Alcohol consumption and the risk of breast cancer

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Abstract
Epidemiologic studies addressing the association of alcohol consumption with breast cancer consistently suggest a modest association and a dose-response relationship. The epidemiologic evidence does not point to a single mechanism to explain the association, and several mechanisms have been proposed. Alcohol consumption is shown to increase levels of endogenous estrogens, known risk factors for breast cancer. This hypothesis is further supported by data showing that the alcohol-breast cancer association is limited to women with estrogen-receptor positive tumors. Products of alcohol metabolism are known to be toxic and are hypothesized to cause DNA modifications that lead to cancer. Recent research has focused on genes that influence the rate of alcohol metabolism, with genes that raise blood concentrations of acetaldehyde hypothesized to heighten breast cancer risk. Mounting evidence suggests that antioxidant intake (e.g. folate) may reduce alcohol-associated breast cancer risk, because it neutralizes reactive oxygen species, a second-stage product of alcohol metabolism. Diets lacking sufficient antioxidant intake, as a result, may further elevate the risk of breast cancer among alcohol consumers. Given that alcohol consumption is increasing worldwide and especially among women in countries of rapid economic growth, a greater understanding of the mechanisms underlying the known alcohol-breast cancer association is warranted. Avoiding overconsumption of alcohol is recommended, especially for women with known risk factors for breast cancer.

Keywords: breast cancer; alcohol consumption; risk factors

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Resumen
Diversos estudios epidemiológicos muestran la asociación del consumo de alcohol con el cáncer de mama de forma consistente, lo que sugiere una modesta asociación, y una relación de dosis-respuesta. La evidencia no apunta a un mecanismo único para explicar la asociación y varios mecanismos han sido propuestos. El consumo de alcohol incrementa los niveles endógenos de estrógeno, un riesgo conocido para cáncer de mama. Esta hipótesis es apoyada por información que muestra que la asociación entre el alcohol y el cáncer de mama está limitada a mujeres con tumores con receptores positivos de estrógeno. Es conocido que los derivados de la metabolización del alcohol son tóxicos, y se ha pensado que causan modificaciones en el DNA que llevan al cáncer. La investigación reciente ha enfocado en genes que influyen la velocidad con que se metaboliza el alcohol, y elevan las concentraciones de acetaldehído que se piensa puede aumentar el riesgo de cáncer de mama. La evidencia actual sugiere que la ingesta de antioxidantes (e.g. folato) puede reducir el riesgo de cáncer asociado al alcohol, porque neutraliza las especies reactivas de oxígeno, un producto de la segunda etapa del metabolismo del alcohol. Las dietas con ingesta insuficiente de antioxidantes, como resultado de esto, pueden elevar el riesgo de cáncer entre los consumidores de alcohol. Dado que el consumo de alcohol está incrementando en todo el mundo, especialmente en mujeres de países con rápido crecimiento económico, un mejor entendimiento de los mecanismos subyacentes a la asociación del cáncer de mama y el alcohol es necesario. Evitar el consumo excesivo es recomendado, especialmente para mujeres con factores de riesgo conocidos para cáncer de mama.

Palabras clave: cáncer de mama; consumo de alcohol; factores de riesgo

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Evidence from a substantial number of epidemiologic and experimental studies suggests that alcohol consumption is a modest risk factor for breast cancer. Worldwide consumption of alcohol has increased substantially in the past two decades, and the increase has been particularly evident among women in countries of rapid economic growth. This article describes the strength of the evidence for the association between alcohol and breast cancer, the primary mechanisms that have been proposed to explain the association, and alcohol consumption patterns worldwide.

Data from a variety of epidemiologic studies suggest that chronic alcohol consumption even in moderate amounts increases a woman’s risk for breast cancer. The vast majority of the case-control studies (84% of 69) and cohort studies (76% of 21) published to-date have shown a positive association between alcohol consumption and breast cancer. Nevertheless, the magnitude of the association is modest: A meta-analysis of data from over 40 reports and 41,477 incident cases of breast cancer estimate that compared to non-drinkers, women who consumed one drink per day (defined as 12g) had a 10% (95% Confidence Interval (CI)= 6%-14%) increased risk of breast cancer. While most studies have reported consistent findings, inconsistencies are thought to be due to the low magnitude of the association, low consumption patterns, and/or the tendency to underreport alcohol consumption.

Epidemiologic data further suggest that consumption of larger amounts of alcohol is associated with a higher risk of breast cancer. Prospective follow-up for an average of 7.3 years of 1.3 million women showed that of women who reported recent alcohol consumption, a 12% (95% CI=9% to 14%) elevation in breast cancer risk was observed for each additional drink (defined as 10g). These findings are consistent with data from a pooled analysis of cohort studies suggesting a dose-response relationship.

The number of cases of breast cancer that can be attributed to alcohol consumption varies by geographic region and depends upon consumption patterns and the prevalence of breast cancer within a given region. In the United States (US), an estimated 2.1 to 4.0% of breast cancers are primarily due to alcohol consumption, accounting for 14,000 to 27,000 new cases per year. In countries with higher average consumption, the attributable risk is much higher; in Italy for example, the attributable risk is estimated to be 10%.

Few studies have examined the relationship between alcohol consumption and specific subtypes of breast cancer, although there is growing recognition that breast cancer is a heterogeneous disease and that different subtypes are associated with unique risk factors, tumor characteristics, and prognoses. One study found differences in the association by tumor histology, noting a 1.8-fold (95% CI: 1.3 – 2.5) excess risk for lobular cancers and only a 1.2-fold (95% CI: 0.9 – 1.4) excess risk for ductal cancers, one other small study reported similar findings. A limited number of studies have examined the known alcohol-breast cancer association by tumors according to the presence of estrogen and/or progesterone receptors; though the results have been contradictory. Future research is needed to further elucidate differences in the association by tumor characteristics.

Evidence for whether the strength of the alcohol-breast cancer association varies by stage of breast cancer detection is lacking. A limited number of epidemiologic investigations have reported that individuals who consume alcohol are more likely to experience late stage detection of breast cancer. High consumers of alcohol, however, are thought to be less likely to receive regular screening for early breast cancer detection, a factor known to result in delayed detection of disease. Other studies have linked alcohol consumption to heightened risk of breast cancer recurrence, although this has been the subject of relatively few published studies.

The strength of the association between alcohol consumption and breast cancer is similar for pre-menopausal and post-menopausal women. While this may weaken the rationale for a hormone-based mechanism, data from controlled feeding studies suggests that alcohol intake leads to immediate elevations in levels of circulating endogenous estrogens (see Proposed Mechanism 1: Effects on estrogen levels and estrogen receptors). Further research in this area is warranted.

There is limited data on whether consumption patterns (i.e. sporadic consumption vs. regular consumption) impact the magnitude of breast cancer risk. Some reports suggest that regular (as low as 1-2 drinks per day) and not sporadic consumption contributes to the increased risk. Nevertheless, data have shown a consistent association across type of alcohol consumed (e.g. wine, beer, hard liquor). Evidence linking breast cancer to the consumption of alcohol during specific time periods of life has been inconsistent; however, there is some evidence that delaying the onset of alcohol consumption can reduce the risk of breast cancer.

**Proposed mechanisms underlying the alcohol-breast cancer association**

Despite consistent evidence linking alcohol consumption to breast cancer, to date the mechanisms explaining the relationship are unclear. Several mechanisms have
been hypothesized; these include effects on estrogen levels and estrogen receptors,24 release of carcinogenic metabolites of alcohol, such as acetaldehyde or reactive oxygen species,25 and decreased absorption of essential nutrients.26 In this section, we describe the strength of evidence for each of these proposed mechanisms

**Proposed mechanism 1: Effects on estrogen levels and estrogen receptors**

*Association with estrogen receptor-positive (ER+ tumors)*

Several epidemiologic studies have shown an association between alcohol and breast cancer exclusively for tumors that express the estrogen receptor, i.e. estrogen receptor-positive (ER+ tumors).15-17,27 Data analyzed from two case control studies of breast cancer cases from the Los Angeles Tumor Registry and neighborhood controls found that the increased risk of breast cancer among postmenopausal women associated with alcohol intake was restricted to ER+/progesterone receptor-positive (PR+) breast cancer.17 The authors concluded that alcohol may preferentially increase the risk of ER+/PR+ breast cancer in postmenopausal women, as a high level of daily alcohol consumption (>27 g/day) was associated with an odds ratio of 1.75 (95% CI 1.14-2.71) for this subtype. Alcohol intake was not associated with other hormone receptor subtypes of breast cancer.17

Similarly, a population-based case control study in western Washington State including women ages 65-79 years found that ever-users of alcohol had an increased risk of ER+/PR+ tumors relative to never-users (OR=1.3, 95% CI 1.1-1.7). No association was observed between alcohol intake and ER+/PR- or ER-/PR- tumors.15 The authors concluded that alcohol was more strongly associated with hormone-receptor positive tumors than with other types of breast cancer, consistent with an underlying hormonal basis for the association between alcohol use and breast cancer.15

Results from the Swedish mammography cohort were similar. The cohort included 51 847 postmenopausal women and 1 188 invasive breast cancer cases and alcohol consumption was found to be associated with increased risk of ER+ tumors, regardless of PR status.27 Compared to non-drinkers, the relative risk for ER+/PR+ breast cancer for those drinking ≥10 g/day was equal to 1.35 (95% CI 1.02-1.80) and the relative risk for ER+/PR- breast cancer was 2.36 (95% CI 1.56-3.56). No association was observed between alcohol intake and ER- tumors. Of note was a significant interaction between alcohol intake and the use of postmenopausal hormones on risk for ER+/PR+ tumors.27

In contrast to these findings, several studies have found no difference in the association between alcohol intake and breast cancer according to ER status.19,28-30 However, critics of these studies suggest that they may have been limited in their ability to detect differences by tumor subtype due to small sample size19,29-30 or non-standardized methods for measuring ER status.28

*Potential pathways*

Alcohol intake has been associated with increased levels of circulating endogenous estrogen,8,31 which may directly contribute to elevated risk for breast cancer. Alcohol increases hormone levels, particularly estrone sulfate and dehydroepiandrosterone (DHEAS), and this is believed to be one of the mechanisms underlying the association between alcohol and breast cancer. In a controlled feeding study of 51 postmenopausal women not taking hormone therapy, when women consumed 8 weeks of 15 or 30 g of alcohol per day, they had increased concentrations of estrone sulfate (increase of 7.5% and 10.7% respectively). DHEAS concentrations also increased by 5.1% and 7.5% respectively, relative to levels when women consumed placebo.31

Among premenopausal women, moderate intake of alcohol can decrease menstrual cycle variability and increase the frequency of long menstrual cycles, increasing exposure to endogenous estrogens.8 Blood levels of the reactive ethanol metabolite acetaldehyde are elevated during the high estradiol phase of menstrual cycle among women who drink, and particularly among women who drink and use oral contraceptive pills. Among postmenopausal women not using hormone therapy, moderate alcohol intake can lead to increased blood estrogen and androgen levels, and among postmenopausal women using hormone therapy, there is an even more pronounced effect of alcohol on blood estradiol levels.5

Alcohol may affect breast cancer risk through the ER signaling pathways as the elevated levels of intracellular estrogens resulting from alcohol intake may act through the estrogen receptor to promote breast tumor growth.31 In human breast cancer cells, ethanol stimulates cell proliferation and enhances ER-alpha and aromatase expression, supporting a role for ER signaling in the proliferation of breast cancer cells. Ethanol has been shown to stimulate proliferation of ER+ but not ER-breast tumors in breast cancer cells in culture, causing a 10- to 15-fold increase in transcriptional activity of liganded estrogen receptors. In addition to increasing the transcriptional activity of ER alpha, ethanol may also affect breast cancer risk by down-regulating the
expression of the tumor suppressor gene BRCA1, an inhibitor of ER-alpha activity.\textsuperscript{32,33}

**Proposed mechanism 2: Alcohol metabolism**

Another proposed mechanism underlying the relationship between alcohol consumption and breast cancer is carcinogenesis resulting from alcohol metabolism. The metabolism of alcohol occurs through a two-stage process. During the first stage, acetaldehyde is a primary product. This and other products of alcohol metabolism are known to induce DNA modifications, by causing strand deletions, chromosomal aberrations, or generating protein adducts. Once DNA modifications occur, acetaldehyde may promote breast tumorogenesis by interfering with DNA repair mechanisms. Several alcohol metabolism genes have been explored for their association with breast cancer. Laboratory and epidemiologic studies have examined genes that result in the rapid metabolism of alcohol to acetaldehyde (during the first stage of metabolism) and genes that result in slow metabolism of acetaldehyde to acetate (during the second stage of metabolism); both are thought to raise blood concentrations of acetaldehyde and result in a higher risk for DNA modifications that can lead to cancer.

The first stage of alcohol metabolism is characterized by the conversion of ethanol to acetaldehyde, which is facilitated by two enzymes: alcohol dehydrogenase (ADH) and cytochrome P4502E1. Nearly 80% of alcohol is metabolized by ADH.\textsuperscript{34} During the second stage of metabolism, acetaldehyde is converted to acetate by three enzymes: aldehyde dehydrogenase (ALDH), xanthine oxidoreductase (XOR), and aldehyde oxidase (AOX).\textsuperscript{33} Acetate is then excreted in the urine.

Both acetaldehyde and free radicals produced in the second stage of metabolism have been implicated for their role in alcohol-associated carcinogenesis. Acetaldehyde is highly toxic and is shown in several laboratory studies to cause DNA modifications through the generation of protein adducts, causing DNA cross-linkage, chromosomal aberrations, and DNA point mutations.\textsuperscript{33,35-37} Importantly, acetaldehyde is thought to interfere with DNA repair machinery,\textsuperscript{5} further increasing the risk of cancer once modifications of the DNA have occurred. It does this by inhibiting enzymes important for the repair of protein adducts and the repair of chromosomal breaks.\textsuperscript{1,33} Similarly, free radicals are thought to lead to carcinogenesis by causing DNA damage, strand breakage and base alterations.\textsuperscript{33}

Levels of acetaldehyde and alcohol-associated free radicals are influenced by levels of enzymes responsible for both their production and for their break-down. For this reason, recent studies have examined the efficiency of alcohol metabolism and genetic factors related to the efficiency. Specifically, alleles for ADH and ALDH have been examined for their relationship to levels of acetaldehyde\textsuperscript{27-29} and alleles for glutathione-S-transferase genes, GSTM1 and GSTT1, have been examined for their relationship to levels of free radicals.\textsuperscript{40} Moreover, genes that influence the process by which DNA modifications are repaired have been examined for their relationship to alcohol-associated breast cancer; one candidate is XRCC1 399Q.\textsuperscript{33} Nevertheless, there remain relatively few published reports on this topic.

One important genetic polymorphism encodes for ADH, the primary enzyme responsible for the oxidation of ethanol to acetaldehyde and thereby plays a rate-limiting role in the metabolic pathway. Data from experimental studies show that polymorphisms in ADH influence the rate of alcohol metabolism, such that individuals having the ADH\textsuperscript{1-1}, ADH\textsuperscript{1-2}, and ADH\textsuperscript{2-2} allele are considered fast, intermediate, and slow metabolizers. Among these, fast metabolizers are thought to experience the greatest risk of breast cancer, likely due to their prolonged exposure to acetaldehyde. Data from three studies support this hypothesis. One study used data from 1047 breast cancer cases and 1101 controls that were part of the Long Island Breast Cancer Study and examined the strength of the alcohol-breast cancer association among fast, intermediate and slow metabolizers (as determined by ADH genotyping).\textsuperscript{37} Analysis from the study showed that among fast metabolizers the odds of breast cancer associated with an average lifetime consumption of 15-30 grams of alcohol per day (the equivalent of 1 to 2 drinks per day) was two-fold (OR: 2.0; 95% CI: 1.1 – 3.5) higher than for non-drinkers. By comparison, the relative odds of breast cancer for intermediate and slow metabolizers associated with similar average lifetime consumption of alcohol was 1.5 (OR: 1.5; 95%CI: 0.9 – 2.4) and 1.3 (OR: 1.3; 95%CI: 0.5 – 3.5), respectively. Data from two additional studies suggest a 1.8-fold higher risk of breast cancer among women with the fast metabolizing alleles.\textsuperscript{38-39} Terry and colleagues further demonstrate that the excess risk was more pronounced among pre-menopausal versus post-menopausal women.\textsuperscript{37} Freudenheim et al. reported a similar finding; specifically, premenopausal women with the ADH\textsuperscript{1-1}, allele who had higher alcohol intake were over 3.5 times likely to develop breast cancer, compared to those with lower alcohol intake.\textsuperscript{39} Among post-menopausal women with the ADH\textsuperscript{1-1}, allele, the relative odds of developing breast cancer were 1.2 among those with higher compared to lower levels of alcohol consumption. These data suggest a possible gene-environment interaction.
As noted above, there is consistent though limited evidence that genetic polymorphisms in regions of the genome responsible for acetaldehyde generation are associated with an elevated risk of breast cancer. Scientists have further hypothesized genetic polymorphisms in the regions responsible for acetaldehyde detoxification may also influence breast cancer risk. Seitz et al. compared blood acetaldehyde levels among individuals who were homozygous for the ALDH allele (ALDH2-2) to those who were heterozygous (ALDH2-1). The findings suggested that those with the homozygous allele had levels of acetaldehyde that were 6 to 20 times higher than among heterozygous individuals. The elevated level of acetaldehyde among homozygous individuals is thought to cause “flush syndrome” and may deter excess alcohol consumption.

During the second stage of metabolisms, the enzymes that catalyze acetaldehyde to form acetate, XOR and AOX, can generate reactive oxidative species (ROS), including superoxide anion (O$_2^-$), hydroxyl radical (•OH), and hydrogen peroxide (H$_2$O$_2$). ROS have been shown to cause DNA damage, strand breakage and base alterations. Notably, •OH modifications are thought to be 8- to 17-fold higher in breast cancer DNA than in normal tissue DNA. Moreover, •OH modified DNA has been directly linked to the progression of human breast cancer and has been proposed as a prognostic indicator of breast disease. Efficient or “fast” metabolizers of acetaldehyde may significantly elevate the risk for ROS-associated DNA modifications. This may explain the reduction in breast cancer incidence among individuals with diets enriched in antioxidants (see Proposed mechanism 3: Alcohol metabolism and nutrient intake).

Because of the role of ROS and other alcohol by-products in carcinogenesis, research has examined polymorphisms in genetic loci associated with the metabolisms of these by-products. The ability to metabolize reactive lipid peroxidases, free radicals, and cytotoxic products of alcohol metabolism is thought to be influenced by glutathione-S-transferase genes (GSTM1 and GSTT1); Park and colleagues report that alcohol-consuming pre-menopausal women lacking these genes were at a 5.3-fold greater risk for breast cancer, compared to women having these genes. Further data on the role of genetic polymorphisms in the metabolism of alcohol are needed.

Polymorphisms in DNA repair genes may also produce excess risk of breast cancer, especially when combined with alcohol consumption. One candidate gene is XRCC1 399Q, which is involved in DNA base excision repair. Further research is needed to elucidate a possible gene-environment interaction.

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**Proposed mechanism 3: Alcohol metabolism and nutrient intake**

The direct association between alcohol consumption and breast cancer risk may be modified, at least in part, by alcohol’s interference with the absorption of folate, a micronutrient known to be important in DNA synthesis and repair. Data from a cohort study of over 35 000 post-menopausal women show that those who consumed 1272 or more dietary folate equivalents per day had a 22% reduction in breast cancer risk, compared to women who consumed less than 345 dietary equivalents. In the U.S. and Canada, mandatory fortification programs started in 1998; this, combined with a higher prevalence of vitamin supplementation, reduces folate deficiency in the population. A randomized, controlled trial of combined folate (2.5 mg), Vitamin B6 (50 mg), and Vitamin B12 (1mg) supplementation compared to placebo among women at high risk of cardiovascular disease reported no overall association between supplementation and invasive breast cancer (HR 0.83, 95% CI 0.60-1.14, P=0.24). Vitamin B12, along with riboflavin and Vitamin B6, are cofactors in the folate pathway converting homocysteine into methionine for DNA methylation. Prior research has also reported no significant associations between Vitamin B6 and breast cancer risk among premenopausal women and postmenopausal women.

It has been observed that the magnitude of the alcohol-breast cancer association differs by levels of folate consumption. Previous epidemiologic studies have suggested that low levels of folate, and other one-carbon methyl group donors such as vitamin B12, may form part of the pathway by which alcohol elevates the risk of breast cancer. Similarly, higher intake of folate or multivitamin use has been shown to attenuate the alcohol-breast cancer association. Since alcohol is a known folate antagonist and could therefore interfere with DNA repair, several studies have investigated joint associations between alcohol and folate and breast cancer, as recently reviewed. The majority of cohort studies provide evidence to support a protective effect of folate on breast cancer among women who consume alcohol. However, data from the Women’s Health Initiative Observational study as well as other large cohort studies reported no evidence for an attenuation of risk in postmenopausal women.

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**Types of alcohol and consumption patterns**

Major types of alcohol include beer, wine, and liquor. The limited evidence available suggests consistency in
the magnitude of the alcohol-breast cancer association across type of alcohol consumed. Nevertheless, the amount of alcohol within a serving varies by source. The United States Department of Agriculture (USDA) reports the mean alcohol content of a serving of beer is 13.9g, wine 15.4g, and liquor 14g (serving defined as 12 oz beer, 5 oz wine, 1.5 oz 80 proof liquor). The actual amount varies by type: the range for beer is 3 to 7%, wine 9 to 15%, and liquor 35 to 50% by volume. Because of this variability, the definition of an alcoholic drink often varies across studies, ranging from ~10-15 grams of alcohol; thus some authors report total grams of ethanol for comparison purposes.

Data from the World Health Organization suggest that an estimated 2 billion people worldwide consume alcoholic beverages. Alcohol consumption patterns among women vary substantially by geographic region (Figure 1). According to data from the World Health Organization, having ever drunk alcohol in the past year was highest in Germany, France, the Czech Republic, and the Netherlands. Among those who drank alcohol in the past year, the proportion of heavy drinkers, as defined by drinking two or more servings of alcohol (>20g) a day, was highest in Nigeria, suggesting relatively high consumption among a smaller proportion of consumers. Notably, consumption of alcohol is reported to be rising in many countries, especially among women in regions of rapid economic growth. Within a given country, drinking patterns vary by subpopulations and across different regions; it is generally believed that those of low education and income consume more alcohol than those of high education and income, resulting in economic disparities in alcohol-associated breast cancer.

Alcohol consumption behaviors are thought to be influenced by migration. Prior epidemiologic research suggests that the proportion of Hispanic women born in the U.S. who drink alcohol is lower than for non-Hispanic whites (60.3% vs. 40.1% report no alcohol consumption, respectively), and the proportion is even lower among women who are recent immigrants (68.9% abstained from alcohol).

![Figure 1. International patterns of alcohol use among women](image-url)
Conclusion

Alcohol consumption is a modifiable risk factor for breast cancer; thus several behavioral recommendations have been offered. Given the dose-response relationship between alcohol consumption and breast cancer, recommendations generally focus on limiting overconsumption of alcohol. Nevertheless, the widely publicized cardiovascular benefit to moderate alcohol consumption suggests that the risks and benefits of alcohol consumption should be weighed in making individual lifestyle choices. Women who are low to moderate consumers of alcohol should consider their overall risk of chronic disease.

Nevertheless, some general recommendations regarding consumption practices should be followed. While definitions vary for what constitutes a low or moderate level of consumption, it is generally recommended that excess consumption be avoided. This is generally thought to amount to three or more drinks per day. Lower intake is recommended for women who have known risk factors for breast cancer; for these women Poschl et al. suggest avoiding regular consumption and that consumption limited to no more than twice weekly in moderate doses (10-20g for women).

In the past two decades, a tremendous amount of research has addressed the association between alcohol consumption and breast cancer. Nevertheless, more research is needed. Future research to elucidate the interaction between alcohol consumption and other breast cancer risk factors and to explain the role of genetic factors in alcohol metabolism will advance the field. Such research can lead to improved health recommendations and more informed decisions about lifestyle and risk, by placing alcohol into a broader context of interactions with other choices. In addition, further research can inform prevention strategies targeting high-risk individuals and communities.

Declaration of conflict of interests: The author declares not to have conflict of interests.

References

The effects of alcohol consumption on breast cancer risk are complex and multifaceted. A recent meta-analysis by Feigelson et al. (2007) indicated that moderate alcohol consumption may increase breast cancer risk in postmenopausal women, whereas heavy consumption appears to be more hazardous. The American Cancer Society (2007) reviewed the evidence and concluded that the association between alcohol consumption and breast cancer is significant but may vary by race and ethnicity.

Among the key points from the literature:

- **Alcohol and Estrogen Receptor Signaling:** Alcohol stimulation of estrogen receptor signaling in human breast cancer cell lines (Coulterio et al., 2005).
- **Folate and One-Carbon Metabolism:** Folate intake, alcohol, and risk of breast cancer among postmenopausal women (Fanslow et al., 2002; White et al., 1999).
- **Gene Polymorphisms:** Alcohol-mediated alterations in p16(INK4A) and hMLH1 genes in spontaneously aborted embryos with Down syndrome (Romieu et al., 2006).
- **Carcinogenesis Models:** Alcohol consumption and risk of breast cancer: the Framingham Study (Gammon et al., 2001).
- **Incorporating Multifactorial Considerations:** The role of nutrients from supplements and diet in relation to breast cancer risk (Nevens et al., 2007).

These studies collectively highlight the intricate relationship between alcohol consumption, hormonal status, and breast cancer development, emphasizing the need for continued research to fully understand the mechanisms at play.