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REVIEW

Epidemiology and Pathophysiology of Alcohol and Breast Cancer: Update 2012

Helmut K. Seitz[1,2,*], Claudio Pelucchi[3], Vincenzo Bagnardi[4,5] and Carlo La Vecchia[3,6,7]

[1]Centre of Alcohol Research, University of Heidelberg, Heidelberg, Germany, [2]Department of Medicine, Salem Medical Centre, Zeppelinstr. 11-33, Heidelberg 69121, Germany, [3]Mario Negri Institute for Pharmacological Research, Milan, Italy, [4]Department of Statistics, University of Milano-Bicocca, Milan, Italy, [5]Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy, [6]International Prevention Research Institute, Lyon, France and [7]Department of Occupational Health, University of Milano, Milan, Italy

*Corresponding author: Tel.: +49-6221-483200; Fax: +49-6221-483494; E-mail: helmut_karl.seitz@urz.uni-heidelberg.de

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Abstract — **Aims:** To update epidemiological data on alcohol and breast cancer, with special emphasis on light alcohol consumption, and to review mechanisms of alcohol mediated mammary carcinogenesis. **Methods:** For epidemiological data, in November 2011 we performed a literature search in various bibliographic databases, and we conducted a meta-analysis of data on light alcohol drinking. Relevant mechanistic studies were also reviewed to November 2011. **Results:** A significant increase of the order of 4% in the risk of breast cancer is already present at intakes of up to one alcoholic drink/day. Heavy alcohol consumption, defined as three or more drinks/day, is associated with an increased risk by 40–50%. This translates into up to 5% of breast cancers attributable to alcohol in northern Europe and North America for a total of approximately 50 000 alcohol-attributable cases of breast cancer worldwide. Up to 1–2% of breast cancers in Europe and North America are attributable to light drinking alone, given its larger prevalence in most female populations when compared with heavy drinking. Alcohol increases estrogen levels, and estrogens may exert its carcinogenic effect on breast tissue either via the ER or directly. Other mechanisms may include acetaldehyde, oxidative stress, epigenetic changes due to a disturbed methyl transfer and decreased retinoic acid concentrations associated with an altered cell cycle. **Conclusions:** Women should not exceed one drink/day, and women at elevated risk for breast cancer should avoid alcohol or consume alcohol occasionally only.

GENERAL INTRODUCTION

Alcohol consumption is a risk factor for cancer of various organs including the upper alimentary tract, the liver, the colorectum and the female breast (Seitz and Stickel, 2007). Among these organs, ethanol-mediated mammary carcinogenesis seems different since even small doses of ethanol stimulate breast cancer development. This is of considerable concern since in Europe and in the USA breast cancer is the most common cancer in women and alcohol use is widespread. In this review, up to date epidemiological data on alcohol and breast cancer have been analyzed with special emphasis on light alcohol consumption. In addition, possible mechanisms of ethanol-mediated mammary carcinogenesis have been briefly discussed. For more detailed information, it is referred to various overview articles (Wright *et al.*, 1999; Mill *et al.*, 2009; Fernandez, 2011).

EPIDEMIOLOGY OF ALCOHOL AND BREAST CANCER

Introduction

An association between alcohol and breast cancer was first suggested in the early 1980s by case–control studies. A network of case–control studies from several areas of North America (Rosenberg *et al.*, 1982) reported a relative risk (RR) of 1.9 (95% confidence interval, CI, 1.5–2.4) for ever vs. never-drinkers. A case–control study from Italy, where alcohol consumption in women was frequent and particularly high at that time (Talamini *et al.*, 1984; Bosetti *et al.*, 2007), gave a corresponding RR of 2.5 (95% CI, 1.7–3.7).

More than 100 epidemiological studies on alcohol consumption and female breast cancer were published afterwards, and a positive association is now established. Two recent International Agency for Research on Cancer (IARC) Monographs considered the effect of alcohol drinking in cancer aetiology, and concluded that female breast cancer is causally related to alcohol consumption (Secretan *et al.*, 2009; IARC, 2010). Several aspects of alcohol consumption on breast cancer risk are, however, still under discussion. Among these are the effects of low amount of drinking (i.e. up to one drink/day) and the risk of breast cancer defined by estrogen receptor (ER) and progesterone receptor (PR) status.

In this section, we review the epidemiological evidence on alcohol drinking—with particular focus on different levels of consumption—and the risk of breast cancer. We also present a meta-analysis of data on light alcohol drinking.

Light alcohol drinking

It is particularly important to quantify the relation between light alcohol drinking and breast cancer risk. In fact, it is still unclear whether there is any threshold in intake below which no effect of alcohol on breast cancer is evident.

We performed a literature search in MEDLINE, ISI Web of Science (Science Citation Index Expanded) and EMBASE for epidemiological studies published prior to November 2011. We also reviewed references cited by the relevant retrieved articles. Articles were included in the meta-analysis only if they satisfied the following criteria: (a) case–control or cohort studies published as original articles; (b) studies that reported findings expressed as odds ratio, RR or hazard ratio (or reporting sufficient data to compute them) for light drinkers (≤12.5 g/day ethanol; ≤1 drink/day) vs. non-drinkers; (c) studies that reported standard errors or CIs of the risk estimates, or provided sufficient data to calculate them. We thus computed a pooled RR of breast cancer for light drinkers vs. non-drinkers, using random-effects models (DerSimonian and Laird, 1986). Statistical heterogeneity among studies was evaluated using I^2, which is the

proportion of total variation contributed by between-study variance (Higgins and Thompson, 2002). Subgroup analyses and meta-regression models were carried out to investigate potential sources of between-study heterogeneity. We used a χ^2 statistics to test for differences of summary estimates among subgroups (Greenland, 1987).

A total of 3431 papers were retrieved from the literature search. Of these, 113 papers reporting breast cancer risk estimates for light drinkers were included in the meta-analysis. The complete reference list is reported in Appendix.

The analysis included 44,552 cases in the reference category of non-drinkers (40,899 incident cases and 3653 deaths) and 77,539 cases in the light drinkers' category (76,303 incident cases and 1236 deaths). These numbers are slightly underestimated, since for six studies the number of exposed and/or non-exposed cases was not reported. Case–control was the most common study design (64% of studies); 51% of the included studies were from North America, 38% from Europe, 6% from Asia and 10% from other regions or from more than one region; 36% of the reported estimates were adjusted for the main risk factors (age, family history, parity, menopausal status, oral contraceptive/hormonal replacement therapy use), while 16% of the estimates included occasional drinkers in the reference category.

Figure 1 shows the RR of breast cancer in light drinkers vs. non-drinkers in each of the 113 included studies. We found substantial heterogeneity among single study estimates ($I^2 = 64\%$). The random-effect summary RR was 1.04 (95% CI, 1.02–1.07). We did not find evidence of heterogeneity in pooled estimates by design ($P = 0.93$) and area in which the study was carried out ($P = 0.71$). Results did not appreciably change from those of the overall analysis when considering only estimates adjusted for the main risk factors (pooled RR = 1.03, 95% CI, 1.00–1.07), as well as including only estimates not considering occasional drinkers in the reference category of non-drinkers (pooled RR = 1.04, 95% CI, 1.01–1.07).

Therefore, this meta-analysis reported a modest but significant association between light drinking and breast cancer. The estimate was based on the results of more than one hundred studies. Women drink less than men (Gronbaek *et al.,* 1994) and therefore low and moderate intakes are usually investigated more frequently and more in detail in women than in men, though the bias due to under reporting of even moderate alcohol consumption may be more relevant for women than for men (Allen *et al.,* 2009). Since several populations show a high prevalence of light drinkers among women, even the small increase in risk we reported—in the order of 5%—represents a major public health issue in terms of breast cancers attributable to alcohol consumption.

Heavy alcohol drinking

High levels (i.e. ≥3 drinks/day) of alcohol consumption were associated with increased risk of breast cancer in the largest available studies (Hamajima *et al.* 2002; Allen *et al.,* 2009; Chen *et al.,* 2011). In the collaborative reanalysis of 53 epidemiological studies on breast cancer (Hamajima *et al.,* 2002), the RRs were 1.32 (95% CI, 1.19–1.45) for consumption of 35–44 g/day and 1.46 (95% CI, 1.33–1.61) for consumption of ≥45 g/day of alcohol, when compared with non-drinkers. The association was similar in never- and ever-smokers. In the Million Women Study (Allen *et al.,* 2009), the RR was 1.29 (95% CI, 1.23–1.35) for the highest level of consumption considered, i.e. ≥21 g/day, after adjustment for smoking and several other covariates. A 51% (95% CI, 35–70%) increase in risk emerged for drinkers of ≥30 g/day vs. non-drinkers in the Nurses' Health Study (Chen *et al.,* 2011). Further, a case–control study of over 2500 women with breast cancer conducted in Italy, in a population characterized by relatively high alcohol drinking, reported an RR of 1.41 (95% CI, 1.17–1.71) for consumption >27 g/day when compared with abstainers (Ferraroni *et al.* 1998). Therefore, these results consistently indicate a 40–50% elevated risk of breast cancer in women consuming three or more alcohol drinks/day.

Dose–risk relation

With reference to the dose–risk relation, the collaborative reanalysis on alcohol and breast cancer (Hamajima *et al.,* 2002) found that the RR of breast cancer increased by 7.1% (95% CI, 5.5–8.7%) for each additional 10 g/day of alcohol intake. In the Million Women Study (Allen *et al.,* 2009), the corresponding increase in alcohol consumption was associated to a 12% (95% CI, 9–14%) increased risk of breast cancer. A meta-analysis based on 49 studies and over 44,000 cases gave a dose–risk function which approached a RR of 1.5 at 40 g/day, and further increased for highest levels of intake (Fig. 2) (Bagnardi *et al.,* 2001). A subsequent meta-analysis of about 100 epidemiological studies provided results according to the degree of control for confounding and the overall quality of the studies identified (Key *et al.,* 2006). The increase in risk for additional 10 g/day of alcohol varied between 10 and 13%, according to the inclusion criteria used. Further, the trend in risk was highly significant ($P < 0.001$). There is, therefore, consistent evidence for a positive dose–risk relation between alcohol drinking and breast cancer.

Breast cancer defined by estrogen and PR status

Since alcohol consumption might affect the risk of breast cancer through hormone-related mechanisms [such as increased estrogen and androgen levels (Sarkar *et al.,* 2001; Singletary and Gapstur 2001) or increased levels of plasma insulin-like growth factor produced by the liver following alcohol drinking (Yu and Berkel, 1999)], several studies examined the association with breast cancer defined by ER and PR status (Deandrea *et al.,* 2008; Suzuki *et al.,* 2008; Lew *et al.,* 2009; Chen *et al.,* 2011). A meta-analysis summarized information on this issue, including 20 epidemiological studies (i.e. 4 cohort and 16 case–control studies) published up to 2007 (Suzuki *et al.,* 2008). The meta-analysis reported an increased risk of 27% (95% CI, 17–38%) of all ER+ and of 14% (95% CI, 3–26%) of all ER-breast cancers for the highest vs. lowest level of alcohol drinking.

When the data were analyzed according to combined ER and PR status, the corresponding summary RRs were 1.22 for ER + /PR+ (95% CI, 1.11–1.34, based on 15 studies and over 11,000 cases of breast cancer), 1.28 for ER + / PR−(95% CI, 1.07–1.53, 11 studies, ~1900 cases), 1.31 for ER−/PR + (95% CI, 0.99–1.74, 8 studies, 580 cases) and 1.10 for ER−/PR− (95% CI, 0.98–1.24, 15 studies, ~4000 cases).

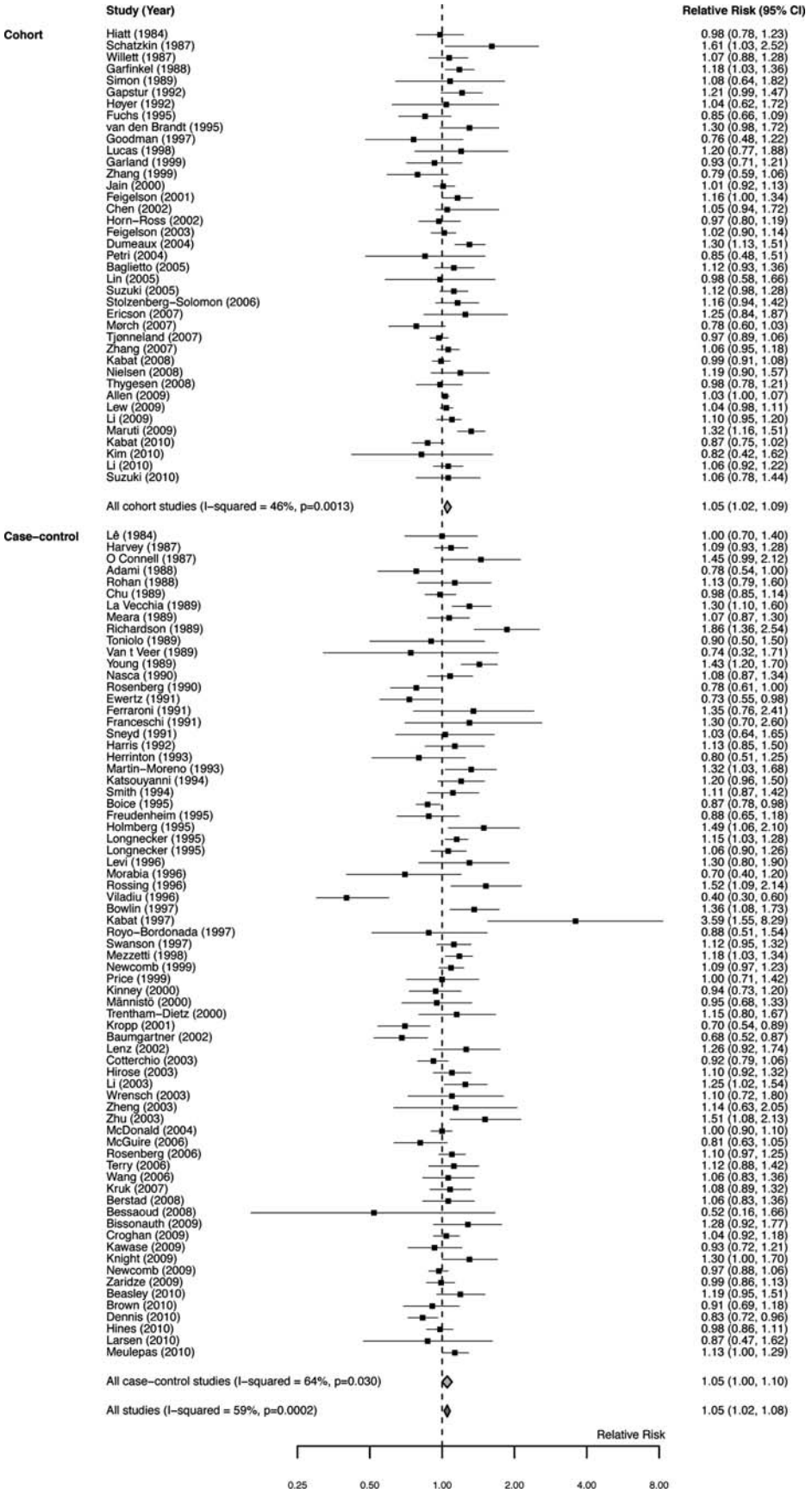

Fig. 1. RRs of breast cancer for light drinkers vs. non-drinkers. Squares indicate study-specific RRs. Horizontal lines indicate the 95% CIs. Diamond indicates pooled RR with its corresponding 95% CI.

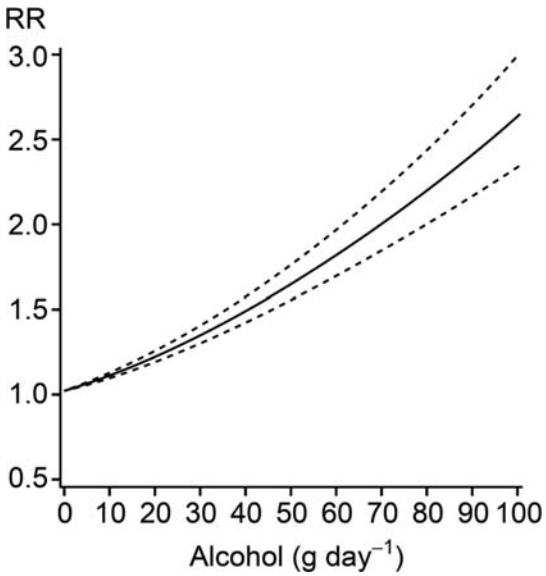

Fig. 2. Dose-risk function between alcohol consumption and breast cancer (extracted from Bagnardi *et al*., 2001).

Subsequent investigations further supported a stronger association between heavy alcohol consumption and ER + (and particularly ER + /PR+) breast cancers (Deandrea *et al.,* 2008; Lew *et al.,* 2009; Chen *et al.,* 2011).

POSSIBLE MECHANISMS OF ETHANOL-MEDIATED BREAST CANCER DEVELOPMENT

The mechanisms by which alcohol stimulates breast carcinogenesis are still not understood. Major pathophysiologic research on the carcinogenic effect of chronic alcohol consumption has focused on the upper alimentary tract, the liver and the colorectum (Baan *et al.,* 2007; Seitz and Stickel, 2007; IARC, 2010). Studies investigating mechanisms of ethanol-mediated breast cancer are rare and thus information is limited. Since a carcinogenic effect of estrogens on breast tissue has been observed, and since alcohol ingestion results in an elevation of serum estrogen concentrations, it is speculated that the carcinogenic effect of ethanol is mediated, at least in part, by estrogens (Fernandez, 2011). In addition, some research has concentrated on acetaldehyde (AA), the first and most toxic metabolite of ethanol oxidation which is by itself carcinogenic (Secretan *et al.,* 2009; Seitz and Stickel, 2010) and on oxidative stress (Seitz and Stickel, 2006). The ethanol effect on epigenetic modifications (Stickel *et al.,* 2006) and on interaction with retinoids (Wang and Seitz, 2004) has not been well studied in the breast when compared with other tissues. Alcohol-related carcinogenesis may also interact with other factors such as smoking, diets, comorbidities and depends on genetic susceptibility.

Animal studies

Only one study demonstrated that ethanol by itself (without the additional administration of a carcinogen) resulted in breast cancer. When 10 and 15% ethanol in the drinking water was given to female ICR mice for 25 months, 45% of the animals developed papillary and medullary adenocarcinomas of the breast ($P = 0.0012$), while no tumours were found in the control group (Watabiki *et al.,* 2000). In addition, a number of animal studies have been performed with alcohol as a modifier of chemically induced mammary carcinogenesis by using either methylnitrosourea (MNU) or dimethylbenzanthracene (DMBA). When MNU (30 mg/kg) or DMBA (5 mg/rat) was used to induce mammary tumours in Sprague Dawley (SD) rats, ethanol as 10–30% of calories in the daily diet significantly increased the incidence of adenocarcinomas (Singletary *et al.,* 1991, 1995), while with higher doses of DMBA (39 mg/kg) no effect on mammary tumourigenesis was seen (Singletary *et al*., 1991). In addition, other studies with 10 and 15 mg of DMBA and ethanol in the drinking water showed either an increased number of mammary tumours per rat ($P < 0.006$) (Rogers and Conner, 1990) or an increased tumour incidence ($P < 0.001$) (Hilakivi-Clarke *et al.,* 2004) Furthermore, *in utero* exposure to ethanol-increased mammary tumourigenesis induced with DMBA in rats (McDermott *et al.,* 1992). Recently, foetal alcohol exposure (6.7% ethanol, equivalent to 3–5 drinks in 2 h for a women) in SD rats from Day 11–21 of gestation decreased mammary tumour latency in adulthood induced by NMU (Polanco *et al.,* 2010).

Another study investigated the interaction of estrogens and ethanol in ovariectomized mice on mammary tumours. While estrogens alone inhibited tumour growth in this model, the addition of ethanol increased insulin sensitivity and increased tumour growth in these obese mice (Hong *et al.,* 2010).

The role of estrogens in ethanol-mediated breast cancer

Long-term exposure to estrogens increases the risk of developing breast cancer in women (Colditz, 1998). In rats, the continuous administration of supra-physiological doses of estrogens resulted in mammary adenocarcinomas, while low doses of estrogens administered over a long-time period lead to fibroadenomas (Russo and Russo, 1996).

The mechanisms by which estrogens induce breast cancer are still not completely clear, although it is well accepted that the binding of estrogens to its nuclear receptor, ER alpha (ERα), initiate a complex intracellular signal sequence, finally stimulating cell proliferation (Suga *et al.,* 2007).

Alcohol-increased plasma estrogen levels had been significantly demonstrated in controlled feeding studies, with human female volunteers (Reichman *et al.,* 1993; Ginsburg *et al.,* 1996; Purohit, 1998; Sarkola *et al.,* 1999, 2000, 2001; Coutelle *et al.,* 2004; Mahabir *et al.,* 2004, Sierksma *et al.,* 2004; Seitz and Maurer, 2007). In postmenopausal women with hormone replacement therapy, 15 or 30 g of ethanol daily consumed over 8 weeks resulted in significantly elevated serum concentrations of oestrone sulphate and dehydroepiandrosterone sulphate (Dorgan *et al.,* 2001). In premenopausal women, not only an acute high dose of ethanol (0.7 g/kg b.wt.) (Mendelson *et al.,* 1988), but also a small dose (0.225 g/kg b.wt.) equivalent to one drink (10–12 g) led to significantly elevated plasma oestradiol levels. When 0.7 g ethanol/kg b.wt. was given, the observed effect was most pronounced during the ovulatory phase of the menstrual cycle and in women using oral contraceptives. With the low dose of ethanol, the elevation has been observed in all phases of the menstrual cycle, but seems to be especially

relevant at mid-cycle where oestradiol concentrations are already high, being further stimulated by ethanol by ~27–38% (Coutelle *et al.,* 2004). There is some evidence that alcohol consumption during adolescence and early adulthood may stimulate breast carcinogenesis more than drinking later in life (Longnecker *et al.,* 1995).

In addition, alcohol at a concentration of 0.06% stimulates the expression of ERα and the oestradiol biosynthesis enzyme aromatase in human breast cancer cell lines (Gavaler and Van Thiel, 1992; Singletary and Gapstur, 2001; Etique *et al.,* 2004). Alcohol stimulates ER signalling in human breast cancer cells (Fan *et al.,* 2000). Alcohol-mediated ER-dependent gene expression may result in cell hyperproliferation in ER-positive Michigan Cancer Foundation-7 (MCF-7) human breast cancer cells (Ginsburg *et al.,* 1996). It has also been reported that crosstalk between adenosine receptor (A2A isoform) and ERα mediates ethanol action in MCF-7 breast cancer cells, which may open new therapy strategies in oestrogen-dependent breast cancer (Etique *et al.,* 2009).

The fact that several studies support the hypothesis that alcohol is more strongly related to ER positive than to ER negative breast tumours underlines the pathogenic role of estrogens in alcohol-mediated breast cancer.

Estrogens may also act directly as tumour initiators. They may be genotoxic both *in vitro* and *in vivo* and they may result in DNA damage including single-strand breaks and DNA adducts (Chakravarti *et al.,* 2001; Liu and Lin, 2004). Catechol estrogen 3,4-quinones (an estrogen metabolite) generates DNA mutations initiating breast cancer (Cavalieri *et al.,* 2004; Yager and Davidson, 2006). The fact that 'ERα knockout mice expressing the Wnt-1 oncogene (ERKO/Wnt-1) develop breast cancer when they receive estrogens' support the direct genotoxic effect of estrogens without ERα-mediated pathways (Bocchinfuso *et al.,* 1999). Furthermore, the administration of estrogens to ovariectomized mice results in more tumours in a shorter period of time when compared with control animals even when antiestrogens are given (Fernandez, 2011). Estrogen treatment of human breast epithelial cells induced gene expression alterations, epigenetic modifications and finally phenotypical changes indicating neoplastic transformation (Fernandez *et al.,* 2005, 2006, 2010; Russo *et al.,* 2006; Huang *et al.,* 2007; Fernandez and Russo, 2010). Since these cells are ER negative, direct genotoxic effects of estrogens must be responsible for the changes observed.

Several mechanisms by which ethanol affects the levels of sex hormones in women have been suggested. These include an ethanol-mediated increase in the hepatic redox state resulting in a decrease of steroid metabolism (Sarkola *et al.,* 1999, 2001). Another explanation for the increased estrogen concentrations after alcohol is the increased aromatase activity following chronic ethanol consumption, which leads to an enhanced conversion of testosterone to oestrogens with reduced testosterone and increased oestrogen concentrations (Gavaler and van Thiel, 1992). Alcohol also inhibits the activity of sulfotransferase and 2-hydroxylase, two enzymes important in estrogen degradation (Eagon, 2010). Alcohol may also decrease melatonin secretion which inhibits estrogen production (Stevens *et al.,* 2000). Furthermore, alcohol may interact with the production of luteinizing hormone from the pituitary gland, which favours estradiol release from the ovaries (Rettori and McCann, 1997). An important study in which rats were exposed to ethanol *in utero* showed an increased number of terminal end buds, which are targets for malignant transformation, suggesting that alcohol when administered during foetal life may modify signals controlling mammary gland development (Hilakivi-Clarke *et al.,* 2004).

Increased estrogen concentrations following ethanol ingestion may not only increase breast cancer risk, it may also explain at least in part the increased susceptibility of the female liver towards alcohol in the pathogenesis of alcoholic liver disease since estrogens may result in enhanced hepatic mitochondrial damage resulting in enhanced fat deposition, apoptosis and the generation of reactive oxygen species (ROS) (Eagon, 2010).

AA, a possible carcinogen for the breast

Alcohol is metabolized via alcoholdehydrogenase (ADH) to AA and further via acetaldehydedehydrogenase (ALDH) to acetate (Fig. 3). AA is toxic, mutagenic and carcinogenic in animal experiments. It binds rapidly to proteins and DNA, forming stable carcinogenic adducts. AA also decreases the anti-oxidative defence system and modifies indirectly epigenetic histone and DNA methylation by decreasing the availability of *S*-adenosinemethionine, the major methyl donator (for review, Seitz and Stickel, 2007). AA has therefore been classified as a carcinogen by the IARC (Secretan *et al.,* 2009). Thus, an increased burden of AA by either enhanced generation or slow degradation may stimulate carcinogenesis. Indeed, this has been shown for other ethanol-mediated cancer sites (Seitz and Stickel, 2007). Approximately 40% of Japanese have a heterozygote mutation at the *ALDH2* gene with a striking reduction of the ALDH2 enzyme activity resulting in a significant elevation AA level in blood and saliva (Vakevainen *et al.,* 2000). Since this increase in AA is associated with side effects such as flushing, tachycardia, nausea, vomiting and sweating, alcohol consumption is reduced below three drinks in heterozygots or close to zero in homozygots. Only a few Japanese men still consume alcohol even when side effects occur. Owing to AA accumulation, these individuals have an increased risk for upper aerodigestive tract cancer (oropharynx, larynx and oesophagus) and for colorectal cancer (Yokoyama *et al.,* 1998). AA may act as a carcinogen only when its concentration exerts mutagenic levels, e.g. only when sufficient alcohol is consumed to reach that level. Owing to the fact that Japanese women drink only small amounts of alcohol, and that Japanese women who are *ALDH2*-deficient tend not drink alcohol (due to the side effects), data for breast cancer in *ALDH2* deficient women who consume sufficient alcohol are not available, and no data are available on AA levels in the breast.

In addition to a decreased metabolism of AA by *ALDH* deficiency, an increased production also favours its accumulation. ADH1C and ADH1B reveal polymorphism. The ADH1B*2 allele codes for an enzyme 40 times more active compared with that encoded by the ADH1B*1 allele. Thus, ADH1B*2 homozygotes produce high AA concentrations, which are associated with severe side effects (flushing syndrome) when these individuals consume ethanol. As a result, these individuals (almost exclusively Asians) do not drink alcohol at all and are protected against alcoholism (Edenberg, 2007). On the other hand, the ADH1C*1 allele

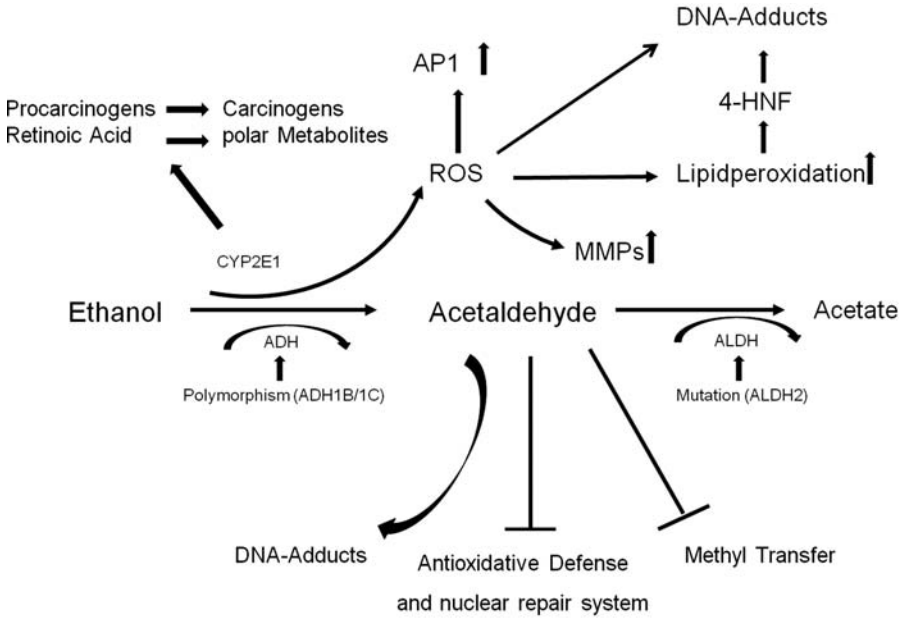

Fig. 3. Ethanol metabolism and its possible role in breast carcinogenesis. Ethanol is metabolized to AA by ADH and further to acetate by ALDH. ADH1B and ADH1C are polymorphic and may generate various amounts of AA. In addition, 50% of Asians have a mutation in the *ALDH2* gene, resulting in low ALDH activity with accumulation of AA when they drink alcohol. Either increased generation or decreased degradation of AA may result in its accumulation. AA reacts with DNA, forming DNA adducts; inhibits the antioxidative defence—and the nuclear repair system and also inhibits DNA methylation. Ethanol is additionally metabolized via CYP2E1 to AA. During this process ROS are formed. ROS binds either directly to DNA or via lipidperoxidation products such as 4-hydroxynonenal (4-HNE), increases the expression of the AP-1 gene (cellular hyperproliferation) and stimulates metalloproteinases (increase invasiveness and metastasis). CYP2E1 also converts various procarcinogens, including those present in cigarette smoke to their ultimative carcinogens and degrades retinoic acid to polar metabolites, resulting in a loss of retinoic acid associated with increased cell dedifferentiation and cellular hyperproliferation.

codes for an ADH enzyme 2.5-fold more active compared with the enzyme encoded by the ADH1C*2 allele. Individuals homozygote for ADH1C*1 seem to have also an increased risk for upper gastrointestinal tract cancer, for the liver and for the colorectum (Visapaa *et al.,* 2004; Homann *et al.,* 2006, 2009). With respect to the breast, contradictory results have been reported. Some studies report an increased breast cancer risk in ADH1C*1 homozygous individuals who consume alcohol chronically (Freudenheim *et al.,* 1999; Coutelle *et al.,* 2004) while others do not (Hines *et al.,* 2000; Breast Cancer Association Consortium, 2006; Terry *et al.,* 2006; Visvanathan *et al.,* 2007). Again, it may be the amount of alcohol leading to higher AA concentrations that determines the risk for breast cancer in alcohol-consuming women. Indeed, in the two positive studies, regular alcohol consumption was found to be higher when compared with the other studies. A recent meta-analysis came to the conclusion that there is not sufficient evidence that women who are ADH1C*1 homozygote have an increased breast cancer risk when they consume alcohol (Ding *et al.,* 2012)

Experimental work has shown that AA accumulates in mammary tissue following a single dose of oral ethanol (Castro *et al.,* 2008). It was therefore hypothesized that AA can be produced from ethanol in mammary tissue but its further detoxification to acetate is lacking (Fanelli *et al.,* 2010).

Ethanol, oxidative stress and breast cancer

Xanthine oxidoreductase and aldehyde oxidase are present in breast tissue (Wright *et al.,* 1999). Thus, AA metabolism may generate ROS, including the superoxide anion free radical, the neutral hydroxide free radical and hydrogen peroxide. It has also been reported that microsomal ethanol oxidation occurs in mammary tissue which could lead to the generation of ROS (Fanelli *et al.,* 2010).

ROS can lead to DNA mutation, base deletion, single- and double-strand breaks. ROS also results in the activation of the AP-1 gene (c-jun and c-fos) with consecutive changes in cell cycle behaviour (Wang and Seitz, 2004). Furthermore, ROS may lead to lipidperoxidation, resulting in the generation of lipidperoxidation products such as 4-hydoxynonenal, which may bind to adenosine or cytosine bases, forming highly carcinogenic exocyclic etheno DNA adducts (Sodum and Chung, 1988). This has been shown for the liver (Wang *et al.,* 2009) and for the oesophagus (Millonig *et al.,* 2011). ROS can also activate metalloproteases and can lead to an increased expression and secretion of metalloprotease 2 and 9 (Etique *et al.,* 2006; Ke *et al.,* 2006; Luo, 2006), resulting in enhanced invasiveness and metastasis.

Other mechanisms

Alcohol results in the activation of various intracellular signalling pathways. For example, alcohol leads to an increased expression of the c-fos transcription factor and results in an increased phosphorylation of the c-jun-terminal protein kinase (JNK), the p38 mitogen-activated protein kinase and the phosphatridylinositol 3-kinase (PI3K) (Ma *et al.,* 2003; Ke *et al.,* 2006). Whether JNK activation is due to an increase in oxidative stress, a decrease in retinoic acid or both still remains to be determined.

Ethanol also stimulates epidermal growth factor receptor (EGFR) signalling via cyclic adenosine monophosphate (c-AMP)-dependent stimulation of amphiregulin transcription (Mill *et al.,* 2009). EGFR signalling modulates ER-dependent signalling via the PI3K/Akt pathway and the IKK phosphorylation of ER (Biswas and Iglehart, 2006). EGFR signalling may also be responsible for the decrease in E-cadherin expression noted after ethanol ingestion (Meng *et al.,* 2000). E-cadherin is a tumour suppressor (Jeanes *et al.,* 2008).

The effect of ethanol on the invasion of breast cancer cells correlated significantly with the expression levels of ErbB2, a receptor tyrosine kinase and the ethanol-mediated overexpression of ErbB2 is associated with an enhanced adhesion of breast cancer cells to fibronectin, an extracellular matrix protein mediated by the focal adhesion kinase-1 pathway (Ma *et al.,* 2003; Ke *et al.,* 2006; Xu *et al.,* 2010). Such an adhesion is an important initial step for cancer cell invasion. Furthermore, epithelial-mesenchymal transition (EMT) plays an important role in cancer progression and metastasis and alcohol stimulates EMT via an EGFR-Snail mediated pathway (Forsyth *et al.,* 2010). Alcohol also stimulates the expression and secretion of metalloproteases (possibly via ROS), leading to the degradation of extracellular matrix resulting in an enhanced tumour cell invasiveness and metastasis (Duffy *et al.,* 2000; Meng *et al.,* 2000; Etique *et al.,* 2006; Luo, 2006). All these mechanisms may explain, at least in part, that ethanol enhances metastasis of breast cancer.

Finally, ethanol may affect epigenetics by changing methylation of DNA and/or histones. This has been shown in other tissues such as the liver and is due to a decrease in the major methyldonor *S*-adenosylmethionine. Chronic ethanol ingestion is associated with folate deficiency, which is important in the generation of methionine, and AA bind and inactivates various enzymes in the generation of *S*-adenosylmethionine (Stickel *et al.,* 2006). DNA methyltransferase is also inhibited by AA. However, these pathomechanisms have been identified for the liver, but data for the breast are not available.

SUMMARY AND CONCLUSIONS

Alcohol consumption is causally related with breast cancer. Increasing evidence indicates a stronger association with ER+neoplasms, though the risk is elevated for ER breast cancers, too. A small but significant increase of the order of 4% in the risk of breast cancer is already present at intakes of up to one alcoholic drink/day. Heavy alcohol consumption, defined as three or more drinks/day, is associated with an increased risk by 40–50%. This translates into up to 5% of breast cancers attributable to alcohol in northern Europe and North America, and up to 10% in countries such as Italy and France, where alcohol drinking was widespread (Ferraroni *et al.,* 1998; Mezzetti *et al.,* 1998), for a total of ~50,000 alcohol-attributable cases of breast cancer worldwide (Boffetta *et al.,* 2006). Up to 1–2% of breast cancers in Europe and North America may be due to light drinking alone, given its larger prevalence in most female populations when compared with heavy drinking.

Mechanisms of ethanol-mediated breast cancer are complex and still not well understood. Since alcohol increases estrogens, estrogen may exert its carcinogenic effect on breast tissue either via the ER or directly.

Other mechanisms for ethanol-mediated breast cancer are still unclear, but may include:

(1) EGFR signalling via c-AMP,
(2) the toxic and genotoxic action of AA,
(3) ROS resulting in oxidative stress and DNA damage,
(4) epigenetic alterations resulting in DNA and/or histone hypomethylation due to a reduced methyl transfer and
(5) lack of retinoic acid resulting in cellular hyperregeneration.

In this context, it is noteworthy that in contrast to other organs, mammary carcinogenesis is already stimulated by ethanol at very low levels which do not affect other tissues. Therefore, the mechanism(s) may be tissue-specific and possibly estrogen-related, since even small serum concentrations of ethanol increase serum estrogens significantly.

RECOMMENDATIONS

Since there is no threshold level of ethanol for breast cancer risk, the breast is one of the most sensitive organs for the carcinogenic action of alcohol. Healthy women should not exceed one drink/day (equivalent to 10–12 g of ethanol). Women at an elevated risk for breast cancer such as those with a positive family history, benign mastopathy or other conditions associated with an increased breast cancer risk should avoid alcohol or consume alcohol only occasionally.

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