Konzumace alkoholu a metabolické změny

Tomáš Zima

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Alcohol Consumption Worldwide

Current Worldwide Alcohol Consumption Among Adults

Alcohol Consumption Among Adults
- Less than 2.1
- 2.1 – 4.6
- 4.6 – 7.6
- 7.6 – 10.8
- 10.8 – 13.66
- 13.66 – 21.5
- No data

in litres of pure alcohol
Alcohol consumption per capita 1990-2014

- African Region 1990
- African Region 2014
- Region of the Americas 1990
- Region of the Americas 2014
- Eastern Mediterranean Region 1990
- Eastern Mediterranean Region 2014
- European Region 1990
- European Region 2014
- South-East Asia Region 1990
- South-East Asia Region 2014
- Western Pacific Region 1990
- Western Pacific Region 2014
- Global 1990
- Global 2014

Litres of pure alcohol
Trends in adults per capita alcohol consumption in different countries

**Figure 3. Trends in Recorded Per Capita Alcohol Consumption by Adults in Selected Countries.**

In addition to recorded consumption, there is unrecorded consumption in some countries. For example, in 2005, adult per capita unrecorded consumption was estimated to be less than 0.5 liters per year in Japan and France; 1 to 2 liters per year in China, the United Kingdom, and the United States; and close to 5 liters per year in Russia. Data are from the WHO Global Information System on Alcohol and Health (http://apps.who.int/gho/data/node.main.GISAH).
Increase of alcohol consumption

- **Germany, Holand**
  - 1950-1990: 4X

- **Czechoslovakia, Czech Republic**
  - 1953: 3.1 l per capita
  - 1982: 8.9 l per capita
  - 1999: 9.9 l per capita
  - 2002: 10.2 l per capita
  - 2005: 9.8 l per capita
  - 2017: 9.9 l per capita
Change in alcohol consumption among adults, 1992-2012 (or nearest year)

Source: OECD Health Statistics 2014.
Trends in alcohol per capita in different region in Europe

* The 95% confidence intervals are represented as shading.
Consumption levels by type of alcohol, and country drinking score

Note: The drinking score is defined as 1 least risky, 2 somewhat risky, 3 medium risky, 4 very risky, 5 most risky.
Metabolisms of etanol in hepatocyte
Metabolisms of ethanol

All systems should lead to toxic damage

- Alcohol dehydrogenase
  - Dimeric proteins, two active site
  - Classes I-V
  - Genes ADH 1-7
  - Proteins – α β γ μ σ χ
  - Chromosome 4

- MEOS – CYP2E1
- Catalase
- Non-oxidative metabolism
Metabolic effect I

Via direct effect
- Membrane alterations
- Malnutrition

Via ADH and AlDH oxidation
- Increasing NADH
- Changing of redox potential
Oxidation of ADH and AI DH

- **Increasing**
  - Lactate
  - Uric acid
  - Ketone bodies

- **Decreasing**
  - Gluconeogenesis
  - Krebs cycle
  - Glucuronidations

- **Acidosis**

- **Oxidative stress**
Metabolic effects II

Via acetaldehyde

- Toxic and reactive substances
- Impairment of mitochondrial transport
- Oxidative stress
- Modification of proteins and DNA
- Interference with DNA repair
- Binds to proteins and forms neoantigens
- Delays cell cycle progression
Metabolic effects III

Via MEOS

- Activation of hepatotoxins and cancerogens
- Changes of oxidation of alcohols – e.g. retinol
- Increasing of beta-oxidation of fatty acids and esterification of fatty acids
OXIDATIVE STRESS AND ETHANOL METABOLISM

- Neutrophils
- Kupffer cells
- CYP2E1
- Aldehyde and xanthine oxidase
- Fe

OXIDANT STRESS ($O_2^{•−}$)

- Fibrosis
- Mitochondrial dysfunction
- Polyunsaturated fat

Depletion of antioxidants (Vit. A, E, GSH)

Lipid peroxidation
Ethanol-induced oxidative stress mechanisms

Peroxidation of lipids, nucleic acids, and proteins

Direct

\[ \text{CH}_3\cdot \text{CH-OH} \]

\[ \cdot \text{OH} \] (Hydroxethyl)

\[ \text{C}_2\text{H}_5\cdot \text{OH} \]

(Ethanol)

Indirect

Glutathione peroxidase activity

Mitochondrial Damage

Reactive oxygen species (ROS)

CYP2E1

Mitochondria

Glutathione pool
Alcohol related diseases

- Liver diseases
  - Alcohol is the most frequent cause of liver cirrhosis in Europe and US
  - Alcoholic liver disease constitutes $\frac{1}{3} - \frac{1}{2}$ of patients indicated for liver transplantation.
- Injuries
- Nutritional deficiencies
- Cardiovascular diseases
- Cancer
Major theories of alcohol liver damage

Steatosis – fibrosis – cirrhosis - carcinoma

- Neutrophil infiltration
- Centrilobular hypoxia
- Genetic factors
- Antigenic adduct formation - derived from lipid peroxidation products 4HNE and MDA
- Action of injurious cytokines, endotoxin,
Acetaldehyde and CYP2E1 as Pathogenetical Factors in ALD

- Gut derived Endotoxines
- Hepatic Kupffer cells
- Mitochondrial Damage
- DNA-Adducts
- Protein Adducts
- Autoantigens
- Functional Impairment
- Carcinogenesis
- Xanthinoxidase
- Retinoid Metabolism
- Procarcinogen Activation
- TNFα, Chemokines, Osteopontin
- NFκB
- STAT-JAK
- JNK
- ALD
- ALD
Alcohol related diseases II

- Damage of nervous system
- Development of osteoporosis
- Pancreas damage
  - Chronic pancreatitis 50%
- Fetal alcohol syndrome
  - 1.3 new born child /1000 child
    - Hypotrofy of fetus
    - Changes of intelect
- Myopathy and cardiomyopathy
  Acute and chronic myopathy,
NADPH-diaphorase positive neurons – stratum griseum superficiale

Controls

Ethanol-fed rats

Zima et al
Alcohol and cancers

- **Upper digestive tract**
  - 25-68 % risk factor – alcohol
  - very common, especially in Europe
  - 5.2% of all cancer cases worldwide
  - 6.4% of all cancer cases in Europe

- **Liver – hepatocellular carcinoma**
  - 5. most frequent cancer
  - 3. most frequent cause of cancer mortality
  - Main risk factors for HCC in Europa and USA - Alcohol abuse, HC, NASH

- **Breast cancer – controversial data**

- **Colon cancer –**
  - WHO concensus conference - higher 20 g/ 12,5 g – metanalysis EtOH/daily increasing the risk
## Alcohol and cancer

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>DAILY ETHANOL (g)</th>
<th>LITERATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEN</td>
<td>WOMEN</td>
</tr>
<tr>
<td>UADT</td>
<td>25-49 (2.3-3-6)</td>
<td>10-20 (4.6)</td>
</tr>
<tr>
<td></td>
<td>(Cirrhosis)</td>
<td>(Cirrhosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bofetta + Garfinkel 1990</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maier + Sennwald 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harty et al. 1997</td>
</tr>
<tr>
<td>LIVER</td>
<td>&gt;24</td>
<td>&gt;12</td>
</tr>
<tr>
<td></td>
<td>(Cirrhosis)</td>
<td>(Cirrhosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burger et al. 2000 (MA)</td>
</tr>
<tr>
<td>BREAST</td>
<td>-</td>
<td>&gt;20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;12 (1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burger et al. 2000 &amp; Smith-Warner et al. 1998 (MA)</td>
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<tr>
<td></td>
<td></td>
<td>Fuchs et al. 1995</td>
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<tr>
<td></td>
<td></td>
<td>Thun et al. 1997</td>
</tr>
<tr>
<td>COLORECTUM</td>
<td>&gt;30-50(2.5)</td>
<td>&gt;30-50(2.5)</td>
</tr>
<tr>
<td>(POLYPS)</td>
<td>&gt;30 (1.8)</td>
<td>&gt;30 (2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scheppach et al. 1999 (MA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cho et al. 2004 (MA)</td>
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<tr>
<td></td>
<td></td>
<td>Keanny et al. 1995</td>
</tr>
</tbody>
</table>
Chronic alcohol consumption is a risk factor for upper alimentary tract cancer, liver cancer.

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Pooled RR (95% Confidence Interval) Associated With Alcohol Consumption*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral and Pharyngeal Cancer</td>
<td>1.75 (1.70–1.82) 2.85 (2.70–3.04) 6.01 (5.46–6.62)</td>
</tr>
<tr>
<td>Laryngeal Cancer</td>
<td>1.38 (1.32–1.45) 1.94 (1.78–2.11) 3.95 (3.43–4.75)</td>
</tr>
<tr>
<td>Esophageal Cancer</td>
<td>1.51 (1.48–1.55) 2.21 (2.11–2.31) 4.23 (3.91–4.59)</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>1.17 (1.11–1.23) 1.36 (1.23–1.51) 1.86 (1.53–2.27)</td>
</tr>
</tbody>
</table>

*The consumption levels analyzed correspond to approximately two, four, and eight standard drinks per day, respectively. A standard drink is frequently defined as 12 fl oz of beer, 5 fl oz of wine, or 1.5 fl oz of 80-proof distilled spirits, all of which contain approximately 0.5 oz (14 g) of pure alcohol.

SOURCE: Bagnardi et al. 2001
Ethanol metabolism and ADH, ALDH Polymorphisms

ADH1B*2/ADH1C*1

ETHANOL ➔ ACETALDEHYDE ➔ ACETATE

ALDH2*2

e.g. - ADH1B, ADH1C, ALDH2 increase in UADT Cancers in central European population – Hashibe 2006
Mechanisms of alcohol-mediated carcinogenesis
Estimated increase in the relative risk of incident cancer per 10-g/d increase in alcohol intake (drinkers only) Million Women Study

<table>
<thead>
<tr>
<th>Cancer site or type (ICD-10)</th>
<th>Number of cases in drinkers</th>
<th>% increase in relative risk (95% CI) per 10-g/day increase in alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx (C32)</td>
<td>99</td>
<td>44 (10 to 88)</td>
</tr>
<tr>
<td>Oral cavity and pharynx (C00-C14)</td>
<td>557</td>
<td>29 (14 to 45)</td>
</tr>
<tr>
<td>Liver (C22)</td>
<td>223</td>
<td>24 (2 to 51)</td>
</tr>
<tr>
<td>Esophagus (C15)</td>
<td>534</td>
<td>22 (8 to 38)</td>
</tr>
<tr>
<td>Breast (C50)</td>
<td>21971</td>
<td>12 (9 to 14)</td>
</tr>
<tr>
<td>Rectum (C19-C20)</td>
<td>1633</td>
<td>10 (2 to 14)</td>
</tr>
<tr>
<td>Malignant melanoma (C43)</td>
<td>1999</td>
<td>4 (-3 to 12)</td>
</tr>
<tr>
<td>Pancreas (C25)</td>
<td>947</td>
<td>4 (-6 to 15)</td>
</tr>
<tr>
<td>Lung (C34)</td>
<td>3468</td>
<td>3 (-2 to 9)</td>
</tr>
<tr>
<td>Leukemia (C91-C93, C95)</td>
<td>742</td>
<td>3 (-8 to 16)</td>
</tr>
<tr>
<td>Brain (C71)</td>
<td>684</td>
<td>1 (-11 to 14)</td>
</tr>
<tr>
<td>Colon (C18)</td>
<td>3122</td>
<td>1 (-5 to 6)</td>
</tr>
<tr>
<td>Cervix (C53)</td>
<td>325</td>
<td>0 (-16 to 19)</td>
</tr>
<tr>
<td>Ovary (C56)</td>
<td>2713</td>
<td>-1 (-7 to 5)</td>
</tr>
<tr>
<td>Endometrium (C54)</td>
<td>2948</td>
<td>-3 (-8 to 3)</td>
</tr>
<tr>
<td>Multiple myeloma (C90)</td>
<td>573</td>
<td>-4 (-16 to 10)</td>
</tr>
<tr>
<td>Bladder (C67)</td>
<td>657</td>
<td>-7 (-18 to 5)</td>
</tr>
<tr>
<td>Stomach (C16)</td>
<td>545</td>
<td>-7 (-19 to 7)</td>
</tr>
<tr>
<td>Renal cell carcinoma (C64)</td>
<td>803</td>
<td>-12 (-22 to -1)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma (C82-C85)</td>
<td>1704</td>
<td>-13 (-19 to -5)</td>
</tr>
<tr>
<td>Thyroid (C73)</td>
<td>305</td>
<td>-25 (-39 to -8)</td>
</tr>
</tbody>
</table>
Alcohol and cancer - conclusion

- Alcoholic beverages are carcinogenic to humans.
- 10% of all cancers in men and 3% in women could be attributed to alcohol consumption.
- The occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus, liver, colorectal cancer and female breast is causally related to alcohol consumption.
- Association is suspected for pancreas and lung cancer.
Mechanisms of Alcohol Induced Tissue Injuries

**Direct and Indirect Effects of Alcohol**

- **Liver damage**
  - Pancreatic damage
  - Gastrointestinal damage

- **Indirect effects of alcohol**
  - Acetaldehyde metabolite formation
  - Metabolic deregulation; e.g., increased catabolism
  - Malnutrition
  - Altered circulating cytokine expression
  - Neurohormonal activation

- **Cardiovascular damage**
  - **Direct effects of alcohol**:
    - Inflammatory markers; e.g., TNF, SDF-1, IL-6, IL-1 INF-g
    - Oxidative stress “ROS”
    - Mitochondrial dysfunction
    - Endoplasmic Reticulum (ER) stress
    - Disruption of Protein biosynthesis
    - Dysregulation of protein metabolism

- **Heart damage**
  - **Inflammatory markers**
  - Contractile dysfunction
  - Cardiac arrhythmia
  - Cardiomyopathy
  - Heart failure

- **CNS damage**
  - **Brain damage**:
    - Neuroinflammation
    - Altered hippocampus structure and function
    - Neuronal damage

*FIGURE 1* | Mechanisms of alcohol-induced tissue injuries.
Estimated future years of life lost by extent of alcohol consumption (compare - 0-100g/week)
Different risk of alcohol-related diseases in Europe – 7 x

Eastern part of the European Region: 1424*
- Liver cirrhosis
- Cancer
- Cardiovascular diseases
- Injuries

Entire European Region: 527*

Mediterranean part of the European Region: 197*

*Annual deaths per million people
Alcohol and Europe

- EU –losses 125 mld EUR/year
- 55 million adults are estimated to drink at harmful levels in the EU (more than 40g of alcohol)
- Harmful alcohol consumption is estimated to be responsible for approximately 195 000 deaths a year in the EU due to e.g. accidents, liver disease, cancers, suicides etc.
- Harmful alcohol use is the 3rd biggest cause of early death and illness in the EU, behind tobacco and high blood pressure.
- 1 in every 7 deaths in men and 1 in every 13 deaths in women in the group aged 15–64 years was due to alcohol consumption
- Alcohol influencing to deaths in young generation (15-29 years) World 5%, Europe 25%, Eastern Europe 33%
Co-operations and support

- **Colleagues and friends**
  - Helmut Seitz
  - Marta Kalousová
  - Otto Lesch
  - Petr Popov
  - Michal Miovský
  - …..

- **Colleagues and laboratory staff from my department**

- **Studies were supported by grants given by the Czech Ministry of Health and the Czech Ministry of Education and Charles University**
Si nimium bibis, non diueris in vivis.
## Hazard ratios for subtypes of cardiovascular outcomes in current drinkers (>100 g/week)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Events/participants</th>
<th>Hazard ratio (95% CI)</th>
<th>Heterogeneity $I^2$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke</td>
<td>12090/585588</td>
<td>1.14 (1.10-1.17)</td>
<td>12 (0-35)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>9910/491050</td>
<td>1.14 (1.10-1.18)</td>
<td>14 (0-40)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>2142/532204</td>
<td>1.13 (1.07-1.19)</td>
<td>0 (0-35)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>6256/491204</td>
<td>1.13 (1.09-1.18)</td>
<td>8 (0-37)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1482/505948</td>
<td>1.17 (1.12-1.23)</td>
<td>0 (0-37)</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>663/412732</td>
<td>1.09 (1.00-1.19)</td>
<td>0 (0-58)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>3215/527729</td>
<td>1.13 (1.06-1.20)</td>
<td>14 (0-40)</td>
</tr>
<tr>
<td>All myocardial infarction</td>
<td>14539/594561</td>
<td>0.94 (0.91-0.97)</td>
<td>12 (0-35)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>11706/515377</td>
<td>0.93 (0.90-0.97)</td>
<td>24 (0-45)</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>2748/538117</td>
<td>0.99 (0.93-1.05)</td>
<td>8 (0-35)</td>
</tr>
<tr>
<td>Coronary disease excluding myocardial infarction</td>
<td>7990/523548</td>
<td>1.06 (1.00-1.11)</td>
<td>26 (0-49)</td>
</tr>
<tr>
<td>Non-fatal coronary disease excluding myocardial infarction</td>
<td>6000/389976</td>
<td>1.00 (0.97-1.03)</td>
<td>0 (0-52)</td>
</tr>
<tr>
<td>Fatal coronary disease excluding myocardial infarction</td>
<td>1889/510147</td>
<td>1.11 (1.04-1.18)</td>
<td>12 (0-40)</td>
</tr>
<tr>
<td>Heart failure (fatal and non-fatal)</td>
<td>2711/447436</td>
<td>1.09 (1.03-1.15)</td>
<td>4 (0-31)</td>
</tr>
<tr>
<td>Death from other types of cardiovascular disease</td>
<td>1121/488122</td>
<td>1.18 (1.07-1.30)</td>
<td>33 (2-53)</td>
</tr>
<tr>
<td>Cardiac dysrhythm</td>
<td>261/71682</td>
<td>1.17 (0.86-1.60)</td>
<td>63 (35-79)</td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>178/383269</td>
<td>1.24 (1.15-1.33)</td>
<td>0 (0-55)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>283/68002</td>
<td>1.12 (0.90-1.41)</td>
<td>29 (0-63)</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>289/423145</td>
<td>1.15 (1.03-1.28)</td>
<td>0 (0-49)</td>
</tr>
</tbody>
</table>

Lower risk of disease with higher alcohol consumption   
Higher risk of disease with higher alcohol consumption
Calculation for protective effective of alcohol

- 100g/week = 15 g/day
- 200g/week = 30 g/day
- 15-30 g/day

- 0,3-0,6 L beer (50g/L)
- 1-2 dl wine (150g/L)
- 0,3-0,9 dl Spirit (400g/L)