ORIGINAL RESEARCH PAPER

Volume-8 | Issue-6 | June-2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF ROLE OF ALCOHOL IN DEVELOPMENT OF BREAST CANCER IN WOMEN IN JHARKHAND

General Surgery

Dr. Mini Sinha* S.R., General Surgery, RIMS, Ranchi *Corresponding Author

Dr.Bikram Kumar S.R., General Surgery, RIMS, Ranchi

Dr. D. K. Sinha Professor; General Surgery, RIMS,Ranchi

ABSTRACT

INTRODUCTION:- Alcohol use appears to be more strongly associated with breast carcinoma specially lobular carcinoma and hormone receptor-positive tumors rather than other types of breast carcinoma.

MATERIAL AND MATHOD:- The study was carried out on 50 patients in Department of Surgery, Rajendra Institute of Medical Sciences, Ranchi from July 2010 to September 2011. The aims of this study regarding local consumption of alcohol in different forms to reinforce the facts related to alcohol consumption and increased risk of carcinoma breast.

DISCUSSION:- In my study out of 21 cases 2 cases having history of alcohol consumption since 5-10 yrs i.e. in 9.52% cases. Out of 21 cases 12 cases drank 5-6 alcoholic beverages per day and having 57.14% risk of getting breast carcinoma. In Jharkhand state most women taking Rice Beer have more risk of getting breast cancer i.e. 52.38% more risk. Out of 21 cases consuming alcohol 15 cases are postmenopausal i.e. 71.43% cases are postmenopausal having breast carcinoma.

CONCLUSION:- Women consuming alcohol since 5-30 years or more and 5-6 drinks per day had increased risk of breast cancer. Alcohol consumption increase the risk of breast cancer in postmenopausal women taking hormone replacement therapy (about 80%). Rice Beer (Handia) had greater risk of breast cancer than other beverages like Toddy and Wine (about 52.38 %) in Jharkhand State as most women of Jharkhand take Rice Beer (Handia).

KEYWORDS

Alcohol, Risk Factor, Mechanism, Benign Breast Disease, Breast Cancer

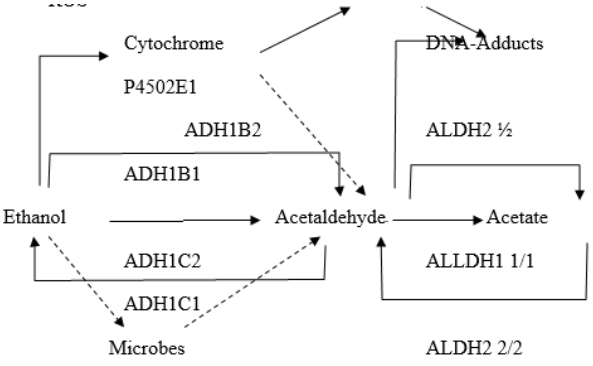
INTRODUCTION:-

Alcohol use appears to be more strongly associated with breast carcinoma specially lobular carcinoma and hormone receptor-positive tumors rather than other types of breast carcinoma.

Mechanism by which **alcohol** increases the risk of breast carcinoma:-

i) Alcohol's interaction and effect on estrogen secretion
ii) Effect on number of estrogen receptor
iii) The generation of acetaldehyde and hydroxyl free radicals
iv) Cell migration and metastasis
v) Interaction with hormone replacement therapy and folate metabolism.

Alcohol metabolism



Ethanol is oxidized to acetaldehyde through the actions of various alcohol dehydrogenase (ADH) enzymes (enzymes encoded by ADH1B and ADH1C genes), through microsomal enzyme cytochrome P4502E1 (CYP2E1) and by microbes living in the human gastrointestinal tract. The relative contributors of these pathways and the differences in activity between enzymes encoded by different ADH1B and ADH1C alleles. Acetaldehyde is oxidized to acetate primarily by aldehyde dehydrogenase 2 (ALDH2).

Cancer- inducing substances (carcinogens) generated during the various pathways of alcohol metabolism are acetaldehyde, highly reactive oxygen-containing compounds i.e. reactive oxygen compound (ROS) generated by CYP2E1 and adducts formed by the interactions of acetaldehyde or ROS with DNA.

ADH and estrogen levels

One of the risk factors for breast cancer is an increased blood level of female sex hormone i.e. estrogen, the most important of which is estradiol.

Alcohol consumption and alcohol metabolism by ADH appear to affect the levels of estrogen and estrogen receptors, which may contribute to alcohol-breast cancer association.

- The enzyme encoded by ADH1C not only metabolizes alcohol to acetaldehyde but also is involved in the metabolism of steroid hormones including estrogen **(McEvily et al 1988)**
- Alcohol enhances the expression of estrogen receptor in breast cell **(Fan et al 2000)**
- Both in women with normal menstrual cycle and in women taking oral contraceptive, blood concentrations of acetaldehyde after alcohol consumption were shown to be particularly high when estradiol levels reached their highest during the menstrual cycle.
- In postmenopausal women an increase of estrogen level following alcohol consumption appears to depend on whether they use hormone replacement therapy.
- Alcohol metabolism causes DNA damage that triggers breast cancer. When alcohol is metabolized in the human body, it is converted to acetaldehyde, a chemical that is structurally similar to formaldehyde, acetaldehyde can cause DNA damage, trigger chromosomal abnormalities in cell culture and act as carcinogen.

Acetaldehyde is itself oxidized predominantly by means of a highly efficient aldehyde dehydrogenase, localized in mitochondrial matrix. As a result both cellular and circulating concentrations of aldehyde are maintained in the low range despite elevated blood ethanol concentration.

The rate of both oxidation and acetaldehyde oxidation is determined by the rate of NADH (reduced from of nicotinamide adenine dinucleotide) oxidation through mitochondrial electron transport.

Excess of alcohol will result in inadequate electron transport activity. This results in an efficient removal of ethanol and acetaldehyde and highly reduced state of both cytosolic and mitochondrial NAD (nicotinamide adenine dinucleotide). This will also promote the overflow of electrons passing through the mitochondrial electron transport chain into formation of reactive oxygen species (superoxide)

Association between alcohol consumption and breast cancer

(1) Dose – dependent association

(a) Drinking larger quantities of alcohol leads to more cases of breast cancer.
(b) Alcohol intake of at least 30gms/day over a period of years increase the risk of breast cancer by 30-40% compared with non-drinkers.
(2) Genetic variations that reduce the alcohol – Metabolizing enzyme alcohol dehydrogenase are linked to an increased risk of breast cancer for premenopausal women who drink heavily.
(3) Alcohol use by women receiving Hormone Replacement Therapy may increase risk.
(4) Risk for women with estrogen-receptor positive tumors increased as alcohol consumption increased.
(5) Alcoholic drinks prevalent to local region/states e.g.-**Handia (Rice Beer)** in **Jharkhand** are taken regularly by womens. These states have high risk of carcinoma breast in women.

MATERIALAND METHODS:

The study was carried out on 50 patients in **Department of Surgery, Rajendra Institute of Medical Sciences, Ranchi** from July 2010 to September 2011.

The aim is to study regarding local consumption of alcohol in different forms to reinforce the facts related to alcohol consumption and increased risk of carcinoma breast.

OBSERVATION:-

Table-1-showing interval between the detection of the lump and reporting of the patient for medical opinion.

Duration of lump of month	No. of Cases	Percentage
Less then 6 months	12	24
7- 12 months	16	32
13-18 months	20	40
More then 18 months	02	04

Table-2- showing side of breast involved

Side involved	No. of cases	Percentage
Right	20	40
Left	28	56
Bilateral	02	04

Table-3-showing the site of origin of lump breast.

Quadrant involved	Upper Outer	Upper inner	Lower inner	Lower outer	Central	Diff. use
Number	28	10	03	05	02	02
Percentage	56	20	06	10	04	04

Table-4-showing clinical presenting features of patient.

Clinical features	Number	Percentage
Painless	43	86
Painful	06	12
Mobility	35	70
Fixity	15	30
Soft	02	04
Firm	30	60
Hard	15	30
Variegated	03	06
Ulcer	06	12
Paeu'd orange	07	14
Nipple discharge	03	06
Nipple retraction	10	20
Axillary lymph node	12	24
Supraclavicular lymph node	01	02
Both lymph node	05	10

Table-5-showing clinical diagnosis of breast lesion.

Type of lesion	No. of cases	Percentage
Carcinoma	21	42
Fibroadenosis	05	10
Fibroadenoma	17	34
Sebaceous cyst	01	02
Hematoma	01	02
Inconclusive	05	10

Table-6-showing USG finding of breast lump.

Breast lump	No. of cases	Percentage
Enlarged breast with normal ecotexture	02	04
Cystic	01	02
Solid benign	21	42
Intermediate	03	06
Malignant	23	46

Table-7- showing mammography finding of breast lump.

Breast lump	No. of cases	Percentage
Benign	22	44
Intermediate	03	06
Malignant	25	50

Table-8-showing cytological study of breast lump by FNAC.

Type of lesion	No. of cases	Percentage
Benign	20	40
Malignant	24	48
Suspicious	04	08
Unsatisfactory	02	04

Table-9-showing histopathological diagnosis of breast lump on biopsy.

Breast lump	No. of cases	Percentage
Carcinoma	31	62
Fibroadenoma	13	26
Fibroadenosis	04	08
Mastitis	01	02
Sebaceous cyst	01	02
	50	100

Table-10-showing comparative incidence of malignant and benign lump.

lump	No. of cases	Percentage
Malignant	31	62
Benign	19	38

Table-11-showing Age incidence of MALIGNANT breast lump (Out of 31 cases).

Age group in years	No. of cases	Percentage
21-30	03	9.67
31-40	06	19.35
41-50	07	22.58
51-60	13	41.94
61-70	02	06.46

Table-12-showing History of ALCOHAL consumption (Out of 31 cases).

History of Alcohol consumption	No. of cases	Percentage
Absent	10	32.26
Present	21	67.74

Table-13- showing DURATION of ALCOHAL consumption (Out of 21 cases).

Duration of Alcohol consumption in years	No. of cases	Percentage
0-5	01	4.76
6-10	02	9.52
11-15	02	9.52
16-20	05	23.81
21-30	11	52.39

Table-14- showing AMOUNT of ALCOHAL consumption (Out of 21 cases).

Amount of Alcohol consumption in per day	No. of cases	Percentage
1-2 drinks	03	14.29
3-4 drinks	06	28.57
5-6 drinks	12	57.14

Table-15-showing risk of breast cancer in POSTMENOPAUSAL and PREMENOPAUSAL women consuming ALCOHOL (Out of 21 cases).

Menopausal status	No. of cases	Percentage
Pre menopausal	06	28.57
Post menopausal	15	71.43

Table-16-showing risk of breast carcinoma in postmenopausal women taking alcohol and hormone replacement therapy (hrt) (out of 15 cases).

Pt. taking Alcohol	No. of cases	Percentage
With HRT	12	80
Without HRT	03	20

Table-17- showing risk of breast carcinoma in women taking different type of Alcoholic beverages (Out of 21 cases).

Type of alcoholic beverages	No. of cases	Percentage
Rice beer	11	52.38
Toddy	4	19.05
Wine	6	28.57

DISCUSSION:-

The results of most studies indicate that there is association between drinking alcoholic beverages and the incidence of breast cancer.

History of Alcohol consumption

All the patient of this series subjected to detail history of Alcohol consumption and tabulated in observation Table- 12 **(Siman Owski 2002).**

In my study out of 31 malignant cases 21 cases having history of alcohol consumption i.e. 67.74% cases. 10 cases having history of alcohol consumption (Table No.-12).

Duration of alcohol consumption

Women who consumed alcohol since long time having increased risk of development of breast carcinoma. **(Herrington et. al. 2001).**

In my study out of 21 cases 11 cases having history of alcohol consumption since 21-30 yrs i.e. about 52.39% cases. (Table No.-13).

Woman who consumed alcohol since 6-10 yrs having low risk of development of breast carcinoma.**(Boyd et. al 2001)**

In my study out of 21 cases 2 cases having history of alcohol consumption since 5-10 yrs i.e. in 9.52% cases. (Table No.- 13).

Amount of alcohol consumption

Women who drank 5-6 alcoholic beverages per day (or 50 grams of alcohol with about 13 grams of standard drink) had higher risk of getting breast cancer. **(D'. Avanzo et al 2000).**

In my study out of 21 cases 12 cases drank 5-6 alcoholic beverages per day and having 57.14% risk of getting breast carcinoma. (Table-14).

Women who drank moderate amount (3-4 drink) per day having moderate risk of getting breast cancer.**(Espina et al 2004).**

In my study out of 21 cases 06 cases drank 3-4 alcoholic beverages per day and having 28.57% risk of getting breast cancer. (Table-14)

Women who drank low amount (1-2 drink) per day having low risk of getting breast cancer. **(Cancer 2004).**

In my study out of 21 cases 03 cases drank 1-2 alcoholic beverages per day and having 14.29% risk of getting breast cancer. (Table- 14).

Breast cancer in postmenopausal women taking alcohol and hormone replacement therapy

Postmenopausal women taking alcoholic beverages having increases risk of getting breast carcinoma. **(Marian and Colleagues 1997).**

In my study out of 21 cases consuming alcohol 15 cases are postmenopausal i.e. 71.43% cases are postmenopausal having breast carcinoma. (Table-15)

Postmenopausal women taking alcohol and taking hormone replacement therapy having increased risk of getting breast carcinoma. **(Peter shields 2004)**

In my study out of 15 cases 12 cases are postmenopausal women taking alcohol and taking hormone replacement therapy i.e. about 80% more risk of getting breast carcinoma.

Type of Alcoholic beverages and breast carcinoma.

Women who drank rice beer having greater risk (18-25 percent) of development of breast carcinoma **(Shred et al 2004).**

In **Jharkhand** state most women taking **Rice Beer** have more risk of getting breast cancer i.e. 52.38% more risk.

CONCLUSION:-

1) Women consuming alcohol since 5-30 years or more had increased risk of breast cancer about 52.39% increased risk.
2) Women consuming 5-6 drinks per day had increased risk of breast cancer about 57.14%.
3) Alcohol consumption increase the risk of breast cancer in postmenopausal women taking hormone replacement therapy (about 80%).
4) Rice Beer (Handia) had greater risk of breast cancer than other beverages like Toddy and Wine (about 52.38 %) in Jharkhand State as most women of Jharkhand take Rice Beer (Handia).

In correlation to other studies done by Miliard (2001), Peter Shields (2004), Jasmine Q Lew (2001) and Shrea et. al. (2005) findings of my study is **similar** to their findings.

The finding of study of Smith-Warner et. al. 1998 i.e. moderate drinking (2-4 drinks/day) increase the risk of breast cancer is **dissimilar** to my study.

REFERENCES

1. Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. JAMA. 2001;286(17):2143–2151. [PubMed] [Google Scholar]
2. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA. 1998;279(7):535–540. [PubMed] [Google Scholar]
3. Seitz HK, Pelucchi C, Bagnardi V, La Vecchia C. Epidemiology and pathophysiology of alcohol and breast cancer: update 2012. Alcohol Alcohol. 2012;47(3):204–212. [PubMed] [Google Scholar]
4. Liu Y, Colditz GA, Rosner B, et al. Alcohol intake between menarche and first pregnancy: a prospective study of breast cancer risk. J. Natl Cancer Inst. 2013;105(20):1571–1578. [PMC free article] [PubMed] [Google Scholar]
5. Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. Ann. Oncol. 2013;24(2):301–308. [PubMed] [Google Scholar]
6. Centers for Disease Control and Prevention Alcohol use and binge drinking among women of childbearing age-United States, 2006–2010. MMWR. 2012;61(28):534–538. [PubMed] [Google Scholar]
7. Brooks PJ, Zakhari S. Moderate alcohol consumption and breast cancer in women: from epidemiology to mechanisms and interventions. Alcohol. Clin. Exp. Res. 2013;37(1):23–30. [PMC free article] [PubMed] [Google Scholar]
8. Suzuki R, Orsini N, Mignone L, Saji S, Wolk A. Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status – a meta-analysis of epidemiological studies. Int. J. Cancer. 2008;122(8):1832–1841. [PubMed] [Google Scholar]
9. Colditz GA, Frazier AL. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. Cancer Epidemiol. Biomarkers Prev. 1995;4(5):567–571. [PubMed] [Google Scholar]
10. Land CE, Tokunaga M, Koyama K, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. Radiat. Res. 2003;160(6):707–717. [PubMed] [Google Scholar]
11. Trichopoulos D, Adami HO, Ekbom A, Hsieh CC, Lagiou P. Early life events and conditions and breast cancer risk: from epidemiology to etiology. Int. J. Cancer. 2008;122(3):481–485. [PubMed] [Google Scholar]
12. Wu AH, Wan P, Hankin J, Tseng CC, Yu MC, Pike MC. Adolescent and adult soy intake and risk of breast cancer in Asian–Americans. Carcinogenesis. 2002;23(9):1491–1496. [PubMed] [Google Scholar]
13. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am. J. Epidemiol. 2000;152(10):950–964. [PubMed] [Google Scholar]
14. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. Nature. 1983;303(5920):767–770. [PubMed] [Google Scholar]
15. Rosner B, Colditz GA. Nurses' health study: log-incidence mathematical model of breast cancer incidence. J. Natl Cancer Inst. 1996;88(6):359–364. [PubMed] [Google Scholar]
16. Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. Am. J. Epidemiol. 1994;139(8):819–835. [PubMed] [Google Scholar]
17. Anderson LN, Cotterchio M, Boucher BA, Kreiger N. Phytoestrogen intake from foods, during adolescence and adulthood, and risk of breast cancer by estrogen and progesterone receptor tumor subgroup among Ontario women. Int. J. Cancer. 2013;132(7):1683–1692. [PubMed] [Google Scholar]
18. Lee SA, Shu XO, Li H, et al. Adolescent and adult soy food intake and breast cancer risk: results from the Shanghai Women's Health Study. Am. J. Clin. Nutr. 2009;89(6):1920–1926. [PMC free article][PubMed] [Google Scholar]
19. Maruti SS, Willett WC, Feskanich D, Rosner B, Colditz GA. A prospective study of age-specific physical activity and premenopausal breast cancer. J. Natl Cancer Inst. 2008;100(10):728–737.[PMC free article] [PubMed] [Google Scholar]
20. Russo IH, Russo J. Pregnancy-induced changes in breast cancer risk. J. Mammary Gland Biol. Neoplasia. 2011;16(3):221–233. [PubMed] [Google Scholar]
21. Meier-Abt F, Milani E, Roloff T, et al. Parity induces differentiation and reduces Wnt/Notch signaling ratio and proliferation potential of basal stem/progenitor cells isolated from mouse mammary epithelium. Breast Cancer Res. 2013;15(2):R36. [PMC free article] [PubMed] [Google Scholar]
22. Medina D. Pregnancy protection of breast cancer: new insights reveal unanswered questions. Breast Cancer Res. 2013;15(3):103. [PMC free article] [PubMed] [Google Scholar]
23. Musey VC, Collins DC, Musey PI, Martino-Saltzman D, Preedy JR. Long-term effect of a first pregnancy on the secretion of prolactin. N. Engl. J. Med. 1987;316(5):229–234. [PubMed] [Google Scholar]
24. Bernstein L, Pike MC, Ross RK, Judd HL, Brown JB, Henderson BE. Estrogen and sex hormone-binding globulin levels in nulliparous and parous women. J. Natl Cancer Inst. 1985;74(4):741–745.[PubMed] [Google Scholar]
25. Russo J, Russo IH. Toward a physiological approach to breast cancer prevention. Cancer Epidemiol. Biomarkers Prev. 1994;3(4):353–364. [PubMed] [Google Scholar]
26. Swanson CA, Coates RJ, Malone KE, et al. Alcohol consumption and breast cancer risk among women under age 45 years. Epidemiology. 1997;8(3):231–237. [PubMed] [Google Scholar]
27. Tjonneland A, Christensen J, Thomsen BL, et al. Lifetime alcohol consumption and

postmenopausal breast cancer rate in Denmark: a prospective cohort study. J. Nutr. 2004;134(1):173–178. [PubMed] [Google Scholar]
28. Horn-Ross PL, Canchola AJ, West DW, et al. Patterns of alcohol consumption and breast cancer risk in the California Teachers Study cohort. Cancer Epidemiol. Biomarkers Prev. 2004;13(3):405–411. [PubMed] [Google Scholar]
29. Holmberg L, Baron JA, Byers T, et al. Alcohol intake and breast cancer risk: effect of exposure from 15 years of age. Cancer Epidemiol. Biomarkers Prev. 1995;4(8):843–847. [PubMed] [Google Scholar]
30. Longnecker MP, Newcomb PA, Mittendorf R, et al. Risk of breast cancer in relation to lifetime alcohol consumption. J. Natl Cancer Inst. 1995;87(12):923–929. [PubMed] [Google Scholar]
31. Berstad P, Ma H, Bernstein L, Ursin G. Alcohol intake and breast cancer risk among young women. Breast Cancer Res. Treat. 2008;108(1):113–120. [PubMed] [Google Scholar]
32. van't Veer P, Kok FJ, Hermus RJ, Sturmans F. Alcohol dose, frequency and age at first exposure in relation to the risk of breast cancer. Int. J. Epidemiol. 1989;18(3):511–517. [PubMed] [Google Scholar]
33. Harvey EB, Schairer C, Brinton LA, Hoover RN, Fraumeni JF., Jr Alcohol consumption and breast cancer. J. Natl Cancer Inst. 1987;78(4):657–661. [PubMed] [Google Scholar]
34. Young TB. A case–control study of breast cancer and alcohol consumption habits. Cancer. 1989;64(2):552–558. [PubMed] [Google Scholar]
35. Masso-Welch PA, Tobias ME, Vasantha Kumar SC, et al. Folate exacerbates the effects of ethanol on peripubertal mouse mammary gland development. Alcohol. 2012;46(3):285–292. [PubMed] [Google Scholar]
36. Singletary K. Ethanol and experimental breast cancer: a review. Alcohol. Clin. Exp. Res. 1997;21(2):334–339. [PubMed] [Google Scholar]
37. Garofalo JM, Bowers DM, Browne RW, et al. Mouse mammary gland is refractory to the effects of ethanol after natural lactation. Comp. Med. 2013;63(1):38–47. [PMC free article] [PubMed] [Google Scholar]
38. Tice JA, O'Meara ES, Weaver DL, Vachon C, Ballard-Barbash R, Kerlikowske K. Benign breast disease, mammographic breast density, and the risk of breast cancer. J. Natl Cancer Inst. 2013;105(14):1043–1049. [PMC free article] [PubMed] [Google Scholar]
39. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N. Engl. J. Med. 1985;312(3):146–151. [PubMed] [Google Scholar]
40. Dupont WD, Parl FF, Hartmann WH, et al. Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer. 1993;71(4):1258–1265. [PubMed] [Google Scholar]
41. London SJ, Connolly JL, Schnitt SJ, Colditz GA. A prospective study of benign breast disease and the risk of breast cancer. JAMA. 1992;267(7):941–944. [PubMed] [Google Scholar]
42. Marshall LM, Hunter DJ, Connolly JL, et al. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol. Biomarkers Prev. 1997;6(5):297–301. [PubMed] [Google Scholar]
43. Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast: a long-term follow-up study. Cancer. 1985;55(11):2698–2708. [PubMed] [Google Scholar]
44. Rohan TE, Cook MG. Alcohol consumption and risk of benign proliferative epithelial disorders of the breast in women. Int. J. Cancer. 1989;43(4):631–636. [PubMed] [Google Scholar]
45. Friedenreich C, Bryant H, Alexander F, Hugh J, Danyluk J, Page D. Risk factors for benign proliferative breast disease. Int. J. Epidemiol. 2000;29(4):637–644. [PubMed] [Google Scholar]
46. Cui Y, Page DL, Chlebowski RT, et al. Alcohol and folate consumption and risk of benign proliferative epithelial disorders of the breast. Int. J. Cancer. 2007;121(6):1346–1351. [PubMed] [Google Scholar]
47. Liu Y, Tamimi RM, Berkey CS, et al. Intakes of alcohol and folate during adolescence and risk of proliferative benign breast disease. Pediatrics. 2012;129(5):e1192–e1198. [PMC free article] [PubMed] [Google Scholar]