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Review

# Alcohol Use and Cancer: A Critical Review

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**ABSTRACT**

The risk of cancer in numerous areas of the human body such as the oral cavity, esophagus, liver, stomach, colon, rectum, and breast is increased by alcohol consumption. The products of the metabolism of ethanol, acetaldehyde, and reactive oxygen species, have genotoxic properties. Chronic alcohol usage may also result in deoxyribonucleic acid (DNA) damage, inflammation, and methylation. Folate deficiency, which can be caused by extended alcohol use, may have an impact on DNA methylation. The consequences of alcohol (ethanol) on colon and breast cancer were discussed in this review article.

**Keywords:** Alcohol metabolism, cancer, ethanol, inflammation

Alcohol consumption is rising year over year. More research is needed to understand the illnesses that this rise in alcohol use might bring on in people. The findings of the research conducted thus far indicate that drinking alcohol raises the risk of cancer in several areas, including the breast, liver, stomach, colon, rectum, and esophagus.[1-3] Alcohol-induced carcinogenesis may be influenced by genetic and epigenetic pathways. Despite the fact that ethanol alone does not cause cancer, acetaldehyde and reactive oxygen species (ROS) have genotoxic or tumor-promoting effects, according to the information that is currently available.[4]

In this review, the effects of alcohol (ethanol) on breast cancer and colon cancer were discussed.

## ALCOHOL METABOLISM

The metabolism of ethanol has a significant impact on cancer by triggering signaling molecules necessary for metastasis and, most significantly, inflammation. Chronic ethanol use may trigger carcinogenesis via a number of pathways and may also have an impact on deoxyribonucleic acid (DNA) methylation due to its potential to result in folate deficiency.[5] Alcohol and breast cancer have also been linked.[2] Not all alcohol consumed orally gets into the systemic circulation. It is initially broken down in the stomach. But when someone is fasting, the majority of the ethanol goes straight from the stomach to the duodenum.

Alcohol absorption is influenced by a variety of variables, including gender, age, ethnicity, and body weight. As shown in Figure 1, alcohol dehydrogenases (ADH), catalase, and cytochrome P450 2E1 (CYP2E1) first convert alcohol (ethanol) to acetaldehyde.

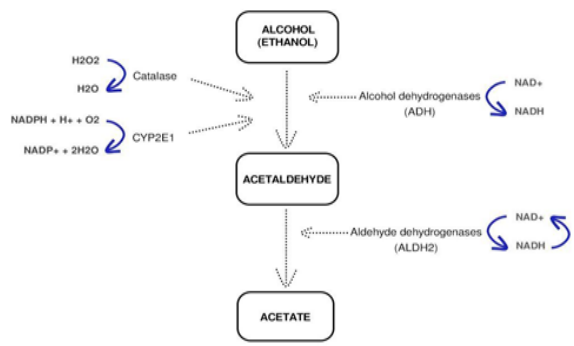


Figure 1. Alcohol metabolism

Aldehyde dehydrogenase (ALDH) then converts it to acetate. Alcohol dehydrogenase 1B (ADH1B),

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alcohol dehydrogenase 1C (ADH1C), and aldehyde dehydrogenase-2 (ALDH2) are the classes of ADH and ALDH isoenzymes that are primarily engaged in ethanol metabolism.[6,7]

## ALCOHOL AND BREAST CANCER

In older women, breast cancer and alcohol use are frequently linked.[2] According to the International Agency for Research on Cancer (IARC), alcohol is causally linked to a higher risk of developing breast cancer.[7] Light alcohol use (less than 1 drink per day or 12.5 g/day) considerably raises the risk of breast cancer by 4–15%.[8–10] Until the first pregnancy happens, the breast experiences a number of physiological changes. According to studies done on animals, breast cancer is more likely to develop as a result of early alcohol consumption. Young virgin rats with undifferentiated mammary glands are more susceptible to developing mammary cancers when exposed to chemical carcinogens when compared to rats with full-term gestation.[11] According to studies, alcohol intake before the age of 30 has been linked to a considerable increase in the risk of breast cancer.[12,13]

Premenopausal breast cancer risk is dose-dependently correlated with alcohol use before the age of 30, and the risk rises by 34% for every 13 g/day (about one drink/day) intake. However, this correlation does not exist for postmenopausal breast cancer risk.[14] According to research conducted on animals, ethanol exposure during puberty causes alterations in the morphology of mouse mammary glands, including an increase in ductal branching as well as epithelial proliferation and density, but has no impact on the nursing mammary gland's return to its resting condition.[15]

In the Nurses' Health Study II (NHS II), a distinct cohort of American female nurses born between 1946 and 1964, closely examines how alcohol use between menarche and the first pregnancy impacts the risk of breast cancer in the future. An evaluation of risks was done concurrently.[8] In a 1989 study, 1609 women were diagnosed with breast cancer over a follow-up period of up to 20 years among fertile women aged 24-44 who had no prior history of the disease. Women who used less than 15 g of alcohol per day (about 1.5 drinks/drink) had a 34% higher risk of breast cancer than those who abstained from alcohol before their first pregnancy. Additionally, the longer the gap between menarche and the first pregnancy, the greater the risk of breast cancer associated with drinking before the first pregnancy. Women aged 10 to 14 years between menarche and their first pregnancy had an increased risk of breast cancer of 14%, while those aged 15 and older had an increased risk of 25% for every 10 g/day of alcohol used before conception. These epidemiological findings, along with evidence from animal studies, imply that alcohol use prior to conception may cause morphological changes in the breast that may increase the risk of breast cancer. Additionally, prolonged alcohol use at this vulnerable time may raise your chance of developing breast cancer. Premenopausal and postmenopausal breast cancer tend to be linked to early alcohol use.[2]

Only a few epidemiological studies have compared the risk of benign breast disease (BBD) with alcohol intake. There was no correlation between alcohol intake in the year before diagnosis and BBD risk, according to two case-control studies on BBD risk variables.[16,17] Compared with non-drinkers the first pregnancy, the risk of proliferative BBD was increased by 26% for those with a daily intake of 5.0-14.9 g (about 0.5-1.5 drinks) before the first pregnancy and 39% for those with a daily intake ≥39%. Each additional 10 g of alcohol taken each day before the first pregnancy raised the probability of proliferative BBD by 16% overall.[2] A 50% increase in the probability of biopsy-confirmed BBD was also linked to a drink of alcohol each day between the ages of 16 and 22.[18] All of the findings point to the possibility that drinking alcohol during adolescence and the early years of adulthood may be more harmful to proliferative BBD risk than drinking alcohol during the later years of adulthood.

Today, mammography is the technique most frequently used to diagnose breast cancer. It is divided into screening and diagnostic mammography. Diagnostic mammography aims to scan asymptomatic patients once a year and find any lesions that may be present. Early detection of breast cancer is greatly reduced by 20% to 40% with early detection via screening mammography. More breast cancer deaths are prevented by annual screening mammography for women 40 to 84 than by biannual screening for those 50 to 74.[19] The use of mammograms also enables the detection of breast defects or malformations. The percentage of radiologically dense fibroglandular tissue in the breast is known as mammographic density. Breast cancer risk is inversely correlated with mammographic density, whether determined by a qualitative technique or a quantitative measurement of the opaque area of the breast.[20] A meta-analysis study of 14000 cases and 226,000 non-cases revealed that women with a mammographic density greater

than 75% had almost five times the risk of breast cancer compared to women with a mammographic density of less than 5%.[21] According to some research, both premenopausal and postmenopausal women who drink more adult alcohol show a weak but substantial positive tendency toward increased mammographic density.[22,23] First and second-degree female relatives of breast cancer patients in the Minnesota Breast Cancer Family cohort, as well as the spouses of male relatives during the follow-up, were questioned regarding their first drinking experience and drinking before the age of 18. Women who admit to drinking before the age of 18 have denser mammograms than those who never drank while growing up. However, when breast cancer risk variables were taken into account, this difference was abolished. In another study, alcohol use was assessed independently for each decade of life (age 21–29, 30-39, and age 40 and older) in the New York City birth cohort (born 1959–1963), and mammograms were collected during follow-up. In this study, consumption of alcohol recently rather than throughout the course of one's lifetime was linked to higher mammographic density. Those who claimed to have consumed seven or more drinks per week over the course of the past year had a 12.3% higher density than non-drinkers. Alcohol drinking before the age of 21 is negatively correlated with mammographic density, but alcohol consumption at subsequent stages of life is favorably correlated. Additionally, there is a lack of information on mammographic density according to alcohol kinds.[24]

Alcohol consumption, which is defined as consuming four or more alcoholic beverages at once, accounts for about 70% of young people's alcohol consumption.[25] Higher alcohol levels are produced by drinking more than one glass of alcohol at once than by drinking one glass of alcohol on consecutive days. Women who regularly consume one drink per day may be at a higher risk of developing breast cancer than those who regularly consume seven drinks on the weekends but abstain from alcohol during the workweek. Epidemiological studies typically measure the risk of breast cancer based on the average alcohol consumption over a specific time period or age group; they do not account for the impact of heavy alcohol use at any given time. Two prospective studies among nurses found an elevated risk of breast cancer to be related to excessive drinking. Weekend and last day of the week drinking patterns were examined in the Danish Nurse Cohort study.[26] Compared to women who reported 1-3 drinks, women who reported binge drinking on weekends had a relative risk of 1.49 for 10-15 drinks and 2.51 for 16-21 drinks, while some women had a lower risk. After accounting for cumulative alcohol consumption, the National Health System found that adult heavy drinkers had a 21% higher chance of developing breast cancer than non-drinkers.[10]

Various forms of alcohol include different compounds, which may alter how alcohol affects breast cancer. Red wine is believed to have a preventative impact on the development of cancer and the cardiovascular system because it contains polyphenolic substances that may be acquired from the grape skin. Red wine polyphenols have antioxidant, anti-inflammatory, and anti-cancer properties that come from numerous molecular and biochemical mechanisms. Mammographic density is positively correlated with beer and white wine consumption in early adulthood and negatively correlated with red wine consumption during adolescence and early adulthood in the New York birth cohort of premenopausal women.[27] White wine consumption and mammographic density have recently been found to have a significant positive association in postmenopausal women. This finding is in line with data from the Minnesota Breast Cancer Family cohort, which showed a positive association between white wine and an inverse association for red wine. Increased wine consumption was found to be positively correlated with mammographic density in a study of Mediterranean women; the link between wine types was not examined.[28]

Three polyphenolic substances-resveratrol, quercetin, and catechin-combine make up 70% of the polyphenols in red wine.[29] They function in the estrogen receptor (ER) as both an antagonist and an agonist and share structural similarities with estrogen.[30,31] Breast cancer type 1 susceptibility protein (BRCA1) reduces epigenetic silencing of the tumor suppressor protein when exposed to resveratrol in breast cancer cells, which inhibits DNA methyltransferases, enzymes that catalyze DNA methylation.[32] Resveratrol prevented lung metastasis in a mouse model containing MDA231 human breast cancer xenografts (cell line) without noticeably altering body weight or liver and kidney function. As a result, these findings suggest that resveratrol prevents MDA231 cells from migrating by reversing transforming growth factor (TGF-β-1) induced epithelial-mesenchymal transition (EMT) and prevents lung metastasis of MDA231 human breast cancer in a mouse model using xenografts.[33]

Barley malt, hops, water, and yeast combine to

make beer, which is a phenolic beverage. Some hop-derived substances, including xanthohumol and hop bitter acids, are thought to be potential cancer chemopreventive agents that may obstruct the beginning, development, and advancement of carcinogenesis. Xanthohumol possesses mixed estrogenic and antiestrogenic characteristics similar to resveratrol, and it inhibits aromatase activity *in vitro*.[34,35] However, the body can only absorb a small amount of these chemicals because they are present in beer in such small amounts.

Overall, epidemiological data shows that it's alcohol content, not the kind of drink, that raises the risk of breast cancer. Although different alcoholic beverage kinds have variable ethanol concentrations, all alcoholic beverage types are claimed to have a similar risk of breast cancer.[10,36,37] The impact of alcohol on circulating estrogen levels, ER in mammary epithelial cells, and the potential carcinogenic effects of ethanol metabolites are among the most extensively studied pathways. Recent in vivo and in vitro research points to additional potential pathways through which alcohol may contribute to the development of mammary tumors, including its impact on EMT, interactions between the epithelium and the stroma, and the epigenetic control of gene expression in the breast.[2]

Elevated estrogen levels are directly correlated with breast cancer. It is widely acknowledged that estrogen's nuclear receptor, the estrogen receptor alpha (ER-α), mediates the proliferative impact of estrogens on mammary epithelial cells.[38] Nevertheless, estrogen has the potential to cause breast cancer via a genotoxic, ER-independent mechanism.[39-42] Alcohol use has been linked to greater levels of circulating estradiol and estrone in premenopausal females.[43-45]

Premenopausal women who drink moderate amounts of alcohol have shorter menstrual cycles than non-drinkers, which may indicate higher exposure to endogenous estrogens.[46] Alcohol use can result in high intracellular estrogen levels that can influence breast tumor growth via the ER. Alcohol promotes the growth of estrogen receptor-positive (ER+) breast cancer cells but not ER+ breast cancer cells. It increases the ER's transcriptional activity by 10 to 15 times.[47,48]

The c-Jun N-terminal kinase (JNK1) pathway ER-α is expressed more when ethanol is present.[49] Numerous epidemiological studies have revealed that alcohol consumption is more strongly linked to hormone receptor-positive breast tumors than to other forms of breast cancer, supporting the hypothesis that the link between alcohol consumption and breast cancer is hormonal in nature.[50] In postmenopausal women, the chances of ER+ and estrogen receptor–negative (ER-) breast cancer and ER+/PR- breast cancer increased by 8% and 12%, respectively, for each beverage eaten per day.[51] Similar results were found in a meta-analysis of 16 case-control studies and four prospective studies that found a 12% increase in ER+ tumor risk per 10 g/day of alcohol usage.[50]

Alcohol usage prior to the first pregnancy is typically more strongly linked to ER+/PR+ tumor risks among women who have given birth to NHS II.[8] Overall, these findings are consistent with the theory that alcohol may increase the breast tissue's susceptibility to estrogens and raise the likelihood of developing breast cancer that mainly expresses hormone receptors. Alcohol is mostly metabolized to acetaldehyde by ADH in the human body. Acetaldehyde dehydrogenase and xanthine oxidoreductase also convert alcohol to acetate.[9,52] Acetaldehyde can result in DNA point mutations, chromosomal abnormalities, and DNA damage. These effects quickly bind to proteins and DNA and form new byproducts.[53–55] Alcohol and acetaldehyde alter DNA methylation patterns by reducing the production and activity of methylation-related enzymes. Acetaldehyde also prevents the healing of oxidative DNA damage brought on by alkylating chemicals.[56] Although acetaldehyde and free radicals are mostly formed in the liver during the alcohol metabolism process, normal human breast tissue has the ability to metabolize modest quantities of ethanol, and human mammary epithelial cells express ADH.[57-59] A single oral dose of ethanol causes the production of acetaldehyde in rats. Then it builds up for a very long time in the breast tissue and eventually reaches a level that is much greater than in the blood.[60,61] The primary causes of this include elevated levels of acetaldehyde generation in breast tissue, the tissue's limited capacity to detoxify acetaldehyde, and acetaldehyde created elsewhere that was transported to the breast tissue by blood.[62] Reactive oxygen species, which are also produced as a result of alcohol metabolism, have a role in the development of alcohol-related breast cancer. They can harm DNA similarly to acetaldehyde by producing strand breakage and mutations, and they are involved in the development and spread of cancer.[63] Two acetaldehyde metabolism-related enzymes, xanthine oxidoreductase, and aldehyde oxidase are also present in breast tissue and can create ROS.[52] As a

result, drinking alcohol may increase the amount of oxidative DNA damage in breast tissue.[2] Salsolinol produced from alcohol has also been shown in some studies to greatly increase the production of the 8-oxo-2'-deoxyguanosine (8-oxodG), a marker of oxidative damage in healthy breast epithelial cells.[64,65] DNA with high concentrations of 8-oxodG inserts is fundamentally implicated in breast cancer.[66] According to a recent *in vitro* study, ethanol stimulates the expression of the integrin alpha-5 (ITGA5) and suppresses the expression of the metastatic suppressor gene (Nm23) in order to promote the adhesion of breast cancer cells to fibronectin, a crucial part of the extracellular matrix.[67] New research demonstrates how alcohol affects the way genes are regulated by epigenetics.[68] The most important epigenetic factor for the development and spread of tumors is epigenetic dysregulation. The best-understood epigenetic cause of the disease is abnormal DNA methylation.

## ALCOHOL AND COLON CANCER

Contrary to popular belief, it is significantly more challenging to comprehend how alcohol affects cancer. It is challenging for us to research how alcohol affects cancer because there are so many confounding variables, including gender, lifestyle choices, and exposure to toxins. Additionally, in many nations, men consume more alcohol than women. Although there is a connection between drinking alcohol and the risk of gastrointestinal cancer, the molecular causes of colon cancer are still poorly understood. Drinking patterns are changing year after year. It is important to conduct further research to comprehend the ailments that an increase in alcohol consumption may bring on in people. According to the findings of the studies conducted thus far, alcohol has been found to raise the risk of cancer in several areas, including the breast, rectum, liver, stomach, colon, and esophagus. The IARC has categorized acetaldehyde as a group 1 human carcinogen. Acetaldehyde is known to cause DNA damage in the digestive system.[69,70]

Ethnic and individual variations in susceptibility to alcohol-related malignancies are closely correlated with polymorphisms in the enzymes that metabolize ethanol and acetaldehyde, particularly ADH and ALDH. According to epidemiological, experimental, and clinical investigations, alcohol misuse has been linked to an increased risk of liver cancer and is a main cause of cirrhosis.[71,72] Recent meta-analyses and case-cohort studies have revealed that drinking alcohol increases the risk of developing stomach cancer.[3]

The third most prevalent type of cancer in the world is colorectal cancer. South Korea, Slovakia, Hungary, and other regions of Europe have significant incidence rates.[73]

Diabetes, diets deficient in fiber, alcohol, smoking, sedentary behavior, colorectal cancer, etc. Numerous things, like, can cause it.[4] Drinking alcohol is also acknowledged as one of the main risk factors for the occurrence of colorectal cancer (CRC).[74-76] More than 30 g of ethanol per day may contribute to CRC, according to reports from the World Cancer Research Fund and the American Institute for Cancer Research.

The primary acetaldehyde-eliminating enzyme, ALDH2, has a variation found in East Asian people as a result of the substitution of lysine (Lys) for glutamate (Glu) at position 487.[77,78] While the Lys allele of ALDH (ALDH2*2) generates an enzyme that is catalytically inactive, the glutamate allele of ALDH2*1 encodes a protein with normal catalytic activity. Therefore, the Lys homozygotes do not have ALDH2 activity that can be seen. Alleles of East Asians frequently have a variation of ADH (ADH1B*2), a mutant version of ADH.[77,79] When drinking the same amount of alcohol as individuals with the wild type of ALDH2, the amounts of acetaldehyde-derived DNA inserts in the blood of alcoholic patients with the ALDH deficiency genotype were substantially higher as shown in Figure 2.

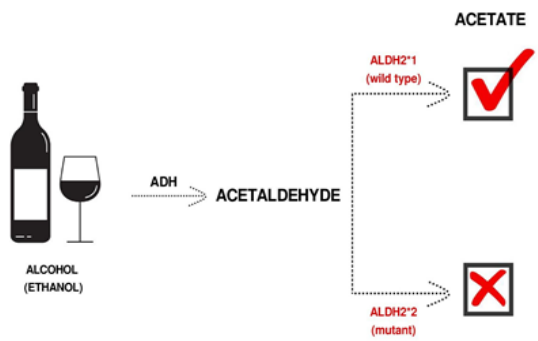


Figure 2. Mutation inhibits the conversion of acetaldehyde to acetate.

By lowering the excretion of carcinogens, alcohol can amplify the effects that are genotoxic. Additionally, it has been demonstrated that alcohol alters one-carbon metabolism by preventing the absorption of folate, which leads to the hypermethylation of tumor suppressor gene islands with 5′-C-phosphate-G-3′" nucleotide sequences

(CpG/CpG sites).[80]

Alcohol consumption led to DNA damage in the mouse stomach, which is influenced by the genotype of ALDH2.[81] In mice treated with ethanol who had ALDH2-/-, ALDH2+/-, or ALDH2+/+ mutations, the number of DNA inserts was measured. Gastric cancer is riskier for ALDH2 carriers who use less than 150 g of alcohol each week.[82] According to this finding, ALDH2 absence might hasten the development of stomach cancer.

Following absorption, oral alcohol is delivered to the colon, where the level of ethanol is the same as in the blood. Although there was detectable ALDH activity in the rat colonic mucosa, it was generally inactive in comparison to the liver, stomach, and small intestine. Additionally, it was discovered that the cytosolic ADH activity in the colonic mucosa was almost six times lower than that of the liver and roughly half that of the stomach ADH activity.[83,84] In Japanese alcoholics with colon cancer, the frequency of the mutant allele ALDH2*2 was found to be 21.7% higher and 9.0% higher than in alcoholics without colon cancer.[85] Similar to the case with gastric cancer, racial or individual differences in susceptibility to alcohol-related CRC are connected with polymorphisms or mutations of genes encoding enzymes involved in acetaldehyde production or removal. The ALDH2 rs886205 polymorphism and the risk of CRC, however, are unrelated, according to a sizable population-based case-control research carried out in Israel.[86] The results of many investigations looking into the connection between the lysine allele polymorphism of ALDH and the risk of colorectal cancer are mixed.[4] Therefore, no definitive results regarding ALDH2*2 and colon cancer could be drawn.

Chronic ethanol use may start or encourage carcinogenesis through a variety of processes. It is thought that the carcinogenesis brought on by alcohol involves both genetic and epigenetic processes.[4] Although data suggest that acetaldehyde and ROS have genotoxic or tumor-promoting effects, ethanol alone is not known to be carcinogenic. Thus, co-administration of ethanol and cyanamide, a strong acetaldehyde dehydrogenase inhibitor, enhanced the incidence of tumors in rats given acetoxymethyl, methylnitramine, offering more proof that acetaldehyde may be involved in ethanol-related carcinogenesis.[87]

## ALCOHOL AND STOMACH CANCER

Gastritis, the etiology of gastric cancer, is known to be brought on by *Helicobacter pylori* (*H. pylori*) infection. Between 1% and 2% of people with *Helicobacter pylori,* infection will develop stomach cancer.[82] We can conclude that some *H. pylori* strains continue to have a sizable level of cytosolic ADH activity and generate a sizable amount of acetaldehyde when exposed to ethanol.[88]

A nasogastric tube was used to administer gastric alcohol infusion to healthy individuals who were both *H. pylori*-negative and ALDH-active. The acetaldehyde levels in the gastric juices of ALDH2 defective people dramatically increased as compared to those of ALDH-active people.[89] A rise in acetaldehyde of this magnitude can cause cancer.

Contrarily, CYP2E1 activation stimulates the metabolism of ethanol, which results in the production of ROS and reactive nitrogen species, and has been linked to a reduction in cellular antioxidant defense.[90] Membrane lipids may oxidatively degrade as a result of ROS. Emerging lipid peroxidation products like 4-hydroxynonenal (4-HNE) can bind to colonic mucosal DNA and form highly carcinogenic exocyclic ethanol DNA adducts.[91] Chronic inflammatory injury and oxidative stress form a vicious cycle that can permanently harm neighboring healthy epithelial and stromal cells and promote carcinogenesis.[92]

Population-based research has shown that persistent alcohol (ethanol) intake can lead to a variety of malignancies, particularly stomach and colon cancers. The gastrointestinal tract can develop cancer as a result of ethanol.[93,94] DNA methylation may be impacted by folate deficiency, which can be brought on by prolonged alcohol use. Therefore, by giving up alcohol for a healthy life, maintaining our ideal flora, eating a balanced diet, and engaging in mild activities, we can protect ourselves against various diseases such as stomach and colon cancer.

In conclusion, alcohol can generally lead to breast cancer, including subtypes that are breast cancer positive. Controlling alcohol use in adolescent girls and women before the first pregnancy is crucial to lowering the risk of breast cancer in the future because the risk of breast cancer reduces after pregnancy. Women should be aware of the issues that can arise from consuming alcohol excessively and over the long term throughout their lives. Teenage girls should monitor their alcohol usage in order to avoid issues in the future because breast cancer affects women all over the world. Although there is

a dose-dependent link between alcohol use and the risk of breast cancer, there is still a lack of information regarding the degree of alcohol consumption at which the risk of breast cancer becomes clinically significant. We will be able to identify a subset of the most vulnerable women and propose therapy targets by having a better knowledge of the molecular changes brought on by alcohol that cause cancer in breast tissue, which will aid in the development of novel markers for cancer prevention.

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