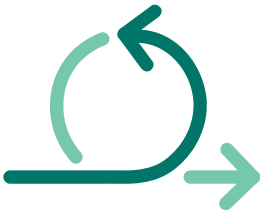
DISCUSSION OF CONCEPTUAL AND METHODOLOGICAL ISSUES

IARD Health Reviews offer a referenced overview of recent peer-reviewed, published research on the relationship between alcohol consumption and health outcomes. They are not intended to be exhaustive representations of all scientific research on a given subject and, as research is constantly evolving, they may not include the most recent findings. These materials do not necessarily reflect the views of IARD or its member companies. The reviews report the findings of the referenced studies and are not intended to advise individuals about their drinking. People with specific questions about their drinking are encouraged to consult a healthcare professional; together, they can determine what is best based on individual risk factors, including family history, genetics, and lifestyle. For some people, the better choice may be to not drink at all. IARD Health Reviews should be read in their entirety and not misrepresented or taken out of context.



The conceptual and methodological issues presented in this chapter of the *IARD Health Review: Drinking and Cancer* reflect several topics raised in the discussion sections of published research studies on alcohol consumption and cancer or other alcohol-related health outcomes. The issues raised in this chapter are intended to inform the reader about some of the challenges and limitations of *epidemiological* research, other issues related to study methods, and how some of these might be addressed in a study's design and analysis. These issues are well-known and described in the alcohol epidemiology research literature and include, but are not limited to, confounding bias, classification errors, and selection bias. IARD has not conducted a systematic review of research studies for the issues described below for this discussion chapter.

There is a glossary of key terms used in this chapter on page 6.

CLASSIFICATION ISSUES AND POTENTIAL ERRORS

The way in which drinkers and nondrinkers are classified in studies may affect observed outcomes for cancer. Some of the issues and examples of different types of potential classification errors include the following:

Drinking patterns

There is little consistency in defining drinking-level categories across research studies on alcohol consumption and health outcomes or describing those levels as light, moderate, or heavy. For example, studies can define categories:

- in 5g increments
- by combining all drinkers consuming up to one full drink and then combining all drinkers consuming more than one drink per day in another category, or
- by combining and describing all drinkers consuming more than one but less than five drinks per day as moderate drinkers, or
- by describing drinkers consuming alcohol occasionally and up to 8g/day as light drinkers, drinkers consuming between 8g/day and 24g/day as moderate, and over 24g/day as heavy.

A wider range of consumption within a single drinking level category can make it difficult to determine more precisely where risk increases. For example, studies that combine occasional, light, and moderate drinkers in a single category fail to provide data on risk associated for each of these different drinking patterns [1, 2].

Discussion of study limitations in meta-analyses and individual studies often includes the inability to assess the role of different drinking patterns on cancer risk, including binge drinking [2-4]. For example, although research has shown an increased risk of breast cancer beginning at light or moderate drinking levels, few studies have investigated the relationship between binge drinking and breast cancer risk [5, 6]. Additional research on refined categories of average alcohol consumption and binge drinking frequency would provide more robust evidence on the relationships among patterns of drinking and cancer risk.

Former drinkers and lifetime abstainers

The "sick-quitter" hypothesis postulates that many former drinkers have stopped drinking for health reasons and was first described in 1988 [7]. If these individuals are classified as non-drinkers in the same group as lifetime abstainers, their existing health conditions may make it appear that nondrinkers are at a higher risk than light or moderate drinkers for a given health outcome or, conversely, that the risk associated with drinking compared with abstaining is lower than it actually is. This effect is sometimes referred to as "abstainer bias". A group of researchers have claimed that this bias (the potential to influence the overall results) applies to all studies that combine lifetime abstainers and occasional and former drinkers in the field of alcohol and cardiovascular disease and all-cause mortality [8, 9], but may not apply to breast cancer studies [10].

Over the past decade, studies have accounted for this potential source of bias by separating former drinkers from lifetime abstainers or testing whether risk estimates differ when former drinkers are included or excluded in the nondrinker category. This bias has often been accounted for in research on alcohol and cardiovascular disease or all-cause mortality [11-16] and in research on alcohol and cancer, including in many studies in the *IARD Health Review: Drinking and Cancer* [1, 5, 17-23].

Another method of addressing this potential bias is to examine results when study participants with a history of a given health condition are first included and then excluded from the analysis, as in Dam et al. 2016 [24].

- **Reporting errors**

Self-reported alcohol consumption data are likely to be subject to inaccuracies due to recall errors (difficulty with accurately remembering past behavior) and social desirability bias (the desire to provide a response viewed favorably by others). The latter may be especially relevant in some cultures for surveys asking questions about potentially sensitive information, such as alcohol consumption. If respondents have underreported their consumption and are misclassified into a lighter drinking category, this would result in an error in the risk estimate [25].

There are methods for minimizing potential underestimation errors:

- Some studies collect multiple measures of alcohol consumption over time [26, 27].
- Other studies collect health data (biomarkers or clinical diagnoses of alcohol-related conditions), which are then used to identify and separate respondents who misreport their consumption from other respondents [23, 28]. This approach has demonstrated that alcohol-related cancer risk associated with "light-moderate" drinking or <1 drink/day appears to be restricted to underreporting; there was no observed association between alcohol consumption at this same level of drinking and cancer risk among unlikely underreporters, as identified by the researchers through previously reported heavier intake or an alcohol-related diagnosis [23, 28].

- **Relevant time period of alcohol consumption**

Another issue that is relevant to cancer epidemiology is the assessment of the timing of exposure to a risk factor of interest.

It is currently unclear whether cancer risk is affected by recent drinking patterns, drinking patterns during a critical period of development (for example, puberty), or the accumulation of drinking patterns over a lifetime.

It is also difficult to discern for any given cancer diagnosis whether carcinogenesis is associated with first exposure to a risk factor, prolonged exposure, only in the presence of an additional risk factor or factors, or whether exposure to a risk factor accelerates cancer development [29].

At present, alcohol assessment varies across research studies, making it difficult to determine whether risk estimates reflect recent or historic drinking patterns.

Few studies have attempted to test whether alcohol consumption in early adulthood, in the recent time period, or over a lifetime is more strongly associated with risk. Additionally, these results have been somewhat inconsistent. More research could help demonstrate whether consumption during one time period is a more accurate predictor of risk than another and whether that reference period differs for various cancer sites. For example:

- One study of cancers of the upper airway and digestive tract found a weak, non-statistically significant association for drinking during early adulthood (aged from 20 to 29 years) and a modest association with both recent and lifetime consumption measures [22].

- A similar finding for male participants was reported in a study of pancreatic cancer [30].

- A 2004 study of Danish women found that recent alcohol consumption was more accurately associated with breast cancer risk than either lifetime consumption or early adulthood consumption [31], a finding confirmed in a larger 2007 multi-cohort study in Europe [32]. A 2011 study in the U.S., however, concluded that a cumulative lifetime alcohol intake measure was more accurate than a baseline or current alcohol measure, and that drinking in early adulthood and later adulthood were both linearly associated with breast cancer risk (although the trend for alcohol intake during early adulthood did not reach statistical significance) [33].

- McNabb and colleagues, in their 2018 meta-analysis, suggest that results indicating that former drinkers have an increased risk of colorectal cancer compared to lifetime abstainers may be due to the impact of a longer-term drinking history on colorectal cancer risk. Their study found a reduced risk of colorectal cancer among light to moderate drinkers, compared with nondrinkers, but the authors acknowledge that the inclusion of former drinkers with lifetime abstainers in the reference group may have influenced their observed protective effect [34].

CONFOUNDING BIAS

Various factors that are related to drinking, or to not drinking, may explain observed associations between alcohol consumption and cancer risk. This potential source of error is referred to as confounding bias.

Many factors may be associated with both drinking behavior and cancer incidence or mortality and should be accounted for in a study's design or in the data analysis as much as possible to minimize confounding bias.

- These include individual factors, such as sex, race, and ethnicity; genetic and physiological factors; behavioral factors, such as smoking, diet, and physical activity; social and economic factors; and existing mental and health conditions.

- Because epidemiological studies are unable to control for all potential confounders, the possibility that the results could be explained by residual confounding cannot be excluded, and the results of observational studies should be interpreted with reasonable caution.

    - When risk estimates exceed 2.0, or are less than 0.5, it is increasingly less likely that the risk association can be explained by unmeasured confounding and more likely that the observed association reflects a true association [35].

Smoking is a strong risk factor for most cancers [36, 37], and there is a high correlation between alcohol consumption and smoking in general and heavier drinking and heavier smoking in particular [38]. Even though smoking can be adjusted for in a study of the relationship between alcohol and cancer, residual confounding may still influence the risk relationship. This means that, in studies that include smokers and nonsmokers, the relationship between alcohol and cancer may be driven by the effect of alcohol in smokers. Studies that separate results for smokers and nonsmokers more effectively examine independent effects of alcohol consumption [37].

SELECTION BIAS

Selection bias may occur when individuals participating in a research study are not representative of the population being studied and can therefore distort (underestimate or overestimate) the relationship between alcohol consumption and cancer risk.

- **Healthy cohorts**

Healthier individuals may be more likely to participate in a research study and continue participating throughout the course of the study than individuals with health issues. This is likely to result in a lower incidence of cancer in the study population over the course of the study, which may make the observed cancer risk lower than it actually is in the general population.

In addition, risky or heavy drinkers can be less likely to be included in a study sample population or to participate in a study due to other factors including social isolation, homelessness, or mental illness. This makes it more likely that a lower incidence of alcohol-related health outcomes will be observed in the study population, making the observed cancer risk lower than it actually is in the general population.

- **Survival bias**

Another type of selection bias relates to survival: drinkers who have died prematurely from an alcohol-related cause cannot be included in a research study, therefore people who are still alive and available to be selected into a research study may not accurately reflect the full population of drinkers. This bias assumes that individuals dying at younger ages are more likely to be drinkers than non-drinkers because alcohol is a leading risk factor for the causes of death that are more prevalent among younger individuals (unintentional injuries and violence) [39].

Selection bias complicates the interpretation of research about other risk factors that are associated with more than one health outcome. This bias cannot be easily adjusted or controlled for by researchers, nor are its potential effects on research outcomes easily quantifiable.

However, "selection" of the study population from a source population does not necessarily produce biases that distorts the risk estimate. Participants in an epidemiological study do not have to be representative of the general population for an association to be *internally valid*. Thus, investigators can study "select" groups and maintain the expectation that results will be meaningful (for example, nurses participating in the Nurses' Health Study). This is why results from large, long-term follow-up studies produce important pieces of evidence; these types of studies focus on the relationship of alcohol to cancer risk by minimizing differences in other factors (socioeconomic or lifestyle) among participants that could affect cancer risk.

Glossary

Epidemiological studies examine the distribution of disease and other health outcomes among human populations and the determinants of those health outcomes. A key feature of an epidemiological study is the measurement of a health outcome (for example, colorectal cancer) among a population at risk, where the measurement of a risk factor (for example, alcohol consumption) and the health outcome are assessed at the same time, longitudinally, or retrospectively, depending on the study design.

Internal validity is the extent to which the results define the true relationship in the study population between a risk factor and a health outcome, and other factors or methodological issues related to study design or implementation are unlikely to have altered the observed relationship. In contrast, a study is said to have external validity if its results can be applied from the study population to the general population.

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