Alcohol and Cancer: Defining the Exposure and Key Milestones in Establishing the Relationship

Susan M. Gapstur, PhD, MPH
Vice President, Epidemiology
American Cancer Society
As required by the Alcohol Policy 18 Conference, I/we have signed a disclosure statement and note the following conflict(s) of interest:

The American Cancer Society accepts support from alcohol industries which is used to support the Society's programs and services, including research.
Archeologic Evidence Shows Alcohol Produced as Early as 7000–6600 BC in China*

• Religious,
• Social
• Cultural

McGovern et al., *Proc Natl Acad Sci*, 101(51), 17593–8; 2004
Types of Alcoholic Beverages Most Commonly Consumed

<table>
<thead>
<tr>
<th>12 fl oz Regular Beer</th>
<th>5 fl oz Table Wine</th>
<th>1.5 fl oz shot 80-Proof Spirits</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% ethanol</td>
<td>12 % ethanol</td>
<td>40% ethanol</td>
</tr>
</tbody>
</table>

A drink that contains about 14 grams of pure ethanol.

Trends in Per Capita Ethanol Consumption (gallons), United States, 1935–2014

1981 = 2.75 gallons

2014 = 2.32 gallons

Trends in Per Capita Ethanol Consumption (gallons) by Beverage Type, United States, 1977–2014.

Alcohol Metabolism

Induced at high amounts
WHO Estimates of Health Effects of Alcohol Consumption

- 5.9% of all deaths
- 5.1% of disease
- 200 health conditions in which harmful alcohol drinking is a component cause, including, for example:
  - Unintentional injuries
  - Burns, falls, motor vehicle crashes
  - Drowning, homicide, suicide
  - Birth defects
  - Depression
  - GI disorders: stomach bleeding, liver and pancreas diseases
  - Sleep disorders
  - Sexually transmitted infection from unsafe sex
  - Seven types of cancer
Early Epidemiologic Evidence that Alcohol Consumption is Associated with Cancer Risk


Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey.

Williams RR, Horm JW.

- **Personal interviews from 7,518 incidence cases of invasive cancer**
  - Lifetime use of cigarettes, cigars, pipes, other tobacco,
  - Wine, beer, liquor
  - Education and family income
- **Consumption for cases of one cancer type compared to other cancer types**
- **Findings showed that alcohol consumption was associated with cancers of:**
  - Oral cavity
  - Larynx
  - Esophagus
  - Colon rectum
  - Breast
  - Thyroid
The IARC Monographs Program

Convenes international panel of experts to evaluate carcinogenic risks to humans posed by “environmental” factors (e.g., chemicals, occupational exposures, physical agents, biological agents, and personal habits).

- Define exposure
- Human evidence
- Animal studies
- Mechanistic studies
Evaluate **Strength of Evidence for Carcinogenicity**

Not **Strength of Association (Relative Risk)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Classification</th>
<th>Parameter</th>
<th>No. of Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>I*</td>
<td>Carcinogenic to humans</td>
<td>Sufficient evidence of carcinogenicity in humans (or in experimental animals and mechanistic studies)</td>
<td>120</td>
</tr>
<tr>
<td>2A</td>
<td>Probably carcinogenic to humans</td>
<td>Limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals</td>
<td>81</td>
</tr>
<tr>
<td>2B</td>
<td>Possibly carcinogenic to humans</td>
<td>Limited evidence of carcinogenicity in humans and less than sufficient evidence in experimental animals</td>
<td>294</td>
</tr>
<tr>
<td>3</td>
<td>Agent is <strong>not classifiable</strong> as to its carcinogenicity to humans</td>
<td>Inadequate evidence of carcinogenicity in humans and in experimental animals</td>
<td>505</td>
</tr>
<tr>
<td>4</td>
<td>Agent is <strong>probably not</strong> carcinogenic to humans</td>
<td>Evidence suggesting lack of carcinogenicity in humans and in experimental animals</td>
<td>1</td>
</tr>
</tbody>
</table>

* An agent can be in Group 1 in the absence of sufficient evidence for carcinogenicity in humans if there is sufficient data in experimental animals and strong evidence that the agent acts through similar mechanism in humans.
IARC Monograph Program: Evaluation of Alcohol and Cancer


2007 Volume 96 (2010)

2009 Volume 100E (2012)
Sufficient Evidence of Carcinogenicity (Group 1) for Alcoholic Beverages, Ethanol in Alcoholic Beverages*, and Acetaldehyde

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Alcoholic Beverages</th>
<th>Ethanol*</th>
<th>Acetaldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectum</td>
<td>2010, 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female breast</td>
<td>2010, 2012</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*2007: “Ethanol” in alcohol beverages is carcinogenic (but no statement about specific type of cancer).
Evidence of Lack of Carcinogenicity (Group 4) for Alcohol with Two Types of Cancer

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Alcoholic Beverages</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL</td>
<td>2007, 2009</td>
</tr>
<tr>
<td>Kidney</td>
<td>2007, 2009</td>
</tr>
</tbody>
</table>
Historic Estimates of Proportion of Cancer Deaths Attributed to Alcohol Consumption in the U.S.

- Rothman et al. (1980): 3% of all US cancer deaths in 1974
- Doll and Peto (1981): 2% to 4% of US cancer deaths in late 1970s
- Nelson et al. (2013): 3.2-3.7% of US cancer deaths in 2009
Proportion and Number of Cancer Cases and Deaths Attributable to Potentially Modifiable Risk Factors in the United States

Farhad Islami, MD, PhD; Ann Goding Sauer, MSPH; Kimberly D. Miller, MPH; Rebecca L. Siegel, MPH; Stacey A. Fedewa, PhD, MPH; Eric J. Jacobs, PhD; Marjorie L. McCullough, ScD, RD; Alpa V. Patel, PhD; Jiemin Ma, PhD, MHSc; Isabelle Soerjomataram, MD, PhD, MSc; W. Dana Flanders, MD, DSc, MPH, MA; Otis W. Brawley, MD, MACP; Susan M. Gapstur, PhD, MPH; Ahmedin Jemal, DVM, PhD

- The proportion and number of invasive cancer cases and deaths,
- Overall (excluding nonmelanoma skin cancers) and for 26 cancer types,
- Adults aged 30 years and older in the United States in 2014
- For major, potentially modifiable exposures

| ✓ cigarette smoking | ✓ secondhand smoke | ✓ excess body weight |
| ✓ physical inactivity | ✓ ultraviolet radiation | ✓ alcohol intake |
| ✓ dietary fiber | ✓ dietary calcium | ✓ consumption of red and processed meat |
| ✓ low consumption of fruits/vegetables | ✓ 6 cancer-associated infections |   |
Incident Cancer Cases
Attributed to Alcohol Consumption in U.S. (2014)

4th in men

3rd in women

3rd in both

Cancer Deaths
Attributed to Alcohol Consumption in U.S. (2014)

PAFs for Specific Types of Alcohol-Related Cancers (U.S., 2014) (men and women combined except breast)

<table>
<thead>
<tr>
<th>Alcohol associated cancers</th>
<th>Incident Cases N (%)</th>
<th>Deaths N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>18,130 (40.9%)</td>
<td>3,640 (38.9%)</td>
</tr>
<tr>
<td>Larynx</td>
<td>2,930 (23.2%)</td>
<td>840 (22.3%)</td>
</tr>
<tr>
<td>Liver</td>
<td>5,750 (21.6%)</td>
<td>3,840 (20.4%)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3,540 (21.0)</td>
<td>2,510 (16.8%)</td>
</tr>
<tr>
<td>Female breast</td>
<td>39,060 (16.4%)</td>
<td>6,350 (15.4%)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>18,090 (12.8%)</td>
<td>6,290 (12.0%)</td>
</tr>
<tr>
<td><strong>TOTAL CANCER</strong>*</td>
<td><strong>87,600 (5.6%)</strong></td>
<td><strong>23,510 (4.0%)</strong></td>
</tr>
</tbody>
</table>

* Excludes non-melanoma skin cancer

Alcohol and Cancer: Possible Biologic Mechanisms

- **Contaminants of alcoholic beverages**
  - introduced during fermentation and production

- **Alcohol Metabolism**
  - Acetaldehyde increases liver cell proliferation
  - Acetaldehyde can lead to DNA adduct formation/DNA and protein damage
  - Reactive oxygen species (ROS) formation

- **Liver cirrhosis**
  - Heavy alcohol consumption causes liver cirrhosis which increases liver cancer risk

- **Estrogen and hormones**
  - Alcohol increase levels of estrogen. (breast cancer)

- **Alcohol and other carcinogens**
  - Alcohol can increase absorption of other cancer causing agents in tobacco

- **Effects on absorption and metabolism of other nutrients**
  - e.g., Alcohol can reduce folate absorption in the gut
Biologic Effects of Alcohol Consumption on CVD Risk Factors

- **Possible Benefit:** up to 1 drink per day
  - Lower risk of CHD
  - Higher levels of HDL cholesterol
  - Improved insulin sensitivity
  - Decreased fibrinogen levels
  - Decreased inflammatory markers (e.g., CRP, IL-6)

- **RISKS:** Drinking too much alcohol
  - Higher risk of hemorrhagic stroke
  - Increased circulating triglycerides
  - Increased blood pressure
  - Increased risk of heart failure, cardiomyopathy and cardiac arrhythmia
Biologic Effects of Alcohol Consumption on CVD Risk Factors

- **BENEFIT**: Moderate consumption
  - Higher levels of HDL cholesterol
  - Improved insulin sensitivity
  - Decreased fibrinogen levels
  - Decreased inflammatory markers (e.g., CRP, IL-6)

- **RISKS**: Drinking too much alcohol
  - Increased circulating triglycerides
  - Increases blood pressure
  - Increases risk of heart failure, cardiomyopathy and cardiac arrhythmia

Recent Mendelian randomization studies have called into question the potential CVD benefits of alcohol consumption (Holmes et al, 2014; Cho et al, 2015).
Alcoholic Beverage Consumption Guidelines

- **American Cancer Society Guidelines for Cancer Prevention**
  “If you do not drink alcohol, do not start drinking. For those who do drink alcoholic beverages limit consumption to no more than 2 drinks per day for men and 1 drink per day for women.”  

- **American Institute for Cancer Research**
  “*For cancer prevention*, AICR recommends not to drink alcohol...If you do drink alcohol, limit your consumption to no more than two drinks a day for men and one drink a day for women...”  

- **American Heart Association**
  If you drink alcohol, do so in moderation. This means an average of 1-2 drinks per day for men and 1 drink per day for women.” (The American Heart Association cautions people NOT to start drinking ... if they do not already drink alcohol).
  http://www.heart.org/HEARTORG/HealthyLiving/HealthyEating/Nutrition/Alcohol-and-Heart-Health_UCM_305173_Article.jsp#.WsURPGPrv1c
Thank You