoints of reported drinking amounts from each study were calculated to reflect number of drinks *per* day. Grams or mililiters were converted into US standard drinks (13.6 g = 1 standard drink) which best reflected the metric used by the majority of these studies.

Table 1 summarizes some of the variables used to test our hypotheses. Methods for obtaining participants' alcohol consumption and the time frames for reporting consumption levels/patterns varied among studies. Most used a combined quantity/frequency measure to record drinking levels/patterns but some used frequency only or quantity only. Time elapsed between baseline and diagnosis/end-point was included in analyses to test hypotheses.

Models were adjusted for estimated median age at time of drinking assessment. Few studies reported *mean* age of participants but most did provide enough information to derive median age – which is a crude indicator of age at measurement. Median age was lower in population case-control studies (Table 3 for level of consumption analysis) compared to cohort studies; all hospital case-control studies had a median age of 60 or older.

Two established predictors of prostate cancer were included: whether the study adjusted for family history of prostate cancer; and whether the study adjusted for ethnicity. Both of these variables failed to reach statistical significance and were dropped from the final models.

In order to test proposed hypotheses 2–5, which specifically related to the effect of study design on apparent outcomes, four specific variables were examined for those studies which used continuous measures of alcohol consumption (n = 156 results):

(a) Pre-existing illness: pre-existing illness was measured according to whether the study excluded one or more illnesses in addition to prostate cancer (*e.g.*, other cancers, coronary heart disease, alcohol, or tobacco-related illnesses) from the control group (population case-control studies) or baseline sample (cohort studies) (in the case of some hospital case-control studies, patients assigned to various hospital departments were excluded). Noteworthy is that few studies comprehensively excluded an array of illnesses that might be associated with changes in drinking patterns and most only excluded a few. Table 1 shows that almost all population case-control studies made some attempt to exclude control subjects with at least one disease other than prostate cancer (97%) whereas slightly over 50% of cohort studies did so. Hospital case-control studies were not analyzed here because, by design, the probability of the inclusion of ill subjects (exclusive of prostate cancer) is likely.

(b) Estimated time elapsed between drinking level assessment and endpoint: for cohort studies only, this variable was defined as the interval (in years) between baseline and endpoint of the study (ranging from 5 to 22 years).

(c) Study definition of current drinking: for case-control designs only, this variable differentiated between studies which measured drinking status up to 1 year before the time of interview *versus* referencing a point before diagnosis/admission in the more distant past or lifetime drinking. There was variation across studies in the reference point used: 5 years before diagnosis; any time in a respondent's lifetime when they drank nearly every day; 1 year prior to interview/diagnosis; lifetime; 3 years prior to diagnosis; prior to illness being diagnosed for cases; 3 years prior to diagnosis and/or change in dietary patterns.

(d) Degree to which false negatives were eliminated from control groups: studies were coded according to the degree to which efforts were made to eliminate men who might have had undiagnosed prostate cancer: (i) histological confirmed nonprostate cancer; (ii) established benign-prostate hypertrophy or nonpalpable node; (ii) prostate-specific antigen levels; (iv) prostatic or urologic problem; (v) self-report of prostate cancer; and (vi) no effort to eliminate false negatives.

(e) Outcome variables (cohort studies only) consisted of morbidity alone, mortality alone, or both while examining

Table 1. Descriptive characteristics of three research designs evaluating the association between alcohol consumption and prostate cancer for number of observations within each research design type

	Population case-control studies (%)	Hospital case-control studies (%)	Cohort studies (%)
Studies evaluating no *vs.* any drinking	**20 Studies**	**14 Studies**	**6 Studies**
Median age 60 or younger	40	0	20
Sample size of 500 or less	50	57	0
Sample size of 2001 or more	20	14	67
Matched by age	100	71	NA
Matched by date of admission to hospital	0	14	NA
Adjusted for ethnicity	20	0	33
Adjusted for family history of prostate cancer	0	0	0
Abstainer category was contaminated with former drinkers	50	86	100
Abstainer category was contaminated with occasionaldrinkers	50	71	67
One or more diseases (other than prostate cancer) excluded from control or baseline sample	20	71	33
Reference point for assessing drinking prior to diagnosis: coincident with diagnosis	50	57	100
Interval between baseline and endpoint in years 9 or fewer Years	NA	NA	67
Proportion showing statistically significant positive results	57	0	31
Studies evaluating no *vs.* former *vs.* any drinking	**5 Studies**	**6 Studies**	**8 Studies**
Median age 60 or younger	0	0	25
Sample size of 500 or less	40	50	0
Sample size of 2001 or more	0	50	62
Matched by age	100	100	NA
Matched by date of admission to hospital	40	0	NA
Adjusted for ethnicity	40	0	21
Adjusted for family history of prostate cancer	60	0	0
Abstainer category was contaminated with former drinkers	100	0	63
Abstainer category was contaminated with occasional drinkers	60	0	63
One or more diseases (other than prostate cancer) excluded from control or baseline sample	0	100	0
Reference point for assessing drinking prior to diagnosis: coincident with diagnosis	0	50	25
Both one or more diseases excluded from control group and reference point for drinking is current	–	–	–
Interval between baseline and endpoint in years 9 or fewer years	NA	NA	25
Proportion showing statistically significant positive results for no *vs.* former drinkers.	100	0	60
Studies evaluating levels of alcohol consumption	**63 Studies**	**34 Studies**	**59 Studies**
Median age 60 or younger	49	0	36
Sample size of 500 or less	22	23	0
Sample size of 2001 or more	36	50	83
Matched by age	97	35	NA
Matched by date of admission to hospital	11	12	NA
Adjusted for ethnicity	38	0	25
Adjusted for family history of prostate cancer	16	0	25
Abstainer category was contaminated with former drinkers	84	68	93
Abstainer category was contaminated with occasional drinkers	73	56	73
One or more diseases (other than prostate cancer) excluded from control or baseline sample	97	0	53
Reference point for assessing drinking prior to diagnosis: coincident with diagnosis	40	29	71
Interval between baseline and endpoint in year 9 or fewer years	NA	NA	44
Proportion showing statistically significant positive results	46	18	35

and controlling for a range of potential confounders. Additional predictor variables included: those used for matching in case-control studies (age, place of residence, and date of admission to hospital); variables used to adjust models (indicators of social class, smoking status, BMI, and physical activity); variables that identified specific exclusions from control or baseline samples (no exclusions, alcohol-related disease exclusions, only other cancers); and whether abstainer categories were contaminated with former drinkers or occasional drinkers. The latter was based on the

notion that apparent higher abstainer risk in the evaluation of some diseases is attributed to the reduction or termination of drinking in older people due to increased illness, disability, frailty, and/or medication use [15, 50], referred to as systematic misclassification error (SME). Studies which defined "abstinence" as not having drunk in the last 30 days or less prior to interview/reference point and which failed to assess past drinking levels/patterns were coded as containing "former drinker" SME. In addition, studies which did not contain a specific category for infrequent or occasional drinkers (*e.g.*, drank less frequently than once in the last 30 days) but which included them among abstainers were coded as containing "occasional drinker" SME.

4.2.2 Analyses

Mixed effects regression models were used to test associations of drinking with prostate cancer outcome [51]. The dependent variable was the log of the odds ratio or relative risk. The alcohol predictor was either the categorized drinking variable or the log of alcohol volume in the case of multiple ordered drinking groups for the continuous measure of alcohol consumption. Median age was also entered as a fixed control variable and study was treated as a random effect. Studies were weighted by the inverse of the estimated variance of the log odds, derived from reported standard errors, confidence intervals, or numbers of incidence of prostate cancer (number of diagnosis or number of deaths). Results are expressed as odds ratios. All analyses were carried out with SAS, Version 9.1.

5 Results

5.1 Is drinking *per se* or former drinking associated with the incidence of prostate cancer?

There were no statistically significant associations differentiating prostate cancer risk for either of two drinking measures: (i) no drinking v. any drinking (20 studies) and (ii) no drinking *versus* former drinking *versus* current drinking (19 studies) (Table 2). This was also true within each of the study design groups (population case-control, hospital case-control, and cohort studies) (table not shown). These results support Hypothesis 1 that drinking *per se* is not associated with prostate cancer.

These findings are tentative, since, according to the criteria identified in Fillmore *et al.* [50], the majority of the studies evaluated were contaminated by SME. Most abstainer groups were contaminated with either former drinkers (in the case of those studies assessing no drinking), or with occasional drinkers (see Table 1). Even the smaller number of studies that specifically evaluated former drinkers showed evidence of SME (Table 1). Thus, although contamination was evaluated in our analyses, it could not compensate for the fact that, ultimately, the vast majority of studies and their results were highly likely to be systematically biased in this way.

Table 2. Meta-analysis of prostate cancer risk for (a) no *versus* any drinking and (b) no *versus* former drinking *versus* current drinking: all studies

	OR	Lower bound 95% CI	Upper bound 95% CI	*p* value
No *vs.* any drinking (*n* = 20 results)				
No drinking	1.00[a)]			
Any drinking	1.11	0.95	1.30	0.16
No *vs.* former *vs.* current drinking (*n* = 19 results)				
No drinking	1.00[a)]			
Former drinking[b)]	1.06	0.65	1.73	0.74
Current drinking	1.04	0.62	1.73	0.85

Based on log OR with weight of 1/variance(log OR).
a) Reference group.
b) The difference between former and current drinkers yielded an OR of 0.97 (0.64, 1.48).

5.2 Is level of alcohol consumption associated with prostate cancer incidence?

Level of alcohol consumption (number of drinks *per* day) was positively associated with prostate cancer incidence for the total sample of 35 studies; Table 3 expresses the summary association for the total sample of relevant studies (OR = 1.158; CI: 1.051, 1.263). This is contrary to the conclusions of most reviews on the subject. The association is primarily due to population case-control studies (OR = 1.239; CI: 1.142, 1.344) and is not statistically significant among either hospital case-control or cohort studies. Overall, the finding supports Hypothesis 2.

Median age of the sample at study recruitment (60 years or older *vs.* 59 years or younger) and level of alcohol consumption interact to significantly predict prostate cancer for the total sample of studies. The borderline statistically significant interaction is due to population case-control studies (OR = 0.794; CI 0.691, 0.913 for older *vs.* younger samples at recruitment) but is not found among cohort studies and could not be tested for hospital case-control studies. Thus, for case-control studies, "heavier" drinking among younger samples at recruitment increases the likelihood of prostate cancer incidence (Table 3 and Fig. 1). The point at which statistical significance is reached is around 2 standard drinks *per* day for the younger population case-control samples (Fig. 1b). The scattergrams (Fig. 1) illustrate how few studies in this research domain have inquired about heavier drinking. Most probably this is not attributable to inattention to these drinking practices but, rather, because most men have decreased their alcohol consumption after age 60 years. Thus, as expected, given that most (but not

Table 3. Meta-analysis of prostate cancer risk for level of alcohol consumption (number of drinks per day), median age of study measurement (baseline for cohort studies) and interaction between level of alcohol consumption and median age: all studies combined and by each study design

	OR	Lower bound 95% CI	Upper bound 95% CI	*p* value
All Studies (35 studies; 115 results)				
Level of alcohol consumption	1.16	1.06	1.26	0.001
Age 59 or younger[a)]	1.00			
Age 60 or older	1.19	0.99	1.42	0.082
Level of alcohol consumption × age 59 or younger[a)]	1.00			
Level of alcohol consumption × age 60 or older	0.89	0.79	1.00	0.047
Population case-control studies (14 studies; 46 results)				
Level of alcohol consumption	1.24	1.14	1.34	<0.0001
Age 59 or younger [a)]	1.00			
Age 60 or older	1.12	0.868	1.45	0.4039
Level of alcohol consumption × age 59 or younger [a]	1.00			
Level of alcohol consumption × age 60 or older	0.79	0.69	0.91	0.002
Hospital case-control studies (7 studies; 25 results)				
Level of alcohol consumption	0.99	0.87	1.13	0.909
Age 59 or younger[a)]	[b)]			
Age 60 or older	[b)]			
Level of alcohol consumption × age 59 or younger[a)]	[b)]			
Level of alcohol consumption × age 60 or older	[b)]			
Cohort studies (14 studies; 44 results)				
Level of alcohol consumption	1.02	0.85	1.23	0.807
Age 59 or younger[a)]	1.00			
Age 60 or older	1.18	0.86	1.65	0.296
Level of alcohol consumption × age 59 or younger[a)]	1.00			
Level of alcohol consumption × age 60 or older	1.05	0.84	1.33	0.645

Based on log OR with weight of 1/variance(log OR).
a) Reference group is age 59 or younger.
b) Could not be calculated.

all) males significantly reduce level of alcohol consumption as they age and become less well, the older the study sample at recruitment, the less likely alcohol consumption will influence prostate-cancer diagnosis. None of the hospital case-control studies had a median age at recruitment of less than 60 years which most probably contributed to the lack of significant findings for this group of studies (Table1).

5.3 Do study-level design characteristics contribute to finding that population case-control studies (*vs.* other designs) demonstrate a positive linear effect between drinking levels and prostate cancer risk?

5.3.1 Exclusion of ill subjects (in addition to those with prostate cancer) among control or baseline samples

Hypothesis 3 stated that efforts to create disease-free control samples (population case-control studies) or baseline samples (cohort studies) would be instrumental in differentiating between studies showing a significant positive effect between level of alcohol consumption and prostate cancer and those that do not (hospital case-control studies are not analyzed because, by design, the probability of the inclusion of subjects ill with conditions other than prostate cancer is high). Exclusion of those in ill health does not show a statistically significant association with prostate cancer for either type of study (Table 4). However, population case-control studies show a trend ($p = 0.156$), very modestly suggesting that when other major illnesses are not removed from control groups, prostate cancer risk is lower. It should be noted that none of the identified studies adequately removed from their baseline or control groups all illnesses that might have impacted on changes in drinking patterns.

5.3.2 The time period between drinking assessment and endpoint among cohort studies

The nonsignificant association in relation to study efforts to create a disease-free sample at baseline and subsequent prostate cancer incidence in cohort studies may be because the time elapsed between baseline and endpoint is typically so long that the advent of new illnesses (apart from prostate cancer) is likely to occur among older subjects. Further-

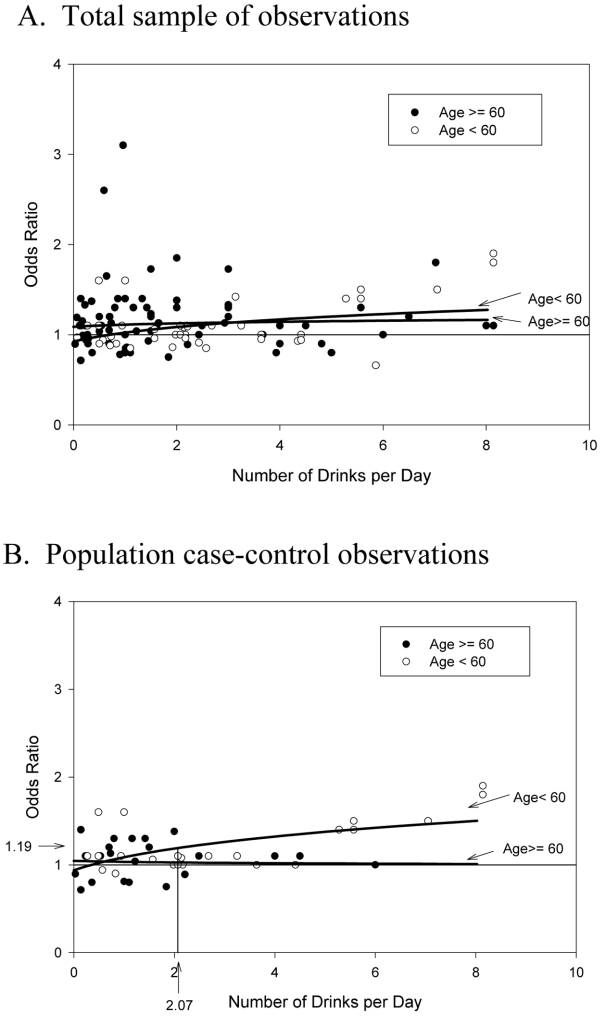

Figure 1. Level of alcohol consumption and prostate cancer incidence/prevalence. Odds ratios for (a) total sample of observations and (b) population case-control observations for those with a median age 60 years and older *versus* 59 or younger. Fitted line is quadratic model in log (drinking amount +1).

more, removal of other illnesses at baseline cannot possibly exclude those who will become ill in the interim and who also, according to the relevant literature, are likely to decrease their level of alcohol consumption. Hypothesis 4 proposed that the longer the interval between measurements, the less likely there would be a significant alcohol-prostate cancer association. However, it should be noted that the interval between baseline and endpoint ranged from 5 to 22 years and, compared to case-control designs, a 5 year interval between drinking assessment and diagnosis is a considerably long period of time. Assessment of the number of years between baseline and endpoint with prostate cancer risk for the cohort studies showed no statistically significant association (Table 5).

We also evaluated the joint effect of years between baseline/endpoint and any efforts to remove ill subjects from the baseline sample (in addition to prostate cancer) (Table 5). Although not statistically significant ($p = 0.109$), the results suggest that efforts to create disease-free samples among studies with shorter intervals between measurements may contribute to finding a higher incidence of prostate cancer.

5.3.3 The proximity of drinking measurement to the diagnosis of prostate cancer among case-control studies

Some case-control studies require participants to predate their responses to specific explanatory variables to a time prior to diagnosis of (or hospitalization for) prostate cancer. The typical rationale is that such a retrospective approach will better mimic the cohort study design and lessen the impact that the disease itself may have on changes in alcohol consumption and other factors (*e.g.*, diet, body weight). The results indicate that such efforts are unrelated to prostate cancer incidence among the sample of population case-control studies but did have an impact among hospital case-control studies (Table 6). Noteworthy is that more hospital case-control studies predate their reference point for explanatory variables to a time prior to diagnosis. Among hospital case-control studies, a potential interaction between level of alcohol consumption and use of a retrospective approach to measuring alcohol consumption suggests that the effect of alcohol consumption is less when such measurements are utilized ($p = 0.089$). Furthermore, for hospital case-control studies, inclusion of this variable alters the effect of drinking amount on prostate cancer risk such that it more closely approaches statistical significance ($p = 0.064$), suggesting that analysts' attempts to capture past drinking levels/patterns of participants are influenced by measurement error.

5.3.4 The elimination of false negatives from control groups

Not surprisingly, cohort and population case-control studies were less likely than hospital case-control studies to include efforts to reduce false negatives in control groups. The latter were more likely to confirm nonprostate cases using rigorous laboratory and/or examination criteria, 40% compared to 11% of population case-control studies and none of the cohort studies. Despite this wide variability, the likelihood of prostate cancer arising among the three study design groups did not appear to be affected by attempts to remove false negatives (Table 7). Interaction effects between levels of alcohol consumption and study efforts to eliminate false negatives also failed to reach statistical significant results (not shown). Alcohol consumption remained significantly associated with prostate cancer incidence despite median age of the studies, design effects and efforts to remove false negatives from control groups.

Table 4. Meta-analysis of prostate cancer risk for level of alcohol consumption (number of drinks *per* day), median age of study measurement (baseline for cohort studies), interaction between level of alcohol consumption and median age and indicator of disease-free control/baseline sample (one or more illness removed): population case-control and cohort studies[c)]

	OR	Lower bound 95% CI	Upper bound 95% CI	*p* value
Population case-control studies (14 studies; 46 results)				
Level of alcohol consumption	1.27	1.17	1.38	<0.0001
No disease-free control sample[a)]	0.70	0.42	1.15	0.156
Level of alcohol consumption × no disease-free control sample	[b)]			
Cohort studies (14 studies; 44 results)				
Level of alcohol consumption	1.16	0.58	2.32	0.659
No disease-free baseline sample[a)]	1.30	0.50	1.48	0.570
Level of alcohol consumption × no disease-free baseline sample	0.86	0.45	1.67	0.647

Based on log OR with weight of 1/variance(log OR).

a) Reference group excluded cancers in addition to prostate cancer and/or other diseases (*e. g.*, coronary heart disease) and/or alcohol-related or tobacco-related diseases.

b) Could not be calculated.

c) Adjusts for median age and interaction between age and level of alcohol consumption. By definition, hospital case-control studies contain ill subjects in their control group and, therefore, are excluded from this analysis.

Table 5. Meta-analysis of prostate cancer risk for level of alcohol consumption (number of drinks per day) for two study-level indicators: (i) interval between baseline and endpoint and (ii) interval between baseline and endpoint and exclusion of the ill at baseline: cohort studies[c)]

	RR	Lower bound 95% CI	Upper bound 95% CI	*p* value
Interval between baseline and endpoint 9 years or <				
Level of alcohol consumption	0.95	0.73	1.22	0.351
Interval 9yrs or < [a)]	1.22	0.88	1.68	0.217
Level of alcohol consumption × interval 9 years or <	1.12	0.85	1.47	0.423
Interval 9 yrs or < and no disease free baseline sample				
Level of alcohol consumption	1.15	0.73	1.79	0.538
Interval 9 years or < and no disease-free baseline sample[b)]	0.74	0.52	1.07	0.109
Level of alcohol consumption × interval 9 years or <and no disease-free baseline sample	0.87	0.59	1.30	0.485

Based on log RR with weight of 1/variance (log RR)

a) Interval >9 yrs is reference point.

b) Reference group consisted of studies with <9 yrs between baseline and endpoint and also excluded cancers in addition to prostate cancer and/or other diseases (*e. g.*, coronary heart disease) and/or alcohol-related or tobacco-related diseases.

c) Adjusts for median age and interaction between age and level of alcohol consumption.

5.4 Studies evaluating lifetime consumption

For most diseases, knowledge of participants' history of drinking behavior is central to identifying and understanding potential associations between alcohol consumption and disease incidence and is driven by the rationale that continued and/or heavy drinking exposure is critical for the development of degenerative-type disease. Some analysts have made attempts to retrospectively capture the complexities of drinking behavior. The methods by which this is done differ so greatly that a meta-analysis of them cannot be reliably performed – with one exception – the duration or number of years drinking assessed. For this variable, controlling for age of measurement, our results indicate an RR of 0.005 (–0.02, 0.03), which, on face value, might suggest that retrospective methods for measuring the duration of number of years drinking either fall short or are not relevant to prostate-cancer incidence. However, it may be in fact that the duration of drinking *per se* is less relevant to prostate cancer incidence than some measures of either frequent and/or heavier drinking over the course of many years. Unfortunately, given the limitations inherent among studies to date it is not possible to test this. Of the five relevant studies identified and examined, only one measured duration of daily drinking for participants. In this case, the results indicated that the number of years *daily* drinking was positively associated with prostate cancer incidence.

Table 6. Meta-analysis of prostate cancer risk for level of alcohol consumption (number of drinks per day) for utilization of a retrospective time frame for drinking of prior drinking *versus* current drinking: case-control studies only[b)]

	OR	Lower bound 95% CI	Upper bound 95% CI	*p* value
All case-control studies				
Level of alcohol consumption	1.15	1.02	1.29	0.021
Retrospective time frame[a)]	0.90	0.74	1.09	0.283
Level of alcohol consumption × retrospective time frame	1.03	1.12	1.18	0.717
Population case-control studies				
Level of alcohol consumption	1.26	1.14	1.39	<.0001
Retrospective time frame[a)]	0.96	0.70	1.31	0.800
Level of alcohol consumption × retrospective time frame	1.03	0.89	1.18	0.717
Hospital case-control studies				
Level of alcohol consumption	1.50	0.97	2.32	0.064
Retrospective time frame[a)]	1.01	0.60	1.70	0.975
Level of alcohol consumption × retrospective time frame	0.67	0.42	1.07	0.089

Based on log OR with weight of 1/variance(log OR).
a) Reference group is current time frame including no time frame specified, current drinking specified or last 1–2 wks specified.
b) Adjusts for median age and interaction between age and level of alcohol consumption.

Table 7. All studies combined meta-analysis of prostate cancer risk for level of alcohol consumption (number of drinks *per* day), median age of study, study design type and rigorous *versus* nonrigorous or no effort to eliminate false negatives from the control groups

	OR	Lower bound 95% CI	Upper bound 95% CI	*p* value
All Studies (35 studies; 115 results)				
Level of alcohol consumption	1.08	1.01	1.16	0.02
Rigorous elimination of false negatives [a)]	1.00			
All other studies including total inattention to false negatives	0.83	0.63	1.09	0.19

Based on log OR with weight of 1/variance (log OR).
a) Reference group.

5.5 Studies of alcoholics

Studies of alcoholics have the advantage of maximizing the effect of heavy drinking and its duration. They are of interest here to determine if they confirm our results from population case-control studies that heavier level of alcohol consumption is associated with prostate cancer risk. Seven such studies were located. Dennis and Hayes [36] estimated the pooled standardized incidence ratio for two of these studies [52, 53] to be 1.22 (1.04, 1.42) and concluded increased risk of prostate cancer due to heavy drinking. Other studies have evaluated these relationships but in general a meta-analysis of them is inappropriate due to differing methods used. Some studies have failed to provide quantitative information on drinkers and others have revealed only very small case frequencies [54, 55]. Another study made the assumption that members of the Danish Brewery Workers Union were either heavy drinkers or alcoholics due to the high availability of beer in that context [56]. Compared to the general Danish population, the incidence was 1.08 (0.96, 1.21) among brewery workers. A Norwegian study of treated alcoholics found that death rates among this population were significantly above that expected for the general population [57]. A somewhat more recent study [58] did not find treated alcoholics to be at higher risk for prostate cancer compared to the general population or to a group of veterans. Despite this small sample of studies utilizing treated alcoholics (or persons exposed to an environment hospitable to heavier drinking) and their design limitations, in accord with Dennis and Hayes [36], we tentatively conclude that there is modest support that heavier daily consumption is associated with prostate cancer risk.

5.6 A template for the study of drinking and prostate cancer incidence

Overall, the results thus far have modestly suggested that retrospective methods (typically used in case-control studies) and measures far in advance of diagnosis (in prospective studies) fall short of reliably assessing the possibility that level of alcohol consumption may influence the development of prostate cancer. This leaves, therefore, the puz-

Table 8. Reproduced from Table 3 from Sesso *et al.* [59] (A) Proportion of respondents reporting stability *versus* change in drinking over a five year period and (B) RRs (95% CI) for each group[a)]

(A) Proportion of stable *vs.* changing drinking at Time 2 (1988) by Time 1 (1977)

	Frequency of drinking 1977 – Time 1				
	Almost never	1/month to <3/week	3/week to <1/day	1/day to <3/day	≥3/day
Frequency of drinking 1988 – Time 2					
Almost never	74	29	50	13	18
1/Month to <3/week	26	47	32	24	
3/Week to <1 day		24	18	51	39
1/Day to <3/day				12	43
≥3/Day					
Total = 100%	(697)	(592)	(1239)	(2760)	(1398)

(B) RR (95% CI) of prostate cancer from 1988 to 1993 for alcohol consumption based on the 1977 and 1988 questionnaires

	Frequency of drinking 1977 – Time 1				
	Almost never	1/month to <3/week	3/week to <1/day	1/day to <3/day	≥3/day
Frequency of drinking 1988 – Time 2					
Almost never	1.00	0.95 (0.31–2.91)	2.10 (1.09–4.02)	1.68 (0.79–3.59)	1.28 (0.53–3.11)
1/Month to <3/week	2.16 (0.92–5.07)	1.86 (0.85–4.09)	1.97 (0.96–4.02)	2.15 (1.14–4.07)	
3/Week to <1 day		3.12 (1.37–7.12)	2.16 (0.97–4.82)	2.51 (1.40–4.49)	2.53 (1.33–4.83)
1/Day to <3/day				2.02 (0.98–4.16)	1.27 (0.62–2.58)
≥3/Day					
Total = 100%	(697)	(592)	(1239)	(2760)	(1398)

a) Adjusted for age, body mass index, physical activity, cigarette smoking, and parental history of cancer.

zling and counter-intuitive finding that only studies assessing drinking behavior relatively close to diagnosis indicate a positive relationship between the two variables.

One study in this literature illustrates why this might be the case and may be regarded as a template for future studies. Sesso *et al.* [59] utilized two "live" measurement points over an 11 year period to predict prostate cancer incidence in a prospective study design. The endpoint of the study was fully 16 years out from the first measurement point.

Table 8 shows the degree of stability and change in drinking frequency occurring between the two live measurement points. The extent of change illustrates that correlation coefficients are inadequate for summarizing this behavior over time and should not be used in future studies to indi-

cate stability. Although there is some consistency of the behavior for some drinking groups (*e.g.*, 74% of the Time 1 respondents reporting almost never drinking also do so at Time 2), the amount of change is remarkable. For example, 50% of those drinking between three times a week and less than once a day in 1977 decreased their drinking 11 years later and 57% of those drinking three or more times a day do the same. These changes – measured only crudely in the Sesso *et al.* [59] study – strongly indicate that the overall observation advanced by Shaper *et al.* [15] regarding changes in drinking over time as impacting on disease development is worthy of serious consideration.

When drinking is used to predict prostate cancer incidence (Table 8), it is clear that, overall, indicators of more frequent drinking (either its stability or increasing over time) is associated with prostate cancer incidence. Had this study also measured the quantity of drinking, in addition to frequency, it is possible that this might have been a stronger finding.

6 Discussion

The results from this study raise a number of issues.

6.1 Differences between our analysis and other reviews and meta-analyses

In contrast to most past analyses which have assessed the association between level of alcohol consumption and prostate cancer, we found an overall significant association, pronounced among population case-control studies.

In a 1998 review of alcohol consumption and prostate cancer risk, Breslow and Weed [10] stated: "Evidence from epidemiologic studies performed over a 25 year time span suggests no association between alcohol consumption and prostate cancer incidence. The studies are so consistently null and the risk estimates so lacking in strength that it seems unnecessary to evaluate the results of this review using formal inferential criteria of causation. The results of cohort studies with positive findings are either not generalizible because they were performed in special populations (Gronberg *et al.*, 1996, Tonnesen *et al*., 1994) or too incompletely described to warrant serious consideration (Hirayama, 1992). The findings of case-control studies with positive findings (De Stefani *et al*., 1995, Hayes *et al*., 1996), although suggestive, cannot overcome the existing body of null evidence (p. 10)."

These authors conclude that while misclassification bias or confounding might account for these results, they dismiss these problems on the grounds that alcohol surveys have been shown to have reasonable validity for the measurement of alcohol consumption over time. However, the wider literature (as discussed above), and the well conducted Sesso *et al.* study [59] in particular, contradict this view. Breslow and Weed [10] failed to heed what Rothman coined as a "towering obstacle" in epidemiological studies namely, the difficulties encountered in assessing actual exposure to a risk factor [60].

Dennis [11] acknowledged the problems referenced above but did not analyze for them. While finding a statistically significant alcohol-prostate cancer dose response for men drinking four or more drinks *per* day, it was concluded that there was no association between alcohol consumption and prostate cancer – possibly because linear estimates were made in order to include studies not reporting higher amounts. His analysis included fewer studies than in the current study which may also have accounted for the different findings. In 2004, Dagnelie *et al.* [61] reviewed ten cohort studies assessing alcohol use and prostate cancer risk finding that the majority found no association and, therefore, concluded that there was no association between alcohol consumption and prostate cancer. Bagnardi *et al.* [12] assessed seven case-control and four cohort studies finding a small positive significant effect.

In 2001, a review was published by Dennis and Hayes [36], pointing to the fact that few studies in this domain of research measure heavy drinking – a particular rarity among the age groups concerned – making it difficult to assess whether this drinking type is associated with prostate cancer. The findings presented here suggest that when heavier drinking measures are employed, there is a statistically significant increase in prostate cancer risk in these groups.

Of considerable importance, Dennis and Hayes [36] also suggested that variation in the time frame of alcohol measurements plays a role in accounting for differences in cross-study findings – reflecting one of the hypotheses tested herein. Apart from the Dennis and Hayes observation, few reviewers have considered some of the extraordinary differences in the designs contributing to this domain of research such as: potential influences of efforts to remove previously undiagnosed prostate cancer from control groups (false negatives); contamination of the abstinence group with former or occasional drinkers; efforts made to exclude diseases other than prostate cancer; and differences in reference group for the explanatory variables. The uneven consideration of such factors across the three major study designs found in this literature may have, in part, led to the typical conclusion that the cross-study results are so mixed that alcohol has no bearing on the incidence of the disease.

6.2 Why population case-control studies appear to be better equipped to assess the association between drinking practices than alternative designs

It has been postulated here that the differences between findings for the population case-control studies versus the two alternative designs may be a function of the degree to

which: (i) efforts were made to create disease-free control groups; and (ii) measurement error associated with the long periods between baseline and endpoint for the cohort studies and the use of retrospective questions among the case-control studies. Our hypotheses were weakly supported but illustrate the possibility that it is the design characteristics typical to the studies themselves which may have contributed to obscuring a positive association between alcohol use and prostate cancer risk. It is not necessarily the case that population case-control studies are "superior" to cohort designs but, rather, that they may be more likely to capture some element of participant drinking history which relates to a positive prostate cancer diagnosis.

We argue that, in all probability, a real association between alcohol consumption and prostate cancer incidence has been concealed by the strong likelihood that drinking patterns change and illness increases during the years in which these men were measured, particularly among the older subjects. In this regard, only very recent measurements may be reliable indicators of a continual pattern of heavier drinkers and "healthier" control/baseline samples are critical. This does *not* mean that long-term drinking patterns do not have an effect on the development of prostate cancer but that currently applied epidemiological methods are typically insensitive to these life course changes – a position supported by studies of alcoholics and by one outstanding study which carefully assessed drinking behavior stability/change over time [59].

Hypotheses advanced here in an attempt to understand why one design shows a positive linear effect in contrast to no effect among alternative designs were only weakly supported, as *none* of the design-level factors explored reached statistical significance. However, the trends were in the direction of the *a priori* hypotheses, suggesting that there is merit to carefully assessing the possibility of serious measurement error in these designs. Attempts to evaluate the degree to which studies eliminated false negatives from their control groups strengthens the conclusion that alcohol use is significantly associated with prostate cancer because the association remained despite the degree to which studies made these efforts.

The lack of statistical significance for these explanatory design factors may be attributed in part to the inadequacies among the studies themselves. We located only one study that might be regarded as the gold standard correcting for the presence of other illness; the majority of studies did not eliminate subjects with the many illnesses, dementia or use of medications that might have influenced changes in drinking behavior and few attempted, except retrospectively, to evaluate changes in drinking behavior. The weak support for design-level hypotheses advanced here may also be attributed to limited, crude coding of these variables due to the small sample of available cases (*e.g.*, studies excluding at least one disease from the control/baseline sample were combined with studies excluding multiple diseases).

It is also possible that other variables not measured in our meta-analyses may have an important role to play. One such variable might be the degree to which the populations sampled by the various studies were exposed to prostate cancer screening such as the prostate specific antigen (PSA) test. With the increasing uptake of PSA over time, especially in developed countries, many new cases which would have otherwise remained undiagnosed are more likely to be captured. It may also be the case that men who drink heavily are less likely to undergo PSA testing. Although we have not been able to explore the possibility here, this is an important area for future research efforts.

6.3 An incongruous outcome

It is ironic that prostate cancer risk should appear to increase at almost the same level of consumption and at the same ages that alcohol is thought to have a "protective effect" for other diseases most notably, coronary heart disease [9, 62–64] although some doubt has been cast on this notion [15, 50]. Consideration of conflicts for the benefits of alcohol for some diseases and detriment to others should be held up to the light of cross-disease analytic approaches.

6.4 The many faces of measurement error and a major problem of contemporary medical epidemiology

Some of the researchers involved with the current study recently published a paper assessing a form of measurement error hypothesized to influence apparent associations between alcohol use and coronary heart disease mortality risk [50]. In that case, it was asserted that measurement of abstinence from alcohol had to be sufficiently *long* so not to miss-classify former or occasional drinkers as long-term abstainers. This hypothesis was advanced on the basis that many former or occasional drinkers had either terminated or reduced their drinking due to ill health or associated factors. Should this particular measurement error occur, the likelihood of a protective effect of alcohol use might be wrongly concluded for coronary heart disease [15]. In sharp contrast, our report herein has suggested that if measurement of drinking is not sufficiently *close to* diagnosis, measurement error is likely to occur because studies will not capture those subjects whose heavier drinking persists despite advancing age and the onset of illness.

On surface, these assertions would appear to be in conflict. However, an underlying problem in medical epidemiological studies assessing drinking behavior (in addition to other behaviors) is that such studies typically make the assertion that *one time* measurement of a behavior is adequate. Typically, analysts do not measure their respondents multiple times or possess large enough samples to carve out groups who change their drinking behaviors from those who do not – a problem magnified in the older years

of the life course. Retrospection about these behaviors is unreliable and correlations of drinking between one measurement point and a subsequent one (even if relatively high) serve to mask the flux in this behavior among many and the relative persistence of it among a few. Many analysts have sought to correct for these problems but, taken as a whole, epidemiological efforts in this domain may be regarded as limited and in large part, suffering from systematic cross-study error biasing toward the null effect. Our attempts to take some of these limitations into account have hopefully provided a clearer account of this complex literature and the actual relationship between levels of alcohol consumption and prostate cancer to be found therein.

6.5 Is alcohol consumption associated with the incidence of prostate cancer?

A statistically significant association was found between level of alcohol consumption and prostate cancer. This association warrants further investigation, especially in relation to heavy drinking and the documentation of alcohol consumption over many years. In this event, we would hypothesize that consistent heavier alcohol consumption will be more strongly associated with prostate cancer risk. Despite the many caveats emanating from our analyses, it is our conclusion that there is a positive linear association between level of alcohol consumption and prostate cancer incidence.

Our warmest thanks to Jinhui Zhao who tracked down and translated a difficult to locate study and to Gerry Shaper who laboriously critiqued our work. We are indebted to Richard Smith (United Health Group; former editor British Medical Journal) for reminding us that serious contamination may exist in the control groups of these studies throwing doubt on any conclusions from them. Support for the project came from the National Drug Research Institute, Curtin University, Perth, Australia.

Conflict of interest statement: Dr. Fillmore has received minor seed money from NordAN and a minor amount of money from the International Center for Alcohol Policies to support an inhouse paper on the nature of contemporary alcohol-related research. In 1980 Dr. Stockwell worked briefly on the project funded by the pharmaceutical company. E. Merck examining the drug nitrefazole as a potential treatment for alcoholism. He has not received personal fees or expenses otherwise from the pharmaceutical industry and has no links to the alcohol industry. Dr. Chikritzhs and Mr. Pascal have no links to the alcohol or potential conflicts of interests. Dr. Bostrom has performed statistical consulting for parmaceutical companies and other industries, none connected with the alcohol beverage industry.

7 References

[1] Haas, G. P., Sakr, W. A., Epidemiology of prostate cancer, *CA Cancer J. Clin.* 1997, *47*, 273 – 87.

[2] Key, T., Risk factors for Prostate Cancer. Preventing Prostate Cancer: Screening versus Chemoprevention, *Cancer Surv.* 1995, *23*, 63 – 77.

[3] Shimizu, H., Ross, P. K., Berstein, L., Yatani, R. *et al*., Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County, *Br. J. Cancer* 1991, *63*, 963 – 966.

[4] Parker, S. L., Davis, K. J., Wingo, P. A., Ries, L. A. G., Heath, C. W., Cancer statistics by race and ethnicity, *CA Cancer J. Clin.* 1998, *48*, 31 – 48.

[5] Gronberg, H., Prostate cancer epidemiology, *Lancet* 2003, *361*, 859 – 864.

[6] Key, T. J., Schatzkin, A., Willett, W. C., Allen, N. E. *et al*., Diet, nutrition and the prevalence of cancer, *Public Health Nutr.* 2004, *7*, 187 – 200.

[7] Wolk, A., Diet, lifestyle and risk of prostate cancer, *Acta Oncol.* 2005, *44*, 277 – 281.

[8] World Cancer Research Fund/American Institute for Cancer Research, *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective*, AICR, Washington DC 2007.

[9] English, D. R., Holman, C. D. J., Milne, E., Winter, M. G. *et al*., *The Quantification of Drug Caused Morbidity and Mortality in Australia*, Commonwealth Department of Human Services and Health, Canberra 1995.

[10] Breslow, R. A., Weed, D. L., Review of epidemiologic studies of alcohol and prostate cancer: 1971 – 1996, *Nutr. Cancer* 1998, *30*, 1 – 13.

[11] Dennis, L. K., Meta-analysis for combining relative risks of alcohol consumption and prostate cancer, *Prostate* 2000, *42*, 56 – 66.

[12] Bagnardi, V., Blangiardo, M., La Vecchia, C., Corrao, G., Alcohol consumption and the risk of cancer: A meta-analysis, *Alcohol Res. Health* 2001, *25*, 263 – 70.

[13] Fillmore, K. M., Stockwell, T., Chikritzhs, T., Bostrom, A., Kerr, W. C., Moderate alcohol use and reduced mortality risk: Systematic error in prospective studies and new hypotheses, *Ann. Epidemiol.* 2007, *17*, S16 – S23.

[14] Longnecker, M. P., Alcohol consumption and risk of cancer in humans: An overview, *Alcohol* 1995, *12*, 87 – 96.

[15] Shaper, A. G., Wannamethee, G., Walker, M., Alcohol and mortality in British men: Explaining the U-shaped curve, *Lancet* 1988, *2*, 1267 – 1273.

[16] Paunio, M., Heinonen, O. P., Virtamo, J., Klag, M. J. *et al*., HDL cholesterol and mortality in Finnish men with special reference to alcohol intake, *Circulation* 1994, *90*, 2909 – 2918.

[17] Suhonen, O., Aromaa, A., Reunanen, A., Knekt, P., Alcohol consumption and sudden coronary death in middle-aged Finnish men, *Acta Med. Scand.* 1987, *221*, 335 – 341.

[18] Klatsky, A. L., Friedman, G. D., Siegelaub, A. B., Alcohol and mortality: A ten-year Kaiser-Permanente experiment, *Ann. Intern. Med.* 1981, *95*, 139 – 145.

[19] Goldberg, I. J., Burchfiel, C. M., Reed, D. M., Wergowske, G., Chiu, D., A prospective study of the health effects of alcohol consumption in middle-aged and elderly men, *Circulation* 1994, *89*, 651 – 659.

[20] San Jose, B., Van DeMheen, H., Van Oers, J. A. M., Mackenbach, J. P., The U-shaped curve: Various health measures and alcohol drinking patterns, *J. Stud. Alcohol* 1999, *60*, 725 – 731.

[21] Cahalan, D., *Problem Drinking and Short-Term Change: A Community*, Dissertation, The George Washington University, Washington DC, 1968.

[22] Stall, R., Change and stability in quantity and frequency of alcohol use among aging males: A 19-year follow up study, *Br. J. Addict.* 1986, *81*, 537 – 544.

[23] Adams, W. L., Garry, P. J., Rhyne, R., Hunt, W. C., Goodwin, J. S., Alcohol intake in the healthy elderly. Changes with age in a cross-sectional and longitudinal study, *J. Am. Geriatr. Soc.* 1990, *38*, 211 – 216.

[24] Seppa, K., Pitkajarvi, T., Sillanaukee, P., Alcohol consumption profile by time in middle-aged men: A longitudinal study based on three different diagnostic instruments, *Alcohol* 1999, *34*, 65 – 70.

[25] Dent, O., Grayson, D., Waite, L., Cullen, J. S. *et al.*, A longitudinal study of alcohol consumption and functional disability in a community sample of older people, *Australas. J. Ageing* 2000, *19*, 185 – 189.

[26] Shaper, A. G., Wannamethee, G., in: Chadwick, D. J., Goode, J. A. (Eds.), *The J-shaped Curve and Changes in Drinking Habit*, *Alcohol and Cardiovascular Diseases*, Wiley Chichester, London 1998.

[27] Kerr, W. C., Fillmore, K. M., Bostrom, A., Stability of alcohol consumption over time: Evidence from three longitudinal surveys from the United States, *J. Stud. Alcohol* 2002, *63*, 325 – 333.

[28] Moore, A. A., Gould, R., Reuben, D. B., Greendale, G. A. *et al*., Longitudinal patterns and predictors of alcohol consumption in the United States, *Am. J. Public Health* 2005, *95*, 458 – 64.

[29] Graham, K., Schmidt, G., The effects of drinking on health of older adults, *Am. J. Drug Alcohol Abuse* 1988, *24*, 465 – 481.

[30] Ruchlin, H. S., Prevalence and correlates of alcohol use among older adults, *Prev. Med.* 1997, *26*, 651 – 657.

[31] Cryer, P. C., Jenkins, L. M., Cook, A. C., Ditchburn, J. S. *et al.*, The use of acute and preventative medical services by a general population: Relationship to alcohol consumption, *Addiction* 1999, *94*, 1523 – 1532.

[32] Cryer, P. C., Saunders, J., Jenkins, L. M., Neale, H. *et al.*, Clusters within a general population of alcohol abstainers, *Int. J. Epidemiol.* 2001, *30*, 756 – 765.

[33] Zarkin, G. A., Bray, J. W., Babor, T. F., Higgins-Biddle, J. C., Alcohol drinking patterns and health care utilization in a managed care organization, *Health Serv. Res.* 2004, *39*, 553 – 570.

[34] Dhom, G., Epidemiologic aspects of latent and clinically manifest carcinoma of the prostate, *J. Cancer Res. Clin. Oncol.* 1983, *106*, 210 – 18.

[35] Greenwald, P., Prostate, in: Schottenfeld, D., Fraumeni, J. F. Jr. (Eds.), *Cancer Epidemiology and Prevention,* PA WB Saunders, Philadelphia 1982, pp. 938 – 946.

[36] Dennis, L. K., Hayes, R. B., Alcohol and prostate cancer. *Epidemiol. Rev.* 2001, *23*, 110 – 114.

[37] Wynder, E. L., Mabuchi, K., Whitmore, W. F., Epidemiology of cancer of the prostate, *Cancer* 1971, *28*, 344 – 360.

[38] Jackson, M. A., Kovi, J., Heshmat, M. Y., Jones, G. W. *et al.*, Factors involved in the high incidence of prostatic cancer among American blacks, *Prog. Clin. Biol. Res.* 1981, *53*, 111 – 32.

[39] Signorello, L. B., Kuper, H., Lagiou, P., Wuu, J. *et al.*, Lifestyle factors and insulin-like growth factor 1 levels among elderly men, *Eur. J. Cancer Prev.* 2001, *9*, 173 – 178.

[40] Pawlega, J., Rachtan, J., Dyba, T., Dietary factors and risk of prostate cancer in Poland. Results of a case-control study, *Neoplasma* 1996, *43*, 61 – 63.

[41] Platz, E. A., Leitzmann, M. F., Rimm, E. R., Willett, W. C., Giovannucci, E., Alcohol intake, drinking patterns and risk of prostate cancer in a large prospective cohort study, *Am. J. Epidemiol.* 2004, *159*, 444 – 453.

[42] Sutcliffe, S., Giovannucci, E., Leitzmann, M. F., Rimm, E. R. *et al.*, A prospective cohort study of red wine consumption and risk of prostate cancer, *Int. J. Cancer* 2007, *120*, 1529 – 35.

[43] Gronberg, H., Damber, L., Damber, J.-E., Total food consumption and body mass index in relation to prostate cancer risk: A case-control study in Sweden with prospectively collected exposure data, *J. Urol.* 1996, *155*, 969 – 974.

[44] Hiatt, R. A., Armstrong, M. A., Klatsky, A. L., Alcohol consumption, smoking and other risk factors and prostate cancer in a large health plan cohort in California (United States), *Cancer Causes Control* 1994, *5*, 66 – 72.

[45] Barba, M., McCann, S. E., Schunemann, H. J., Stranges, S. *et al.*, Lifetime total and beverage specific – alcohol intake and prostate cancer risk: A case-control study, *Nutr. J.* 2004, *3*, 1 – 8.

[46] Crispo, A., Talamni, R., Gallus, S., Negri, E. *et al.*, Alcohol and the risk of prostate cancer and benign prostatic hyperplasia, *Urology* 2004, *64*, 717 – 722.

[47] Schoonen, W. M., Salinas, C. A., Kiemeney, L. A., Stanford, J. L., Alcohol consumption and risk of prostate cancer in middle-aged men, *Int. J. Cancer* 2005, *113*, 133 – 140.

[48] Sharpe, C. R., Siemiatycki, J., Case-control study of alcohol consumption and prostate cancer risk in Montreal, Canada, *Cancer Causes Control* 2001, *12*, 589 – 598.

[49] Tavani, A., Negri, E., Franceshci, S., Talamini, R., La Vecchia, C., Alcohol consumption and risk of prostate cancer, *Nutr. Cancer* 1994, *21*, 24 – 31.

[50] Fillmore, K. M., Kerr, W. C., Stockwell, T., Chikritzhs, T., Bostrom, A., Moderate alcohol use and reduced mortality risk: Systematic error in prospective studies, *Addiction Res. Theory* 2006, *14*, 101 – 132.

[51] Normand, S.-L., Meta-Analysis: Formulating, evaluating, combining and reporting, *Stat. Med.* 1999, *18*, 321.

[52] Tonnesen, H., Moller, H., Ancersen, J. R., Jensen, E., Juel, K., Cancer morbidity in alcohol abusers, *Br. J. Cancer* 1994, *69*, 327 – 332.

[53] Adami, H. O., McLaughlin, J. K., Hsing, A. W., Wolk, A. *et al.*, Alcoholism and cancer risk: a population-based cohort study, *Cancer Causes Contr.* 1992, *3*, 419 – 425.

[54] Pell, S., D'Alonzo, C. A., A five-year mortality study of alcoholics, *J. Occup. Med.* 1973, *15*, 120 – 125.

[55] Hirayama, T., Life-style and cancer: from epidemiologic evidence to public behaviour change to mortality reduction of target cancers, *J. Natl. Cancer Inst. Monogr.* 1992, *12*, 65 – 74.

[56] Thygessen, L. C., Albertsen, K., Johansen, C., Gronbaek, M., Cancer incidence among Danish brewery workers, *Int. J. Cancer* 2005, *116*, 774 – 778.

[57] Sundy, P., *Alcoholism and Mortality*, National Institute for Alcohol Research, Publication no. 6. Oslo, Universitersforlager 1967.

[58] Schmidt, W., Popham, R. E., The role of drinking and smoking in mortality from cancer and other causes in male alcoholics, *Cancer* 1981, *47*, 1031 – 1041.

[59] Sesso, H. D., Paffenbarger, R. S., Lee, I.-M., Alcohol consumption and risk of prostate cancer: The Harvard alumni health study, *Int. J. Epidemiol.* 2001, *30*, 749 – 755.

[60] Rothamn, G., Taubes, G., *Epidemiology Faces its Limits*, *Science* 1995, *269*, 164 – 169.

[61] Dagnelie, P. C., Schuurman, A. G., Goldbohm, R. A., Van Den Brant, P. A., Diet, anthropometric measures and prostate cancer risk: A review of prospective cohort and intervention studies, *BJU Int.* 2004, *93*, 1139 – 1150.

[62] Holman, C. D. J., English, D. R., Milne, E., Winter, M. G., Meta-analysis of alcohol and all-cause mortality: A validation of NHMRC recommendations, *Med. J. Aust.* 1996, *164*, 141 – 145.

[63] Corrao, G., Rubbiati, L., Bagnardi, V., Zambon, A., Poikolainen, K., Alcohol and coronary heart disease: A meta-analysis, *Addiction* 2000, *95*, 1505 – 1523.

[64] Rehm, J., Gutjahr, E., Gmel, G., Alcohol and all-cause mortality: A pooled analysis, *Contemp. Drug Probl.* 2001, *28*, 337 – 361.

