DRINKING AND BREAST 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 necessarily 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 health care 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.

This Health Review focuses cancer sites associated with alcohol consumption as identified by the World Cancer Research Foundation 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.

There is a glossary of key terms used in this chapter on page 9.

Last Reviewed: July 2019

Introduction

BREAST CANCER IN WOMEN

13%

Lifetime risk of diagnosis (U.S.)

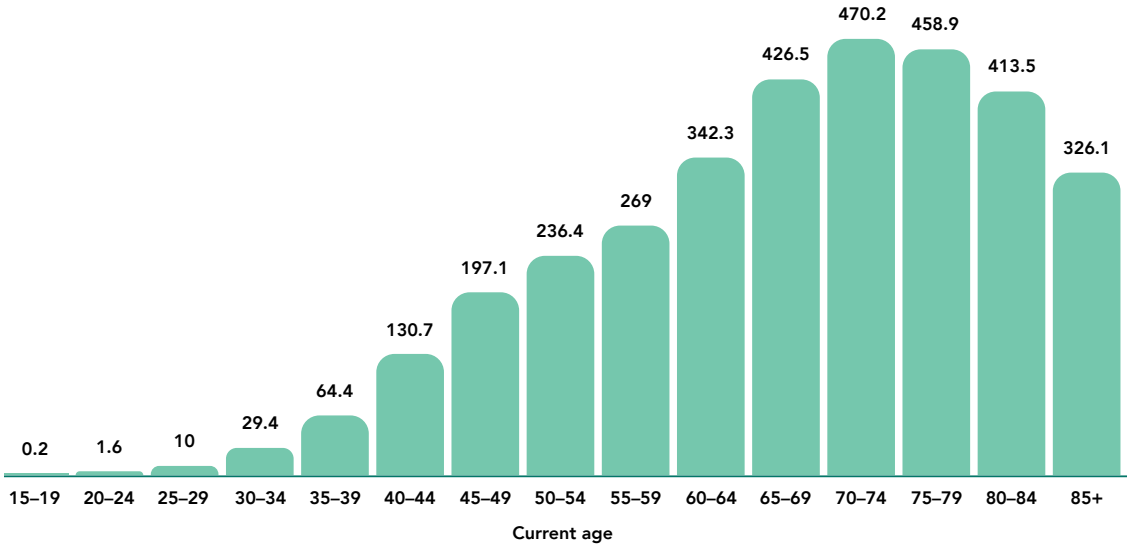
46

Global incidence per 100,000

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

Breast cancer is the most-diagnosed cancer among women and accounts for 24% of all incident cases of cancer among women globally [3]. Incidence rates vary across countries, from a high of 113 per 100,000 persons in Belgium to a low of 5 per 100,000 persons in Bhutan [3]. Incidence increases with age, and 80% of all female breast cancer cases diagnosed in the U.S. occur in women aged 50 years or older (postmenopausal women) (see Figure 1) [4].

Figure 1: Age-specific incidence of breast cancer among women in the U.S. per 100,000



Source: *Table 4.11, Age-specific SEER incidence rates 2013-2017* [2]

Several factors may affect breast cancer risk, some of which may mediate or modify the relationship between alcohol consumption and breast cancer risk (see Table 1).

Table 1: Common risk factors for breast cancer*

Modifiable risk factors	Non-modifiable risk factors
Age at first pregnancy/number of pregnancies	Age
Alcohol consumption	Age of first menstrual period
Body mass index (BMI)	Breast tissue density
Breastfeeding	Ethnicity
Breast implants	Family history
Hormonal contraceptives	Height
Hormone replacement therapy (HRT)	Race
Length and frequency of physical activity	Sex
Radiation exposure	

Source: *American Cancer Society* [5] and *The World Cancer Research Fund / American Institute for Cancer Research's Third Expert's Report 2018* [6]

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

The importance (that is, magnitude, 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 BREAST CANCER

The mechanisms that explain the relationship between alcohol and breast cancer are complex and still being studied [6-8].

- Evidence from experimental and epidemiological studies indicate that exposure to *acetaldehyde* in breast tissue may result in *oxidative DNA damage*, thus initiating and promoting cancer growth [7-10].

- Alcohol consumption may also increase estrogen levels or sensitivity to estrogen in breast tissue, which may increase the likelihood of hormone receptor expression on cancerous cells [7-10].

- Alcohol may also increase *enzymatic activity* and weaken the structure and integrity of cell tissue. In addition, changes in proteins involved in maintaining tissue integrity may lead to increased invasiveness of carcinogens into cells [6, 9].

- The role of alcohol in breast cancer risk may also be partly due to the dietary patterns of alcohol consumers. Heavy alcohol consumption has been associated with deficiencies in antioxidants (such as Vitamins A, C, E, folate, and thiamin) and other nutrients that support the process of repairing DNA damage and neutralizing *reactive oxygen species* [7-10]. The inability to support these processes may, independently and jointly, increase susceptibility for cancer growth. [8, 10].

- For moderate consumers, alcohol may increase *insulin-like growth factor* (IGF-1), which may increase production of breast tissue cells: both cancerous and non-cancerous [9, 10].

- Alcohol consumption may contribute to structural breast tissue changes during the "critical period of increased biologic vulnerability" between first menstrual period and first full-term pregnancy, which may increase risk of future breast cancer development [8]. Additionally, emerging evidence suggests that alcohol may impact gene expression regulation, which is a key factor of *cell proliferation* [8].

Summary of recent breast 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 breast 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, and prospective cohort studies
Publication dates: from 2007 through June 2019
Outcomes: 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 "Methodological issues" chapter.*

Breast cancer, unspecified
In this first section we present results of studies reporting *relative risk* estimates for breast cancer in general, without further classification of subtype or subgroup. The results of studies by subtype or subgroup are summarized in the next section of this review. (Please see the Glossary on page 9 for a definition of relative risk and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.)

META-ANALYSES AND POOLED PROSPECTIVE COHORT STUDIES

The findings from seven meta-analyses and pooled prospective cohort studies published in the past 12 years suggest an increase in breast cancer risk associated with alcohol consumption. Compared with nondrinkers, risk appears to increase at low drinking levels [11-17]. Results also show that the magnitude of risk increases with higher levels of alcohol consumption. Compared to nondrinkers, the lowest levels of average alcohol consumption defined by these studies (up to 13g/day) are associated with a 4% to 5% increase in risk (this is equivalent to a relative risk of 1.04 and 1.05, respectively), while the highest levels of consumption (more than 50g/day) are associated with a 61% increase in risk (equivalent to a relative risk of 1.61), compared to nondrinkers. (Relative risk estimates of 1.05 are considered "weak" and 1.61 are considered "modest"; see, for example, Schoenbach and Rosamond (2000) [18] and the Glossary for additional references).

Some studies reported no increase in risk for their lightest drinking categories compared with not drinking but reported a statistically significant increase starting at 2g/day [17], 5g/day [14], and 12g/day [15].

One meta-analysis included in the literature review reported risk estimates comparing highest to lowest consumption categories but was excluded from the summary above because it did not quantify those categories in number of drinks or grams of alcohol [19].

INDIVIDUAL PROSPECTIVE COHORT STUDIES

The results from 20 prospective cohort studies, many of which are included in the meta-analyses mentioned above, similarly indicate that risk for breast cancer increases as alcohol intake increases, potentially starting at low levels of alcohol consumption.

Thirteen studies found an association between some level of alcohol consumption and increased breast cancer risk [20-32], and a minority of the studies (seven) reported no association (null results) [33-39].

- Eight studies reported an increased risk associated with drinking less than 14g/day [20, 21, 23-26, 29, 31], including one study that used a lifetime consumption estimate [29].
- Five studies reported an increased risk above, but not below, 14g/day [22, 27, 28, 30, 32].
- As with the findings from meta-analyses, the magnitude of risk for drinkers compared to nondrinkers ranges from a "weak" association to a "moderate" association; see Glossary for relative risk and descriptions of magnitude of risk. For example, results from the 13 prospective cohort studies included risk estimates ranging from 1.05 to 1.76.

Differences in risk estimates at given drinking levels across prospective cohort studies are to be expected, given the different characteristics, prevalence of and average level of alcohol consumption, and prevalence of breast cancer, across different populations.

Cancer subtypes

Cancers have historically been described and classified according to the site or tissue of origin. More recently, cancers have been further classified by certain features that may be related to type of diagnoses and underlying conditions [6]. Two of these features – diagnosis in relation to menopause (menstruation cessation) status and hormone receptor type – are discussed below.

MENOPAUSE

The etiology of breast cancer and the impact of risk factors may differ when diagnosed in women before menopause then when diagnosed after menopause [6]. According to the National Cancer Institute, from 2015 to 2017, the probability of developing postmenopausal breast cancer was over four-times more likely than premenopausal breast cancer [40]. There are many factors that can contribute to this difference: for example, production of sex hormones that stimulate cell growth, such as estrogen and progesterone, increases with age until menopause. Breast tissue is increasingly exposed to hormones over time, thus increasing chances of tumor growth [6, 41]. Furthermore, the difference in risk may be explained by hormone receptor status (discussed below) and other modifiable risk factors that change over the life-course such as dietary patterns, level of physical activity, body mass index, and use of hormone replacement therapy [22, 42].

Postmenopausal breast cancer

According to WCRF, there is "convincing" evidence of an association between alcohol consumption and increased risk of developing postmenopausal breast cancer. WCRF could not determine a threshold of alcohol intake at which risk appears to increase [6].

Seventeen prospective cohort studies in this review examined postmenopausal breast cancer risk associated with multiple drinking categories.

- The majority of studies reported an increased risk associated with drinking, starting at or below 14g/day [42-49], above 14 g/day [22, 50-52] and at 30g/day [53].
- Only one study found no association between alcohol consumption and postmenopausal breast cancer [54].
    - However, this study found that alcohol use among postmenopausal women who used HRT increased the risk of breast cancer, compared to women who did not use HRT [54].
- One study reported a reduced risk for nondrinkers and those consuming less than 14g/day, compared to 28g or more per day [55].

Premenopausal breast cancer

According to WCRF, there is "probable" evidence that alcohol is associated with an increase in risk of premenopausal breast cancer. WCRF could not determine a threshold of alcohol intake at which risk appears to increase [6].

Two prospective cohort studies in this review examined the association between premenopausal breast cancer and multiple drinking level categories.

- Both studies reported no association between any level of alcohol consumption and premenopausal breast cancer, when compared to nondrinkers [22, 52].

The results from these two studies cannot be directly compared with the findings reported by WCRF due to different selection criteria and methods of analysis. WCRF summarized risk for premenopausal breast cancer by comparing undefined highest to lowest alcohol consumption groups and by calculating a *dose-response* trend analysis per 10g increase in alcohol consumption [6]. IARD did not include studies that used unquantified highest and lowest alcohol consumption categories in this review.

HORMONE RECEPTOR STATUS

There are several breast cancer subtypes that differ in potential causal factors and response to treatment [26, 45, 56]. Hormone receptors are proteins that bind hormones circulating throughout the body; breast cancer subtypes may be defined by the absence or presence of one or more hormone receptor types on the surface and inside breast cells [57]. The most common types of hormone receptors found on breast cells are estrogen receptors and progesterone receptors. When a receptor binds to a hormone, it promotes cell growth, potentially leading to cancerous cells [57].

The following abbreviations in Table 2 will be used in the summary of the research below.

Table 2: Abbreviations of different breast cancer hormone receptor cell types

Hormone receptor cell type	Abbreviation
Estrogen-positive receptor	ER+
Estrogen-negative receptor	ER-
Progesterone-positive receptor	PR+
Progesterone-negative receptor	PR-
Human epidermal growth factor-positive receptor	HER2+
Human epidermal growth factor-negative receptor	HER2-
Estrogen-positive and progesterone-negative receptor	ER+/PR-
Estrogen-negative and progesterone-positive receptor	ER-/PR+
Estrogen-negative and progesterone-negative receptor	ER-/PR-
Estrogen-positive and progesterone-positive receptor	ER+/PR+
Estrogen-negative, progesterone-negative, and human epidermal growth factor-negative receptor	ER-/PR-/HER2-

Several studies have stratified their analysis by hormone receptor status type to determine if hormone receptor status modifies or mediates the relationship between alcohol consumption and breast cancer risk.

Only two studies, a meta-analysis and a pooled cohort study, provide summary-level evidence by hormone receptor status, but they offer conflicting results; a 2016 pooled-cohort study found that risk associated with alcohol did not differ by hormone receptor status [14], whereas a 2008 meta-analysis reported increased risk estimates for ER+, ER-, ER+/PR+, and ER+/PR-, and null results for other receptor types when comparing highest to lowest alcohol consumptions [58].

Eleven prospective cohort studies grouped breast cancer risk by hormone receptor type [21, 22, 27, 29, 30, 37, 45-48, 59]. Results from these studies, presented below, suggest that hormone receptor subtype may modify the relationship between alcohol consumption and breast cancer risk. However, the limited number of individual studies and smaller sample sizes for some breast cancer subtypes make it difficult to draw any conclusions.

- Nine of these studies looked at the combination of ER/PR subtypes [21, 22, 27, 29, 30, 37, 45, 47, 48]. Seven studies reported an increased risk among women with ER+/PR+ subtypes [21, 22, 27, 29, 45, 47, 48] associated with alcohol consumption, compared to nondrinkers (or light drinkers [29]), including two studies that examined postmenopausal breast cancers only [45, 47]. Results for other combinations of ER/PR were less consistent.

- ER+/PR+ breast cancers are the most common combination of hormone receptor subtypes [60], which may explain why the results for ER+/PR+ mirrored results for all unspecified breast cancers within most of the nine studies described above.

- Five studies looked at subtypes for ER or PR cancers separately [27, 30, 45, 46, 59]. Again, the hormone-positive receptor subtype (ER+ or PR+) was linked with an increased risk associated with alcohol, but the negative subtype (ER- or PR-) was not. This was true for four out of five studies examining ER cancers [27, 45, 46, 59] and three out of four studies examining PR cancers [27, 45, 59]. Two of these studies, Key et al. (2019) and Falk et al. (2014), included postmenopausal breast cancers only.

FUTURE RESEARCH

Some researchers have focused on examining the joint effect of modifiable risk factors that tend to cluster together by comparing the presence or absence of multiple risk factors combined. While threshold values defining risk may vary from study to study, modifiable risk factors commonly included in joint effect analyses for breast cancer are [43, 50, 55, 56, 61]:

- Alcohol consumption
- Body mass index
- Dietary patterns
- Hormone replacement therapy
- Physical activity
- Smoking

Collectively, these individual modifiable risk factors may have a larger effect than as individual factors [50, 55]. A full analysis of studies examining multiple risk factors simultaneously was outside the scope of this review, but the results of recent studies have shown that adherence to the "healthier" levels of at least five of these modifiable factors (as defined by each study) was associated with a 24% to 35% reduced risk for breast cancer compared to no healthy behaviors [50, 55, 61]. Further research is needed to understand the joint effect of multiple risk factors on breast cancer risk.

Glossary

- **Acetaldehyde** is a product of ethanol metabolism, which takes place in the liver and breast tissue and leads to DNA damage.
- **Carcinogen** is any agent or substance that can cause cancer.
- **Cell proliferation** is the multiplication of cells due to cell division.
- **Dose-response** describes the relationship between the amount of exposure and the amount of risk of the outcome.
- **Enzymatic activity** consists of proteins reacting together to speed up the rate of a chemical reaction.
- **Human epidermal growth factors** are proteins that control breast cell growth and repair. If mutated, they can reverse their activity and contribute to increased cell growth instead.
- **Insulin-like growth factor (IGF)** are proteins that have a similar sequence to insulin and mediate hormone growth activity.
- **Hormone replacement therapy (HRT)** – also known as menopausal hormone therapy (MHT) – is treatment with estrogen and progesterone to relieve menopause symptoms.
- **Oxidative damage** occurs when free radicals are produced, resulting in damage to cells and tissues potentially causing DNA mutations.
- **Reactive oxygen species** are a group of highly-reactive molecules containing oxygen that are an important part of metabolism and inflammatory response at low levels. 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** is a measure that compares the probability of a given outcome (for example, breast 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 [18, 62-65], however, the risk estimates associated with each term may differ or overlap (see Figure 2A-C). For example, according to Schoenbach and Rosamond 2000 [18], a moderate risk is equivalent to a relative risk of 1.8 to 3.0, while Craun and Calderon n.d., states that moderate to strong risk is equivalent to a relative risk greater than 1.5 [62, 65].

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

Adapted from *Schoenbach and Rosamond 2000* [18]

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

Adapted from *Hopkins 2002* [63]

Figure 2C. Descriptions of magnitude of risk

Table 1
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	.41	1.15	2.70
Strength of association	r, R, φ, ρ, partial r, β, r_b, tau	.2	.5	.8
Squared association indices	r^2, R^2, η^2, adjusted R^2, ω^2, ϵ^2	.04	.25	.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 outcome 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* [64]

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