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Influence of alcohol on breast cancer risk

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Abstract
One of the most significant recognized and controllable risk factors for cancer in humans is alcohol consumption. Breast cancer is the most prevalent malignancy in women globally and the main factor in cancer-related deaths. It has long been understood that severe drinking plays a part in breast cancer risk, and even moderate drinking is linked to the disease. Even light alcohol usage (less than 1 drink per day or 12.5 grams per day), which does not considerably raise the risk of cancer in other female organs, dramatically raises the risk of breast cancer by 4–15%. Because nearly half of women of childbearing age drink alcohol and 15% of drinkers at this age consume four or more drinks at once. Early menopause, early pregnancy, and late menstruation are all linked to a lower risk of breast cancer. Women with a gap of 10–14 years between menarche and their first pregnancy and those with a gap of 15 or more years had a risk of breast cancer that rose by 14% for every 10 g/day of alcohol they drank before being pregnant and by 25% overall. Alcohol drinking increases the chance of developing breast cancer via altering hormone levels and the biological processes that are connected to them, metabolizing ethanol to produce carcinogens. The purpose of the present review is to give an overview of the association between alcohol intake and the risk of developing breast cancer in women.

Keywords: Alcohol consumption, breast cancer, early menopause and pregnancy, late menstruation, altering hormone levels

Introduction
Epidemiological research has shown that poor lifestyle variables have a significant impact on the development of breast cancer. For instance, daughters of immigrant Asian women to the USA showed an increased risk of getting breast cancer, which was linked to exposure to several lifestyle and nutritional factors. The gradual rise in breast cancer prevalence in Asian nations over the past few centuries provides additional proof that shifting living habits have an impact on the development of breast cancer. Once more, this discovery is connected to a trend toward a more contemporary and "Western" lifestyle. Consequently, when formulating a strategy for breast cancer prevention, modifiable and lifestyle risk factors should be taken into account. This manuscript excludes non-modifiable risk factors such older age, hereditary hazards, family history of breast cancer, breast density, thorax radiation, and lifetime menstrual cycle frequency. (Dieterich *et al.* 2014) [5]. The International Agency for Research on Cancer considers that alcohol is causally connected to the chance of developing breast cancer, with a 7–10% increase in risk for every 10 g (about one drink) of alcohol that adult women consume daily. Both premenopausal and postmenopausal women display this relationship. Alcohol intake causes 9000–23, 000 new cases of invasive breast cancer annually in the USA, or 4–10% of all breast cancers (Liu *et al.* 2015) [1]. Early menopause, early pregnancy, and late menstrual onset are all linked to a lower risk of breast cancer. During a follow-up period of up to 20 years, 1609 women received a breast cancer diagnosis. When compared to women who refrained from alcohol prior to their first pregnancy, those who consumed less than 15 grams of alcohol per day (or 1.5 drinks per day) had a 34% higher risk of breast cancer (Liu *et al.* 2015) [1]. Women of 60 years of age and older account for 51.7% of all breast cancer deaths, which occurs at a relatively young age. Geographically, age-standardized rates (ASR) of breast cancer incidence and mortality show that breast cancer incidence and mortality rates may increase in the future in developing countries due to changes in reproductive patterns, increased use of screening technologies, and lifestyle changes. (Shield *et al.* 2016) [3]. The well-known activators of cellular proliferation that are estrogens and androgens are linked to a higher risk of breast carcinogenesis.

Drinking alcoholic beverages increases endogenous estrogen levels in women, which has been linked to an increased risk of breast cancer. ADH-mediated alcohol oxidation has been proposed as the mechanism for the alcohol-mediated augmentation of steroid levels. This process raises the hepatic redox state, which in turn slows the catabolism of sex steroids. A total of 5% of breast cancer diagnoses among women in eight European nations are thought to be caused by alcohol (Scoccianti *et al.* 2014) [2]. Breast cancer risk is enhanced by cumulative exposure to elevated levels of endogenous hormones, specifically estrogens, androstenedione, dehydroepiandrosterone sulfate, and testosterone. (Shield *et al.* 2016) [3]. The impacts of sex hormones (estrogen and androgen levels) and the mutagenic properties of alcohol's first metabolite, acetaldehyde, are thought to be the mechanism by which alcohol exerts its carcinogenic effect (Vegunta *et al.* 2020) [6]. Now, most significantly, the main core of treatment focuses on quitting smoking and drinking & avoid taking any unnecessary postmenopausal hormones. Eating several servings of vegetables and fruit each day, consuming a diet high in fiber such as cereals and soy products, maintaining an ideal body weight (BMI = 20–25 kg/m^2), limiting the amount of red meat that we eat each day to 140 g, exercising frequently (2–3 hours per week of moderate exercise) also helps to control breast cancer risk (Dieterich *et al.* 2014) [5]. Chemoprevention is one such method used where the use of pharmaceutical or natural agents prevents the growth of invasive breast cancer. (Advani *et al.* 2014) [7]. Certain medications to reduce the risk factors in women with a high and moderate personal risk for breast cancer may be prescribed anti-estrogen medicines at specialized clinics (Daly *et al.* 2021) [8].

Materials and Methods: The relevant data for this review study was discovered by searching Google Scholar, PubMed, PubMed Central, and published research papers and review articles from throughout the world on how alcohol consumption influences the development of breast cancer in women. Only publicly available data were used, and speculative assertions concerning exposure were disregarded. Utilizing information from reputable sources of information on the issue is one of these inclusion criteria. The study excluded all other languages than English.

Results and Discussions

Factors effecting in the development of breast cancer

Binge drinking: The drinking behavior described as binge drinking is defined as the sporadic ingestion of >60 g of pure alcohol on at least one occasion over the course of the previous 7 days (Scoccianti *et al.* 2014) [2]. In comparison to women reporting 1-3 drinks, women reporting binge drinking on weekends had a relative risk of 1.49 for 10-15 drinks and a relative risk of 2.51 for 16-21 drinks. However, a decreased risk was seen for a small subset of women who drank more. The highest relative risk of 1.55 for binge drinking on the previous weekday was noted for consumption of four to five drinks as opposed to one drink. After accounting for cumulative alcohol intake, the NHS found that adult binge drinkers had a 21% higher chance of developing breast cancer than non-drinkers (Liu *et al.* 2015) [1].

Estrogen and Estrogen receptor: According to several studies, exposure to elevated levels of endogenous hormones over time—particularly estrogens, androstenedione, dehydroepiandrosterone sulfate, and testosterone—increases the risk of breast cancer. The nuclear estrogen receptor (ER) alpha, which in turn encourages cellular proliferation, is thought to play a role in how exposure to high estrogen levels raises the risk of breast cancer. Estrogen specifically increases ER signaling in human breast cancer cell lines, as well as the production of ER alpha and aromatase. In addition, elevated serum estrogen levels cause abnormal DNA methylation, which has been linked to both *in vivo* and *in vitro* breast cell carcinogenesis (Shield *et al.* 2016) [3].

Role of insulin growth factor and breast density: The proliferation of both breast cancer cells and healthy breast epithelial cells is impacted by insulin-like growth factor (IGF)-1, according to a significant body of experimental data. By raising ovarian estrogen levels and lowering sex hormone binding globulins, IGF-1 also raises the risk of breast cancer. A meta-analysis of 17 studies further supported the relationship between circulating levels of IGF-1 and the risk of developing breast cancer. IGF-1 levels in the blood have a complicated association with alcohol consumption. IGF-1 levels are elevated in individuals who consume moderate amounts of alcohol; however, IGF-1 levels are temporarily lowered after alcohol consumption and are decreased in individuals who consume large amounts of alcohol (due to alcohol-induced liver function damage). Thus, although only for moderate drinkers, alcohol may have an impact on the risk of breast cancer via raising IGF-1 serum levels and increasing breast cancer density (Shield *et al.* 2016) [3].

Role of ethanol metabolism: The first and most dangerous metabolite of ethanol is acetaldehyde, which is thought to be carcinogenic. Through a variety of processes, such as disruption of DNA replication, induction of DNA damage, and production of DNA adducts, acetaldehyde encourages the development of cancer. Aldehyde dehydrogenase (ALDH) enzymes oxidize acetaldehyde from ethanol, and alcohol dehydrogenase (ADH) enzymes convert acetaldehyde to the non-toxic compound acetate. Alcohol-related malignancies are more likely to develop in individuals who have ADH (alcohol dehydrogenase) alleles that encode highly active ADH enzymes or ALDH alleles that encode enzymes with abnormally low activity. People of East Asian heritage are particularly likely to have low activity ALDH enzymes. By preventing DNA methylation and interacting with retinoid metabolism, ethanol may also promote cancer (Cao *et al.* 2016) [4].

Other mechanisms: High levels of MMP-2 and MMP-9 expression in tumor tissue have been linked to worse outcomes and accelerated metastases in patients with breast cancer. A culture media made from fibroblasts exposed to ethanol greatly changes the invasive behavior of breast cancer cells and mammary epithelial cells. Ethanol dose-dependently increases MMP-2 synthesis by fibroblasts. Additionally, alcohol and acetaldehyde alter DNA methylation patterns by suppressing the production and activity of the methylation-related enzymes. Alcohol can have a negative impact on the metabolism of folate by

lowering hepatic storage, increasing renal excretion, and limiting intestinal absorption. Folate is necessary for DNA synthesis and methylation because it acts as a methyl donor in one-carbon metabolism. Several prospective studies revealed that the protective effect of high folate intake (generally 600 g/day) on breast cancer risk was primarily seen in women with high alcohol consumption. In contrast, the harmful effect of alcohol consumption on breast cancer risk was limited to women with low folate intake (Liu *et al.* 2015) [1].

Prevention

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) offers the following advice for reducing alcohol consumption: Keep track of your drinking, accurately count and measure your drinks, set goals for how many days a week you'll have drinks, pace yourself to have no more than one standard drink in an hour, avoid drinking on an empty stomach, fill your free time with healthy activities, hobbies, and relationships, or resume ones you've missed, avoid "triggers," and prepare to deal with urges by reminding yourself of your motivation. Know when to say "no" when being given a drink when you don't want one. Along with the aforementioned advice, persons who are dependent on alcohol should also consider the following: 1) inform family and friends; 2) establish new interests and social groups; 3) find fulfilling activities that don't include alcohol; and 4) ask for assistance from others. Many medical practitioners advise patients undergoing chemotherapy or biological therapy to abstain from drinking while undergoing treatment. However, current recommendations for cancer survivors from prominent organizations including the American Cancer Society, American Institute for Cancer Research, and American Society for Clinical Oncology recommend that women limit their alcohol use to no more than one drink per day (Cao *et al.* 2016) [4].

The role of resveratrol

Due to its chemo preventive effects on breast cancer cells, resveratrol, sometimes known as "the red wine chemical," has been recommended for both breast cancer prevention and therapy. In particular, it has been discovered that resveratrol inhibits the transcription of AP-1, which prevents procarcinogens from becoming carcinogens, and NF-kB, which has an anti-inflammatory impact. In addition, resveratrol has been shown to be capable of inducing apoptosis and cell cycle arrest, as well as having antioxidant and anti-angiogenesis characteristics (Shield *et al.* 2016) [3].

Risk-reducing Medications

Chemoprevention: In specialized clinics, anti-estrogen drugs may be prescribed to women who have a high or moderate personal risk for breast cancer. The use of these drugs is referred to as "chemoprevention" therapy. Tamoxifen use for 5 years in premenopausal women decreased breast cancer risk by 33%, and the reduction remained for at least 15 years after the anti-hormonal medicine was stopped. To check for medication-induced side effects, a patient may find a six to eight-week trial of tamoxifen more tolerable than a five-year treatment. Although it has been demonstrated that raloxifene and aromatase inhibitors can lower the incidence of breast cancer in high-risk post-menopausal women, these medications are not advised for use in premenopausal women (Daly *et al.* 2021) [8].

Screening: Early diagnosis is one of the most effective breast cancer prevention strategies. Chemotherapy and surgical removal of the tumors are both successful outcomes if the disease is identified at an early stage of metastasis and as primary tumors. Mammography is a screening technique that offers several important benefits and is used for breast diagnosis and routine screening. Magnetic Resonance Imaging (MRI) is a further technology that is frequently employed in the treatment of breast cancer. Which breast cancer examination technique is the most difficult? For diagnosing invasive ductal carcinoma, it is particularly useful. MRI is useful in the diagnosis of tiny tumors, auxillary nodal metastases, and residual tumors after neoadjuvant treatment, and hidden primary breast cancer (Das 2022) [9].

Surgery: Mastectomy and Breast-conserving surgery (BCS) are the two main types of surgical procedures that remove cancerous tissue. BCS, also known as a lumpectomy, quadrantectomy, partial/segmental mastectomy, or extensive local excision, enables the removal of breast malignant tissues in conjunction with oncoplasty procedures in plastic surgery. However, in the majority of situations, a mastectomy entails the immediate reconstruction of the breast following the entire removal of the breast. Although BCS appears to be more advantageous, patients who have BCS frequently demonstrate a subsequent need for a total mastectomy (Das 2022) [9].

Radiation therapy: It is a local treatment for breast cancer that is essential to the disease and is typically given after chemotherapy and/or surgery. Radiation therapy is administered to both ensure that the cancer cells are still eliminated and lower the likelihood of breast cancer recurrence. If the breast cancer is metastatic and unable to be removed, radiation therapy is an option. Fatigue, lymphoedema, skin darkening, and skin irritation are all common side effects of radiation therapy used on patients with breast cancer. However, radiation treatment dramatically reduced the likelihood of breast cancer returning (Das 2022) [9].

Conclusion

Alcohol may contribute to the development and progression of breast tumors by elevating sex hormone levels, promoting breast epithelial cells, generating the genotoxic metabolite acetaldehyde, and inducing oxidative stress. Healthcare professionals should talk to their patients about their drinking habits and assess the advantages and disadvantages of consuming low to moderate amounts of alcohol. In addition to the patient, breast cancer also affects the patient's family, friends, and community. The development of tools that accurately identify women, who are at high risk of breast cancer, preventive drugs with few side effects, effective education and communication of the risks and benefits of chemotherapies, and ways to combine different risk-reduction strategies are numerous issues that researchers need to consider. Additionally, because the disease affects a woman's life in numerous manners than one, including her mental state and social standing, family and social support can lessen the negative effects of the

illness. Breast cancer is a disease that may be prevented, and industrialized nations have access to enough medical resources to do so, such as annual mammograms or daily usage of chemo preventative medications. It is advisable to perform a screening, especially for acquired cancer susceptibility genes like BRCA1 or BRCA2, if a woman has a family history of breast cancer. Based on the screening results, the risk of breast cancer may then be evaluated, and personal prevention recommendations might be given. Future breast cancer preventive strategies may include individual genome sequencing as a standard practice. To reduce the incidence of breast cancer, environmental factors include ingesting exogenous estrogen, abusing alcohol, and eating an excessive amount of fat should be avoided. Women from both developed and developing countries may find that regular exercise is an easy and affordable strategy to avoid breast cancer. In conclusion, breast cancer can be prevented. Taking chemoprevention and lowering risk factors are the two main ways to avoid breast cancer. The public still has to be made more aware about breast cancer, though.

Future scope: In order to identify a subgroup of the most vulnerable women and provide therapy targets, it would be helpful to have a better understanding of the biological changes induced by alcohol that cause cancer in breast tissue. This would aid in the development of novel indicators that could be utilized in cancer prevention. It would be especially helpful to pinpoint the molecular mechanisms that link alcohol intake to breast cancer because this knowledge could help women make educated choices about how often and how much alcohol they should consume.

Conflict of Interest: There is no conflict of interest related to the study.

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