Can Meat Take the Heat or Should it Get Out of the Kitchen?

Meat Cooked at High Temperature and Cancer Risk

Thursday, December 12, 2019
1:00 pm – 2:00 pm ET

Sponsored by the National Cattlemen’s Beef Association, a contractor to the Beef Checkoff
A Few Reminders

CPE Credit
ASN designates this educational activity for a maximum of 1 CPEUs. Dietitians and Dietetic Technicians, Registered should only claim credit commensurate with the extent of their participation in the activity.

To claim credit, please take the post webinar evaluation to be emailed after the webinar. The survey also is accessible on nutrition.org (search “webinar: can meat take the heat”).
Questions & Answers

- Please use the “questions” box on your “Go To Meetings” screen to submit questions to our presenters.
- Please submit your questions at any time during today’s webinar.
- After the webinar, we will post answers to frequently asked questions on nutrition.org.
Speakers

Robert Turesky, PhD, BSc
University of Minnesota
Pathways Linking Dietary HAAs from Meat to Cancer Risk: Is the Evidence Compelling?

Jane Pouzou, PhD
EpixAnalytics
Uncertainty in Dietary Exposure Assessment of PAH and HCA

Steven Clinton, MD, PhD
The James, The Ohio State University Comprehensive Cancer Center
Meat and Cancer Risk: Findings from the WCRF/AICR Expert Panel Reports

Moderator

Richard C. Baybutt, PhD
East Carolina University
Learning Objectives

At the end of this session, attendees will be able to:

▪ Communicate current World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations regarding meat intake and cancer risk
▪ Describe strengths and limitations of mechanistic evidence linking meat HAAs to human cancer incidence
▪ Describe strengths and limitations of common methodology used to estimate HCA and PAH exposure in epidemiologic studies
▪ Review strengths and limitations of epidemiological evidence on meat intake and cancer risk
Pathways Linking Dietary Heterocyclic Aromatic Amines (HAAs) from Meat to Cancer Risk: Is the Evidence Compelling?

Robert J. Turesky, PhD
Masonic Cancer Center
Department of Medicinal Chemistry
University of Minnesota, Minneapolis, MN 55455
No conflicts to disclose.
Chemical exposures are thought to contribute to cancer risk.
Meat Consumption Risk of Colorectal, Prostate and Pancreatic Cancer

“The Working Group of IARC classified consumption of processed meat as ‘carcinogenic to humans’ (Group 1)

Red meat as ‘probably carcinogenic to humans’ (Group 2A) …after considering substantial epidemiological data and strong mechanistic evidence”

“Consumption of processed meat was also positively associated with gastric cancer and red meat was also positively associated with pancreatic and with prostate cancer”
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)

Bouvard et al., *Lancet*. 2015
Exposure Biomarkers for Molecular Epidemiology Studies

Traditional Epidemiology

External Exposure → ? → 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
Cooking Time and Temperature-Dependence on Heterocyclic Aromatic Amine Formation in Fried Beef

More than 20 HAAs are formed in cooked meats, poultry, and tobacco smoke

Concentrations: <0.03 – 500 ng/g in cooked meat

Exposure:
6.3 – 20.1 ng/kg/day (USA)
2.3 – 6.6 ng/kg/day (Western Europe)
0.5 – 1.0 ng/kg/day (China and Japan)
Mechanisms of colorectal DNA damage by meat

Exogenous

Processed meat

N-nitroso compounds

Endogenous formation

DNA damage

N-Nitroso compounds, lipid peroxides, bacteria flora

Red meat

Heme iron

PAHs

B[a]P

HAAs

Cooked meat mutagens

DNA Damage and Repair

DNA damaging agents
- DNA replication stress
- Oxygen radicals (O₂, O₂⁻, OH, HO₂, H₂O₂)
- Ionizing radiation
- Polycyclic aromatic hydrocarbons
- UV light
- Chemotherapeutics

Types of DNA damage
- Base mismatches
- Insertions / deletions
- ssDNA breaks
- Abasic sites
- 8-Oxoguanine
- DNA adducts
- Intrastrand crosslinks
- Interstrand crosslinks

DNA repair mechanisms
- Mismatch repair
- Base-excision repair
- Nucleotide-excision repair
- dsDNA break repair
- Transcription-coupled / global genome repair
- Homologous recombination / non-homologous end-joining

Helena et al., *Int. J. Mol. Sci.* 2018
DNA Damage and Genotoxicity Assays

**Bacteria**
- S. typhimurium
- E. Coli
- +/- Enzymes
- Ames test
- Mutants

**Cell assays**
- Micronucleus test
- Bi-nucleated cell
- Chromosomal aberrations
- γH2Ax test
- Double strand breaks
- Comet test
- DNA damage

**Rodents**
- Bone marrow
- Micronucleus
- Tumor formation and mutation in organs

**Humans**
- Exfoliated cells
- Blood
- Urine
- Saliva

Cooked meat mutagens
DNA Adducts and Mutations

DNA and RNA isolation from plasma

Peripheral blood

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

cfDNA, miRNAs

Colon polyp removal

Finotti et al., J Oncol. 2018
**Caveat:** Chemical biomarkers represent recent exposures whereas mutations are an accumulation of exposures over time.

LPO: lipid peroxidation
Mass spectrometry-based approaches to identify and measure biomarkers of exposure

- Low quantities of sample
- Wide-range in analyte levels
- Absolute and semi-quantitation
- Structural identification

DNA, proteins and metabolite extraction

LC/MS analysis

Human tissues

Human fluids

Blood

Exfoliated urinary cells

PhIP-HO-N²-Gluc
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

Biomonitoring of PhIP in Animal Fur and Human Hair

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

---

**PhIP Standard, MS²**

**[1H₃C]-PhIP**

- m/z 228.1 > 210.1
- \( t_R: 8.2 \)
- A: 2.3E6

**PhIP, 351 pg/g hair**

- m/z 225.1 > 210.1
- \( t_R: 8.2 \)
- A: 3.9E5

---

**Black Fur**

- PhIP/[^1H₃C]-PhIP
- m/z 225.1/228.1

---

**Fur/Hair Collection**

- Skin
- Cortex
- Artery
- Vein

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**Solid-phase Extraction**

- Hair Digestion

---

**Liquid-liquid Extraction**

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**Bessette, E. E. et al., Chem. Res. Toxicol. 2009.**


Turesky et al., Cancer Epidemiol. Biomarkers & Prev. 2013
Biomonitoring a Carcinogenic Heterocyclic Aromatic Amines in Hair

Does kibble containing PhIP contribute to canine cancer?
The epidemiology data on dietary factors and prostate cancer risk are not consistent.

Biomarkers of exposure (PhIP in hair) and DNA damage (adducts) may help us to understand the chemical agents that contribute to genetic damage of the prostate genome and cancer risk.
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?
Histogram of PhIP in Hair, and Scatter Plot of dG-C8-PhIP in the Genome of PC patients

LOQ
PhIP (454 ng/day)
75%
Patients

Histogram of PhIP in Hair

PhIP (pg/g hair)

Number of values

0 25 50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525

PhIP (pg/g hair)

# values

0

10

20

30

40

50

60

15

10

5

0

PhIP (pg/g hair)

LOQ

PhIP (454 ng/day)

75%

Patients

dG-C8-PhIP

dG-C8-PhIP per 10^8 nts

0

5

10

15

PhIP (pg/g hair)
Conclusions and Future Directions

- Does frequent consumption of cooked red meat increase cancer risk?
- Well-done cooked red meat and poultry contains HAAs
- Human enzymes (P450s) **bioactivate HAAs to genotoxicants** that damage DNA to form DNA adducts, which can induce mutations
- **Biomarkers** (PhIP in hair, HAA urinary metabolites, and DNA adducts) can be employed in *epidemiology studies* to link exposures to cancer risk
- **Signature mutations** of HAAs in cancer-driver genes must be established

*Acknowledgement of Support: NCI/NIH RO1 CA122320:Chemical markers of heterocyclic aromatic amines for human biomonitoring*
Question and Answers
Uncertainty in Dietary Exposure Assessment of PAH and HCA

Jane Pouzou*, Solenne Costard, Francisco Zagmutt
Health Risk Analysis Consultant
December 12, 2019
# Faculty Disclosure

<table>
<thead>
<tr>
<th>Financial Relationship (prior 12 months)</th>
<th>Commercial Interest</th>
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<tr>
<td>Grant/Research Support</td>
<td>In the last twelve months, as an employee of EpiX Analytics, Dr. Pouzou has received research support from the Beef Checkoff and from MatPrat Norway. These organizations had no role in the design, creation, or editing of this material.</td>
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<td>Other</td>
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What does exposure mean?

• How much of a hazard gets to (sometimes into) the body?

• In a risk assessment, must be combined with dose-response to know the health impact

• Exposures have many forms and three classic routes
  • Also injection, and physical hazards like noise, vibration

• Accurate and **specific** past exposure measurements are challenging
  • Memory is unreliable, repeat measures are expensive or impossible, proxies can mislead
Common Approaches to Dietary PAH and HCA Exposure

- Typically carried out within an epidemiological study (cohort or case-control)

- Diet is evaluated for food groups using surveys/diaries at intervals

- Approximation of annual diet may or may not be carried out

- Previous measurements of chemical concentrations in food groups are combined with food group consumption (CHARRED)
  - Concentration data in CHARRED are point estimates of 3 HCAS and 1 PAH measured by meat type (beef, pork, or chicken dishes), cooking method, and degree of ‘doneness’
True Exposure vs Estimated Exposure

“True” BaP from red meat

Advanced methods can somewhat extrapolate to lifetime servings and estimate uncertainty... but better data is needed for improvement on current methods

Usually point values per food (1.52 pg/g in a well-done grilled 60g burger)

Uncertainty and variability distributions better reflect what we know of “true” exposure

Estimated BaP from red meat
Project Goals

• **For >100 food “strata”** (meat and bread categories)

• **1: Quantify concentrations of 2 HCA (PhIP and MelIQx) and PAH8 (BaP, ChY, BaA, BkF, BbF, DahA, IP, BghiP)**
  - Concentrations (mean with uncertainty) predicted through random effect meta-regression multivariate models using as many different source studies as possible

• **2: Quantify probabilistic dietary exposure to PAH and HCA**
  - Calculate the uncertainty in the mean dietary exposure to PAH and HCA based on goal above and NHANEs
  - Understand exposure trade-offs between HCAs and PAHs between different foods (based on actual portions)
Compiled 21 studies of HCA concentrations in food and 9 for PAH (CHARRED data and others)

- Used Bayesian RE meta-regression to model concentration based on:
  - Cooking Method
  - Time
  - Temperature (surface or surrounding)
  - Form of the food and type of meat (e.g. ground beef or pork)
  - Flame used and type of fuel for barbecuing
  - Raw meat fat percentage

- Interpolation <LOD and Imputation

- Food concentrations show substantial statistical uncertainty (e.g. standard errors)

- Main drivers of concentration were cooking method and conditions rather than the type of protein
Concentrations

- PAH concentrations were less uncertain overall except in a few categories

- PAH were lower on average but with more extreme outliers (especially open flame methods)
Dietary Exposures

- HCA and PAH statistically different between multiple cooking methods.

- Few significant differences based on meat types: Higher exposures driven by cooking preference for meats (e.g. barbecuing/broiling) and concentration.
Exposure Tradeoffs between meals

- If a typical portion of food A were exchanged for a typical portion of B, how does exposure to both compound groups change?

- BBQ is a higher PAH method across all foods.

- Not many tradeoffs, where a significantly higher exposure from PAH might be exchanged with one for HCA, by switching foods.
  - A pan-fried, un-breaded chicken breast vs a broiled hamburger would give lower PAH but higher HCA, as one example.

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<th>BBQ Beef</th>
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<th>What if I switch?</th>
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<td>Fried Fish</td>
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<tr>
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<th>Beef Steak</th>
<th>Pork Chop</th>
<th>Chicken Breast</th>
<th>Salmon Steak</th>
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<tr>
<td><strong>BBQ/Grilled</strong></td>
<td>HCA: 1138</td>
<td>HCA: 538</td>
<td>HCA: 2031</td>
<td>HCA: 1077</td>
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<tr>
<td></td>
<td>PAH: 1270</td>
<td>PAH: 748</td>
<td>PAH: 5259</td>
<td>PAH: 1210</td>
</tr>
<tr>
<td><strong>Pan-Fried</strong></td>
<td>HCA: 1020</td>
<td>HCA: 715</td>
<td>HCA: 1750</td>
<td>HCA: 1210</td>
</tr>
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<td>PAH: 20</td>
<td>PAH: 18</td>
<td>PAH: 19</td>
<td>PAH: 81</td>
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</table>
Conclusions

- Use of point estimate food group concentrations ignores uncertainty in resulting exposures

- Not all food categories have equal certainty in PAH or HCA concentration estimates

- Cooking methods are the most important distinguisher of HCA and PAH concentration in foods and the resulting dietary exposure

- In dietary exposure assessments, uncertainty can answer:
  - Are population exposure groups (quartiles, high vs low, etc) actually different in their exposure?
  - Does diet composition or residue content drive exposure?
For any questions or comments about these slides, please contact:

Jane Pouzou, MPH, PhD
Health Risk Analysis Consultant
EpiX Analytics
jpouzou@epixanalytics.com
www.epixanalytics.com
Question and Answers
Meat and Cancer Risk:

What have we learned from the AICR/WCRF Third Expert Report in 2018 on Diet, Nutrition, Physical Activity and Cancer

Steven K Clinton MD PhD

The James
Financial Conflicts of Interest
None

Personal Opinions
Many

Research Support
Government: National Institutes of Health, Department of Defense, United States Department of Agriculture.

The Ohio State University:
Comprehensive Cancer Center, Pelotonia, Center for Advanced Functional Foods Research, Foods for Health Discovery Themes

Other: American Institute for Cancer Research (AICR), American Cancer Society (ACS), The National Cattleman’s Beef Association
What is the American Institute for Cancer Research and World Cancer Research Fund?

The Vision
To live in a world where no one develops a preventable cancer.

The Mission
Investigate the causes of cancer and provide recommendations for prevention.
AICR / WCRF: The Strategy

**Fund** scientific research.

**Analyze** all the research within the field from around the world to ensure all messages are based on the latest evidence.

**Education:** Give practical, understandable advice to the public and cancer survivors about how to reduce cancer risk.

**Promote collaboration** between nutrition and cancer research communities.

**Impact:** Work with governments and decision-makers to influence public policy.
The AICR / WCRF Expert Reports: History
Distinguishing Evidence from Opinion and to Improve Transparency

1997

Online access:
http://www.aicr.org/
dietandcancerreport.org
What Comprises the 2018 Third Expert Report?

Rigorous Systematic Literature Review
Assessment of Evidence
Recommendations

Evaluation:
17 Cancers, 51 million people examined, and 3.5 million cancer cases
The AICR / WCRF Process: Judging the Evidence

- Multidisciplinary teams (CUP)
- Grading criteria
  - Strength of evidence / causality
- Guidelines for systematic literature review
- Peer review (external control)
- Internal quality control (review process)
- Process of findings documented:
  - Protocols
  - CUP database and inference
  - Library of statistical programs
  - Systematic literature reviews
  - Meta-analysis
The Process

One central database for cancer prevention research

- Prepare protocols
- Update central database
- Prepare reports

External review of protocols & reports

- Schedule update initiated

AICR/WCRF Network

- Public health recommendations
- Set research priorities

CUP Expert Panel

- Draw conclusions from evidence
- Review Cancer Prevention Recommendations

Dr. Teresa Norat
Imperial College London

CUP Panel
The Continuous Update Program (CUP)

2010: Breast Cancer
2011: Colorectal Cancer
2012: Pancreatic Cancer
2013: Endometrial Cancer
2014: Ovarian Cancer
2014: Prostate
2014: Breast Cancer Survivors
2015: Liver
2015: Gallbladder
2015: Kidney
2015: Bladder
2016: Lung
2016: Esophagus
2016: Stomach
2017: Breast
2017 Colorectal
2018: Lung
2018 Mouth, Pharynx, Larynx

2,000 Total Pages
# Judging the Evidence – Grading Criteria

## Evidence Matrix

<table>
<thead>
<tr>
<th></th>
<th>Decreases Risk</th>
<th>Increases Risk</th>
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</thead>
<tbody>
<tr>
<td><strong>Strong evidence</strong></td>
<td></td>
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</tr>
<tr>
<td>Strong evidence</td>
<td>Convincing</td>
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<tr>
<td>Probable</td>
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<tr>
<td><strong>Limited evidence</strong></td>
<td>Limited - suggestive</td>
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</tr>
<tr>
<td>Limited – no conclusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Strong evidence</strong></td>
<td>Substantial effect on risk unlikely</td>
<td></td>
</tr>
</tbody>
</table>

- **Basis for Recommendations**
- **Basis for Additional Research**

### Pre-defined requirements determining grading of evidence:
- Number and types of studies
- Quality of exposure and outcome assessment
- Heterogeneity within and between study types
- Exclusion of chance, bias or confounding
- Biological gradient
- Evidence of mechanisms
- Size of effect

wcrf.org/judging-evidence
Summarizing
the
AICR and
WCRF
Evidence

Red and
Processed Meat
and
Cancer Risk
# Diet, Nutrition, Physical Activity and Colorectal Cancer

<table>
<thead>
<tr>
<th>Strong Evidence</th>
<th>Decreases Risk</th>
<th>Increases Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convincing</td>
<td>Physical activity&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Processed meat&lt;sup&gt;3&lt;/sup&gt;, Alcoholic drinks&lt;sup&gt;4&lt;/sup&gt;, Body fatness&lt;sup&gt;5&lt;/sup&gt;, Adult attained height&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Probable</td>
<td>Wholegrains, Foods containing dietary fibre&lt;sup&gt;7&lt;/sup&gt;, Dairy products&lt;sup&gt;8&lt;/sup&gt;, Calcium supplements&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Red meat&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Limited – suggestive</td>
<td>Foods containing vitamin C&lt;sup&gt;11&lt;/sup&gt;, Fish, Vitamin D&lt;sup&gt;12&lt;/sup&gt;, Multivitamin supplements&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Low intakes of non-starchy vegetables&lt;sup&gt;14&lt;/sup&gt;, Low intakes of fruits&lt;sup&gt;14&lt;/sup&gt;, Foods containing haem iron&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>Limited – no conclusion</td>
<td>Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine; beta-carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern</td>
<td></td>
</tr>
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<td>Strong Evidence</td>
<td>Substantial effect on risk unlikely</td>
<td></td>
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</table>

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<sup>1</sup>Physical activity includes vigorous physical activity, moderate physical activity, and leisure-time physical activity.  
<sup>2</sup>Physical activity decreases risk of colorectal cancer, but the strength of the evidence is stronger for physical activity performed at leisure time compared with occupational physical activity.  
<sup>3</sup>Processed meat increases risk of colorectal cancer.  
<sup>4</sup>Alcoholic drinks increase risk of colorectal cancer.  
<sup>5</sup>Body fatness increases risk of colorectal cancer.  
<sup>6</sup>Adult attained height increases risk of colorectal cancer.  
<sup>7</sup>Wholegrains decrease risk of colorectal cancer.  
<sup>8</sup>Dairy products increase risk of colorectal cancer.  
<sup>9</sup>Calcium supplements decrease risk of colorectal cancer.  
<sup>10</sup>Red meat increases risk of colorectal cancer.  
<sup>11</sup>Foods containing vitamin C decrease risk of colorectal cancer.  
<sup>12</sup>Fish decrease risk of colorectal cancer.  
<sup>13</sup>Vitamin D decreases risk of colorectal cancer.  
<sup>14</sup>Multivitamin supplements decrease risk of colorectal cancer.  
<sup>15</sup>Low intakes of non-starchy vegetables increase risk of colorectal cancer.  
<sup>16</sup>Low intakes of fruits increase risk of colorectal cancer.  
<sup>17</sup>Foods containing haem iron increase risk of colorectal cancer.  

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The table above summarizes the evidence for various dietary and lifestyle factors in relation to colorectal cancer risk, with notes on the strength of evidence (strong, convincing, probable, limited – suggestive, limited – no conclusion) and the specific factors that either decrease or increase risk.
AICR / WCRF Summary Chart 2018 (dietandcancerreport.org)

Diet, Nutrition, Exercise Variables

Type of Cancer

Red Meat  Processed Meat  Alcohol  Body Fatness

Conclusions Key
- Decreasing decreases risk
- Probable decreases risk
- Limited - suggestive decreases risk
- Substantial effect on risk unlikely
Judging the Evidence (wcrf.org/judging-evidence)

Red Meat and Processed Meat and Cancer Risk

<table>
<thead>
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<th>RED MEAT</th>
<th>Processed Meat</th>
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<tr>
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<td>Convincing</td>
<td>Colorectum</td>
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<tr>
<td>Probable</td>
<td>Colorectum</td>
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<tr>
<td>Limited evidence</td>
<td>Limited – suggestive</td>
<td>Nasopharynx Lung Pancreas</td>
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NOTE: The 2018 AICR/WCRF report downgraded the previous conclusion that the red meat and colon cancer demonstrated a convincing relationship.
**Basis for Recommendations**

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<tr>
<td></td>
<td>Nasopharynx</td>
<td>Nasopharynx Esophagus (Squamous) Lung Stomach Pancreas</td>
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</table>

The 2018 reports downgraded the previous conclusion that the red meat and colon cancer demonstrated a convincing relationship.
### Processed meat (RR for 50g/day or 1.76 oz/day)

<table>
<thead>
<tr>
<th></th>
<th>Colorectal</th>
<th>Colon</th>
<th>Rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N cohorts, cases</td>
<td>RR (95% CI)</td>
<td>I² %</td>
<td>N cohorts, cases</td>
</tr>
<tr>
<td>10,738</td>
<td>1.16 (1.08-1.26)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>8,599</td>
<td>1.23 (1.11-1.35)</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>3,029</td>
<td>1.08 (1.00-1.18)</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

### Red meat (RR for 100g/day or 3.53 oz/day)

<table>
<thead>
<tr>
<th></th>
<th>Colorectal</th>
<th>Colon</th>
<th>Rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N cohorts, cases</td>
<td>RR (95% CI)</td>
<td>I² %</td>
<td>N cohorts, cases</td>
</tr>
<tr>
<td>6,662</td>
<td>1.12 (1.00-1.25)</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>4,081</td>
<td>1.22 (1.06-1.39)</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>1,772</td>
<td>1.13 (0.96-1.34)</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

### Combined Red and Processed Meat (100g/day or 3.53 oz/day)

<table>
<thead>
<tr>
<th></th>
<th>Colorectal</th>
<th>Colon</th>
<th>Rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N cohorts, cases</td>
<td>RR (95% CI)</td>
<td>I² %</td>
<td>N cohorts, cases</td>
</tr>
<tr>
<td>31,551</td>
<td>1.12 (1.04-1.21)</td>
<td>70</td>
<td>15</td>
</tr>
<tr>
<td>10,010</td>
<td>1.19 (1.10-1.30)</td>
<td>63</td>
<td>10</td>
</tr>
<tr>
<td>3,455</td>
<td>1.17 (0.99-1.39)</td>
<td>48</td>
<td>6</td>
</tr>
</tbody>
</table>
# Red and processed meat/ colorectal cancer: example of forest plot

## RR (95% CI) of colorectal cancer for 100g/day increase of red and processed meat

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sex</th>
<th>per 100g RR (95% CI)</th>
<th>% Weight</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shin</td>
<td>2014</td>
<td>M/W</td>
<td>1.23 (1.11, 1.37)</td>
<td>10.39</td>
<td>KNHIC</td>
</tr>
<tr>
<td>Wie</td>
<td>2014</td>
<td>W</td>
<td>1.10 (0.35, 3.71)</td>
<td>0.41</td>
<td>CSECK</td>
</tr>
<tr>
<td>Bamia</td>
<td>2013</td>
<td>M/W</td>
<td>1.07 (0.99, 1.17)</td>
<td>11.39</td>
<td>EPIC</td>
</tr>
<tr>
<td>Ollberding</td>
<td>2012</td>
<td>M/W</td>
<td>0.94 (0.86, 1.02)</td>
<td>11.21</td>
<td>MEC</td>
</tr>
<tr>
<td>Kim</td>
<td>2011</td>
<td>M/W</td>
<td>1.29 (1.15, 1.46)</td>
<td>9.86</td>
<td>Korean Cohort Study</td>
</tr>
<tr>
<td>Cross</td>
<td>2010</td>
<td>M/W</td>
<td>1.30 (1.19, 1.42)</td>
<td>11.14</td>
<td>NIH-AARP</td>
</tr>
<tr>
<td>Fung</td>
<td>2010</td>
<td>W</td>
<td>1.10 (0.99, 1.21)</td>
<td>10.68</td>
<td>NHS</td>
</tr>
<tr>
<td>Fung</td>
<td>2010</td>
<td>M</td>
<td>1.07 (0.97, 1.17)</td>
<td>11.00</td>
<td>HPFS</td>
</tr>
<tr>
<td>Kabat</td>
<td>2007</td>
<td>W</td>
<td>1.10 (0.56, 2.16)</td>
<td>1.18</td>
<td>NBSS</td>
</tr>
<tr>
<td>Berndt</td>
<td>2006</td>
<td>M/W</td>
<td>1.39 (0.84, 2.30)</td>
<td>1.95</td>
<td>CLUE II</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>W</td>
<td>1.20 (0.99, 1.45)</td>
<td>7.21</td>
<td>SMC</td>
</tr>
<tr>
<td>Lin</td>
<td>2004</td>
<td>W</td>
<td>0.73 (0.55, 0.99)</td>
<td>4.41</td>
<td>WHS</td>
</tr>
<tr>
<td>Flood</td>
<td>2003</td>
<td>W</td>
<td>1.14 (0.74, 1.75)</td>
<td>2.54</td>
<td>BCDDP</td>
</tr>
<tr>
<td>Pietinen</td>
<td>1999</td>
<td>M</td>
<td>1.05 (0.75, 1.49)</td>
<td>3.55</td>
<td>ATBC</td>
</tr>
<tr>
<td>Chen</td>
<td>1998</td>
<td>M</td>
<td>1.11 (0.76, 1.63)</td>
<td>3.07</td>
<td>PHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.12 (1.04, 1.21)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis

---

## Forest Plot Example

- Example of forest plot for the RR (95% CI) of colorectal cancer for 100g/day increase of red and processed meat.

### Study Details:

- **Shin, 2014, M/W**: RR = 1.23 (1.11, 1.37), Weight = 10.39, KNHIC
- **Wie, 2014, W**: RR = 1.10 (0.35, 3.71), Weight = 0.41, CSECK
- **Bamia, 2013, M/W**: RR = 1.07 (0.99, 1.17), Weight = 11.39, EPIC
- **Ollberding, 2012, M/W**: RR = 0.94 (0.86, 1.02), Weight = 11.21, MEC
- **Kim, 2011, M/W**: RR = 1.29 (1.15, 1.46), Weight = 9.86, Korean Cohort Study
- **Cross, 2010, M/W**: RR = 1.30 (1.19, 1.42), Weight = 11.14, NIH-AARP
- **Fung, 2010, W**: RR = 1.10 (0.99, 1.21), Weight = 10.68, NHS
- **Fung, 2010, M**: RR = 1.07 (0.97, 1.17), Weight = 11.00, HPFS
- **Kabat, 2007, W**: RR = 1.10 (0.56, 2.16), Weight = 1.18, NBSS
- **Berndt, 2006, M/W**: RR = 1.39 (0.84, 2.30), Weight = 1.95, CLUE II
- **Larsson, 2005, W**: RR = 1.20 (0.99, 1.45), Weight = 7.21, SMC
- **Lin, 2004, W**: RR = 0.73 (0.55, 0.99), Weight = 4.41, WHS
- **Flood, 2003, W**: RR = 1.14 (0.74, 1.75), Weight = 2.54, BCDDP
- **Pietinen, 1999, M**: RR = 1.05 (0.75, 1.49), Weight = 3.55, ATBC
- **Chen, 1998, M**: RR = 1.11 (0.76, 1.63), Weight = 3.07, PHS
- **Overall**: RR = 1.12 (1.04, 1.21), Weight = 100.00
Hypothesized Mechanisms / Relationships: Red and Processed and Cancer

- Production and husbandry practices may result in carcinogenic or pro-carcinogenic environmental contaminants and pharmaceutical to be incorporated into meat.
- Meat contains iron which may potentiate reactive free-radical formation and propagation contributing to a carcinogenic process.
- Cooking may lead to carcinogen production or incorporation into meat.
  - Heterocyclic amines due to high temperatures
  - Polycyclic aromatic hydrocarbons due to grilling/smoking
- Nitrate/Nitrite and/or other preservatives (salt/smoking) and processing may promote carcinogen formation
- Dietary patterns rich in meat:
  - Meat as a rich source of calories may displace anti-cancer foods
  - Meat rich dietary patterns may impact the host microbiome in a manor to alter microbial function and impact host carcinogenic processes
  - Confounding: Meat may be a indicator of dietary patterns associated with cancer risk, but not causal
Summary of the Recommendations: AICR/WCRF 2018

- Be a healthy weight
- Be physically active
- Eat a diet rich in wholegrains, vegetables, fruits and beans
- Limit ‘fast foods’, and other processed foods high in fat, starches or sugars
- Limit consumption of red and processed meat
- Limit consumption of sugar-sweetened drinks
- Limit alcohol consumption
- Do not use supplements for cancer prevention
- For mothers: breastfeed your baby, if you can
- After a cancer diagnosis: follow our recommendations and those of trained medical experts
RECOMMENDATION 2018

Limit consumption of red and processed meat

Eat no more than moderate amounts of red meat\(^1\), such as beef, pork and lamb. Eat little, if any, processed meat\(^2\)

**GOAL**

If you eat red meat, limit consumption to no more than about three portions per week. Three portions is equivalent to about 350 to 500 grams (about 12 to 18 ounces) cooked weight of red meat.\(^3\) Consume very little, if any, processed meat.

1. “Red Meat” refers to all types of mammalian muscle meat (beef, veal, pork, lamb, horse, goat).
2. “Processed Meat” refers to meat that has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavor or improve preservation.
3. 500 grams of cooked red meat is approximately equal to 700-750 grams of raw meat, but the exact conversion depends on the cut of meat, the proportions of lean meat and fat, and the methods and degree of cooking.
Interpretation of the AICR / WCRF Recommendation: Limit consumption of red and processed meat

https://www.wcrf.org/dietandcancer/recommendations/limit-red-processed-meat

- **Red Meat**
  - Greater risk of colorectal cancer is suggested for consumption exceeding
    - 350 to 500 gms per week
    - 12-18 oz cooked weight per week

- **Processed Meat**
  - No level of intake was confidently associated with a lack of cancer risk.

https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1516.pdf

- **Current Average American Intakes (adults >20 yrs of age)**
  - Red Meat = 11.41 oz-eq / week
  - Processed Meat = 6.93 oz-eq / week (included cured poultry foods)
  - Weekly total intake of red and processed meat combined
    - 18 oz-eq / week (510 gams)

- Illustrates a need for improved communication and education regarding red meat to the public, those at risk of cancer, as well as cancer patients and survivors.
Example:

Quality Educational Materials

Limit red meat

Red meat contains substances that have been linked to colorectal cancer. Pork, lamb, deer, buffalo and beef, including hamburgers, are all red meat.

Here’s what 18 ounces looks like broken down into multiple servings for the week.

<table>
<thead>
<tr>
<th>Item</th>
<th>Serving Size</th>
<th>Per Serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 golf balls</td>
<td>2.25 oz</td>
<td></td>
</tr>
<tr>
<td>6 decks of cards</td>
<td>3 oz</td>
<td></td>
</tr>
<tr>
<td>6 bars of soap</td>
<td>3 oz</td>
<td></td>
</tr>
<tr>
<td>4 tennis balls</td>
<td>4.5 oz</td>
<td></td>
</tr>
<tr>
<td>2 softballs</td>
<td>9 oz</td>
<td></td>
</tr>
</tbody>
</table>

Eat no more than 18 oz of cooked red meat per week.

www.mdanderson.org/food
The Future:

Investment in research is necessary to improve our understanding of meat intake and health outcomes.
Improving the Quality of Research: Meats in Health and Disease

- **Patterns of intake:**
  - Application to populations/countries of varied social/economic states

- **Classification:**
  - Improving precision for assessment of meat sources, production, preservation, processing, quality (fat content), and preparation (cooking) throughout the life course

- **Measurement:**
  - Improving quantitative estimates of meat intake
  - Enhancing data-bases for nutrients and other constituents

- **Terminology:**
  - Address the lack of clear definitions (processes meat)

- **Cancer outcomes**
  - Improve assessment of cancer subtypes
    - Histopathology (e.g. ER +/-, breast cancer) (e.g. squamous/adenoc. esoph)
    - Anatomy (e.g. gastric cardia and non-cardia) (e.g. cervix and uterine)
    - Genomic (and other “omics”) signatures (e.g. HPV associated)
Improving the Quality of Research: Meats in Health and Disease

- **Continue to enhance study designs/methodology:**
  - Hierarchy of evidence
    - Cohort, case-control, ecological, etc.
  - Pooling studies
  - Systematic reviews and meta analysis

- **“Shape” of the Association**
  - Intake of meat and cancer risk may not be linear
  - Define thresholds, plateaus, and J- or U-shaped curves

- **Confounding and Effect modification**
  - Define lifestyle, dietary components, or dietary patterns associated with meat intake that impact risk of cancer and health outcomes.
  - Determine if meat relationships on cancer vary over exposure to another variable or modifier (e.g. body fatness on breast cancer depends on menopausal status)
Improving the Quality of Research: Meats in Health and Disease

- Complement epidemiology with quality clinical trials and mechanisms research focusing upon risks and benefits
  - Define risks and benefits of meat intake as well as mechanisms of action.
  - Red meat is nutrient dense: essential amino acids, bioavailable iron, zinc, selenium, and B vitamins (particularly B12)

- Reducing reporting bias / systematic bias:
  - Greater concern in retrospective compared to prospective studies
    - Self reporting by assessment tools
      - Over-reporting of foods believed to be healthy
      - Under-reporting foods believed to be un-healthy
  - Improved assessment of energy intake and expenditures
    - Key to confounding and effect modification
  - Publication / access to studies with “non-significant” findings

Note:

This presentation is not intended to evaluate and discuss social, economic, and environmental aspects of meat production and consumption.
Thank You
Question and Answers
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