LETTER TO THE EDITORS

ALCOHOL EXPOSURE IN UTERO AND BREAST CANCER RISK LATER IN LIFE

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Since the pioneering work of Hiatt and Bawol (1984), there has amassed a considerable amount of evidence that moderate-to-heavy alcohol consumption increases risk of breast cancer in women (Willett et al., 1987; Longnecker, 1999). A plausible mechanism is by alcohol’s effects on circulating hormone levels. Alcohol administration has been reported to increase circulating oestriadiol levels in pre-menopausal women (Reichman et al., 1993); the evidence is mixed in post-menopausal women (Purohit, 1998). In a cross-sectional study of pre-menopausal women, Muti et al. (1998) determined an association between reported alcohol consumption and serum oestradiol levels during the luteal phase of the menstrual cycle, and found an 18% elevation in drinkers, consuming an average 1 drink per day, compared to abstainers. It is not clear how alcohol affects circulating oestradiol levels. Alcohol has been reported to increase aromatase activity; i.e., the conversion of testosterone to oestrogens, resulting in reduced testosterone and increased oestrogen levels (Gavaler and Van Thiel, 1992). Alcohol also might interact with luteinizing hormone production from the pituitary (Röttiri and McCann, 1997), resulting in increased oestradiol release from the ovaries.

In addition to affecting oestrogen levels, alcohol appears to influence melatonin. Alcohol administration has been reported to reduce the nocturnal rise in serum melatonin in rats (Moss et al., 1986), and in humans (Ekman et al., 1993; Rojmark et al., 1993) under experimental conditions. In a large cross-sectional study, Stevens et al. (2000) found a significant inverse association of alcohol consumption and urinary 6-sulphatoxymelatonin, a good indicator of nocturnal blood levels (Cook et al., 2000), in healthy women living under normal conditions in the Seattle area. Importantly, there was no effect of one drink on melatonin level, but a 9% reduction with 2 drinks, 15% with 3 drinks, and 17% with 4 drinks or more. It may be that an increase in circulating oestriadiol levels and a reduction in melatonin levels after alcohol exposure, are not just simultaneous events, but causally related. Stevens and Hiatt (1987) suggested that alcohol ingestion may result in lowered melatonin levels which, in turn, may lead to elevated circulating oestriadiol concentration in blood (Cohen et al., 1978). Specifically, decreased concentrations of melatonin might increase release of gonadotrophins, leading to an increase in ovarian oestrogen production (Kauppila et al., 1987; Penny et al., 1987; Voordouw et al., 1992; Brzezinski, 1997).

Both high oestrogen levels and low melatonin levels have been implicated in increasing the risk to develop breast cancer. Findings in human breast cancer cells growing in culture and in animal models (Clarke et al., 1992), as well as in epidemiological studies, at least in post-menopausal women (Key, 1999; Kabuto et al., 2000), link elevated circulating oestrogen levels to increased breast cancer risk. In addition, in vivo data indicate that reduced melatonin levels can increase chemically induced mammary cancer in rats (Tamarkin et al., 1981; Blask et al., 1991). The epidemiology is, however, quite sparse (Tamarkin et al., 1982) due in part to the fact that there has not, until recently, been a reliable technique for estimating nocturnal circulating melatonin levels that is feasible to use in large-scale epidemiological studies.

These observations can be considered in the context of the hypothesis that an elevated exposure to oestrogens in utero will increase the lifetime risk of breast cancer (Trichopoulos, 1990) by altering normal breast development. This hypothesis was subsequently supported in a number of epidemiological studies (Potischman and Troisi, 1999). Animal models also support the hypothesis and show that elevated in utero oestriadiol levels lead to altered mammary gland development (Hilakivi-Clarke et al., 1997); further, an exposure of pregnant rats to oestradiol, or feeding them a diet high in n-6 polyunsaturated fatty acid (PUFA), which significantly raises circulating oestriadiol levels, results in increased 7,12-dimethylbenz[a]anthracene-induced mammary tumour incidence in their female offspring.

For women who are pregnant, ingestion of alcohol, even in moderation, may lead to elevated circulating oestriadiol levels, either through a reduction of melatonin or some other mechanism. This may then affect the developing mammary tissue such that the lifetime risk of breast cancer is raised in their daughters.

REFERENCES


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