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Colorectal Cancer and Alcohol

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1. Introduction

Chronic alcohol consumption may lead to a variety of diseases and may deteriorate a great number of existing health problems. Among all these diseases the development of certain types of cancer is of major concern. Since decades it has been known that chronic alcohol consumption is a risk factor for cancer of the upper aerodigestive tract (oral cavity, pharynx, larynx and oesophagus), the liver and the female breast. Data with respect to alcohol and cancer concerning other organs do not show such clear correlations. In February 2007 an international group of epidemiologists and alcohol researchers met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the role of alcohol and its first metabolite acetaldehyde as potential carcinogens in experimental animals and humans. The working group has concluded from the epidemiological data available that the occurrence of malignant tumours mentioned above is related to the consumption of alcoholic beverages. In addition, at this time epidemiologic and experimental data showed that alcohol is also a risk factor for colorectal cancer (Baan et al., 2007).

Worldwide a total of approximately 389,000 cases of cancer presenting 3.6 % of oral cancers (5.2 % in men and 1.7 % in women) derive from chronic alcohol consumption (Rehm et al., 2004). Besides the fact that alcohol is a co-carcinogen and may act as a promoter alcohol can also accelerate tumour spread as exemplified for liver metastases of colorectal cancer possibly due to immune suppression and induction of angiogenesis by the expression of vascular endothelial growth factor (VEGF) (Seitz & Stickel, 2010). In addition, it is important to know that ethanol also interacts with the metabolism of chemo-therapeutic drugs which can result in a decreased respond to medication and increased side-effects (De Bruijn & Slee, 1992).

This review focuses solely on the effect of chronic alcohol consumption on colorectal cancer, a cancer which is wide spread in Western societies and is No. 3 cancer in men and women in Germany. The present review will, therefore, discuss epidemiology of alcohol and colorectal cancer, will briefly address possible mechanism by which alcohol stimulates colorectal carcinogenesis and may finally give some suggestions and recommendations with respective to earlier detection and identification of high risk groups.

2. Epidemiology

An increased risk for the development of colorectal cancer associated with chronic alcohol ingestion has been considered for decades. In 1974 Breslow and Enstrom emphasized a

correlation between beer consumption and rectal cancer occurrence (Breslow & Enstrom 1974). In 1992 Kune and Vitetta summarized the results of more than 50 epidemiologic studies between 1957 and 1991 including 7 correlational studies, more than 40 case control studies and 17 prospective cohort studies on the role of alcohol on the development of colorectal tumours (Kune & Vitetta 1992). Most of these studies reported a positive association of large bowel cancer with alcohol consumption. In addition a positive trend with respect to dose-response was found in 5 out of 10 case control studies and in all prospective cohort studies in which a dose-response analysis has been performed.

In the nineties of the last century another 12 epidemiological studies have been published with inconsistent results (Seitz et al., 2006). Most importantly a prospective cohort study in Japan reported a positive dose-response relationship between alcohol intake and colon cancer risk in men and women (N. Shimizu et al., 2003), while a Danish population based cohort study showed no association (Pedersen et al., 2003).

A panel of experts at a WHO consensus conference on nutrition and colorectal cancer reviewed in 1999 the epidemiology on alcohol and colorectal cancer and it was concluded that alcohol ingestion even in a low dose-intake between 10 and 40 grams especially consumed as beer resulted in a 1.5-fold increased risk for colorectal cancer and to a lesser extend for colonic cancer in both sexes but predominantly in men (Scheppach et al., 1999).

Cho et al showed in a meta-analysis of 8 cohort studies from the US and Europe a trend between the increased amount of alcohol intake and the risk for colorectal cancer. In this meta-analysis a consumption of more than 45 grams per day was associated with an increased risk of 45 % (Cho et al., 2004).

A huge prospective follow-up study of more than 10,000 US citizens concluded that alcohol consumption of one or more alcoholic beverages per day is associated with a 70 % greater risk of colonic cancer with a strong positive dose-response relationship (Su & Arab, 2004).

Most recently it was proposed that the alcohol colorectal cancer association is more apparent in Japanese than in Western populations. A pooled analysis of results from 5 cohort studies from Japan showed a strong and highly significant association between alcohol intake and colorectal cancer not only in men but also in women (Mizoue et al., 2008). Twenty five per cent of colorectal cancer cases in men were attributable to an alcohol intake of more than 23 grams per day. A recent meta analysis from the IARC of 34 case control and 7 cohort studies provides strong evidence for an association between alcohol consumption of more than 1 drink per day and the risk for colorectal cancer (Fedirko et al., 2011). Similar results were reported from the Netherlands (Bongaerts et al., 2008, 2010) and the US (Thygesen et al., 2008) but not from Great Britain (Park et al., 2009, 2010).

The accumulation of all these convincing epidemiologic data on alcohol and colorectal cancer resulted by the IARC that chronic alcohol consumption is a risk factor for colorectal cancer (Baan et al., 2007).

3. Animal experiments

Various animal experiments have been performed to study the effect of alcohol on chemically induced colorectal cancer. The results of these experiments depend on the experimental design, the type of carcinogen used, its time duration of exposure and dosage as well as the route of alcohol administration. While alcohol alone does not induce colorectal tumours, the administration of alcohol together with a colorectal carcinogen does under certain experimental conditions result in a stimulation of carcinogenesis (Seitz et al., 2006).

This is especially relevant when a carcinogen such as acetoxymethylmethylnitrosamine (AMMN) is locally applied to the rectal mucosa (Seitz et al., 1990). Some evidence exist that acetaldehyde (AA) is an important factor since inhibition of its degradation stimulates colorectal cancer (Seitz et al., 1990).

For a detailed summary of the animal experiments performed so far we refer to the following review article (Seitz et al., 2006).

4. Risk factors in alcohol mediated colorectal carcinogenesis

Various risk factors for ethanol-mediated colorectal carcinogenesis exist. Five out of 6 studies of the effect of alcohol on the occurrence of adenoma polyps in large intestine showed a positive association with alcohol (Kune et al., 1992; Seitz et al., 1998). In addition, also the occurrence of hyperplastic polyps is enhanced when more than 30 grams of alcohol per day were consumed. The relative risk for men was 1.8 and for women 2.5 (Kearney et al., 1995).

Alcohol affects the adenoma/carcinoma sequence at the different early steps (Boutron et al., 1995). High alcohol intake favours high risk polyps or colorectal cancer occurrence among patients with adenoma (Bardou et al., 2002). It has also been reported that a reduction in alcohol consumption for individuals with genetic predisposition for colorectal cancer had large beneficial effects on tumour incidence (Le Marchand et al., 1999). Thus, patients with tendency towards colorectal polyps have an increased risk to develop carcinoma when they consume additional alcohol.

Another additional risk is possibly the presence of ulcerative colitis, although the data are not completely clear. Alcohol by itself may additionally enhance inflammation and may thus favour carcinogenesis.

Another important factor is that alcohol reduces the availability of folate which results in a decrease of methylation and thus, a decrease of thymidine generation, DNA synthesis and cellular regeneration, in a situation of enhanced need. Therefore, folate, methionine and vitamin B6 deficiency are risk factors for ethanol mediated colorectal carcinogenesis (Giovannucci et al., 1995; Larsson et al., 2005; Schernhammer et al., 2008; Weinstein et al., 2008; Yamaji et al., 2009; Figueiredo et al., 2009; Lee et al., 2010).

It is well known that tobacco smoking is associated with a higher risk for colonic adenoma and hyperplastic polyp formation as well as increased incidence of colorectal carcinoma (Seitz & Cho, 2009).

Age, another risk factor for colorectal cancer may also affect ethanol mediated cancer development in the large intestine. It has been shown in animal experiments that mucosal damage induced by chronic alcohol ingestion is more pronounced with advanced age compared to youth (Simanowski et al., 1994).

Finally, genetic risk factor with respect to alcohol metabolism and colorectal cancer has to be taken into consideration. Alcohol is metabolised by alcohol dehydrogenase (ADH) to AA. Seven different ADHs exist and two of them (ADH1B and ADH1C) reveal polymorphism. Among the two ADH1C is of considerable interest (see below) (Edenberg, 1997). Individuals with increase metabolism of ethanol via ADH1C due to homozygosity of the ADH1C*1 allele seem to have a significantly increased risk for colorectal cancer when they consume more than 30 grams alcohol per day (Homann et al., 2006).

5. Possible mechanisms of alcohol mediated colorectal carcinogenesis

5.1 Acetaldehyde (AA)

Most recently the IARC has identified AA as an important carcinogen for humans (Secretan et al., 2009). AA is produced from ethanol via ADH. In the gastrointestinal mucosa various ADHs are present and capable to produce AA from alcohol. In addition, gastrointestinal bacteria of the upper gastrointestinal tract and of the large intestine can metabolize ethanol to AA (Salaspuro, 2003) (Figure 1).

AA is highly toxic and carcinogenic and causes point mutations in the hypoxanthine-guanine phosphoribosyltransferase localized in human lymphocytes, induces sister chromatid exchanges and cross-chromosomal aberration (Seitz & Stickel, 2010). AA forms stable adducts with DNA. One of these adducts is especially generated in hyperregenerative tissues (in the presence of spermine and spermidine) such as the upper gastrointestinal tract and the colon where chronic alcohol consumption results in tissue hyperregenerativity. This propane DNA adduct is highly carcinogenic (Brooks & Thiruvathu, 2005). There is significant evidence that AA is responsible for the carcinogenic effect of alcohol in the upper gastrointestinal tract, oesophagus, larynx, pharynx and oral cavity (Baan et al., 2007; Seitz & Stickel, 2010). For more details about the role of AA on upper gastrointestinal cancer we refer to the following review article (Baan et al., 2007; Stickel et al., 2006).

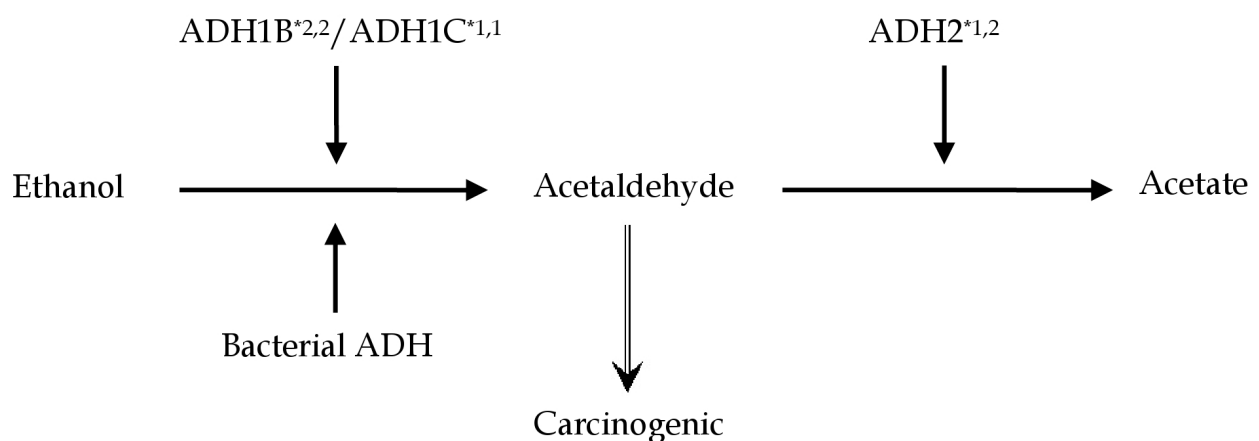


Fig. 1. Ethanol metabolism by mucosal enzymes and gastrointestinal bacteria. Ethanol is first metabolized by alcohol dehydrogenase (ADH) to acetaldehyde (AA) which is toxic and carcinogenic. AA is then further converted by acetaldehyde dehydrogenase (ALDH) to acetate which is non-toxic and is channelled into the intermediary metabolism of the cell. Accumulation of AA may either occur with rapid generation through ADH or slow degradation through ALDH. ADH1B and ADH1C are polymorphic. While the ADH1B*2 allele encodes for ADH enzymes approximately 40-fold more active as compared to the enzymes encoded by the ADH1B*2 allele, the ADH1C*1 allele encodes for an enzyme approximately 2.5-fold more active than the enzyme encoded by the ADH1C*2 allele. Thus, ADH1B*2,2 and ADH1C*1,1 homozygotes may accumulate AA. In addition, 40 % of Asians are heterozygote for the ALDH2 gene (ALDH2*1,2) encoding for an enzyme with very low ALDH activity resulting in AA accumulation.

In the colonic mucosa ADH1 and ADH3 are present and are involved in AA generation. On the other hand acetaldehyde dehydrogenase (ALDH), the enzyme responsible for AA

degradation is detectable at relative low activities only (Seitz & Oneta, 1998). The net amount of AA present in the tissue may determine its toxic and carcinogenic action. Thus, individuals with an increased production and decreased degradation of AA are especially at risk for colorectal cancer development. It has been proposed that the ALDH activity of colonic mucosa may be sufficient for the removal of AA produced by colonic mucosal ADH during ethanol oxidation but it is insufficient for the removal of AA produced by intracolonic bacteria.

The most striking evidence of the causal role of AA in ethanol-associated carcinogenesis derives from genetic linkage studies in alcoholics and / or heavy drinkers. Individuals who accumulate AA due to polymorphism and / or mutation in the gene coding for enzymes responsible for AA generation and detoxification have been shown to have an increased cancer risk. In Japan as well as in other Asian countries a high percentage of individuals carry a mutation of the ALDH2 gene which codes for an enzyme with low activity leading to elevated AA levels after alcohol consumption. While homozygotes are completely protected against alcoholism and alcohol associated diseases due to the fact that they cannot tolerate alcohol even at very small doses, heterozygotes (ALDH2*1,2) have an increased risk for alimentary tract cancer including the colon and the rectum (Yokoyama et al., 1998) (Figure.1).

In addition, polymorphism of the ADH1C gene may also modulate AA levels. ADH1C*1 transcription leads to an ADH isoenzyme 2.5 times more active than that from ADH1C*2 (Figure1). We evaluated whether the association between alcohol consumption and colorectal cancer development is modified by ADH1C polymorphism. We recruited 173 individuals with colorectal tumours diagnosed by colonoscopy and 788 control individuals without colorectal tumours and determined their genotypes. Genotype ADH1C*1/1 was more frequent in patient with alcohol associated colorectal neoplasia compared to patients without cancer (Homann et al., 2006). In addition, only individuals drinking more than 30 grams ethanol per day with a genotype ADH1C*1/1 had an increased risk for colorectal tumours. These data identify ADH1C homozygosity as a genetic risk marker for colorectal tumours in individuals consuming more than 30 grams alcohol per day and emphasize further the role of AA as a carcinogenic agent in alcohol mediated colorectal carcinogenesis.

It has been shown that after alcohol administration, the amount of AA per gram of tissue is highest for the colonic mucosa compared to all other tissues in the body (Seitz et al., 1987). This is primarily due to the production of AA by the faecal bacteria. AA has toxic effects on the colon mucosa resulting in secondary compensatory hyperregeneration with increased crypt cell production rates and an extension of the proliferative compartment towards the lumen of the crypt (Simanowski et al., 1994, 2001). This change in crypt cell dynamics represents a condition associating with increased risk for colorectal cancer.

The alcohol associated hyperregeneration of the colonic mucosa is especially pronounced with increasing age (Simanowski et al., 1994). As already pointed out, this may have practical implications since age by itself is a risk factor for CRC.

High AA levels have been found after alcohol administration in the colon of rats and these concentrations were significantly lower in germ free animals as compared to the conventional rats suggesting that faecal bacteria are capable of producing AA (Seitz et al., 1990). Indeed, the reversed microbial ADH reaction produces under aerobic or microaerobic conditions striking amounts of AA when human colonic contents or some microbes representing normal colonic flora are incubated in vitro at 37°C with increasing ethanol

concentrations (Jokelainen et al., 1996, 1994; Salaspuro et al., 1999). This reaction is already active at comparatively low ethanol concentrations (10-100 mg %) which exist in the colon following social drinking (Jokelainen et al., 1996). AA formation catalysed by microbial ADH takes place at a pH normally found in the colon and is rapidly reduced with decreasing pH (Jokelainen et al., 1994).

The administration of antibiotics to animals has significantly decreased colonic bacteria and colonic AA production (Jokelainen et al., 1997).

- a. high AA levels occur in the colon due to bacterial and mucosal ethanol oxidation
- b. animal experiments show an increased occurrence of colorectal tumours induced by the specific locally acting carcinogen AMMN when cyanamide, an ALDH inhibitor, is applied and AA levels are elevated,
- c. crypt cell production rate correlates significantly with AA levels in the colonic mucosa,
- (d) colonic AA levels show a significant inverse relationship with mucosal folate concentration which supports in vitro data showing a destruction of folate by AA,
- d. individuals with the inactive form of ALDH2 resulting in elevated AA concentrations exhibit an increased risk for CRC when they consume alcohol,
- e. individuals homozygous for the ADH1C*1 allele coding for an enzyme with a 2.5 times higher AA production have also an increased risk for colorectal cancer, the action of AA seems the major mechanism of ethanol-mediated colorectal cancer development.

5.2 Oxidative stress

Chronic ethanol consumption results in the induction of cytochrome P4502E1 (CYP2E1) predominantly in the liver (Seitz & Stickel, 2010) but also in other tissues including the colorectal mucosa (Shimizu et al., 1990). This CYP2E1 induction is associated with an increased metabolism of ethanol through CYP2E1 and the generation of AA but also of reactive oxygen species (ROS). For more details we refer to the following review article (Seitz & Stickel, 2007). ROS may attack lipids and result in lipidperoxidation with the generation of lipidperoxidation products such as 4-hydroxy-nonenal or malondialdehyde. These lipidperoxidation products may bind to proteins but also to DNA and form exocyclic etheno DNA adducts with a high carcinogenic potency (Wang et al., 2009).

The effect of chronic ethanol consumption on the induction of CYP2E1 and the activation of procarcinogens has been convincingly demonstrated by the use of azoxymethane (AOM), a procarcinogen for the colon. The metabolism of AOM to its ultimate carcinogen has been inhibited in the presence of ethanol in the body since ethanol competes for the binding site at CYP2E1 but significantly enhanced when ethanol is withdrawn in a condition where CYP2E1 is induced and completely available for the metabolism of AOM (Sohn et al., 1987).

The induction of CYP2E1 in the colonic mucosa may lead to an enhanced activation of dietary (nitrosamines) and cigarette smoke derived (polycyclic hydrocarbons) procarcinogens and may be one mechanism by which ethanol enhances colorectal carcinogenesis (Seitz & Osswald, 1994).

In this context it is interesting that alpha tocopherol, a radical scavenger, prevents mucosal cell hyperproliferation induced by ethanol suggesting that ROS may be involved in this process (Vincin et al., 2003).

5.3 Epigenetics

There is increasing evidence that alcohol related epigenetic changes of DNA methylation and histone acetylation do occur which may potentially modulate tumour development (Stickel et al., 2006). Epidemiologic data have clearly shown that folate deficiency alone or together with methionine deficiency increases the risk for ethanol mediated colorectal cancer (Giovannucci et al., 1995; Larsson et al., 2005; Schernhammer et al., 2008; Weinstein et al., 2008; Yamaji et al., 2009; Figueiredo et al., 2009; Lee et al., 2010). Similarly, vitamin B6 deficiency also enhances tumour risk. All these factors are involved in methyl transfer. Their deficiency results in DNA hypomethylation, a condition relevant in carcinogenesis. In addition, histone acetylation is also favoured by chronic ethanol consumption (Kim & Shukla, 2006; Choudhury & Shukla, 2008) since ethanol metabolism leads to the accumulation of acetate on one hand and to a change in the intracellular redox potential with increasing concentrations of NADH and decreasing concentrations of NAD on the other hand. This change in redox potential also favours histone acetylation. In addition, histone deacetylation is blocked by ethanol through its inhibitory effect on histone deacetylase (HDA).

Indeed, animal experiments have shown DNA hypomethylation in the colon following chronic ethanol ingestion (Choi et al., 1999). However, site specific hypomethylation have not been demonstrated so far.

5.4 Other mechanisms

Other mechanisms of ethanol mediated carcinogenesis in the colon may including deficiency of retinoic acid (Wang X.D. & Seitz, 2004), effect of ethanol on intracellular signalling (Dunty, 2010) including various pathways such as Mitogenic signals (MAPK, RAS), Insensitivity to anti-growth signals (Rb and Cell cycle control, TGF β), Apoptosis (p53, PTEN), Angiogenesis, Metastasis (ECM, Osteopontin, Wnt) and an ethanol effect on inflammation (Wang, J., 2010).

6. Summary, conclusion and recommendations

Chronic ethanol consumption at a dose of more than 30 grams ethanol per day is a risk factor for colorectal cancer. Chronic ethanol consumption also increases the risk for colorectal cancer in individuals with polyps and colorectal inflammation as well as in those with an ALDH mutation (ALDH2* 1,2, only Asians) and ADH1C*1 homozygosity since they accumulate AA following ethanol ingestion.

The mechanisms of ethanol mediated colorectal carcinogenesis may involve AA produced by mucosal ADH and intestinal bacteria. In addition, oxidative stress induced by ethanol may also play a role.

As a clinical consequence, chronic alcohol consumers should be screened earlier as the general population for colorectal cancer either by faecal blood test or colonoscopy depending on the methods available.

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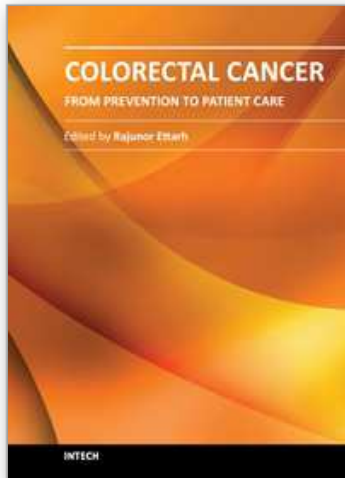
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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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