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Breast cancer and its association with alcohol

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Worldwide, more than a million women are diagnosed with breast cancer every year, accounting for 10% of all new cancers and 23% of all female cancer cases. Breast cancer incidence rates vary considerably, with the highest rates in the developed countries and the lowest rates in developing countries (Cancer Research UK 2008). Breast cancer is the most common cancer in women in Australia, UK and the USA, where one in eight women will be diagnosed with breast cancer in Australia before the age of 85 (AIHW 2008), one in nine will be diagnosed at some stage in their life in the UK (UK Office for National Statistics 2007), and one in four will be diagnosed at some stage in their life in the USA (CDC 2007). Breast cancer incidence rates continue to increase with age, with the greatest rate of increase immediately prior to the menopause.

An association between alcohol consumption of breast cancer

The first purported positive association between alcohol consumption and breast cancer was reported in 1977 (Williams and Horm 1977), and since then approximately 100 epidemiological studies have been published, which consistently support such as association (Longnecker 1994, Key et al. 2006). This association has been observed for both pre- and post-menopausal women of all ages, and is observed to be independent of the type of alcoholic beverage consumed (Rosenberg et al. 1993, Longnecker 1994, Bowlin et al. 1997, Hamajima et al. 2003, Petri et al. 2004, Key et al. 2006). The association may also be more significant for certain subtypes of breast cancer for example, hormone-sensitive rather than hormone-insensitive subtypes (Millikan et al. 2008, Dolle et al. 2009, Kwan et al. 2009, Li et al. 2010, Kabat et al. 2011).

However, while the association is consistent and considered confirmed for consumers of three or more drinks per day (Rosenberg et al. 1993, Longnecker 1994, van den Brandt et al. 1995, Swanson et al. 1997, Suzuki et al. 2010, Zhang and Holman 2011), for consumers of one to two drinks per day, the data is less consistent or erratic (Flatt et al. 2010). Indeed, it has been suggested that the relationship between alcohol consumption and breast cancer is linear (Bowlin et al. 1997, Smith-Warner et al. 1998, Hamajima et al. 2003, Thygesen et al. 2008, Chen et al. 2011) or increases monotonically (Ellison et al. 2001, Tjonneland et al. 2003, Thygesen et al. 2008) for the average daily amount of alcohol consumed. The highest risk has been associated with consumption of six or more drinks per day (Chen et al. 2011). It has also been suggested that consumption patterns may modify risk (Morch et al. 2007, Chen et al. 2011), such that the consumption of four to five drinks consumed per session may increase/double risk by 50% compared to only one drink consumed per session. Paradoxically, alcohol dependence does not increase the risk of breast cancer (Kuper 2000).

It has also been suggested, but not substantiated, that there is a positive relationship between the duration (and hence accumulated amount) of alcohol consumption over the lifespan of a woman and her risk of breast cancer, although age at commencement of alcohol consumption appears to be irrelevant (Longnecker et al. 1995a, 1995b, Bowlin et al. 1997, Swanson et al. 1997, Terry et al. 2006, Chen et al. 2011). For example, the risk of breast cancer appears similar for cumulative alcohol consumption prior to 40 years of age and after 40 years of age (Chen et al. 2011). Again it has been suggested but not substantiated that there is long latency between onset of alcohol consumption

and onset of breast cancer of approximately 20 years (Willett and Stampfer 1997, Thygesen et al. 2008), although some studies conversely suggest that recent consumption is a better predictor of risk compared to retrospective consumption due to confounders such as aging, hormonal/ menopausal status and body mass index (Ellison et al. 2001, Horn-Ross et al. 2004, McDonald et al. 2004, Tjonneland et al. 2004, 2007).

In addition, light to moderate alcohol consumption after diagnosis of breast cancer generally does not appear to be associated with a recurrence of breast cancer (Reding et al. 2008, Flatt et al. 2010), although increased body mass index may influence any association (Homes et al. 1999, Kwan et al. 2010). Further, light to moderate alcohol consumption after diagnosis of breast cancer also appears also not be associated with overall mortality (Holmes et al. 1999, Dal Maso et al. 2008, Franceschi et al. 2009, Kwan et al. 2010), or it may actually reduce the risk of overall mortality (Reding et al. 2008, Barnett et al. 2008). There may, however, be an association with heavier consumption in developing, for example, estrogen receptor positive breast cancer in the contralateral breast (Li et al. 2009).

Risk factors for breast cancer and alcohol

The errancy of the data suggests that causation of breast cancer may be multi-factorial. The primary risk factors for breast cancer are purported to be: lifestyle; inherited gene mutations and hence family history; medical history; reproductive history (such as early menarche, nulliparity and late menopause); endogenous/exogenous hormones (such as hormone replacement therapy); body mass index; and environmental exposure to carcinogens. It has been proposed that alcohol may modify the significance of these risk factors, and in particular, act additively with those risk factors that influence the concentration of hormones in plasma. It has also been proposed that the factors other than family history, may act additively with the family history risk factor, and also, that some of these risk factors may be limited to those women who have a positive family history of breast cancer (Gapstur et al. 1992, Horn-Ross et al. 2004). Consequently, it has been proposed but not proven that the positive association between alcohol and breast cancer may be restricted primarily to women who have a positive family history of breast cancer (Vachon et al. 2001).

Potential interaction between steroid hormones and alcohol

Concerning the plasma concentration of the sex or steroid hormones as a risk factor for breast cancer, there is a positive association between the risk of development of breast cancer and the concentration of these hormones for both pre- and post-menopausal women; the steroid hormones include androgens, such as testosterone, and estrogens, such as estradiol, estrone and estriol (Brinton et al. 1986, Bergkvist et al. 1989, Colditz et al. 1990, Steinberg et al. 1991, Colditz et al. 1995, Dorgan et al. 2001, The Endogenous Hormones and Breast Cancer Collaborative Group 2002, Kaaks et al. 2005a,b, Eliassen et al. 2006). One source of endogenous estrogens is the aromatization of androgens to estrogens, and alcohol has been observed to increase this aromatization; the conversion occurs primarily in the ovary for pre-menopausal women and peripherally for post-menopausal women (Figure 1).

Figure 1. Primary mechanisms for the production of estrogens

In pre-menopausal women:

dehydroepiandrosterone (DHEA) ——> androgens (testosterone) ————> estrogens (estradiol) aromatization

In post-menopausal women:

androgens (androdstenedione) ————> estrogens (estrone) aromatization

Where:

oxidation

estrone <————> estradiol

reduction

An elevated concentration of testosterone or estradiol may increase the risk of breast cancer approximately six- and five-fold, respectively (Dorgan 1994, 1996), where the risk may be proportional to concentration (The Endogenous Hormones and Breast Cancer Collaborative Group 2002). Indeed, Reichman et al. (1993) observed in pre-menopausal women that the concentration of DHEA sulfate, testosterone and estradiol increased across the menstrual cycle following the consumption of alcohol as did Muti et al. (1997) and Rinaldi et al. (2006). The increase in sulfated DHEA implies that alcohol may also increase the production of DHEA sulfate in the adrenal cortex through its effect on the hypothalamic-pituitary-adrenal axis (Rivier 1996, Dorgan 2001). Gavaler and van Thiel (1992) and Rinaldi et al. 2006 reported similar observations in post-menopausal women and Hankinson et al. (1995, 1998) also reported an increase in the plasma concentration of estrone, which is purported to be a primary source of estradiol in breast cancer cells, following the consumption of alcohol. Furthermore, the effect of alcohol on the sex hormones is both acute and chronic.

The data shows also that there is a dose dependent response to alcohol on the aromatization of testosterone and on the subsequent concentration of estradiol in plasma, which then peaked and plateaued (Longnecker et al. 1995); this was consistent with the risk of breast cancer in consumers of alcohol compared to abstainers (Longnecker et al. 1988). Purported mechanisms by which alcohol may increase the concentration of steroid hormones include: stimulation of ovarian theca cells to produce androgens through increased pituitary luteinizing hormone secretion; induction of androgen catabolism in the liver; and/or increased liver aromatase activity leading to an increased conversion of androgens to estrogens.

The question remaining is at what level of moderate consumption the elevation of risk occurs, and then relative risk (risk benefit ratio) when compared with other causes of death, such as cardiovascular disease, which increases in post-menopausal women as a consequence of a reduced concentration of estradiol in plasma; estrogens significantly lower the concentration of cholesterol in plasma which is positively associated with a decreased risk of mortality from cardiovascular disease. For example, from a meta-analysis of 38 epidemiological studies by Longnecker in 1994, daily consumption of one alcoholic drink was associated with an 11% (7 to 16%) increased risk of breast cancer compared with abstainers while from a subsequent meta-analysis of 53 studies by Clavel-Chapelom in 2002, daily consumption of one alcoholic drink was associated with only a 7.1% (5.5 to 8.7%) increased risk. Furthermore, the pattern of alcohol consumption influences the concentration of the steroid hormones circulating in plasma, such that chronic and heavy intake of alcohol is observed to lead to early menopause, a lower concentration of gonadotrophins post-menopausally and an increased concentration of the steroid hormones post-menopausally (Gavaler and van Thiel 1987).

Potential interaction between hormone replacement therapy and alcohol

Post-menopausal women on estrogen replacement therapy (ERT) who consume alcohol are generally observed to have a significantly elevated plasma concentration of estradiol as compared with women not using ERT (Ginsberg et al. 1996 and Gavalar 1998). Ginsberg et al. (1996) observed an increase of approximately 300%, which corresponds to the preovulatory peak in the menstrual cycle, where the changes in the circulating concentration of estradiol significantly correlated with changes in the blood concentration of alcohol on both the ascending and descending limbs of the blood alcohol curve. The plasma concentration of this steroid hormone, which correlated with the plasma concentration of follicle stimulating hormone (FSH), is correlated with total amount of alcohol consumed per week (Gavalar 1998); interesting Gavalar also observed an increase in the concentration of estrone. However, the interaction of alcohol and ERT is not simple as the dose-response relationship of ERT is inverse when a moderate amount of alcohol is consumed (Gavaler 1998).

Consequently, accumulating data suggests that alcohol consumption is most strongly associated with the risk of breast cancers that are hormonally responsive, such as lobular (5-10% of all cancers) and hormone receptor positive tumors (estrogen receptor positive (ER+), such as ER+PR+ and ER+PR-

subtypes) (66%) (Enger et al. 1999, Li et al. 2003, Terry et al. 2006, Suzuki et al. 2008, Li et al. 2010, Kabat et al. 2011) as well as with the risk of tubular (2%) (Rosenberg et al. 2006); this is consistent with data suggesting that ERT is most strongly associated with lobular cancers (Li et al. 2000, 2008, 2010, Zanetti-Dallenbach et al. 2008). Data also suggests that no or a negative association observed for triple negative breast cancer (ER-/PR- or ER-/PR) or basal-like breast cancer (Millikan et al. 2008, Dolle et al. 2009, Kwan et al. 2009, Trivers et al. 2009, Kabat et al. 2011).

The suggestion of a further increased risk of breast cancer by post-menopausal woman who use ERT and who are also light to moderate consumers of alcohol remains controversial (Suzuki et al. 2005, Nielsen and Gronbaek 2008), in particular as ERT decreases the risk of other diseases such as cardiovascular disease (Ross et al. 1981, Szklo et al. 1984, Stampfer et al. 1985), osteoporosis (Hutchinson et al 1979, Weiss et al. 1980, Paganini-Hill et al. 1981), and dementias such as Alzheimer's disease (Tang et al. 1996, Zuccala et al. 2001, Ganguli, et al. 2005, Stampfer et al. 2005, McDougall et al. 2006, Reid et al. 2006, Wright et al. 2006) and hence decreases the risk of death from all causes (Bush et al. 1983, Criqui et al. 1988, Thun et al. 1997).

Potential interaction between folate and alcohol

An adequate consumption of folate, however, may reduce the increased risk of breast cancer associated with alcohol consumption (Zhang et al. 1999, 2005, Rohan et al. 2000, Sellers et al. 2001, Baglietto et al 2005, Stolzenberg-Solomon et al. 2006, Tjonneland et al. 2005, 2006). For example, while alcohol interferes with DNA synthesis and repair, folate is involved in DNA synthesis, repair and methylation. In animal models, folate supplementation reduces DNA strand breaks in the p53 gene (Kim et al. 2000); the P53 protein regulates the cell cycle to prevent genome mutation, and hence functions to suppress tumors. It can activate DNA repair proteins when it recognizes damaged DNA, hold the cell cycle at the G1/S regulation point on DNA damage recognition to prevent uncontrolled cell division and can initiate apoptosis, the programmed cell death, if the DNA damage proves to be irreparable. Cancer occurs when the rate of proliferation of mutated cells greatly exceeds the rate of apotosis. In breast cancer, the gene has been observed to be mutated in 15 to 50% of tumors (Olivier and Hainaut 2001).

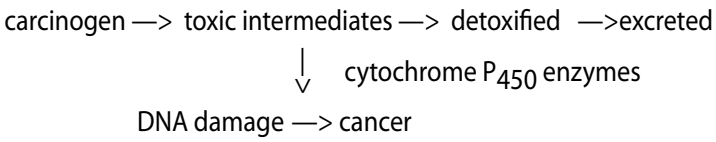
The concurrent consumption of alcohol and folate (at least 300 mg/day) has been observed to reduce the relative risk of alcohol-induced breast cancer to 1.05 for women consuming greater than 15 g alcohol/day or one and a half standard drinks, but was only 0.55 for women consuming greater than 600 mg/day of folate. Indeed, the concurrent consumption of folate-containing vitamin supplements reduces the relative risk to 0.74 for women consuming greater than 15 g alcohol/day compared to those not using vitamins (Zhang et al. 1999). The interaction between alcohol and folate has been observed to be primarily limited to estrogen receptor negative (ER-) breast cancer tumors (Zhu and Williams 1998, Sellers et al. 2002, Zhang et al 2005), which is consistent with an interaction of alcohol and folate on breast tissue tumors being mainly through the primary metabolite of alcohol, acetaldehyde, which is directly carcinogenic as well as indirectly carcinogenic via folate depletion, independent of circulating estrogens and estrogen receptor-mediated events.

Potential interaction between inherited gene mutations and alcohol

Inherited mutations in the BRCA-1 and BRC-2 genes confer significantly increased lifetime risks of breast cancer, in particular for BRCA-1 mutation carriers less than 50 years of age (Wooster et al. 1995; Tavtigian et al. 1996, Antoniou et al. 2003). In contrast to the general population, light to moderate alcohol consumption does not appear to increase the risk of breast cancer in women carrying a BRCA-1 gene mutation although higher amounts may be multiplicative (McGuire et al. 2006, Dennis et al. 2010, Dennis et al. 2011), which may reflect hormone receptor status; estrogen receptor negative tumors account of 80% of tumors in BRCA-1 mutation carriers (Foulkes et al. 2004, McDonald et al. 2004, Zhang et al l 2007). Risk appears increased in women carrying a BRC-2 gene mutation and appears additive with increased body mass index (Dennis et al, 2011). Light to moderate wine consumption, however, actually may be protective for BRCA-1 but not BRCA-2 mutation carriers (Dennis et al. 2010, 2011).

Other potential mechanisms of action for alcohol in breast cancer

Concerning biological or environmental exposure, alcohol is purported to influence the local and systemic metabolism of mammary carcinogens. Risk is the sum of numerous factors, each with a small risk, such that the summed risk is high from the enhancing or synergistic effects or influences of the risk factors. It is suggested that approximately 50% of breast cancer is not related to genetic/hormonal risk factors, but is related to the environment as observed from cultural/geographic correlations for risk. With respect to environmental exposure to carcinogens, metabolism in the body may either activate or detoxify the carcinogen. For example:



whereby, a decrease in or inhibition of metabolism, increases the exposure of the circulating carcinogen in the blood to organs/tissues, such as the breast.

Because alcohol is not itself genotoxic and nor tumorigenic in animals, potential mechanisms for the positive association between alcohol and breast cancer include the facilitation of carcinogens into cells, the induction of carcinogen activating enzymes, the inhibition of DNA repair and the promotion of tumors. Potential ubiquitous carcinogens include N-nitrosamines, to which people are exposed from sources such as tobacco and N-nitrosodimethylylamine (NDMA). The former carcinogen is metabolized by cytochrome P4502E1 enzymes in the liver, such that in the presence of alcohol, this metabolism is inhibited and the unmetabolized carcinogen circulates in the blood together with the alcohol. The coexposure of the carcinogen and alcohol to tissues has been observed to promote tumors in these tissues.

In addition, cytochrome P4502E1 enzymes have been observed in animal breast tissue and there is greater expression of these enzymes in breast tissue tumors compared to normal breast tissue, such that high concentration of circulating carcinogen may be activated by the cytochrome P4502E1 enzymes and/or alcohol may induce the activation of these enyzmes (Anderson et al. 1995). While these observations are yet to be confirmed in human breast tissue, the induction of cytochrome P4502E1 is associated with an increased production of reactive oxygen species that are associated with DNA damage including single and double strand breakage (Wright et al. 1999, Koch et al. 2004), where breast tissue tumors contain an approximate nine-fold higher concentration of these DNA modifications (Li et al. 1999).

Alcohol may additionally influence alterations in cell cycle behaviour such as cell cycle duration leading to the hyperproliferation of mutated cells, that is, uncontrolled cell division; nutritional deficiencies, such as methyl-, vitamin E-, folate- pyridoxal phosphate-, zinc- and selenium-deficiencies; and alterations of the immune system eventually resulting in an increased susceptibility to certain virus infections such as hepatitis B virus and hepatitis C virus (Poschl and Seitz 2004).

There is also accumulating data that the primary metabolite of alcohol, acetaldehyde, is partly responsible for alcohol-associated carcinogenesis. Acetaldehyde is directly carcinogenic and mutagenic interfering with both DNA synthesis and repair. It also binds to cellular proteins and DNA forming stable protein and DNA adducts, which result in physical and functional impairment of the cell and consequently in an immunological cascade reaction, and in the occurrence of replication errors and/or mutations in oncogenes or tumor suppressor genes (Dellarco 1988, Fang and Vaca 1995, Nakamura et al. 2003). Acetaldehyde also degrades folate in the colon, where a folate dietary deficiency has been associated with an increased risk of breast, pancreatic and colon cancer (Gloria et al. 1997, Duthie et al. 2000, Hussien et al. 2005).

Alcohol is metabolised to acetaldehyde by the enzyme alcohol dehydrogenase (ADH), where approximately 96-98% of ADH activity occurs in the liver but it also expressed and regulated by other tissues including breast tissue (Seitz et al. 1998, Wright et al. 1998, Triano et al. 2003). Individuals differ in their ability to metabolise alcohol because of genetic differences in ADH; ADH is encoded by at least five different genes that result in enzyme classes of different metabolic activity for alcohol and

hence concentration of circulating acetaldehyde (Bosron and Li 1986). For example, Class 1 ADH polypeptide subunits are encoded by three specific gene loci, ADH1A (a), ADH1B (b) and ADH1C (y) where, in vitro, the (y)-a polypeptide subunit encoded by the ADH1C*1 variant metabolises alcohol to acetaldehyde 2.5-times faster than the ADH1C*2 variant (Lee et al. 2006), and the b-1 polypeptide subunit encoded by the ADH1B*2 variant metabolises alcohol to acetaldehyde 100-times faster than the subunits encoded by the ADH1B*1 variant, but has a lower affinity for alcohol (Hurley et al, 1990). Several studies have examined an association between the different polypeptide subunits and risk of breast cancer with conflicting and hence inconclusive results (Freudenheim et al. 1999, Hines et al. 2000, Lilla et al. 2005, Sturmer et al. 2005, Terry et al, 2006, Visvanathan et al. 2007, Kawase et al. 2009, Larsen et al. 2010). Results from one recent study supports an association between 'fast' metabolisers of alcohol per se and hence the 'fast' appearance of acetaldehyde and an increased risk of breast cancer (Terry et al. 2006), where women with the fast metabolising ADH1C*1 variant and hence ADH1C*1,1 genotype have been observed to be 1.8-times more at risk for breast cancer than women with other genotypes (Coutelle et al. 2004). Intriguingly, the expression of ADH1 is breast tissue is decreased in invasive breast cancers (Triano et al. 2003). The results of another recent study, however, also suggests that slow converters of alcohol to acetaldehyde may also be at increased risk of developing breast cancer, which implies that both alcohol and its primary breakdown product acetaldehyde could be contributing compounds (Larsen et al. 2010).

Although animal studies show that alcohol does not initiate or promote tumorogenesis and may actually decrease the incidence of tumors, some studies also show that alcohol may effect or enhance metastasising tumors (Weiss et al. 1995, Swanson et al. 1997), and that this effect is dependent on the stage of alcohol consumption, that is, pre- or post-treatment with a carcinogen, and on the amount of alcohol consumed. While it is unknown what stage of carcinogenesis is affected by alcohol, recent research implies that alcohol acts at a late stage of carcinogenesis (Weiss et al. 1995, Swanson et al. 1997).

Conclusions

While there is an indisputable association between alcohol consumption and the risk of breast cancer, the mechanisms behind the association require further elucidation. This risk of breast cancer should not, however, be considered in isolation from the risk of other factors for mortality, such as cardiovascular disease, whereby cardiovascular disease is the primary cause of mortality in the industrialised or westernised world. Indeed, the light to moderate consumption of alcohol is associated with a significantly reduced risk of mortality from cardiovascular disease and from all causes, for both men and women, irrespective of age and ethnicity (Boffetta and Garfinkel 1990, Marmot and Brunner 1991). Thus, it may be advisable for women to enumerate and evaluate their risk factors for cardiovascular disease and for breast cancer, in addition to the amount and pattern of their alcohol consumption, before considering abstaining from alcohol.

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