

# DRINKING AND BREAST CANCER IN WOMEN



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.

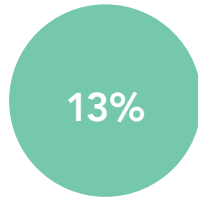
This Health Review focuses on cancer sites associated with alcohol consumption as identified by the World Cancer Research Fund and the International Agency for Research on Cancer. Due to the limited availability of national cancer statistics in many countries, U.S. data – which is publicly available 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 17.

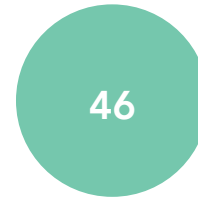
**Last Reviewed:** July 2019

**Update 05/12/2022:** Result tables have been added and content in the Biological mechanisms section has been updated.

# Introduction



**Lifetime risk of diagnosis (U.S.)**

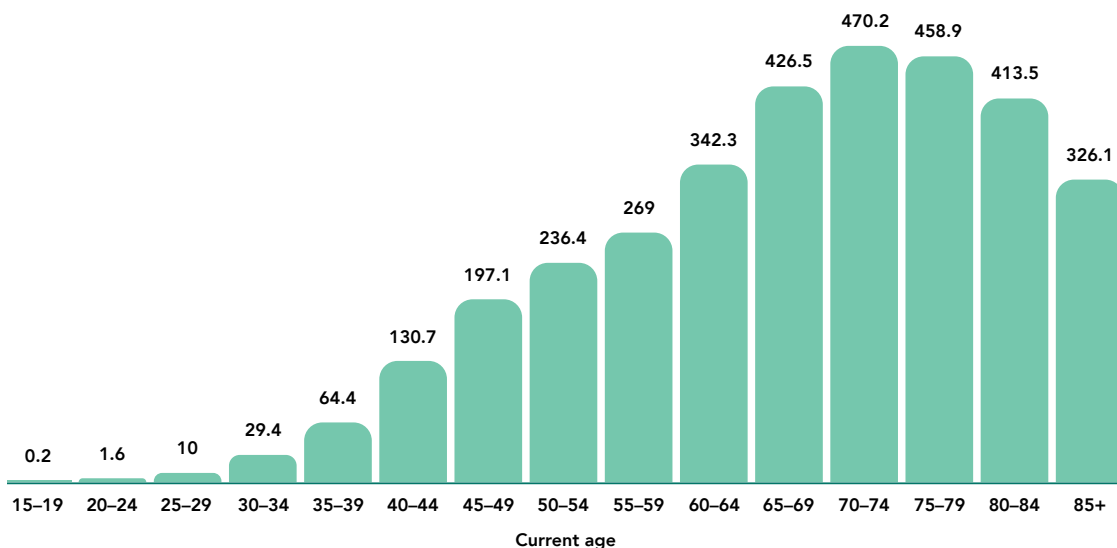


**Global incidence per 100,000**

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]

According to the World Cancer Research Fund (WCRF), alcohol consumption is a risk factor for breast cancer [5]. In addition, several other 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
<i>Hormone replacement therapy (HRT)</i>	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

Researchers are continuing to explore several plausible biological mechanisms that may explain the potential role of alcohol as a risk factor for breast cancer [5, 7, 8], and some of these are:

##### Acetaldehyde

Alcohol (ethanol) is primarily metabolized in the liver by two important families of enzymes: *alcohol dehydrogenase (ADH)* and *acetaldehyde dehydrogenase (ALDH)* and, to a lesser extent, CYP2E1. Alcohol is converted to acetaldehyde by ADH, which is then converted to acetate by ALDH [9, 10]. 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, 8, 11, 12].

##### Tissue integrity

Alcohol may act as a solvent by changing proteins involved in maintaining tissue integrity and lead to increased invasiveness of toxic substances into cells [5, 11].

- ▶ 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].

### **Nutritional deficiencies**

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, 8, 11, 12]. The inability to adequately support these processes may, independently and jointly, increase susceptibility for cancer growth. [8, 12].

- ▶ 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 [11, 12].

### **Interaction with estrogen**

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, 8, 11, 12].



# 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; 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:** breast 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".*

## BREAST CANCER, UNSPECIFIED

In this 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 17 for a definition of relative risk (RR) 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 non-drinkers, risk appears to increase at low drinking levels [13-19] (see Table 2)

- ▶ Four studies reported an increased risk starting at more than 0g/day [13-15, 18].
- ▶ Three 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 [19], 5g/day [16], and 12g/day [17].
- ▷ Three meta-analyses compared nondrinkers with drinkers in a light-to-moderate drinking category, up to 12.5g/day [13, 18] and up to 30g/day [15] only. These studies did not include drinking categories above these limits.

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 [20]

Results from these studies indicate that the magnitude of risk grows larger as alcohol consumption increases. 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, which would be described as “weak” [21]), while the highest levels of consumption (more than 50g/day) are associated with a 61% increase in risk (this is equivalent to a relative risk of 1.61 which would be described as “modest” in magnitude [21]). See for example Schoenbach and Rosamond (2000) [21] and the Glossary for descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.

Table 2. Relative risk estimates for alcohol consumption associated with breast cancer for women combined from meta-analyses and pooled cohort studies\*

Study reference	Former drinker	Non-drinker	Average alcohol grams per day																																																								
			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
Bagnardi et al., 2015		ref.†	1.04											1.23																							1.61																						
Choi et al., 2018		ref.†	1.04				1.09					1.13										Grey shading																																					
Bagnardi et al., 2013		ref.†	1.05											Grey shading																																													
Seitz et al., 2012		ref.†	1.05											Grey shading																																													
Zeisser et al., 2014	ns	ref.‡	ns	1.15																1.38																		Grey shading																					
Jung et al., 2016		ref.†	ns				1.10					1.19										1.32																																					
Maas et al., 2016		ref.†	ns	ns	ns	ns	ns					1.16					1.24																																										

\* All meta-analysis study designs published between January 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 abstainers)

#### 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.
- ▶ Purple shading indicates a statistically significant increase in relative risk compared to the reference group.
- ▶ 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.

**Individual prospective cohort studies**

Twenty prospective cohort studies, many of which are included in the meta-analyses mentioned above, met the review inclusion criteria. These studies indicate that risk for breast cancer increases as alcohol intake increases, potentially starting at low levels of alcohol consumption (see Table 3).

Thirteen studies found an association between some level of alcohol consumption and increased breast cancer risk [22-34], and a minority of the studies (seven) reported no association (null results) [35-41].

- ▶ Seven studies reported an increased risk associated with drinking less than 14g/day [22, 23, 25-27, 30, 32].
- ▶ Six studies reported an increased risk above, but not below, 14g/day [24, 28, 29, 31, 33, 34].
- ▶ 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 [21]; see Glossary for definitions of relative risk and 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.



Table 3. Relative risk estimates for alcohol consumption associated with breast cancer for women from individual prospective cohort studies\*

Study reference	Occasional drinker	Former drinker	Non-drinker	Average alcohol grams per day																																																																												
				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
Kabat et al., 2008			ref.†	ns				ns				ns									ns									ns																																																		
Kawai et al., 2011			ref.‡	ns				ns									ns									ns																																																						
Shin et al., 2015			ref.†	ns				ns									ns									ns																																																						
Kim et al., 2017			ref.†	ns				ns									ns									ns																																																						
White et al., 2017		ns	ref.†	ns				ns									ns									ns																																																						
Betts et al., 2018			ref.†	ns				ns									ns									ns																																																						
Zhang et al., 2007			ref.†	ns				ns				ns									ns									ns																																																		
Hippisley-Cox et al., 2015			ref.†	1.05				1.11									1.21									1.31									ns																																													
Klatsky et al., 2014		1.31	ref.‡	1.14				1.23									1.35									ns																																																						
Allen et al., 2009			ns†	ref.	1.08				1.13									1.29									ns																																																					
Romieu et al., 2015			ns†	ref.	1.09				1.18									ns									ns																																																					
Chen et al., 2011			ref.†	ns				1.15				1.22									1.20									1.51																																																		
Kunzmann et al., 2018			ref.‡	ns	ns				1.31				ns									1.26									ns																																																	
Thygesen et al., 2008			ref.	ns				1.36									ns									4.64																																																						
Li et al., 2008		ns	ref.‡	ns	ns				1.20									1.40									ns																																																					
Klatsky et al., 2015		1.31	ref.‡	ns				1.20									1.30									ns																																																						
Fagherazzi et al., 2015			ref.†	ns				ns									1.19									ns																																																						
Suzuki et al., 2010	ns	1.41	ref.†	ns				1.76									ns									ns																																																						
Tjønneland et al., 2007			ns†	ref.	ns				ns				ns									1.36									ns																																																	
Morch et al., 2007			ns	ref.				ns				ns									ns				2.30				1.62																																																			

\* All individual prospective cohort 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)

‡ Nondrinker (lifetime abstainers)

## 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 [5]. 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 [5]. 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 [42]. 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 [5, 43]. Furthermore, the difference in risk may be explained by hormone receptor status (discussed below) or modifiable risk factors that change over the life-course such as dietary patterns, level of physical activity, BMI, and use of HRT [24, 44].

### Postmenopausal breast cancer

According to the WCRF, there is “convincing” evidence of an association between alcohol consumption and increased risk of developing postmenopausal breast cancer. The WCRF could not determine a threshold of alcohol intake at which risk appears to increase [5]. (Please see [Background chapter](#) for an explanation on the WCRF definitions of strength of evidence.)

Eighteen prospective cohort studies that examined postmenopausal breast cancer risk associated with multiple drinking categories met the review criteria (see Table 4).

- ▶ The majority of studies reported an increased risk associated with drinking, starting at or below 14g/day [44-53], above 14 g/day [24, 54-56] and at 30g/day [57, 58].
- ▶ Only one study found no association between alcohol consumption and postmenopausal breast cancer [59].
  - ▷ However, this study found that alcohol use among postmenopausal women who used HRT, a potential risk factor, increased the risk of breast cancer, compared to women who did not use HRT [59].
- ▶ One study reported a reduced risk for nondrinkers and those consuming less than 14g/day, compared to 28g or more per day [60].

Table 4. Relative risk estimates for alcohol consumption associated with breast cancer based on menopause status for women from individual prospective cohort studies\*

Study reference	Former drinker	Non-drinker	Average alcohol grams per day																																																																																				
			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+														
<b>Diagnosis premenopause</b>																																																																																							
Nitta et al., 2016		ref.†	ns	ns													ns																																																																						
Fagherazzi et al., 2015		ref.†	ns	ns	ns													ns																																																																					
<b>Diagnosis postmenopause</b>																																																																																							
Nielsen et al., 2008		ref.†	ref.	ns													ns														ns														ns																																										
Falk et al., 2014	ns	ref.†	ns	1.23	1.26													1.35																																																																					
Tamimi et al., 2016		ref.†	ns	1.13													1.32																																																																						
Park et al., 2014		ref.†	ns	1.23	ns	ns													1.53																																																																				
Key et al., 2018		ns†	ns	ref.	1.05													1.23																																																																					
Lew et al., 2009		ref.†	ns	ns	1.13													1.23														1.35																																																							
Maruti et al., 2009			ref.	ns	ns	1.60																																																																																	
Masala et al., 2017		ref.†	ref.													1.30																																																																							
Dam et al., 2016			ns	ref.													1.27														ns														ns																													1.45													
Akinyemiju et al., 2017			ref.													1.33														1.78																																																									
Li et al., 2010	ns	ref.‡	ns	ns	ns	ns													1.27														ns																																																						
Nitta et al., 2018		ref.†	ns	ns													2.74																																																																						
Arthur et al., 2018		ns†	ref.	ns	ns													1.17																																																																					
Fagherazzi et al., 2015		ref.†	ns	ns	ns													1.24																																																																					
Horn-Ross et al., 2012		ref.†	ns													1.26																																																																							
Ericson et al., 2007		ref.†	ns													ns														2.52																																																									
Hahn et al., 2018		ref.†	ns	ns													ns														1.72																																																								
Cifu et al., 2018		0.78†	0.84													ns														ref.																																																									

\* All individual prospective cohort 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)

‡ Nondrinker (lifetime abstainers)

§ Nondrinker (may include occasional drinkers)

**Premenopausal breast cancer**

According to the WCRF, there is “probable” evidence that alcohol is associated with an increase in risk of premenopausal breast cancer. The WCRF could not determine a threshold of alcohol intake at which risk appears to increase [5].

Two prospective cohort studies that met the inclusion criteria for this review examined the association between premenopausal breast cancer and multiple drinking level categories (see Table 4).

- ▶ Both studies reported no association between any level of alcohol consumption and premenopausal breast cancer, when compared to nondrinkers [24, 56].

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 [5]. 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 [47, 51, 61]. 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 [62]. 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 [62].

The following abbreviations in Table 5 will be used in the summary of the research below.

**Table 5: 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-
<i>Human epidermal growth factor-positive receptor</i>	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 meta-analyses or pooled cohort studies met the inclusion criteria for this review and 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 [16], 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 [63].

Eleven individual prospective cohort studies grouped breast cancer risk by hormone receptor type [23, 24, 28, 30, 31, 39, 47-49, 53, 64]. Results from these studies, presented below (see Table 6 and Appendix Table A1), 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 [23, 24, 28, 30, 31, 39, 47, 49, 53]. Seven studies reported an increased risk among women with ER+/PR+ subtypes [23, 24, 28, 30, 47, 49, 53] associated with alcohol consumption, compared to nondrinkers (or light drinkers [30]), including three studies that examined postmenopausal breast cancers only [47, 49, 53] (see Appendix Table A1). Results for other combinations of ER/PR were less consistent.
  - ▷ ER+/PR+ breast cancers are the most common combination of hormone receptor subtypes [65], 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 [28, 31, 47, 48, 64]. 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 [28, 47, 48, 64] and three out of four studies examining PR cancers [28, 47, 64]. Two of these studies, Key et al. (2019) and Falk et al. (2014), included postmenopausal breast cancers only (see Appendix Table A1).

Table 6. Relative risk estimates for alcohol consumption associated with breast cancer among women from individual prospective cohort studies based on hormone receptor status\*

Study reference	Receptor cell type	Occasional drinker	Former drinker	Non-drinker	Average alcohol grams per day																																																																					
					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
Wang et al., 2015	ER+			ref.†	ns	ns	ns	ns	1.51																																																																	
	ER-			ref.†	ns	ns	ns	ns	ns																																																																	
	PR+			ref.†	ns	ns	ns	ns	1.43																																																																	
	PR-			ref.†	ns	ns	ns	ns	ns																																																																	
Suzuki et al., 2010	Overall results	ns	1.41	ref.‡	ns	1.76																																																																				
	ER+	ns	ns	ref.‡	ns	ns																																																																				
	ER-	ns	2.39	ref.‡	ns	[hatched]																																																																				
	ER+/PR+	ns	ns	ref.‡	ns	ns																																																																				
	ER+/PR-	ns	ns	ref.‡	ns	[hatched]																																																																				
	ER-/PR-	ns	2.08	ref.‡	ns	[hatched]																																																																				
Shin et al., 2015	Overall results			ref.†	ns	ns	ns																																																																			
	ER+/PR+			ref.†	ns	ns	ns																																																																			
	ER+/PR-			ref.†	ns	ns	ns																																																																			
	ER-/PR-			ref.†	ns	ns	ns																																																																			
Romieu et al., 2015	Overall results			ns <sup>§</sup>	ref.	1.09	1.18	1.08																																																																		
	ER+/PR+			ns <sup>§</sup>	ref.	ns	1.18	ns																																																																		
	ER+/PR-			ns <sup>§</sup>	ref.	ns	ns	ns																																																																		
	ER-/PR-			ns <sup>§</sup>	ref.	ns	ns	ns																																																																		
	ER-/PR+			ns <sup>§</sup>	ref.	ns	ns	ns																																																																		
	ER-/PR-/HER-			ns <sup>§</sup>	ref.	ns	ns	ns																																																																		

Continued on next page

**Table 6. (Continued) Relative risk estimates for alcohol consumption associated with breast cancer among women from individual prospective cohort studies based on hormone receptor status\***

Study reference	Receptor cell type	Occasional drinker	Former drinker	Non-drinker	Average alcohol grams per day																																																																									
					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+			
Fagherazzi et al., 2015	Overall results			ref.†	ns														1.19																																																											
	ER+/PR+			ref.†	ns														1.32																																																											
	ER-/PR-			ref.†	ns														ns																																																											
Chen et al., 2011	Overall results			ref.†	ns				1.15				1.22				1.20										1.51																																																			
	ER+/PR+			ref.†	ns				1.14				1.27				1.20										1.58																																																			
	ER+/PR-			ref.†	ns				ns				1.39										ns																																																							
	ER-/PR-			ref.†	ns				1.25				ns										ns																																																							
	ER-/PR+			ref.†	ns				ns				ns										2.45																																																							
Li et al., 2008	Overall results		ns	ref.‡	ns				1.20										1.40																																																											
	ER+			ref.‡	ns				1.40										1.70																																																											
	ER-			ref.‡	ns				ns										ns																																																											
	PR+			ref.‡	ns				ns										1.60																																																											
	PR-			ref.‡	ns				ns										ns																																																											
	ER+/PR+			ref.‡	ns				ns										1.70																																																											
	ER+/PR-			ref.‡	ns				ns										ns																																																											
	ER-/PR+			ref.‡	ns				ns										ns																																																											

\* All individual prospective cohort 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)

‡ Nondrinker (lifetime abstainers)

## 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 [45, 54, 60, 61, 66]:

- ▶ 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 [54, 60]. 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 [54, 60, 66]. Further research is needed to understand the joint effect of multiple risk factors on breast cancer risk.

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 breast 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.





## Glossary

- ▶ **Acetaldehyde** is a product of ethanol metabolism, which takes place in the liver and breast tissue and leads to DNA damage.
- ▶ **Acetaldehyde dehydrogenase (ADH)** is an enzyme that breaks down acetaldehyde into smaller molecules such as acetate, which are further broken down into carbon dioxide and water molecules.
- ▶ **Alcohol dehydrogenase (ALDH)** is an enzyme involved in metabolism of ethanol which breaks down alcohol into acetaldehyde molecules.
- ▶ **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 stress** occurs when there is an imbalance between the accumulation of reactive oxygen species (see below for definition) and the body's ability to detoxify and eliminate these molecules through an antioxidant (for example, glutathione, vitamin C, vitamin E) defense.
- ▶ **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** 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 [21, 67-70], however, the risk estimates associated with each term may differ or overlap (see Figure 2A-C). For example, according to Schoenbach and Rosamond 2000 [21], 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 [67, 70].

**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

Source: Schoenbach and Rosamond 2000 [21]

**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 [68]

**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, $\Delta$ , g	0.41	1.15	2.70
Strength of association	r, R, $\phi$ , p, partial r, $\beta$ , rh, tau	0.2	0.5	0.8
Squared association indices	$r^2$ , $R^2$ , $\eta^2$ , adjusted $R^2$ , $\omega^2$ , $\epsilon^2$	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 [69]

# Appendix

## Appendix 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.
- ▶ Purple shading indicates a statistically significant increase in relative risk compared to the reference group.
- ▶ 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.

**Table A1: Relative risk estimates for alcohol consumption associated with breast cancer among postmenopausal women from individual prospective studies based on hormone receptor status\***

Study reference	Receptor cell type	Former drinker	Non-drinker	Average alcohol grams per day																																																																							
				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	
Key et al., 2018	Overall results		ns	ns	ref.	1.05														1.23																																																							
	ER+		ns	ns	ref.	1.09														1.28																																																							
	ER-		ns	ns	ref.	ns														ns																																																							
Li et al., 2010	Overall results	ns	ref. <sup>§</sup>	ns	ns	ns				ns				1.27												ns																																																	
	ER+/PR+	ns	ref. <sup>§</sup>	ns	ns	ns				ns				1.32												ns																																																	
	ER+/PR-	ns	ref. <sup>§</sup>	ns	ns	ns				ns				ns												ns																																																	
	ER-/PR-	ns	ref. <sup>§</sup>	ns	ns	ns				ns				ns												ns																																																	
Park et al., 2014	Overall results		ref. <sup>†</sup>	ns				1.23				ns				ns												1.53																																															
	ER+/PR+		ref. <sup>†</sup>	ns				ns				1.35												1.61																																																			
	ER+/PR-		ref. <sup>†</sup>	ns				1.89				ns												1.72																																																			
	ER-/PR-		ref. <sup>†</sup>	ns				1.57				ns												1.58																																																			
Falk et al., 2014	Overall results	ns	ref. <sup>‡</sup>	ns	ns	1.26				1.35																																																																	
	ER+	ns	ref. <sup>‡</sup>	ns	ns	1.29				1.48																																																																	
	ER-	ns	ref. <sup>‡</sup>	ns	ns	ns				ns																																																																	
	PR+	ns	ref. <sup>‡</sup>	ns	ns	1.37				1.64																																																																	
	PR-	ns	ref. <sup>‡</sup>	ns	ns	ns				ns																																																																	
	ER+/PR+	ns	ref. <sup>‡</sup>	ns	ns	1.36				1.63																																																																	
	ER+/PR-	ns	ref. <sup>‡</sup>	ns	ns	ns				ns																																																																	
	ER-/PR-	ns	ref. <sup>‡</sup>	ns	ns	ns				ns																																																																	

\* All individual prospective cohort 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)

‡ Nondrinker (lifetime abstainers)

§ Nondrinker (may include occasional drinkers)

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