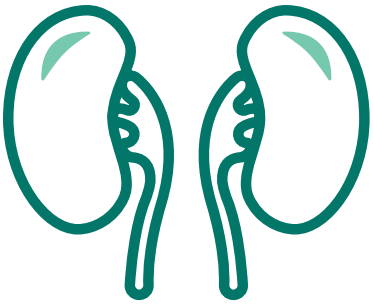
DRINKING AND KIDNEY CANCER



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. IARD and its member companies do not recommend that anyone drink alcohol for its potential health benefits and would encourage those with specific questions about their drinking to consult their healthcare professionals; 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.

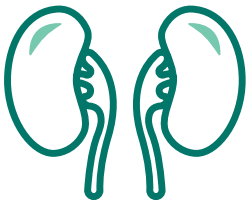
This Health Review focuses on cancer sites associated with alcohol consumption as identified by the World Cancer Research Fund and the International Agency for Research on Cancer. Due to the limited availability of national cancer statistics in many countries, U.S. data – which is publicly available and annually updated – is sometimes used to illustrate cancer risk in this review.

A glossary of key terms used in this review can be found on page 11.

Last literature review: July 2019

Note: Cancers that start in the kidney and renal pelvis are commonly combined when reported in national and international data. The renal pelvis is located in the center of the kidney and funnels urine to the ureter. Most studies refer to renal cell carcinoma, which is the most common type of kidney and renal pelvis cancer, as "kidney cancer." Therefore, this review uses the term "kidney cancer" to indicate the combination of kidney and renal pelvis cancer, or renal cell carcinoma, or both unless otherwise noted.

Introduction



KIDNEY CANCER IN MEN AND WOMEN

1.7%

Lifetime risk of diagnosis (U.S.)

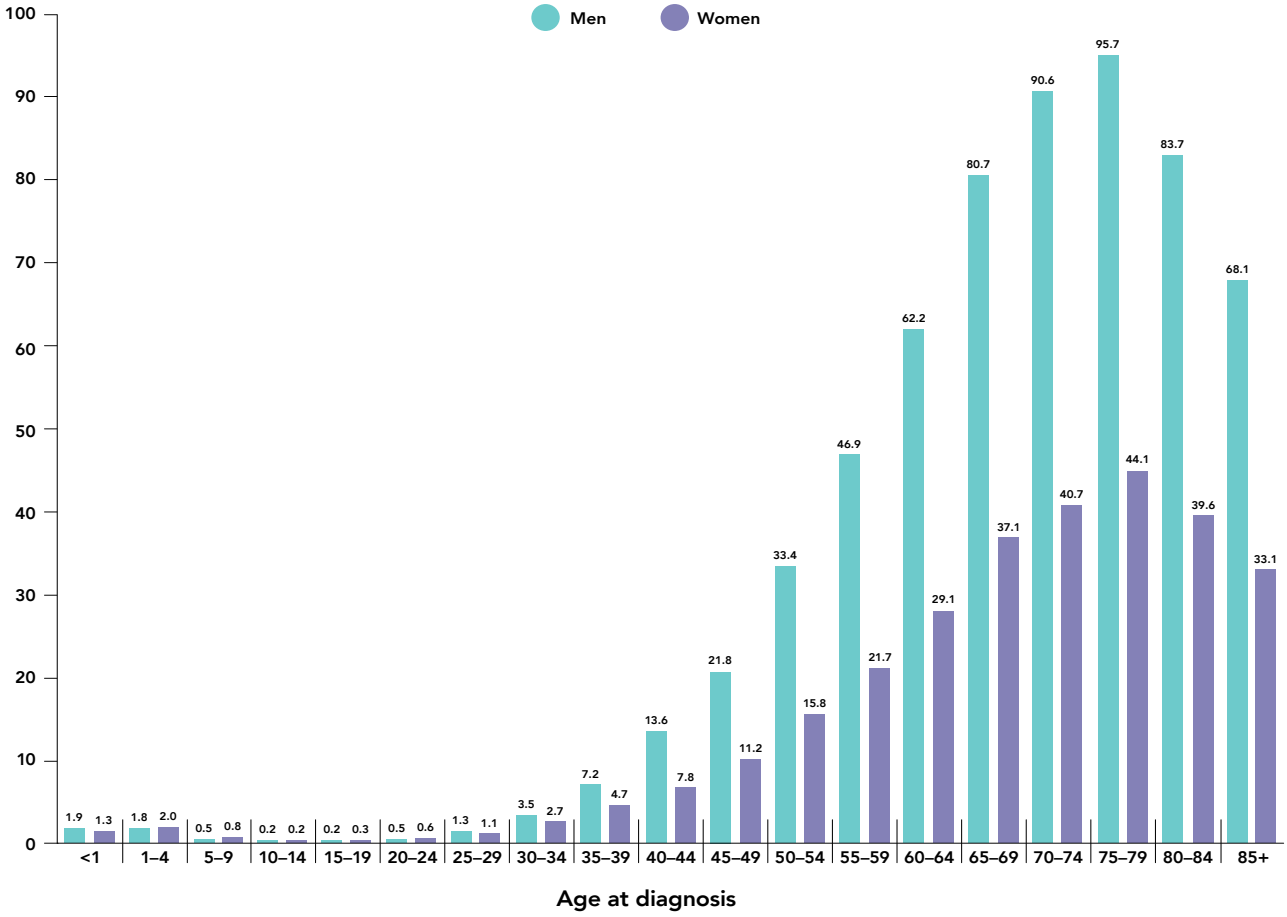
4.55

Global incidence per 100,000

Sources: *Global Burden Disease study 2019 (age-standardized data) [1] and the National Cancer Institute SEER Report [2]*

Kidney cancer is the 14th most common cancer in the world for men and women combined and accounts for 2.2% of all incident cancer cases globally [3]. Incidence rates vary across countries, from a high of 14.5 per 100,000 persons in Lithuania to a low of zero in the Maldives, the Republic of the Gambia, and Vanuatu [3]. In the U.S., the average age at diagnosis is 64 years, with 77% of new diagnoses occurring among those aged 55 years and older; incidence rates are twice as high among men than women (see Figure 1) [2].

Figure 1. Age-specific incidence of kidney cancer among men and women in the U.S. per 100,000



Source: *Seer 21 Areas, Kidney SEER Incidence and U.S. Mortality Rates by Age at Diagnosis, 2014-2018 [2]*

According to the World Cancer Research Fund (WCRF), alcohol consumption is a risk factor for kidney cancer [4]. In addition, several other risk factors are associated with kidney cancer risk, some of which may mediate or modify the relationship between alcohol consumption and kidney cancer risk (see Table 1).

Table 1. Common risk factors for kidney cancers*

Modifiable risk factors	Non-modifiable risk factors
Alcohol consumption Body mass index Hypertension Smoking Taking painkillers with phenacetin	Age Personal/family history Genetics Kidney disease Race Sex

Source: *American Cancer Society [5] and The World Cancer Research Fund / American Institute for Cancer Research's Third Expert's Report 2018 [4]*

**Items are listed alphabetically and not according to importance or magnitude of risk.*

The importance (that is, magnitude or prevalence) of any given risk factor relative to other risk factors may differ by population due to environmental, socio-economic, behavioral, or genetic differences.

BIOLOGICAL MECHANISMS OF KIDNEY CANCER

Researchers are continuing to explore several plausible biological mechanisms that may explain the potential role of alcohol as a risk or mitigating factor for kidney cancer [4, 6], and some of these are:

- Alcohol consumption may reduce kidney cancer risk by modifying the relationship between insulin and diabetes. Studies have shown that low-to-moderate alcohol consumption increases insulin sensitivity [7-9], especially among women, [10, 11] and is associated with a reduced risk of diabetes [12-14]. Studies have identified an association between diabetes and increased risk of kidney cancer [15, 16].

- Alcohol is a known diuretic [17] and is hypothesized to reduce the risk of kidney cancer by inducing urination and reducing the length of time that epithelial cells are exposed to carcinogens [4, 18, 19].

    - Studies have shown that drinking water suppresses vasopressin, which is a hormone that retains fluid in the kidney; this results in higher urinary output among hydrated individuals, compared to dehydrated individuals [17]. In the presence of alcohol, vasopressin suppression is prolonged despite water volume [19] leading to higher urinary output [17, 19]; however the diuretic effect of alcohol may be reduced in dehydrated individuals [17].

- Some alcohol beverages contain phenolic compounds such as tannins, which can affect their color, taste, and texture. These compounds may exhibit protective properties [20]; however, research in this field of interest is still evolving.

- Limited research has shown that the antioxidant phenolic compounds resveratrol and xanthohumol may reduce oxidative stress through suppression of cell proliferation, induced cell death, anti-inflammation, and inhibition of *reactive oxygen species* production [21, 22], however their bioavailability (concentration in the blood) is low [22, 23].

Summary of recent kidney cancer research

This chapter of the *IARD Health Review: Drinking and Cancer* includes studies that examine the association between alcohol consumption and risk of being diagnosed with kidney cancer.

For this chapter, the following criteria were used to select studies following a literature search using the IARD Research Database and PubMed.

Study designs: meta-analyses (a type of study that pools data from multiple studies), pooled cohort studies, pooled case-control studies, prospective cohort studies, and case-control studies; systematic reviews were excluded from the summary of results section because of the absence of new or pooled risk estimates
Publication dates: from 2007 through June 2019
Outcomes: kidney cancer incidence; combined incidence and mortality (for meta-analyses only)
Exposure: at least three quantified levels of alcohol consumption; or at least two quantified levels of alcohol consumption if a study examined a limited range of alcohol consumption (for example, up to one drink per day only)
Sample size: 1,000+

When multiple analyses were presented in a study, we included results from models that were fully adjusted, used a lifetime alcohol consumption assessment (versus a single assessment), and separated former drinkers from lifetime abstainers. Results of meta-analyses and pooled cohort studies are presented first, followed by results of individual studies to allow comparison of risk estimates across both types of study designs.

Note: The time frame of alcohol exposure assessment varies from study to study (for example, researchers could assess a study participant's lifetime, recent past, or current consumption), making it difficult to determine whether risk estimates reflect recent drinking patterns or the accumulation of drinking patterns over a lifetime. *This topic is discussed in the chapter "**Discussion of conceptual and methodological issues**".*

KIDNEY CANCER

In this section we present results of studies reporting *relative risk* estimates for kidney cancer. (*Please see the Glossary on page 11 for a definition of relative risk and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.*)

According to the WCRF, there is "probable" evidence of a reduced risk of kidney cancer associated with alcohol consumption up to 30g/day; insufficient evidence is available for intake above 30g/day [4]. (*Please see **Background chapter** for an explanation on the WCRF definitions of strength of evidence.*)

Meta-analyses

Five meta-analyses met the inclusion criteria for this review. Compared to nondrinkers, four meta-analyses found a reduced risk of kidney cancer [6, 18, 24, 25] and one meta-analysis found no association [26] between kidney cancer and alcohol consumption when results are reported for both sexes combined. None of the five meta-analyses found an increased risk associated with any level of alcohol consumption (see Table 2).

When stratified by sex, results for women were found to be generally consistent with those reported for men and women combined [18, 24-26], whereas no association was reported for men at or below 13g/day [18, 24-26] (see Table 2).

- No association was reported by Choi et al., 2018, between kidney cancer and alcohol consumption when both sexes were combined, or for men separately, but a reduced risk was reported for women only [26].
    - Choi et al., 2018 limited the study to comparing nondrinkers to drinkers who consume up to 30g/day; there are no risk estimates for drinkers who consume more than 30g/day [26].

Results from these meta-analyses indicate that the magnitude of the risk estimate is considered "weak" across the alcohol consumption spectrum (see, for example, Schoenbach and Rosamond (2000) [27] and the Glossary for additional resources). Compared to nondrinkers, the lowest levels of average alcohol consumption defined by these studies (up to 12.5g/day) are associated with an 8% to 10% decrease in risk (this is equivalent to a relative risk of 0.92 to 0.90), whereas the highest levels of consumption (more than 15g/day) are associated with a 28% decrease in risk (this is equivalent to a relative risk of 0.72).

Individual prospective cohort and case-control studies

Eleven individual prospective cohort or case-control studies met the review criteria for examining the association between alcohol consumption and kidney cancer among men and women combined [20, 28-37] (see Table 3).

- Three of six cohort studies found a reduced risk of kidney cancer associated with alcohol consumption for men and women combined starting at less than 15g/day [20, 29, 32] but two of these reported no association with consumption greater than 15g/day [29, 32].
- Four out of five case-control studies reported a reduced risk starting at alcohol consumption above 0g/day [33, 34], 21g/day [35], and 48g/day [36].
- Four of 11 studies reported no association between alcohol consumption and kidney cancer for men and women combined [28, 30, 31, 37].

Table 2. Relative risk estimates for alcohol consumption associated with kidney cancer from meta-analyses*

Study reference	Nondrinker	Average alcohol grams per day
Combined sexes		
Choi et al., 2018	ref.†	ns (0.5–4) | ns (5–9) | ns (10–14) | ns (15–29) | 30+
Bellocco et al., 2012	ref.†	0.90 (0.5–4) | 0.79 (5–49) | ns (50+)
Bagnardi et al., 2015	ref.†	0.92 (0.5–4) | 0.79 (5–49) | ns (50+)
Lee et al., 2007	ref.†	ns (0.5–4) | 0.82 (5–14) | 0.72 (15+)
Xu et al., 2015	ref.†	ns (0.5–4) | 0.75 (5–39) | ns (40+)
Men		
Choi et al., 2018	ref.†	ns (5–9) | ns (10–14) | ns (15–29) | 30+
Bagnardi et al., 2015	ref.†	ns (0.5–4) | 0.83 (5–49) | ns (50+)
Xu et al., 2015	ref.†	ns (0.5–4) | 0.76 (5–49)
Lee et al., 2007	ref.†	ns (0.5–4) | ns (5–14) | 0.71 (15+)
Women		
Xu et al., 2015	ref.†	0.87 (0.5–4) | 0.72 (5–39)
Bagnardi et al., 2015	ref.†	0.85 (0.5–4) | 0.65 (5–49)
Lee et al., 2007	ref.†	ns (0.5–4) | ns (5–14) | 0.73 (15+)
Choi et al., 2018	ref.†	ns (0.5–4) | ns (5–9) | 0.93 (10–29) | 30+

*All meta-analysis study designs published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.
† Nondrinker (may include former or occasional drinkers or both)

Table Notes:

- Vertical bars correspond to the lower and upper limits of each drinking level as defined by the study, converted, if necessary, to grams of pure alcohol per day.
- Green shading indicates a statistically significant decrease in relative risk, compared to the reference group.
- Grey shading indicates that the study did not assess risk at this drinking level.
- "ns" indicates that risk for that drinking level was not statistically different from risk for the reference group.
- Dashed line indicates that upper and lower limits of two drinking categories overlapped.

Table 3. Relative risk estimates for alcohol consumption associated with kidney cancer for men and women combined from individual prospective cohort and case-control studies*

Study reference	Former drinker	Nondrinker	Average alcohol grams per day
Prospective studies			
Schouten et al., 2016		ref.†	ns
Klatsky et al., 2015	ns	ref.‡	ns
Macleod et al., 2013		ref.†	ns
Schouten et al., 2008		ref.†	ns
Wozniak et al., 2015	ns	ns‡	ref.
Karami et al., 2015		ref.†	ns
Case-control studies			
Hsu et al., 2007		ref.‡	ns
Antwi et al., 2018		ref.†	0.54
Hu et al., 2009		ref.†	0.8
Greving et al., 2007		ref.†	ns
Pelucchi et al., 2008		ref.†	ns

Study reference	0.5 1 2 3 4	5 6 7 8 9	10 11 12 13 14	15 16 17 18 19	20 21 22 23 24	25 26 27 28 29	30 31 32 33 34	35 36 37 38 39	40 41 42 43 44	45 46 47 48 49	50 51 52 53 54	55 56 57 58 59	60 61 62 63 64	65 66 67 68 69	70 71 72 73 74	75 76 77 78 79	80 81 82 83 84	85 86 87 88 89	90 91 92 93 94	95 96 97 98 99	100+
Schouten et al., 2016	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Klatsky et al., 2015	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Macleod et al., 2013	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Schouten et al., 2008	ns	0.66	0.66	0.66	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Wozniak et al., 2015	ref.	0.73	0.73	0.73	0.73	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Karami et al., 2015	ns	ns	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67
Hsu et al., 2007	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Antwi et al., 2018	0.54	0.54	0.54	0.54	0.54	0.54	0.54	0.54	0.54	0.43	0.43	0.43	0.43	0.43	0.43	0.41	0.41	0.41	0.41	0.41	0.41
Hu et al., 2009	0.8	0.78	0.78	0.78	0.78	0.78	0.78	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65
Greving et al., 2007	ns	ns	ns	ns	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
Pelucchi et al., 2008	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	0.76	0.76	0.76	0.76	0.76	0.76	0.70	0.70

*All individual prospective cohort and case-control studies published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.
†Nondrinker (may include former or occasional drinkers or both)
‡Nondrinker (lifetime abstainer)

Nine individual prospective cohort or case-control studies met the review criteria and reported risk estimates for men and women separately: eight for men [20, 32, 33, 36, 38-41] and eight for women [20, 32, 33, 36, 38, 39, 41, 42] (see Tables 4 and 5).

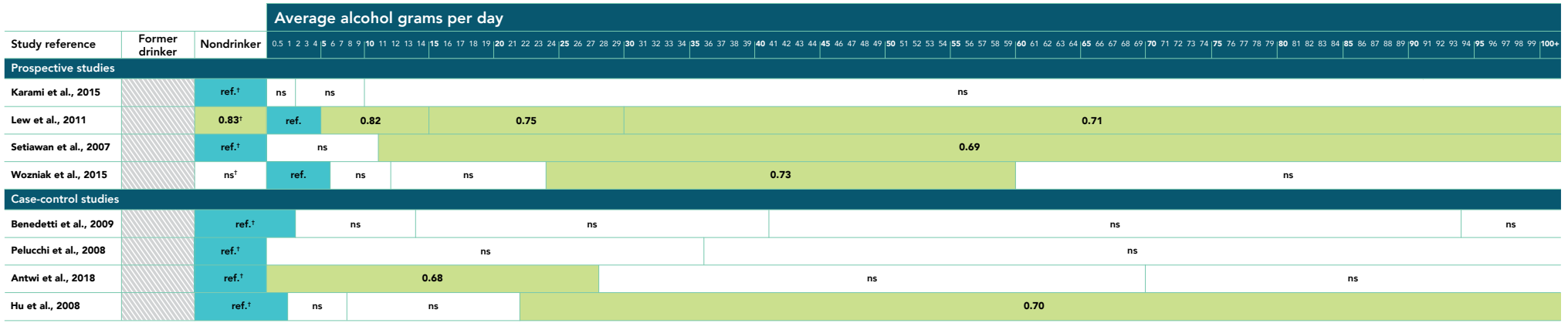
- Among men, five studies reported a reduced risk associated with alcohol consumption starting at more than 0g/day [33], 5g/day [38], 11g/day [39], 22g/day [41] and 24g/day [32], and three reported no association [20, 36, 40].
    - Wozniak et al., 2015 reported a reduced risk associated with alcohol consumption between 24g/day and 60g/day, but otherwise found no association with kidney cancer at any other level of consumption [32].
- Among women, five studies reported a reduced risk associated with alcohol consumption starting at more than 0g/day [33], 2g/day [20], 8g/day [41], 16g/day [42], and 30g/day [38], and three reported no association [32, 36, 39].
    - Karami et al., 2015 reported a reduced risk associated with alcohol consumption between 1.75g/day and 9.75g/day, but otherwise found no association with kidney cancer at any other level of alcohol consumption [20].

FUTURE RESEARCH

The plausible biological mechanisms that may explain the potential role of alcohol as a risk or mitigating factor for kidney cancer remain unclear. To obtain a better understanding, more research is needed. Additionally, to obtain a precise estimate of a potential threshold of alcohol consumption associated with kidney cancer risk, more refined drinking categories would need to be included.

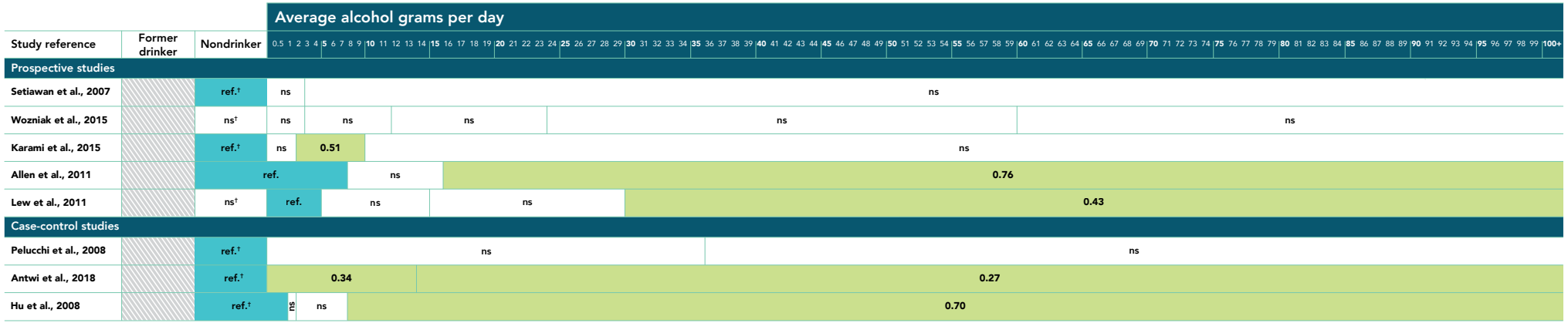
This review did not evaluate risk of bias or overall study quality as this was out of the scope of the review, and instead left interpretation of study quality and findings to the reader. However, future systematic reviews could contribute to a greater understanding of the relationship between alcohol consumption and kidney cancer risk by assessing study quality. Such an exercise may help readers interpret individual study results in the context of other published research and assess the overall quality of evidence from the existing body of research.

Table 4. Relative risk estimates for alcohol consumption associated with kidney cancer for men only from individual prospective cohort and case-control studies*



*All individual prospective cohort and case-control studies published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.
†Nondrinker (may include former or occasional drinkers or both)

Table 5. Relative risk estimates for alcohol consumption associated with kidney cancer for women only from individual prospective cohort and case-control studies*



*All individual prospective cohort and case-control studies published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.
†Nondrinker (may include former or occasional drinkers or both)

Glossary

- **Reactive oxygen species** are a group of highly-reactive molecules containing oxygen that, at low levels, are an important part of metabolism and inflammatory response. An excess of reactive oxygen species can damage cellular proteins, lipids, or DNA, and has been linked with chronic diseases, such as cancer, diabetes, and cardiovascular disease.

- **Relative risk (RR)** is a measure that compares the probability of a given outcome (for example, kidney cancer) among a group of people with a given risk factor (for example, alcohol consumption) with the probability of that outcome among a group of people without the risk factor (for example, nondrinkers). A risk estimate above one (RR>1) indicates an increased risk of the outcome associated with the exposure and a risk estimate below one (RR<1) indicates a reduced risk of the outcome associated with the exposure. If the risk estimate is equivalent to one (RR=1) then there is no association between the outcome and the exposure.

    - The magnitude of relative risk describes the strength of the association between the exposure and outcome of interest, or the relative risk estimate. There are several terms used to describe or interpret different relative risk estimates. Some commonly used descriptors are weak, small, moderate, medium, strong, or large [27, 43-46], however, the risk estimates associated with each term may differ or overlap (see Figures 2A-C). For example, according to Schoenbach and Rosamond 2000 [27], a moderate risk is equivalent to a relative risk of 1.8 to 3.0, while Craun and Calderon 2006, state that moderate to strong risk is equivalent to a relative risk greater than 1.5 [43, 44].

Figure 2A. Descriptions of magnitude of risk

1.0	No association (null value)
1.1–1.3	Weak
1.4–1.7	Modest
1.8–3.0	Moderate
3–8	Strong
For inverse associations (risk ratio is less than 1.0), take the reciprocal and look in above table, for example, the reciprocal of 0.5 is 2.0, which corresponds to a "moderate" association.	

Source: *Schoenbach and Rosamond 2000 [27]*

Figure 2B. Descriptions of magnitude of risk

	Trivial	Small	Moderate	Large	Very Large	Nearly perfect	Perfect
Correlation	**0.0**	**0.1**	**0.3**	**0.5**	**0.7**	**0.9**	**1**
Diff. in means	**0.0**	**0.2**	**0.6**	**1.2**	**2.0**	**4.0**	**infinite**
Freq. diff.	**0**	**10**	**30**	**50**	**70**	**90**	**100**
Rel. risk	**1.0**	**1.2**	**1.9**	**3.0**	**5.7**	**19**	**infinite**
Odds ratio	**1.0**	**1.5**	**3.5**	**9.0**	**32**	**360**	**infinite**

Source: *Hopkins 2002 [45]*

Figure 2C. Descriptions of magnitude of risk

Effect size: Interpretation suggestions for social science data

Type of effect size estimate	Included indices	RMPE	Moderate effect	Strong effect
Group difference	d, Δ, g	0.41	1.15	2.70
Strength of association	r, R, ϕ, p, partial r, β, r_h, tau	0.2	0.5	0.8
Squared association indices	r^2, R^2, η^2, adjusted R^2, ω^2 ε^2	0.04	0.25	0.64
Risk estimates	RR, OR	2.0*	3.0	4.0

Note. RMPE = recommended minimum effect size representing a "practically" significant effect for social science data. For effects with highly valid dependent measures (e.g., death) and using rigorous controlled outcomes trials, lower values may have practical value. RR = relative risk; OR = odds ratio.
*These are not anchored to *r* and should be interpreted with caution

Source: *Ferguson 2016 [46]*

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