Diet and Lifestyle Factors in Cancer Risk

Robert J. Turesky, Ph.D.
Professor
Masonic Chair in Cancer Causation
Masonic Cancer Center
Department of Medicinal Chemistry
Disclosure

- I have no actual or potential conflict of interest in relation to this program/presentation.
A lot of research focuses on agents that can cause cancer.
“Alle Dinge sind Gift und nichts ist ohne Gift; allein die Dosis macht, dass ein Ding kein Gift ist.”

("All things are poison and nothing is without poison; only the dose makes a thing not a poison.")

Paracelsus
1493-1541

Paracelsus (born Philippus Aureolus Theophrastus Bombastus von Hohenheim)
Swiss physician, alchemist
Diet and cancer: many cancers are caused by lifestyle factors, not genetics

- Change in phyto-estrogen profiles from plants, soy?
- Exposures to “new” carcinogens

N-nitroso compounds from salted fish, pickled vegetables (nitrates)

What are carcinogens?

- Carcinogens generally cause damage after repeated or long-duration exposure. They may not have immediate apparent harmful effects, with cancer developing only after a long latency period.

- **Dose:** amount and duration of exposure. The lower the dose the least likely you are to develop cancer or related diseases.

- Carcinogens increase the risk of cancer by altering cellular metabolism or damaging DNA directly in cells, by forming DNA adducts, which interfere with biological processes, and induce mutations resulting in the uncontrolled, malignant division, ultimately leading to the formation of tumors.

- Chemicals formed endogenously, i.e. free radicals, lipid peroxidation can damage DNA too!
Examples of carcinogens

- Chemicals in the diet or environment that damage DNA (directly or indirectly)
- Lifestyle factors: tobacco, alcohol, diet, obesity
- Sunlight – irradiation
- Bacteria
- Viruses
Dietary & Environmental Exposures

Processed meat  Grilled meat  Bacon  Air pollution  Car exhaust

Coffee  Herbal medicine  Drugs  Plastic food containers  Pesticides

Alcohol  Plastic water bottles  Food packaging

Biospecimens

Urine  Blood  Hair  Saliva  Finger nails  Breast milk  Biopsy tissue
What is DNA?

- Biochemical information storage and retrieval system (a cell’s hard drive)
- Contains only 4 different components (A, C, G, and T) linked in two anti-parallel strands.
- DNA encodes for the information to produce our cells and our body
How do mutations and cancer occur and what is chemical carcinogenesis?

Chemicals in the environment or diet “latch-on” to DNA and induce a mutation when the cell divides.

Mutations that occur to genes that are tumor suppressor proteins (enzymes) are particularly bad!

![DNA Helix diagram](image)
Exposure Biomarkers for Molecular Epidemiology Studies

Traditional Epidemiology

External Exposure → Question Mark → Disease

Molecular Epidemiology

Biomarkers of Genetic Susceptibility

Exposure → Internal Dose → Biological Effective Dose → Early Biological Effects → Altered Function → Clinical Disease

Biomarkers of Exposure

Biomarkers of Diseases

Adducts

Mutation Spectra
How we measure chemicals and biomarkers in human studies?

A mass spectrometer measures the molecular weight of chemical like a scale measures our body weight.
What is the International Agency for Research on Cancer (IARC)?


- Leading experts in fundamental research and epidemiologists review the impact of chemicals and lifestyle factors on health risk for IARC

- IARC Monograph Vol 114: Red and Processed Meats: 22 experts from 10 countries – evaluated over 800 studies
Cancer Incidence and Mortality in the United States*

New Cancer Cases per Year

- Breast: 179,900
- Prostate: 186,300
- Lung & bronchus: 111,800
- Colon & rectum: 74,500
- Urinary bladder: 52,200
- Uterus: 41,500
- Non-Hodgkin lymphoma: 37,300
- Melanoma: 37,300
- Thyroid: 27,700
- Ovary: 20,800
- Oral cavity: 22,400
- Kidney: 29,800
- Leukemia: 22,400
- Pancreas: 159,000
- All other sites: 149,000

*Estimated numbers from the American Cancer Society, Inc., 2008.
Causes and risk factors of breast cancer

- Family history
- Gene mutation
- Late childbearing
- Early Menstruation & Late Menopause / Obesity
- Increased breast density
- Prolonged use of oral contraceptives
- Hormone replacement therapy after menopause
- Alcohol intake / tobacco
Alcohol (ethanol) is a risk factor for oral cavity, pharynx, larynx, esophagus, liver, colon and *breast cancer*

- The European Prospective Investigation into Cancer and Nutrition (EPIC) study reported that *10% of all cancers in men could be attributed to alcohol consumption*. 
Relative risk for breast cancer with alcohol consumption

Pooled analysis of data from 53 studies that included 58,515 women with breast cancer (adjusted by study, age, parity, age at first birth and tobacco smoking)
Alcoholic Beverages and Cancer Risk

What does cancer have to do with hangover?

- Ethanol
- Acetaldehyde
- Acetate

ADH: alcohol dehydrogenase
ALDH: aldehyde dehydrogenase

Energy that the body can use

Mistakes in DNA
DNA to bind and form clumps
Chromosome rearrangements
Estrogen and progestogens are required for normal development and function of multiple tissues.

Estrogen also can promote breast cancer development mostly via activation of growth factor pathways that prompt cells to divide.

[Image showing healthy growth and breast cancer processes related to estrogen and progestogen binding to receptors]

Packaging Materials and Breast Cancer Risk

- Bisphenol A can increase cell proliferation and increase risk of breast cancer
- The risk is controversial because high levels of exposure are needed to induce the effect!!
- Other synthetic chemicals also may contribute to breast cancer

https://doi.org/10.1016/j.gene.2016.05.009
Chemicals in plastics, such as Bisphenol A, can increase cell proliferation and increase risk of breast cancer – but the data is controversial!!

- The U.S. EPA established a reference dose (RfD) for humans at 50 µg BPA/kg body weight (BW) per day based on a 1000-fold reduction of the lowest observed adverse effect level (LOAEL) in rodent studies.

- The daily human intake of BPA is less than 1 µg per kg body weight per day, rendering the RfD to be considered safe to humans.

- Other studies suggest biological effects of Bisphenol A may occur at lower concentrations, or that there is a critical time window of exposure where bisphenol exerts toxic effects.
Mechanisms of breast carcinogenesis

**Inherited Mutations**

- About 12% of women in will develop breast cancer during their lives.
- About 72% of women who inherit a harmful \textit{BRCA1} mutation and about 69% of women who inherit harmful \textit{BRCA2} mutation will develop breast cancer.
- Ashkenazi Jewish harbor \textit{BRCA1} (8-10%) and \textit{BRCA2} (1%); White (non-Ashkenazi Jewish) harbor \textit{BRCA1} (2-3%) and \textit{BRCA2} (2%).
Cigarette smoke and cancer risk

**Chemical Compounds in Cigarette Smoke**

This graphic offers a summary of a selection of hazardous compounds in cigarette smoke and their effects.

**Estimated Number of Chemical Compounds in Cigarette Smoke**

- **Nicotine**: Approx. 90g per cigarette
  - Addictive
  - Increased heart rate
  - Increases blood pressure
  - Increases blood glucose
  - Lethal dose around 500-1000mg

- **Acetaldehyde**: Approx. 680-1571mg per cigarette
  - Reverses mental confusion
  - Adequate from re-cycling
  - Inescapable to skin & eyes
  - Inimical to respiratory tract

- **1,3-Eutadiene**: Approx. 36-99mg per cigarette
  - Reverses human carcinogen
  - Inimical to eyes & skin
  - Inimical to upper respiratory tract

- **Benzene**: Approx. 43-77mg per cigarette
  - Known human carcinogen
  - Damages hair & marrow
  - Looms red blood cell count
  - May cause reproductive damage

- **Acrolein**: Approx. 69-990mg per cigarette
  - Possible human carcinogen
  - Known DNA damage
  - Irreversible to skin & nasal passages
  - May contribute to heart disease

- **Polycyclic Aromatics**: Large class of compounds
  - Includes benzo(a)pyrene
  - Known human carcinogen
  - Linked with bladder cancer
  - Approx. 0.14g per cigarette
  - Up to 0.14g per cigarette

**Number of these compounds with confirmed carcinogenic activity**: 70

© Compound Interest 2015 - www.compoundchem.com | Twitter: @compoundchem | Facebook: www.facebook.com/compoundchem

This graphic is shared under a Creative Commons Attribution-NonCommercial-NoDerivatives Licence.
Other Life-style Factors and Chemical Exposures that Contribute to Cancer Risk

• Cigarettes (lung, esophagus, liver, pancreas, colon, mammary gland)

• Traditional herbal medicines (kidney, bladder, liver)

• Cooked meats and cooking fumes (lung, colon, pancreas, prostate, mammary gland)

• UV light, excessive sun exposure (skin cancer)
Some traditional Chinese herbal medicines cause cancer of the kidney, bladder, and liver. Aristolochia herbs are known to be particularly problematic.

**Drugs affected:**
- Cyclosporin
- Antidepressants
- Birth control pills
- Indinavir (HIV)
- Irinotecan (Cancer)
- Warfarin (anticoagulant)
Traditional Chinese Herbal Medicines and Aristolochia

- AA exposure occurs world-wide through herbs used in traditional herbal medicines.
- Despite FDA banning, the sale of herbs containing Aristolochia, AA is prevalent in products sold over the internet in USA.
- AA causes rare urothelial carcinomas of the upper urinary tract (UUC).
- AA induces the uncommon A:T-to-T:A transversions in P53 and other cancer driver genes throughout the genome in patients with UUC.
- AA is responsible for Aristolochic Acid Nephropathy (AAN), a chronic kidney disease, frequently accompanied by UUC.
- Aristolochic acid is Group 1 carcinogen (IARC, 2002).
Role of AA DNA Adducts in Mutations and Chemical Carcinogenesis

- dA-AL adducts induce an otherwise rare A to T transversion mutation in TP53 gene of patients with Aristolochic Acid Nephropathy (AAN) and Balkan Endemic Nephropathy (BEN)

- AA-I also contributes to hepatic, bladder and renal cell cancer

Grollman et al., Proc Natl Acad Sci. 2007
Chen et al., Proc Natl Acad Sci. 2012
Aristolochic acid nephropathy (AAN): a worldwide problem

Collin, et al., Transl Androl Urol, 2016

Heinz H. Schmeiser, Cancer Res. 56, 2025-2028,

Medicinal herbs containing Aristolochia

Contaminated wheat

Collin, et al., Transl Androl Urol, 2016
dA-AL-I Levels in Renal Cortex in Taiwan and Other Countries

132 out 148 (89%) Taiwan subjects were positive for dA-AL-I

B-H Yun et al., Toxicol. Res. 2015; unpublished data
Aristolochic DNA Adducts in Renal Cancer Patients Across Europe and Russia
Proportion of A:T > T:A mutations according to the quantity of 7-(deoxyadenosin-N^6-yl) aristolactam I (dA-AL-I)


Summary of Aristolochic Acid

- Aristolochic Acid (AA) exposure occurs predominately in Asia and the Balkans, but also throughout the world.
- Despite banning by regulatory agencies, some traditional medicines still contain Aristolochia.
- Mutation data show that AA contributes to UUC, but also renal cell, bladder, and liver cancers.
- Mass spectrometry can measure AA exposure through dA-AL-l adducts in human tissues.
- Herbal products are “natural” but that does not mean they are safe!
Meat Consumption and Colorectal Cancer (CRC)

International Agency for Research on Cancer (IARC) Monographs, Oct. 2015:

- Processed meat is ‘carcinogenic to humans’ (Group 1)
- Red meat is ‘probably carcinogenic to humans’ (Group 2A)
- Red meat is associated with pancreatic and prostate cancer

**CRC-causing agents**

- N-nitroso compounds in processed meats
- Heterocyclic Aromatic Amines (HAAs) in cooked red meat
- HAAs are multisite carcinogens in rodents
- HAAs are Group 2A or 2B carcinogens
What is red and processed meat?

- **Red meat:** unprocessed mammalian muscle meat, e.g. beef, veal, pork, lamb, horse or goat meat—including minced or frozen meat.

- **Processed meat:** Meat that has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavor or improve preservation (e.g. bacon, sausage, hot dogs, lunch meats)
Mechanisms of colorectal DNA damage by meat

- **Exogenous**
  - Processed meat
    - N-nitroso compounds
- **Endogenous formation**
  - DNA damage

**Red meat**
- Heme iron
- N-Nitroso compounds, lipid peroxides, bacteria flora

**Processed meat**
- HAAs
- PAHs
- B[a]P

Cooked meat mutagens

A food frequency questionnaire is used in epidemiology studies to gauge an individual's eating habits.
Metabolism of Genotoxicants

Caveat: Chemical biomarkers represent recent exposures whereas mutations are an accumulation of exposures over time.

LPO: lipid peroxidation
Biomarkers for HAA Exposure

- PhIP DNA adduct: dG-C8-PhIP
- Urinary metabolites: PhIP-HO-N2-Gluc, PhIP-HN2-O-Gluc
- Caffeine CYP1A2 phenotype
- PhIP albumin-Cys34 adduct
- Sulfinamide

PhIP in hair

Skin

Cortex

Artery

Vein

Sulfinamide
Dietary nitrites form $N$-nitroso compounds (NOCs): Do NOCs in processed meats contribute to colon cancer?

- Nitrite in processed meat can react with amines to form $N$-nitroso compounds (NOCs)
- Acidic conditions in the stomach can promote NOC formation
- NOCs can be metabolized into species which can alkylate DNA
- Alkylation of $O^6$ of dG is a major mutagenic lesion of NOCs

DNA Adducts and Mutations

The biomarkers represent the primary pathological site object of the clinical intervention.

The biomarkers represent the sum of all the heterogenous tumor sites, including possible changes of geno/phenotype.

Colon polyp removal

Finotti et al., J Oncol. 2018
How much meat can I eat?
How bad is eating meat?

The World Health Organization has determined that eating processed meat is unhealthy.

Is bacon really as bad as tobacco?
Meta-Analysis of Red & Processed Meat and Colorectal Cancer

Relative Risk

Red meat

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Subgroup</th>
<th>RR (95% CI) per 100g/day increase</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pietinen</td>
<td>1999</td>
<td>Male</td>
<td>0.83 (0.43, 1.61)</td>
<td>2.92</td>
</tr>
<tr>
<td>Jarvinen</td>
<td>2001</td>
<td>Mixed</td>
<td>1.37 (0.92, 2.06)</td>
<td>7.74</td>
</tr>
<tr>
<td>Tiemersma</td>
<td>2002</td>
<td>Mixed</td>
<td>1.69 (0.88, 3.23)</td>
<td>2.98</td>
</tr>
<tr>
<td>English</td>
<td>2004</td>
<td>Mixed</td>
<td>1.19 (0.89, 1.56)</td>
<td>16.79</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>Female</td>
<td>1.23 (0.90, 1.67)</td>
<td>13.11</td>
</tr>
<tr>
<td>Norat</td>
<td>2005</td>
<td>Mixed</td>
<td>1.21 (1.02, 1.43)</td>
<td>44.43</td>
</tr>
<tr>
<td>Lee</td>
<td>2009</td>
<td>Female</td>
<td>0.80 (0.52, 1.23)</td>
<td>6.78</td>
</tr>
<tr>
<td>Nothlings</td>
<td>2009</td>
<td>Mixed</td>
<td>1.00 (0.64, 1.57)</td>
<td>6.25</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>(I-squared = 0.0%, p = 0.483)</td>
<td>1.17 (1.05, 1.31)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Processed meat

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Subgroup</th>
<th>RR (95% CI) per 50g/day increase</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pietinen</td>
<td>1999</td>
<td>Male</td>
<td>1.01 (0.80, 1.27)</td>
<td>9.87</td>
</tr>
<tr>
<td>Flood</td>
<td>2003</td>
<td>Female</td>
<td>1.17 (0.76, 1.61)</td>
<td>3.13</td>
</tr>
<tr>
<td>English</td>
<td>2004</td>
<td>Mixed</td>
<td>1.61 (1.12, 2.30)</td>
<td>4.44</td>
</tr>
<tr>
<td>Lin</td>
<td>2004</td>
<td>Female</td>
<td>0.56 (0.24, 1.33)</td>
<td>0.80</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>Female</td>
<td>1.13 (0.85, 1.51)</td>
<td>6.77</td>
</tr>
<tr>
<td>Norat</td>
<td>2005</td>
<td>Mixed</td>
<td>1.15 (1.03, 1.28)</td>
<td>33.90</td>
</tr>
<tr>
<td>Balder</td>
<td>2006</td>
<td>Mixed</td>
<td>1.21 (0.91, 1.61)</td>
<td>6.88</td>
</tr>
<tr>
<td>Cross</td>
<td>2007</td>
<td>Mixed</td>
<td>1.26 (1.13, 1.40)</td>
<td>31.84</td>
</tr>
<tr>
<td>Nothlings</td>
<td>2009</td>
<td>Mixed</td>
<td>1.21 (0.74, 2.00)</td>
<td>2.36</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>(I-squared = 12.2%, p = 0.333)</td>
<td>1.18 (1.10, 1.28)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Chan, PLoS ONE 2011
Non-linear dose-response meta-analysis of red and processed meats consumption and risk of colorectal cancer

Chan et al., PLoS One 2011
Smoking a pack of cigarettes for 40 years increases your risk of developing lung cancer by ~30-fold.
Meat preference, metabolic genotype and phenotype, and Smoking Status in Colorectal Cancer

- Tobacco smoke contains chemicals which induce CYP1 activity
- CYP1A2 and NAT2 are important enzymes for bioactivating HAAs
- A group of smokers stratified by cooked meat preference, CYP1A2 phenotype, and NAT2 phenotype for CRC risk, shown on the right

Well-done cooked red meats linked to prostate cancer

- What chemical/s contained in red meat is/are responsible for DNA damages of human colon and prostate?
- Looking for biomarkers to understand the chemical agents that contribute to DNA damage of the prostate
- Develop strategies for cancer prevention
Bioactivation of HAAs and DNA Adduct Formation in Human Prostate

- LOQ, 2 adducts/10^9 DNA bases
- Thus far, only DNA adducts of PhIP and not other cooked meat mutagens have been detected in prostate DNA of cancer patients

Bellamri, M., et al., Tox. Sci, 2018
One-third of Prostate Cancer Patients have PhIP-DNA Adducts

Biomonitoring Carcinogenic Heterocyclic Aromatic Amines in Hair

The Turesky Family

PhIP Levels in Hair of Human Omnivores, and Vegetarians, and Fur of Canines

PhIP is present in canine fur too!

Does kibble containing PhIP contribute to canine cancer?
Biomonitoring of PhIP in Animal Fur and Human Hair

**PhIP Standard, MS^2**

**[^2H_3]C-PhIP**

$m/z$ 228.1 > 210.1

$t_R$: 8.2

A: 2.3E6

**PhIP**

$m/z$ 225.1 > 210.1

$t_R$: 8.2

A: 3.9E5

**HPLC-QqQ-MS**

- LOQ: 25 pg PhIP/g hair
- % CV (within-day and between day): <10%


Turesky et al., Cancer Epidemiol. Biomarkers & Prev.
Does a dog’s diet contribute to **cancer**?

- High temperature cooking of meat or fish produces **heterocyclic aromatic amines**.
- Do dogs eat food that has been exposed to high temperatures? Yes!
- **Acrylamide** is also formed at high temperature cooking.

[https://healthypets.mercola.com/sites/healthypets/archive/2013/05/27/cooked-meat-carcinogens.aspx](https://healthypets.mercola.com/sites/healthypets/archive/2013/05/27/cooked-meat-carcinogens.aspx)
Scientist Accidentally Discovers a Possible Culprit in the Growing Incidence of Cancer

May 27, 2013  |  40,812 views

Spread the Word to Friends And Family By Sharing this Article!

1,034  |  74  |  15  |  17  |  3  |  248

Dr. Becker Interviews Dr. Turesky

https://healthypets.mercola.com/sites/healthypets/archive/2013/05/27/cooked-meat-carcinogens.aspx
PhIP and human cancer

• PhIP is formed in well-done cooked red meats

• ~10% of prostate cancer patients have their DNA damaged by PhIP

• We can measure PhIP in human hair

• Comparing increased levels of PhIP with VERY AGGRESSIVE prostate cancer

• Can a snip of hair identify individuals at risk?
Hair as a Biomarker for PhIP Exposure from a Semi-Controlled Cooked Meat Feeding Study

The accrual of other prototypical HAAs in hair is very low

Dose-dependent increase in PhIP hair levels/melanin
\( (\rho = 0.68, P < 0.0001) \)

\[ y = 8.6974x + 13.215 \]

\( R^2 = 0.441 \)

PhIP in hair

Hair Collection → Hair Digestion

Solid-phase Extraction → Liquid-liquid Extraction

HPLC-QqQ-MS

LOQ: 1.25 pg PhIP/50 mg hair

Turesky et al., CEBP, 2013
Le Marchand, et al., Carcinogenesis, 2016

Dose-dependent increase in PhIP hair levels/melanin

\( (\rho = 0.68, P < 0.0001) \)

\[ y = 8.6974x + 13.215 \]

\( R^2 = 0.441 \)
PhIP in Scalp Hair of Prostate Cancer Patients at UMN

Do PhIP hair levels correlate to
• DNA damage?
• Gleason Score and tumor aggressiveness?

Are there other chemicals in hair linked to Prostate Cancer? Or other diseases?
Safe Cooking and Handling of Barbeque Grills

• Avoid exposure to the smoke generated from cooked meats as they can contain mutagens and potential carcinogens

• Don’t over-cook meat!! Avoid eating well-done, charred meat

• Flip meat samples often and use marinades to minimize formation of carcinogens

• Use gloves when removing charred residues on grilled surface - burnt residues may contain carcinogens too!
Radiation

- **Ultraviolet** (UV-B light 280-320 nm) from the sun can increase the risk of squamous carcinoma, basal cell carcinoma and malignant melanoma of the skin.

- **Ionizing X-rays** in high dosage & gamma rays, alpha- and beta-particles and radiation from thermonuclear devices.
Irradiation and DNA Damage: indoor tanning and UV radiation link

Deanne Lazovich, University of Minnesota
Not everything we eat or drink is going to kill us!

There are many beneficial foods – some are anti-carcinogenic
Preventive (Anti-carcinogenic) Foods
The diet contains essential nutrients for health and sustenance. Many beneficial chemicals in food can protect against DNA damage and may decrease cancer risk.

**Minimize alcohol intake**: AICR recommends about the equivalent of one beer or glass of wine per day.

AICR recommends **not more than 18 ounces of red meat per week** (about 3 “Quarter Pounders” from MacDonalds).

Some types of foods and methods of cooking can produce hazardous chemicals. **Don’t eat burnt meat!**

Use common sense! Eat a **varied diet** containing fish, poultry, soy, eggs, and limiting quantities of meats.

There are no “magic bullets”. We can minimize exposures to hazardous chemicals in the diet. Enjoy life and enjoy eating. Everything in moderation.

**Don’t smoke!**
Acknowledgements

- Turesky Lab
- Masonic Cancer Center’s Analytical Biochemistry Shared Resource
- Dr. Chris Weight and Dr. Paari Murugan, Departments of Urology and Laboratory Medicine and Pathology, University of Minnesota
- Dr. Badrinath Konety, and Department of Urology Staff, UMN
- Bionet, UMinn
- Dr. L. Le Marchand, Dr. L. Wilkens, Dr. K. White, Univ. Hawaii
- The Patients!!
  Funding:
  R01CA122320, R01ES019564, R01CA220367
  R01CA134700, R33CA186795, P01CA160032
  Cancer Center Support grant CA077598
- Masonic Chair in Cancer Causation (RJT)
Advancing Knowledge, Enhancing Care