

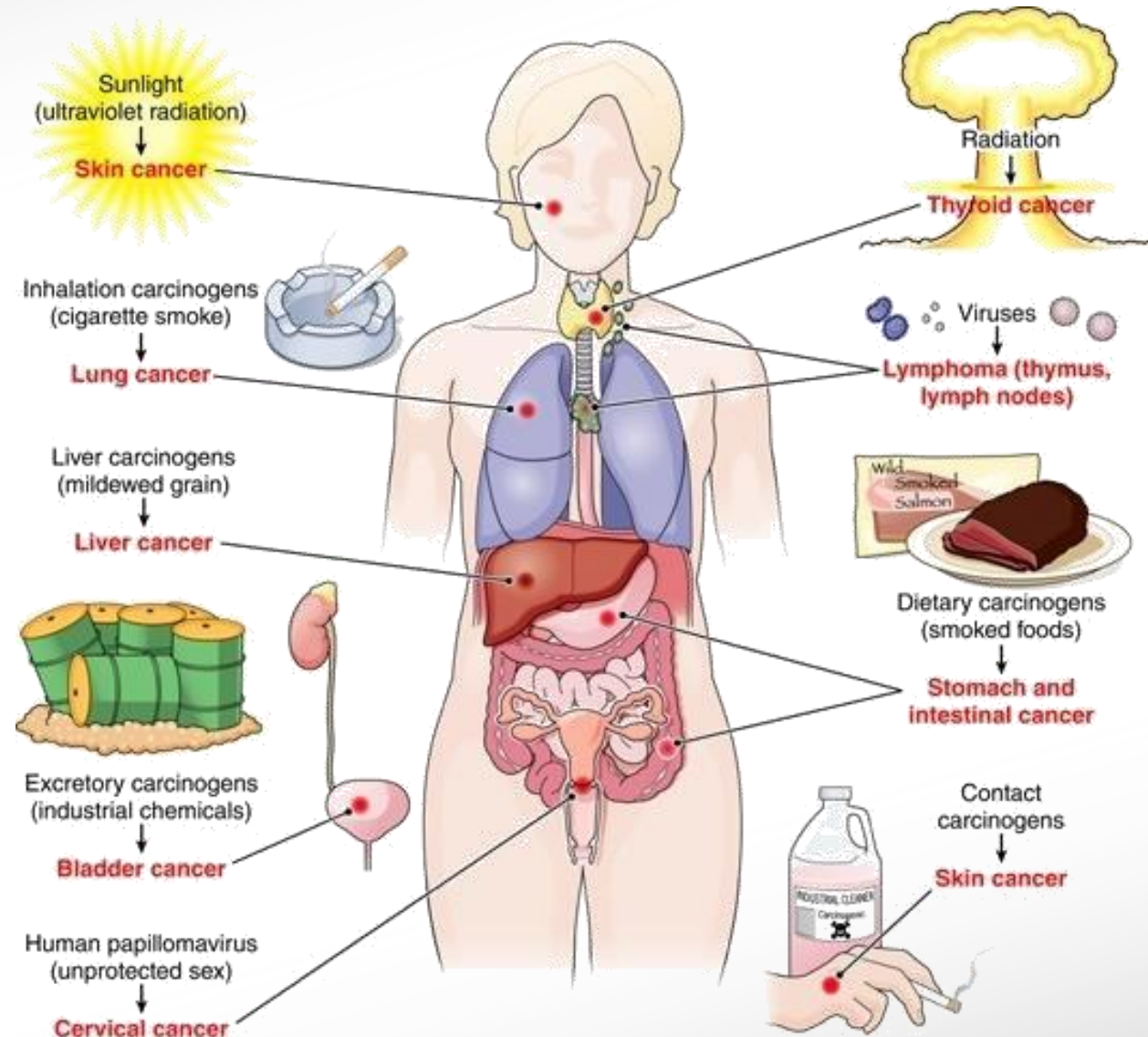
Dietary and Environmental Carcinogens – What to Avoid?

The Breast Cancer Education Association Annual Conference
St. Paul, Minnesota
October 6, 2018

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Masonic Cancer Center
Department of Medicinal Chemistry
University of Minnesota, MN



A lot of research focuses on agents that can cause cancer



Paracelsus



Drug Safety

"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**

Outline of Presentation

- Introduction to research in the Turesky Laboratory at the University of Minnesota
- The World Health Organization (IARC)
- What is DNA and a mutation?
- Chemicals in the environment and diet that may cause cancer
 - Contraceptives, tobacco, alcohol, meat, chemicals in packaging materials (multiple sites including mammary gland)
 - Alcohol (liver, colon, mammary gland)
 - Cigarettes (lung, esophagus, liver, pancreas, colon, mammary gland)
 - Traditional herbal medicines (kidney, bladder, liver)
 - UV light, excessive sun exposure (skin cancer)
 - Cooked meats and cooking fumes (lung, colon, pancreas, prostate, mammary gland)
- Lifestyle factors
 - Physical exercise
 - Obesity (multiple cancers)

Turesky Lab: identifying hazardous chemicals in the environment and diet

Exhaust gas

- Aldehydes
- PAHs
- Nitro PAHs
- HAAs



Cigarette smoke

- N-Nitroso Compounds
- AAs, HAAs
- PAHs
- Aldehydes
- Oxidants



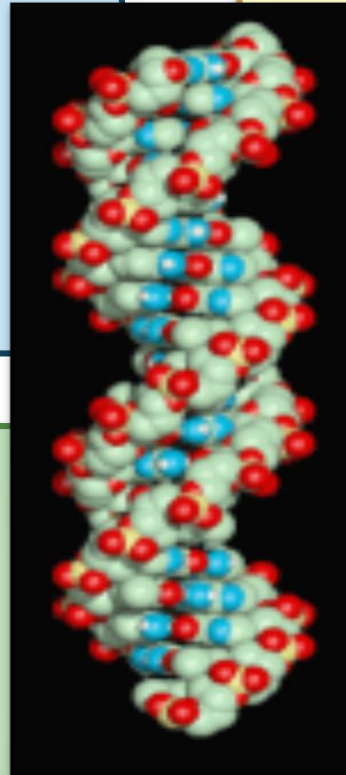
Aristolochic Acids



Aflatoxin B₁

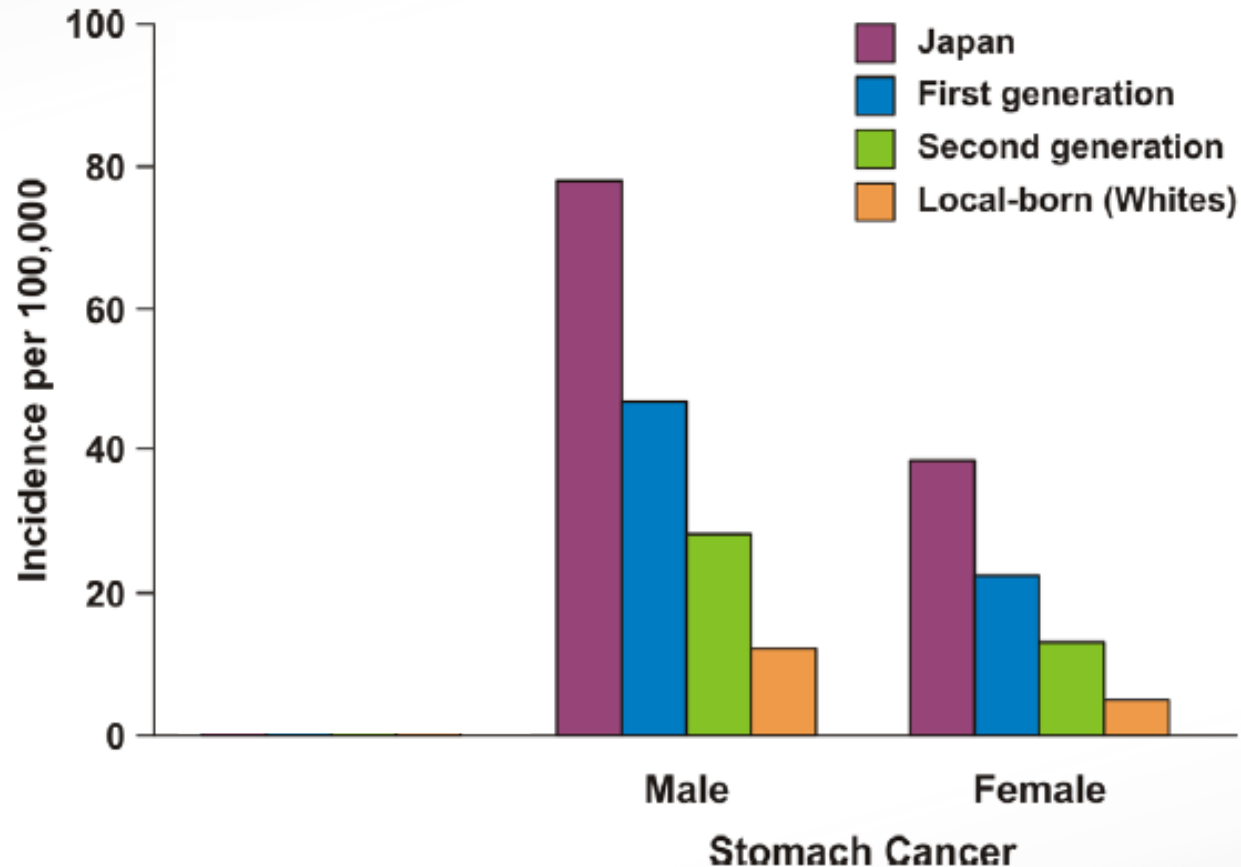
Cooked meats

- HAAs
- PAHs
- N-Nitroso Compounds
- Lipid Peroxides



➤ **Chemical exposures** are thought to contribute to **cancer in humans**

Diet and cancer: many cancers are caused by lifestyle factors, not genetics



L.N. Kolonel and L.R. Wilkens, *Migrant Studies*, ch. 11 in: *Cancer Epidemiology and Prevention*, 3rd Edition, D. Schottenfeld and J.F. Fraumeni, Jr., eds, 2006

Dietary & Environmental Exposures



Processed meat



Grilled meat



Bacon



Air pollution



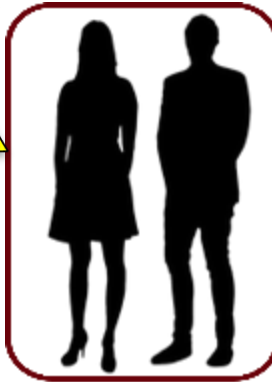
Car exhaust



Drugs



Coffee



Alcohol



Herbal medicine



Plastic food containers



Pesticides



Plastic water bottles



Food packaging

Biospecimens



Urine



Blood



Hair



Saliva



Finger nails



Breast milk



Biopsy tissue

How we measure chemicals and biomarkers in human studies?

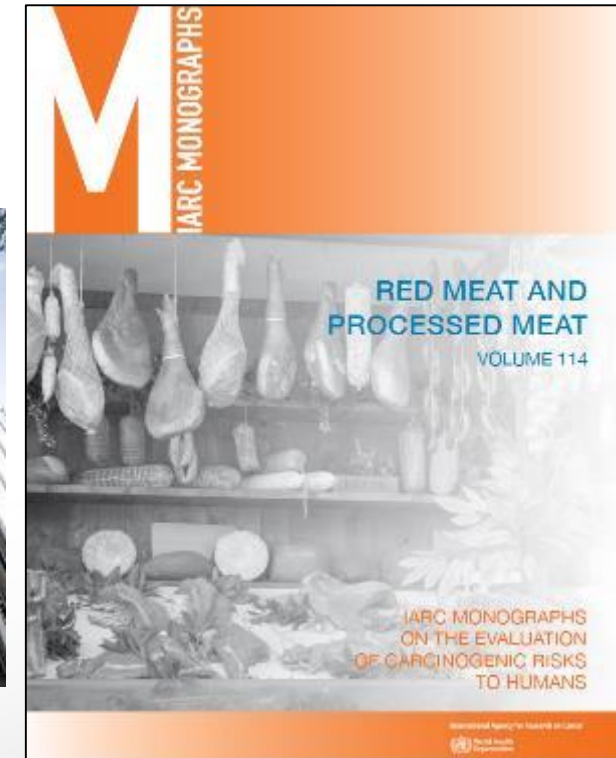


A mass spectrometer measures the molecular weight of chemical like a scale measures our body weight

What is the International Agency for Research on Cancer (IARC)?

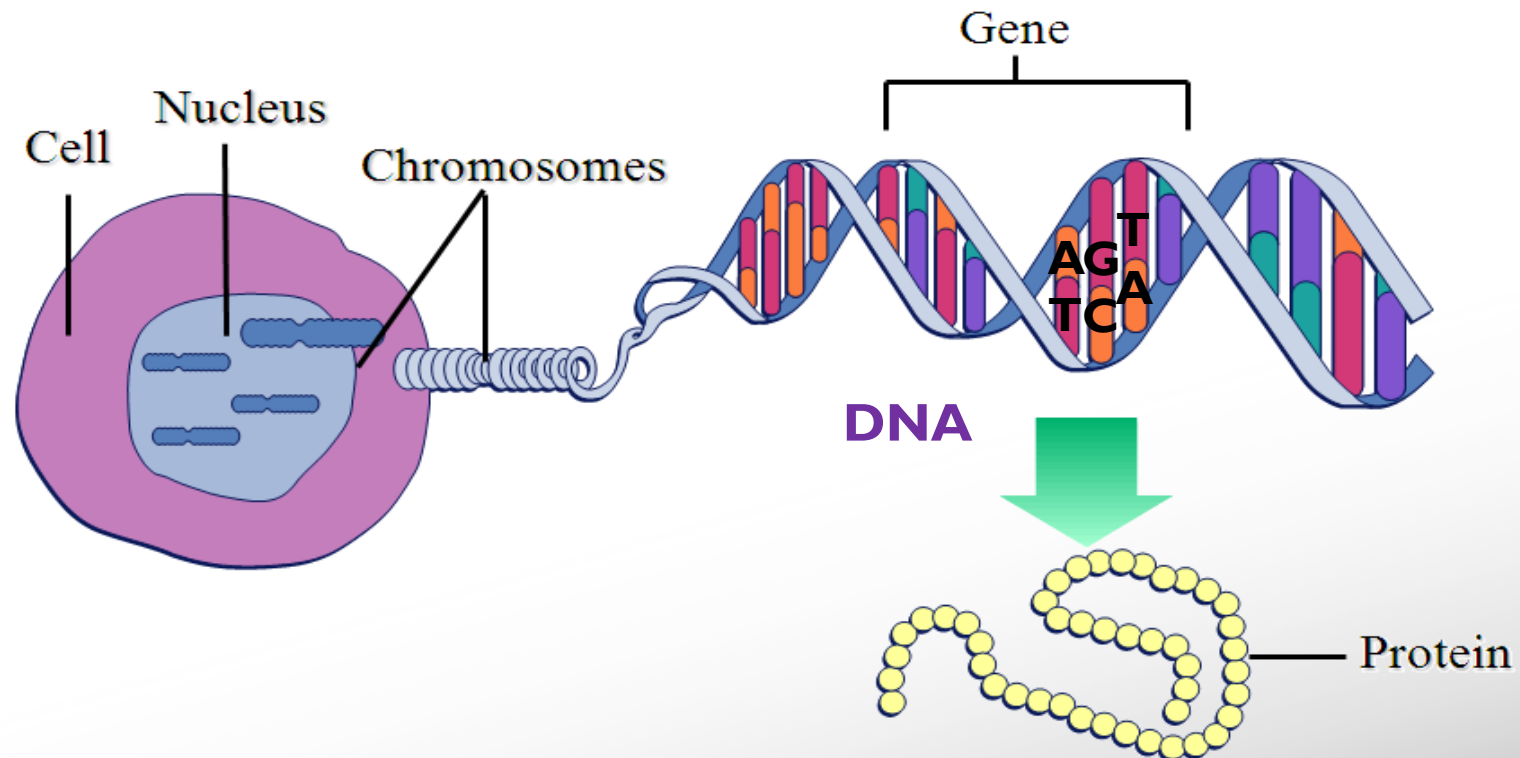
- 1969: IARC Monographs on the Evaluation of Carcinogenic Risk of **Chemicals** to Humans
- Leading experts in fundamental research and epidemiologists review the **impact of chemicals and lifestyle factors on health risk** for IARC
- IARC Monograph Vol 114: Red and Processed Meats: 22 experts from 10 countries – evaluated over 800 studies

International Agency for Research on Cancer



What is DNA?

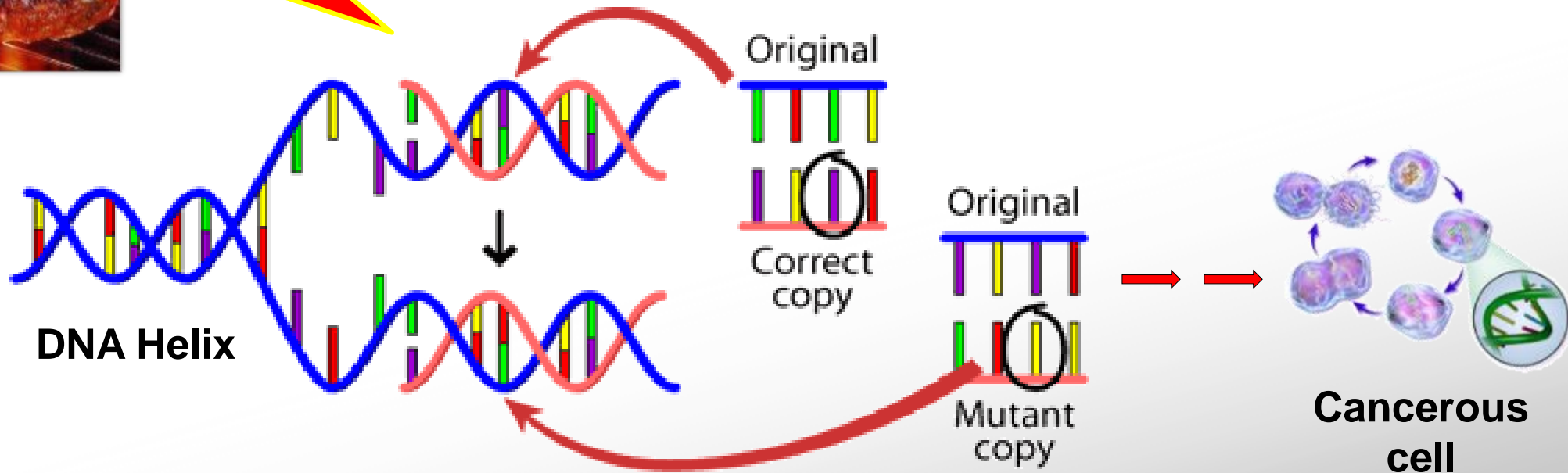
- Biochemical information storage and retrieval system (a cell's hard drive)
- Contains only 4 different components (A, C, G, and T) linked in two anti-parallel strands.
- DNA encodes for the information to produce our cells and our body



How do mutations and cancer occur and what is chemical carcinogenesis ?

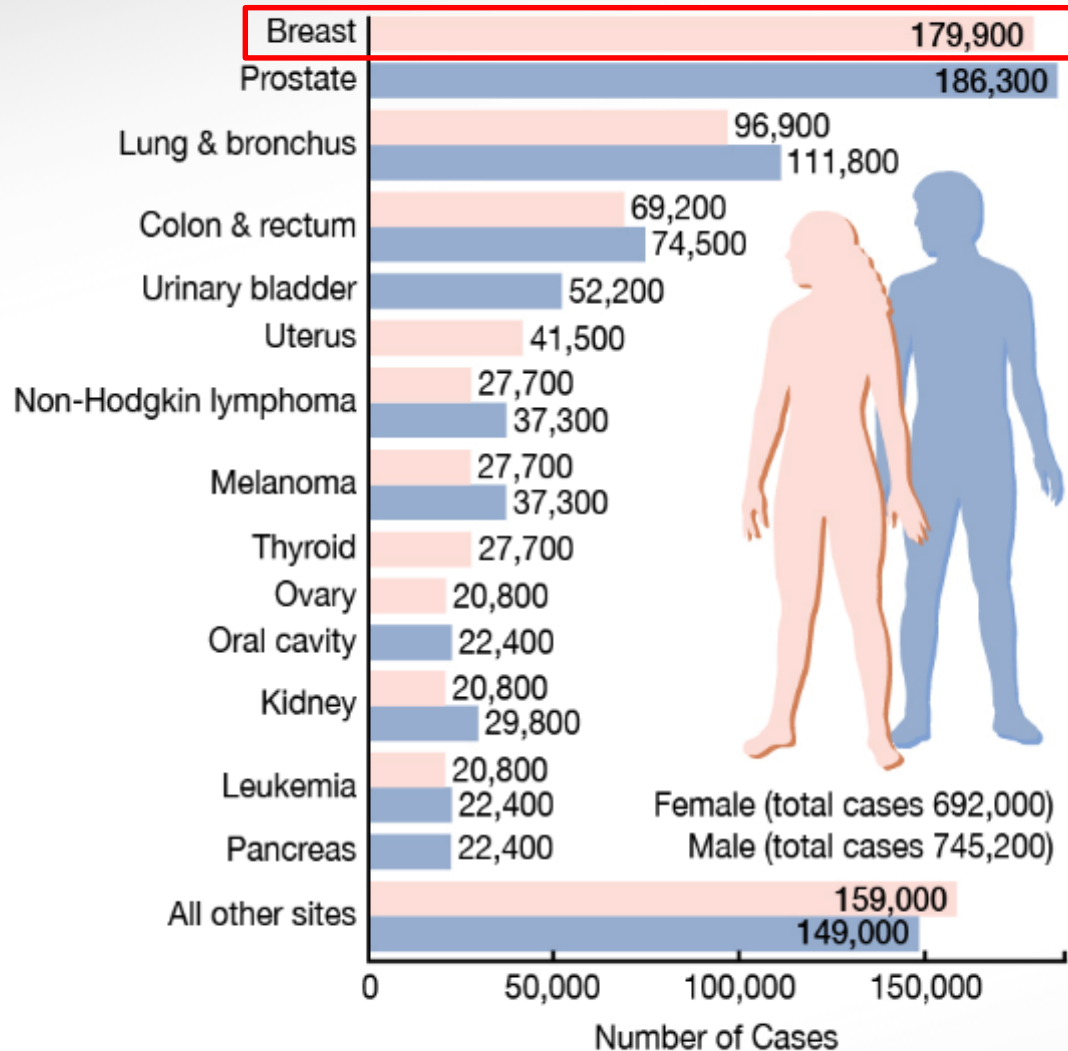
Chemicals in the environment or diet “latch-on” to DNA and induce a mutation when the cell divides

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



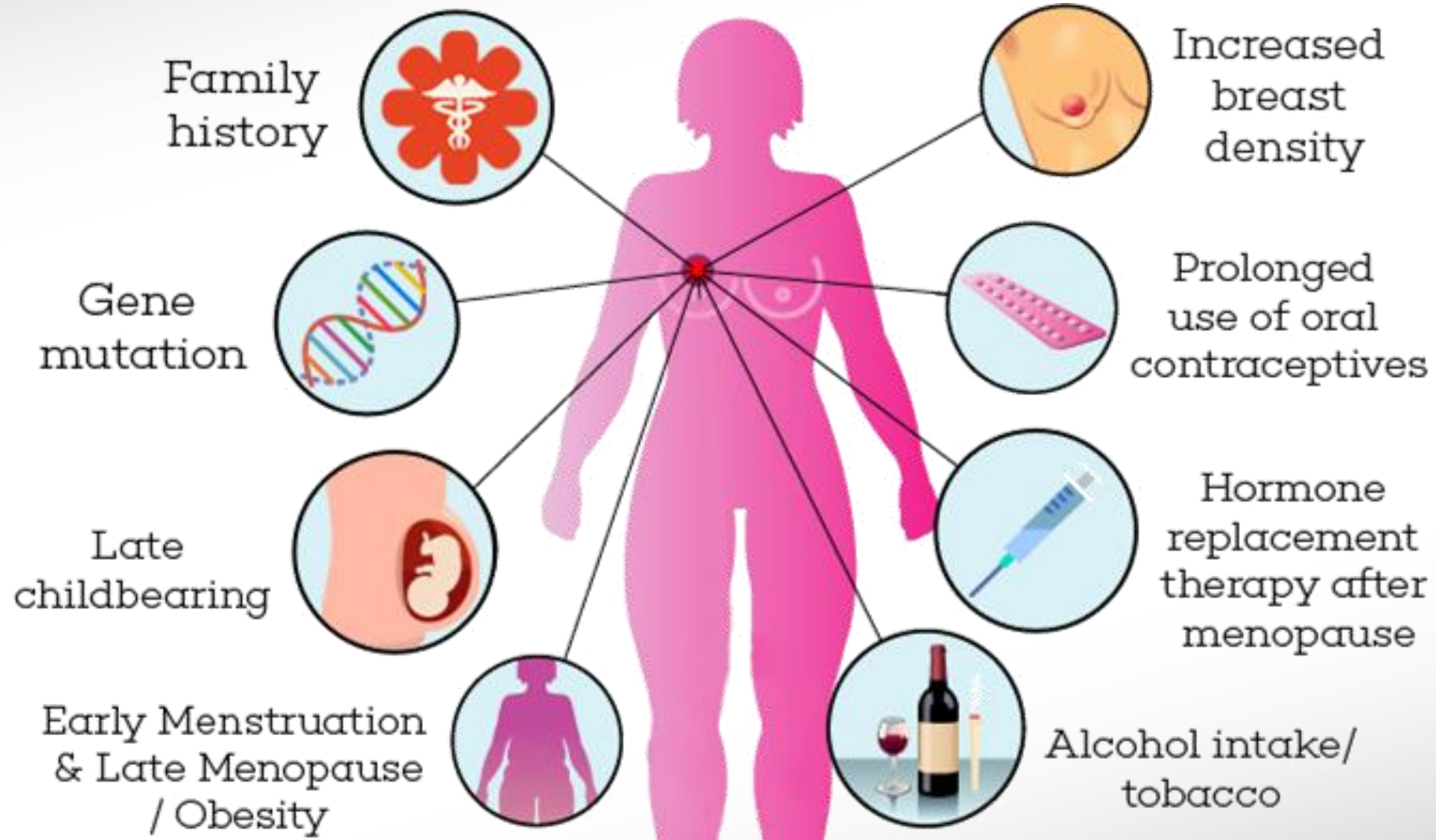
Cancer Incidence and Mortality in the United States*

New Cancer Cases per Year



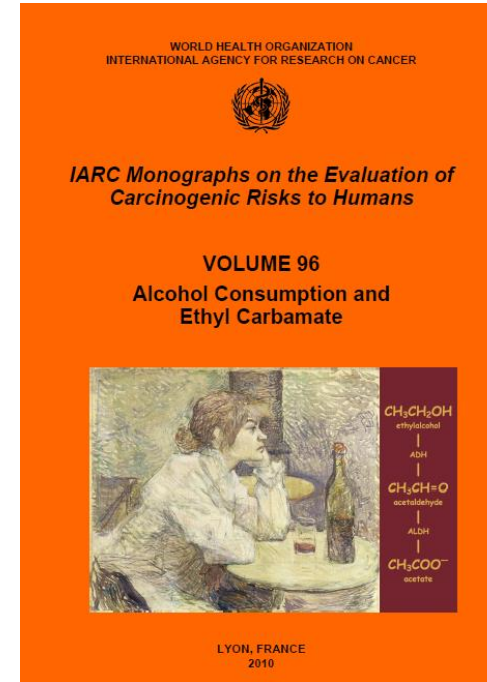
*Estimated numbers from the American Cancer Society, Inc., 2008.

Causes and risk factors of breast cancer

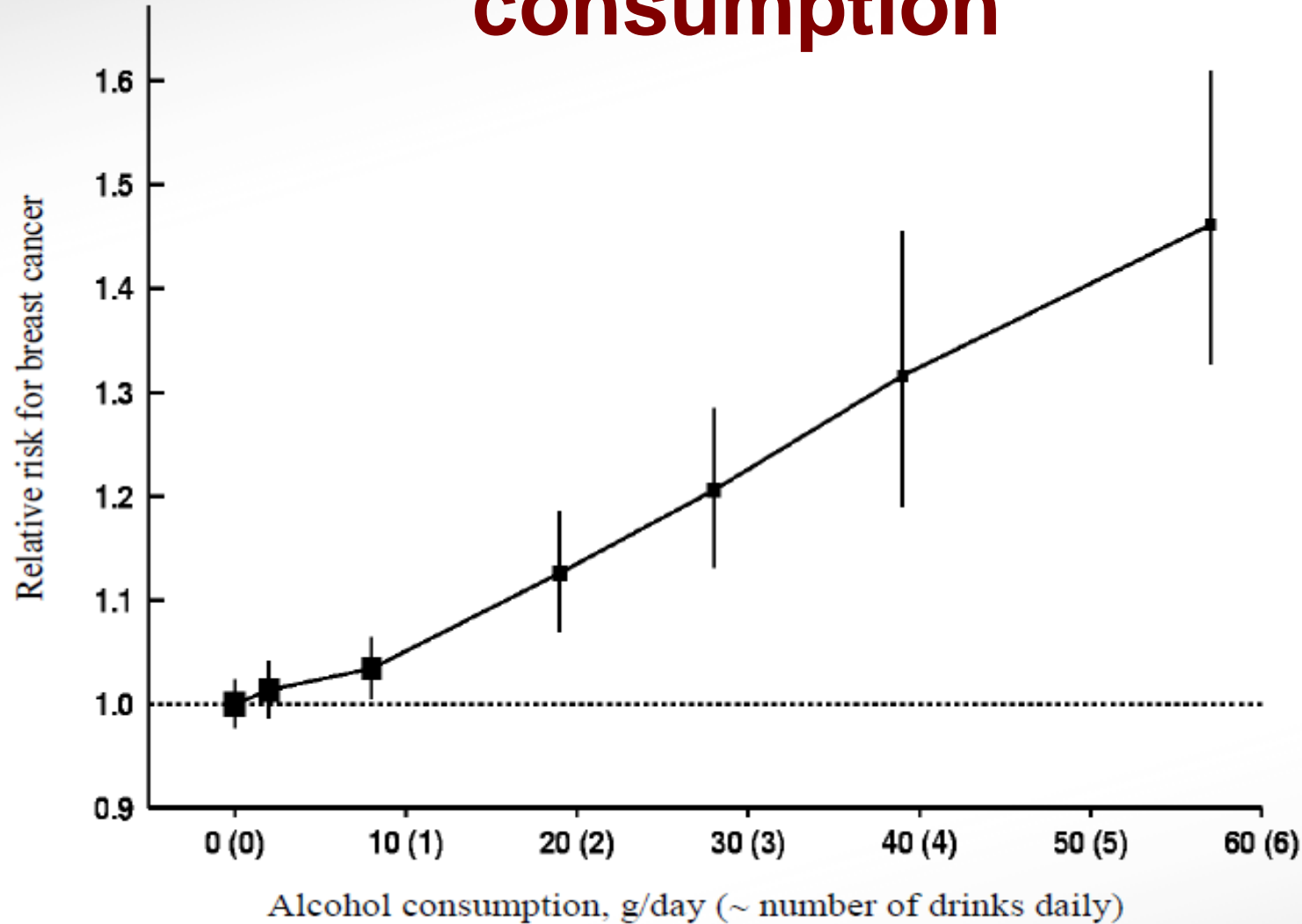


Alcoholic Beverages and Cancer Risk

- 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**



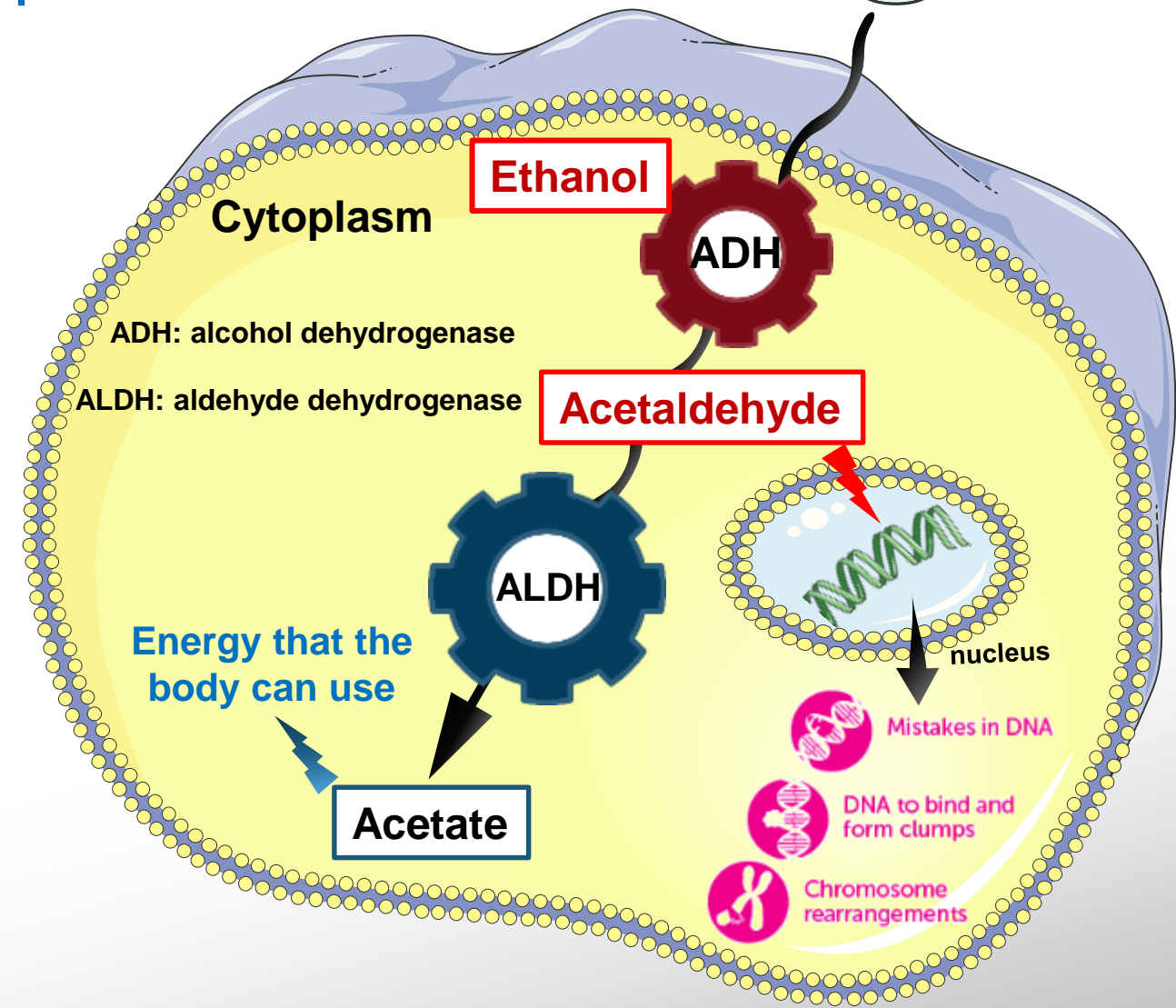
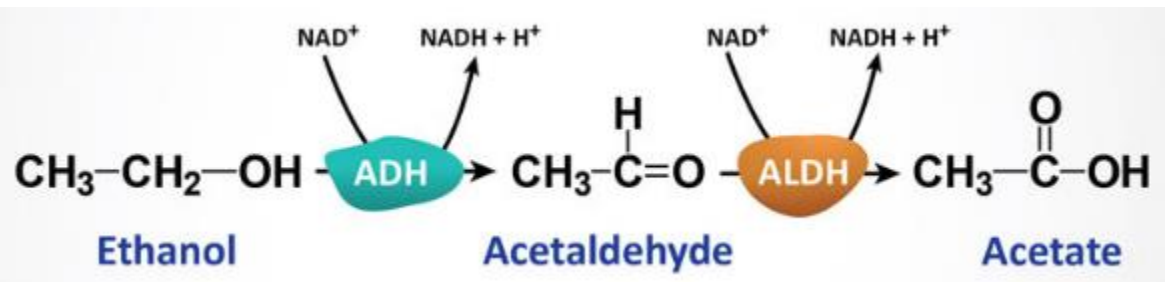
Relative risk for breast cancer with alcohol consumption



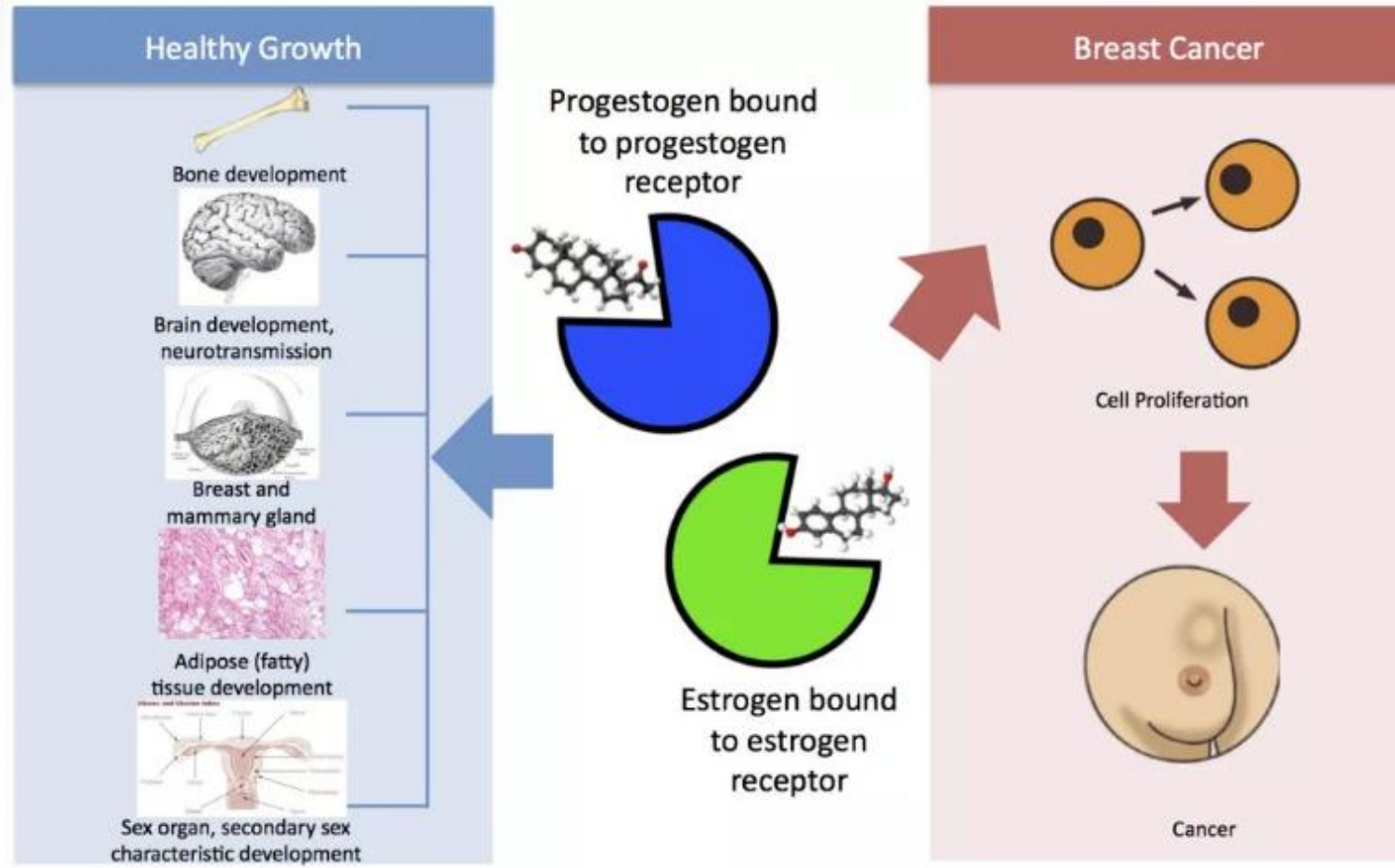
Pooled analysis of data from **53 studies** that included **58,515 women with breast cancer** (adjusted by study, age, parity, age at first birth and tobacco smoking)

Alcoholic Beverages and Cancer Risk

What does cancer have to do with hangover ?



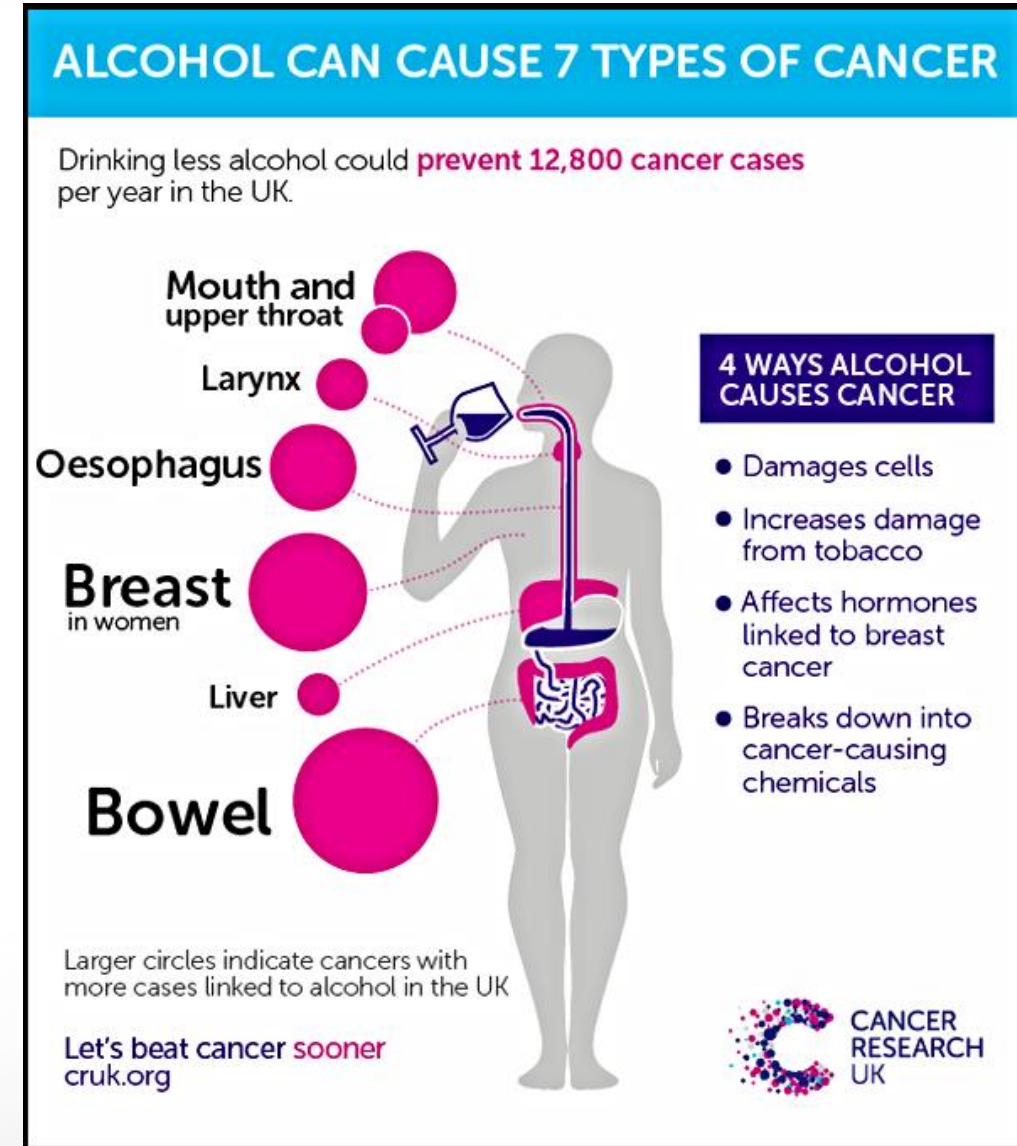
Estrogen and progestogens are required for normal development and function of multiple tissues



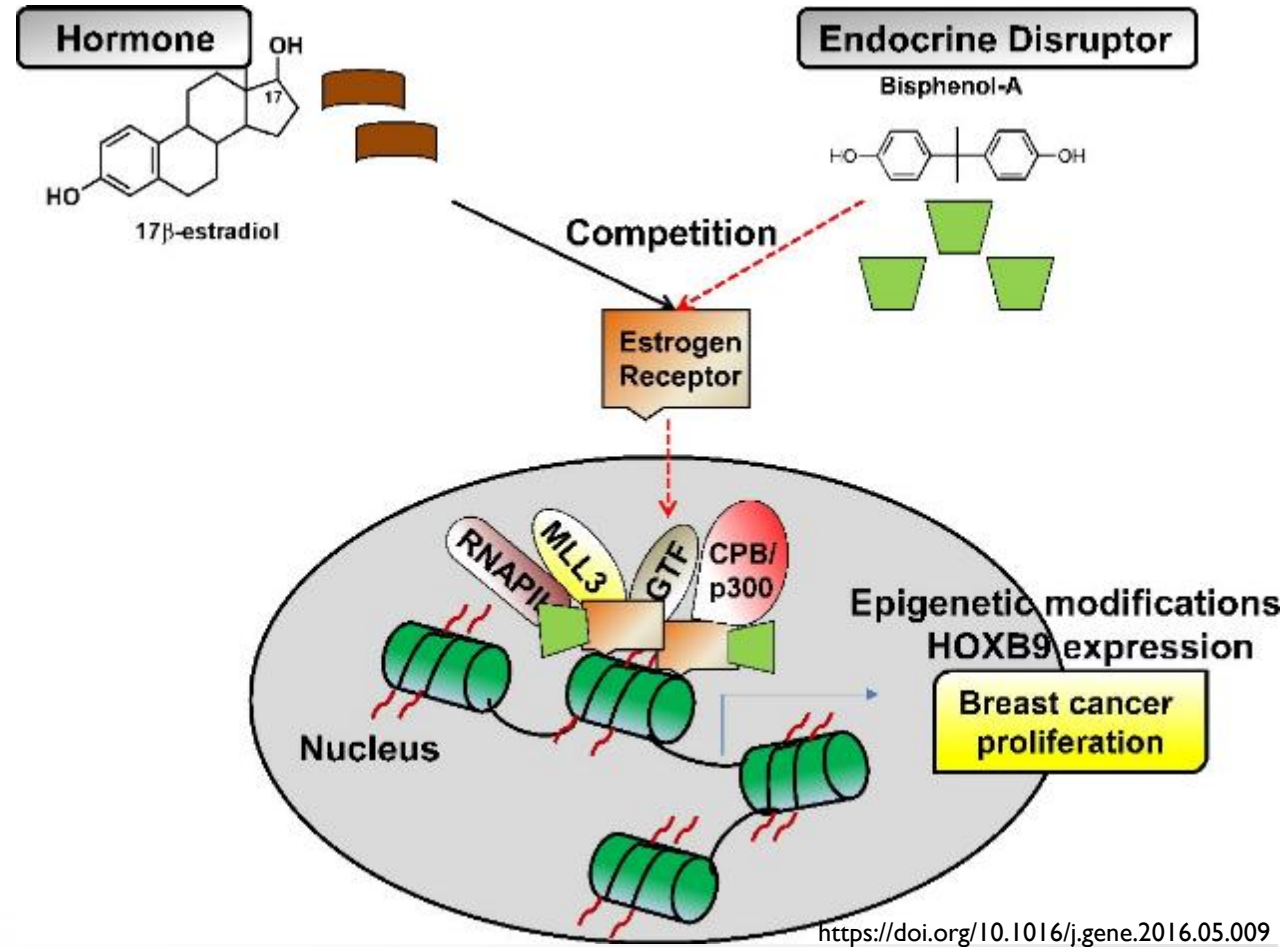
Estrogen also can **promote breast cancer** development mostly via activation of growth factor pathways that prompt cells to divide

Alcohol and Cancer Risk: The Good and the Bad

- Ancient **Egyptian Papyri** and **Sumerian** tablets dating back to 2200 BC detail the medicinal role of wine, making it the world's oldest documented man-made medicine
- Moderate consumption of some alcoholic beverages, red wine in particular, may have beneficial effects, which contains a chemical called resveratrol that may be “anti-carcinogenic”
- Moderate wine drinking can improve the balance of **low-density lipoprotein** (LDL or "bad" cholesterol) to **high-density lipoprotein** (HDL "good" cholesterol), which may clean up or remove LDL from **blocking arteries**
- Social interactions, relaxation, release of anxiety and stress – can be impacted by consumption of alcoholic beverages
- Binge **drinking is not beneficial !!!**



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 !!

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

Avoiding Exposures to Endocrine Disruptor Chemicals

- Don't cook foods in plastic containers or use roasting/steaming bags
- Use glass, porcelain, enamel-covered metal, or stainless steel pots, pans, and containers for hot foods and beverages
- Plastics with recycling symbol 2, 4, and 5 are generally considered OK to use. Plastics with recycling symbol 7 are OK
- Recycling symbol 1 is also OK to use.

■ Avoid bottles labeled 3 or 7 (PVC and PC) as they exude **toxic chemicals** able to penetrate your food and drinks, and lengthy exposure can even result in severe health problems.



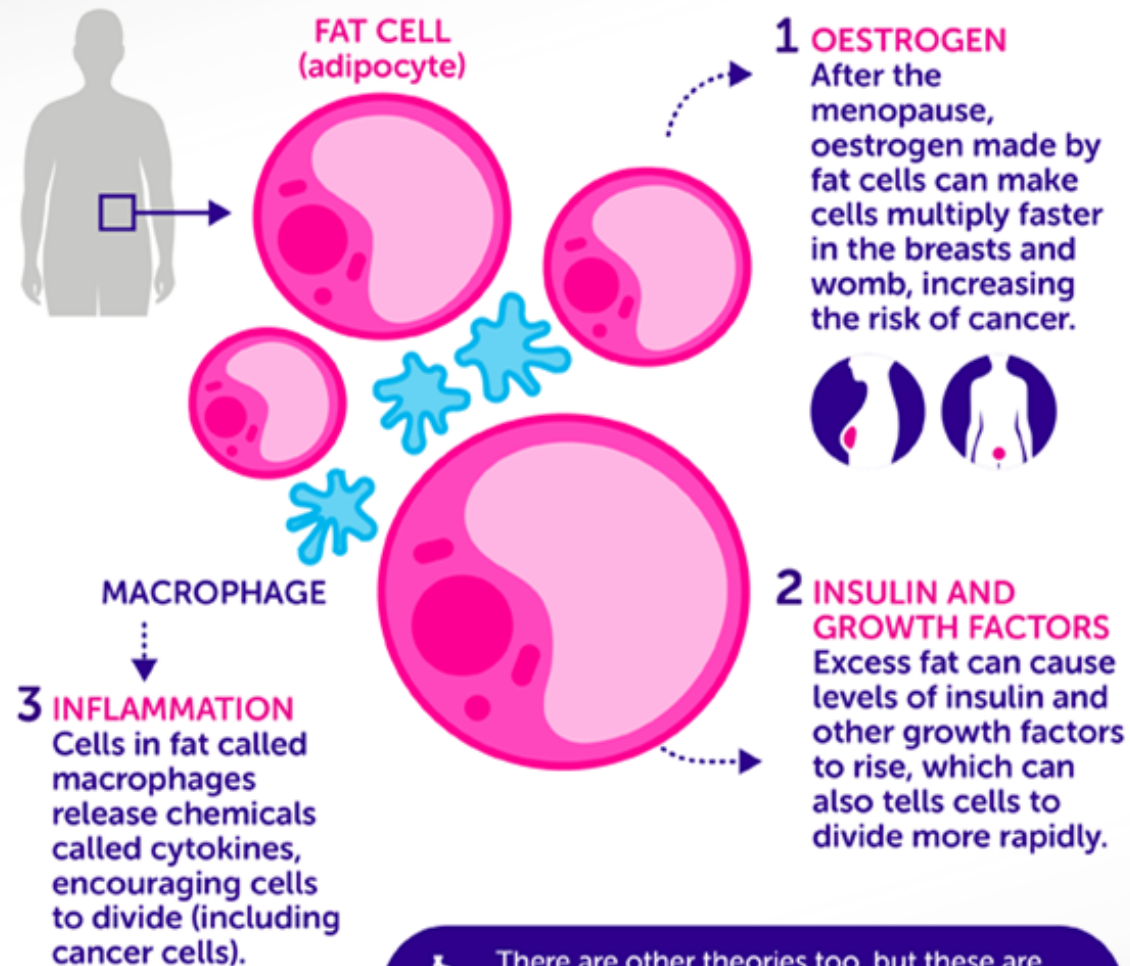
Bottles made of polyethylene (2 and 4) and polypropylene (5 and PP) are **suitable for multiple uses**. They're relatively safe if you only store cold water in them and regularly disinfect them.



<p>polyethylene terephthalate</p> <p>soft drink bottles, mineral water, fruit juice container, cooking oil</p>	<p>high-density polyethylene</p> <p>milk jugs, cleaning agents, laundry detergents, bleaching agents, shampoo bottles, washing and shower soaps</p>	<p>polyvinyl chloride</p> <p>trays for sweets, fruit, plastic packing (bubble foil) and food foils to wrap the foodstuff</p>	<p>low-density polyethylene</p> <p>crushed bottles, shopping bags, highly-resistant sacks and most of the wrappings</p>	<p>polypropylene</p> <p>furniture, consumers, luggage, toys as well as bumpers, lining and external borders of the cars</p>	<p>polystyrene</p> <p>toys, hard packing, refrigerator trays, cosmetic bags, costume jewellery, CD cases, vending cups</p>	<p>other plastics, including acrylic, polycarbonate, polyactic fibers, nylon, fiberglass</p>
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How could obesity lead to breast cancer

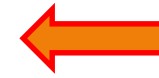
Research has identified three main ways



There are other theories too, but these are the main ideas being studied. More research is needed to understand this in more detail.

Mechanisms of breast carcinogenesis

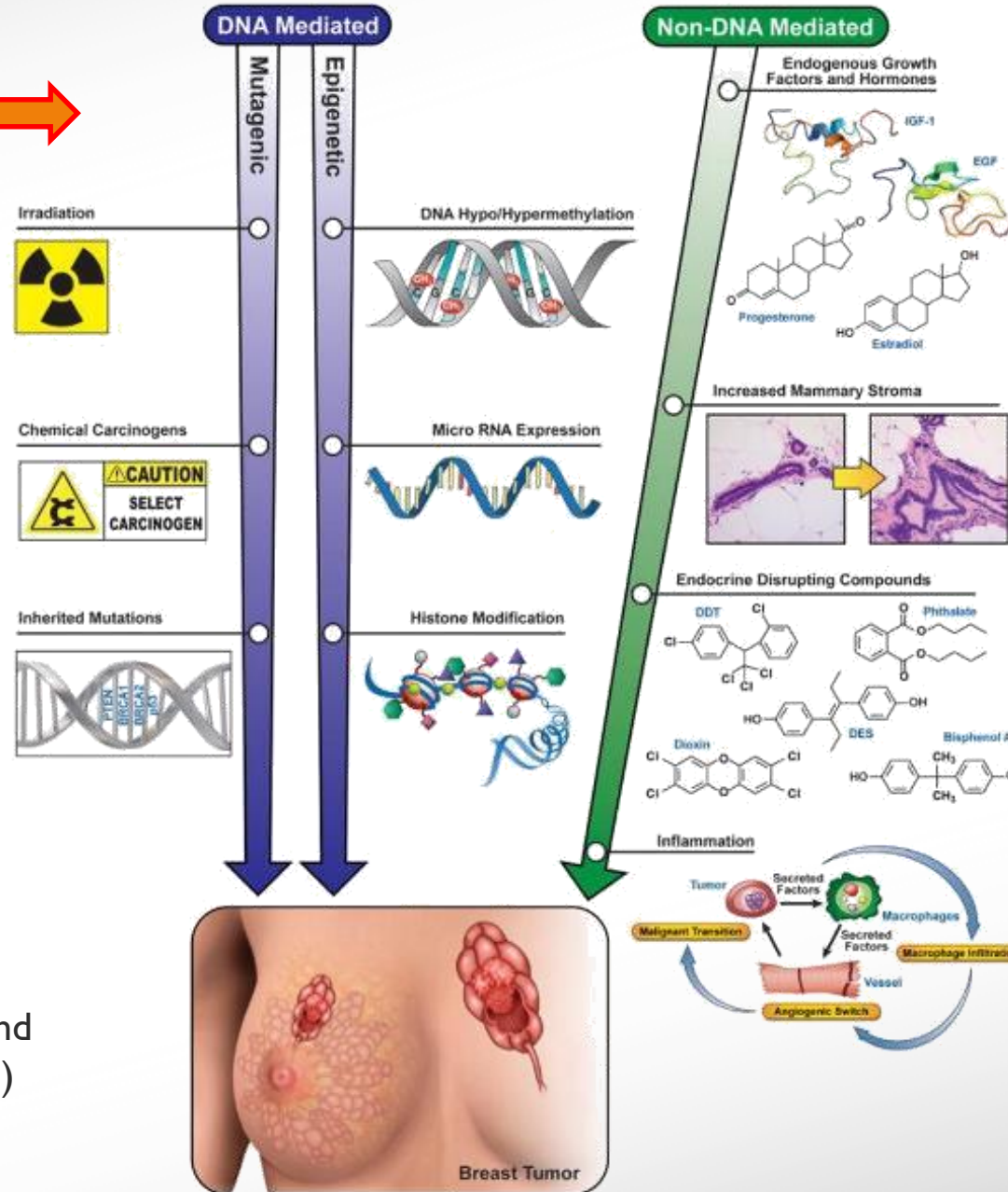
DNA damage and mutations



Hormonal

Inherited Mutations

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



How to reduce chemical exposures linked to breast cancer

- Limiting exposure to fumes from gasoline
- Limiting exposure to exhaust from diesel and other fuel combustion, such as from vehicles or generators
- Use electric instead of gas-powered lawn mowers
- Use a ventilation fan to remove fumes when cooking; reduce consumption of charred or burned food
- Avoid stain-resistant rugs, fabrics and furniture
- Use a solid carbon block drinking water filter
- Avoid drinking plastic bottled water and consuming foods from metal cans with plastic liners



Other Life-style Factors and Chemical Exposures the Contribute to Cancer Risk

- Cigarettes (lung, esophagus, liver, pancreas, colon, mammary gland)
- Traditional herbal medicines (kidney, bladder, liver)
- UV light, excessive sun exposure (skin cancer)
- Cooked meats and cooking fumes (lung, colon, pancreas, prostate, mammary gland)

Cigarette smoke and cancer risk

CHEMICAL COMPOUNDS IN CIGARETTE SMOKE

THIS GRAPHIC OFFERS A SUMMARY OF A SELECTION OF HAZARDOUS COMPOUNDS IN CIGARETTE SMOKE & THEIR EFFECTS

ESTIMATED NUMBER OF CHEMICAL COMPOUNDS IN CIGARETTE SMOKE

7,357

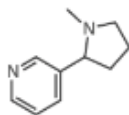


70

NUMBER OF THESE COMPOUNDS WITH CONFIRMED CARCINOGENIC ACTIVITY

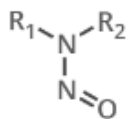
The compounds shown below are all found in cigarette smoke. The mass figures, given in μg , take into account both mainstream (inhaled) and sidestream smoke. 1 μg is equal to 1 millionth of a gram. Amounts of these compounds vary in different brands of cigarettes - these figures are approximate.

NICOTINE



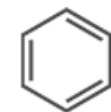
- Approx. 919 μg per cigarette
- Addictive
- Increases heart rate
- Increases blood pressure
- Increases blood glucose
- Lethal dose: around 500-1000mg

N-NITROSAMINES



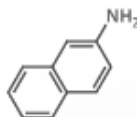
- Large class of compounds
- Several are tobacco-specific
- **Known human carcinogens**
- Most carcinogenic: NNK & NNN
- NNK: approx. 0.3 μg per cigarette
- NNN: approx. 2-50 μg per cigarette
- May cause reproductive damage

BENZENE



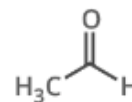
- Approx. 46-272 μg per cigarette
- **Known human carcinogen**
- Damages bone marrow
- Lowers red blood cell count
- May harm reproductive organs

AROMATIC AMINES



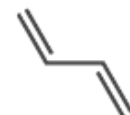
- Large class of compounds
- Includes 2-aminonaphthalene:
- **Known human carcinogen**
- Linked with bladder cancer
- Approx. 0.04 μg per cigarette

ACETALDEHYDE



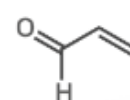
- Approx. 680-1571 μg per cigarette
- **Known animal carcinogen**
- **Probable human carcinogen**
- Irritant to skin & eyes
- Irritant to respiratory tract

1,3-BUTADIENE



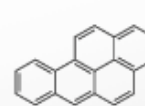
- Approx. 36-191 μg per cigarette
- **Known human carcinogen**
- **Suspected human teratogen**
- Irritant to eyes & skin
- Irritant to upper respiratory tract

ACROLEIN



- Approx. 69-306 μg per cigarette
- **Possible human carcinogen**
- **Known DNA mutagen**
- Irritant to skin & nasal passages
- May contribute to heart disease

POLYAROMATICS



- Large class of compounds
- Includes benzo(a)pyrene:
- **Known human carcinogen**
- **Known DNA mutagen**
- Affects reproductive capacity
- Up to 0.14 μg per cigarette



Some Traditional Chinese Herbal Medicines Cause Cancer, Others Effect Enzymes in Our Bodies and Efficacy of Prescribed Drugs

Science
Translational
Medicine

International Agency
Research on Cancer



Aristolochia herbs

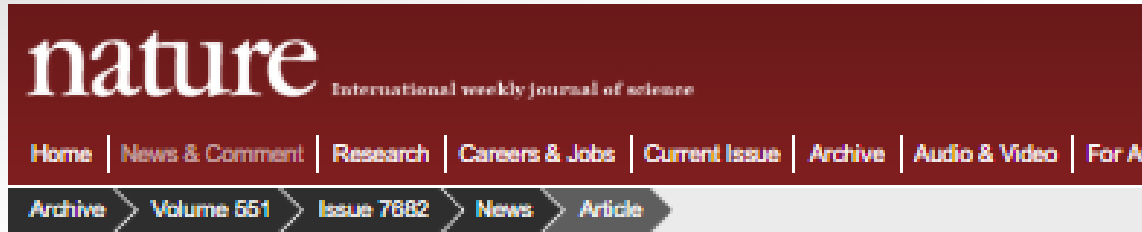


Drugs affected:

- Cyclosporin
- Antidepressants
- Birth control pills
- Indinavir (HIV)
- Irinotecan (Cancer)
- Warfarin (anticoagulant)

- Some traditional Chinese herbal medicines cause **cancer of the kidney, bladder, and liver**

Some Traditional Chinese Herbal Medicines Cause Cancer



NATURE | NEWS



China to roll back regulations for traditional medicine despite safety concerns

Scientists fear plans to abandon clinical trials of centuries-old remedies will put people at risk.

David Cyranoski

29 November 2017



David Grey/REUTERS

The Chinese government is promoting traditional Chinese medicines as an alternative to expensive Western drugs.



NATURE | NEWS



Screen uncovers hidden ingredients of Chinese medicine

Genetic audit reveals that some traditional remedies contain endangered animals and toxic plants.

Ewen Callaway

12 April 2012

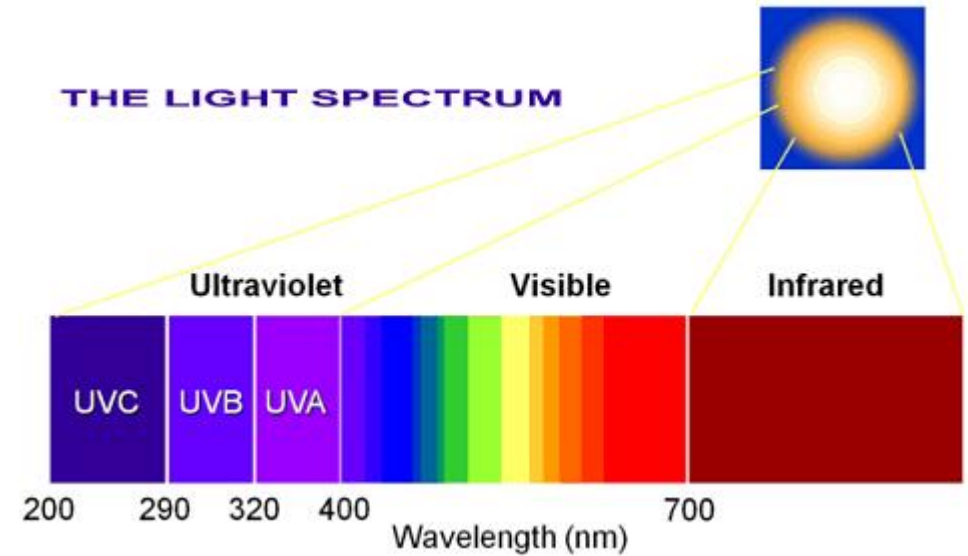
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Chinese herbal medicines contain ingredients derived from endangered animals, toxic plants and livestock, a genetic audit has discovered. Few of these ingredients were listed on the packaging.

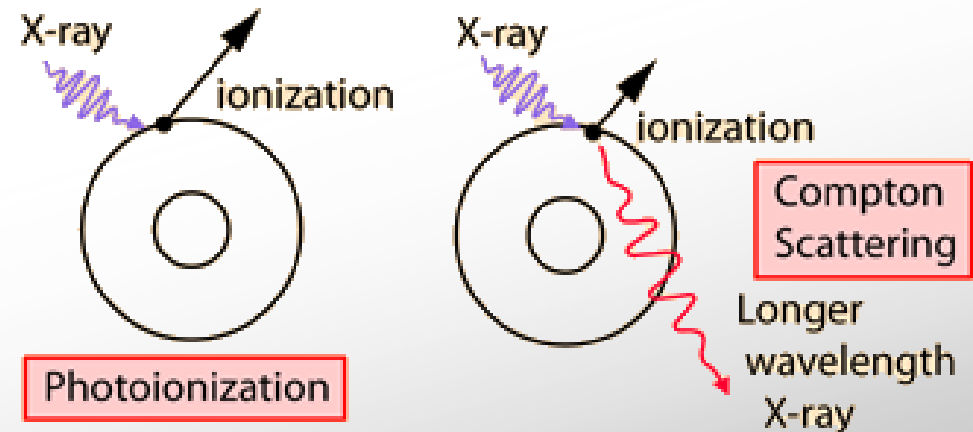
"There's absolutely no honesty in the labelling of these products. What they declare is completely at odds with what's in there," says Mike Bunce, a geneticist at Murdoch University near Perth, Australia, who led the study. The results are published today in *PLoS Genetics*¹.

Radiation

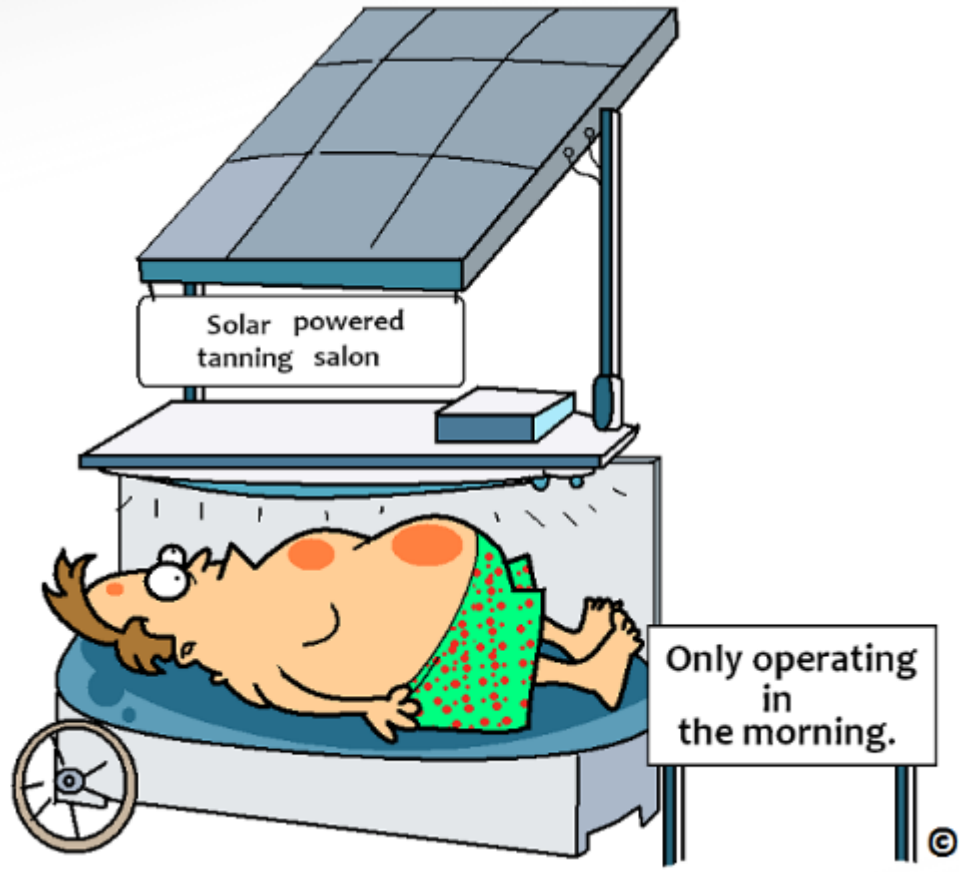
- **Ultraviolet** (UV-B light 280-320 nm) from the sun can increase the risk of squamous carcinoma, basal cell carcinoma and malignant melanoma of the skin.



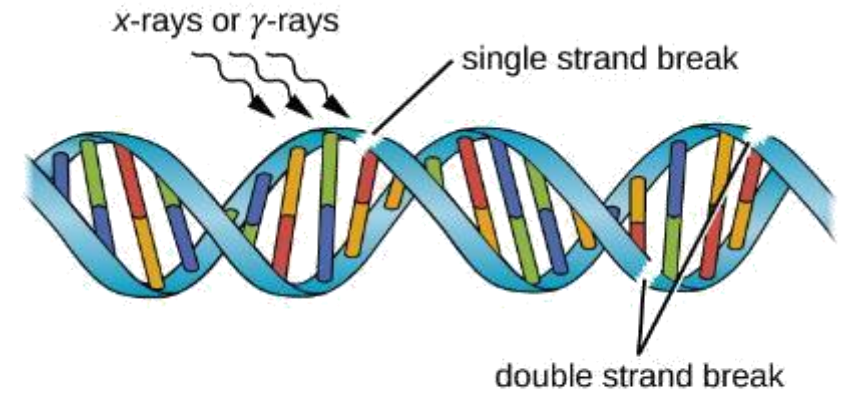
- **Ionizing X-rays** in high dosage & gamma rays, alpha- and beta-particles and radiation from thermonuclear devices.



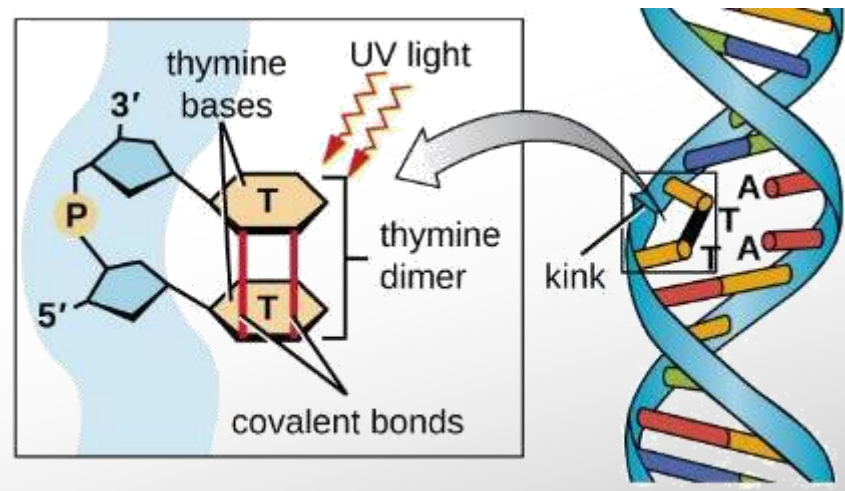
Irradiation and DNA Damage: indoor tanning and UV radiation link



Deanne Lazovich, University of Minnesota

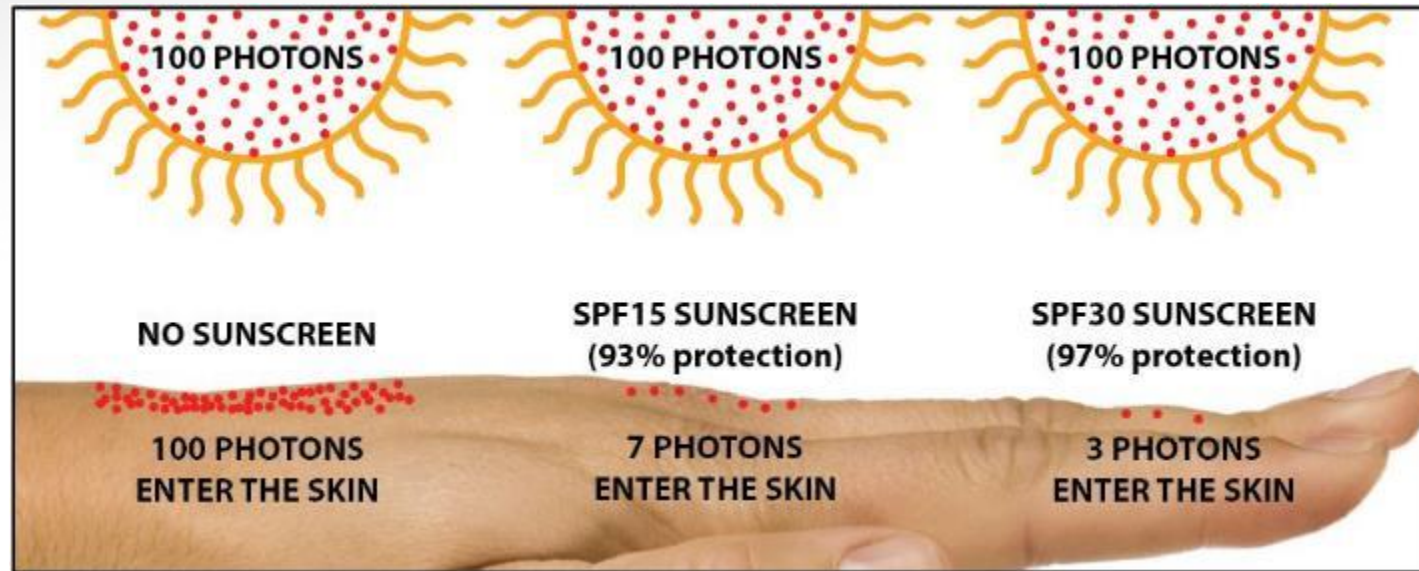


(a) Ionizing radiation



(b) Non-ionizing radiation

The SPF (Sun Protection Factor) Sunscreen



The SPF (Sun Protection Factor) scale is not linear:

SPF 15 blocks 93% of UVB rays

SPF 30 blocks 97% of UVB rays

SPF 50 blocks 98% of UVB rays

Or:

SPF 15 (93% protection) allows 7 out of 100 photons through

SPF 30 (97% protection) allows 3 out of 100 photons through

SPF 75 or SPF 100, do not offer significantly greater protection than SPF 30

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)



Anatomy of a Hot Dog

What's in a hot dog, and why does it pose health risks?



- **Nitrates and Nitrites** produce carcinogenic N-nitroso compounds. They also cause the hardening of arteries and may increase risk of diabetes.
- **Heme Iron** is related to the formation of N-nitroso compounds that may lead to colorectal cancer.
- **Heterocyclic Aromatic Amines (HAAs)** are carcinogens formed by cooking and grilling at high temperatures.
- **Saturated Fat and Cholesterol** lead to LDL deposits in arteries, causing narrowing and blockage which can result in heart attacks or strokes.
- **Salt** is linked to both high blood pressure and stomach cancer.
- **Trimethylamine N-oxide (TMAO)** is a chemical that increases the risk of heart disease.

Reasons to avoid processed meats

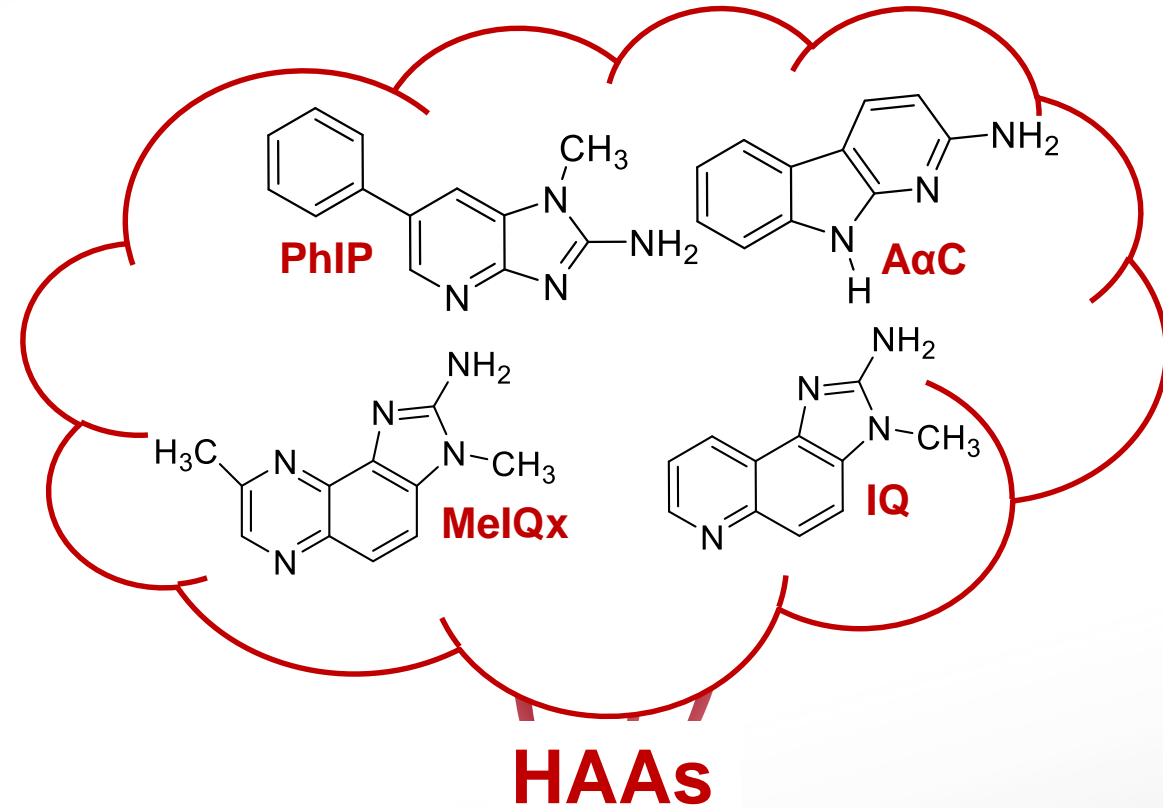


Eating processed meat

- increases risk for **colorectal cancer**
- Increases risk for **heart disease**
- Increases risk for **type 2 diabetes**

Heterocyclic Aromatic Amines (HAAs) genotoxic chemicals formed in well done cooked meats

- More than **20 HAAs** are formed in well-done cooked meats and poultry
- Some HAAs arise in tobacco smoke
- HAAs are multisite carcinogens in rodents
- HAAs are **Group 2A or 2B** carcinogens
- HAAs induce **mutations** in rodents
- HAAs induce colorectal, pancreatic and mammary cancers in rodents



Well-done cooked red meats linked to colon and prostate cancer



Health » Well-done red meat linked to aggressive prostate cancer

Well-done red meat linked to aggressive prostate cancer

By Amanda Gardner, Health.com

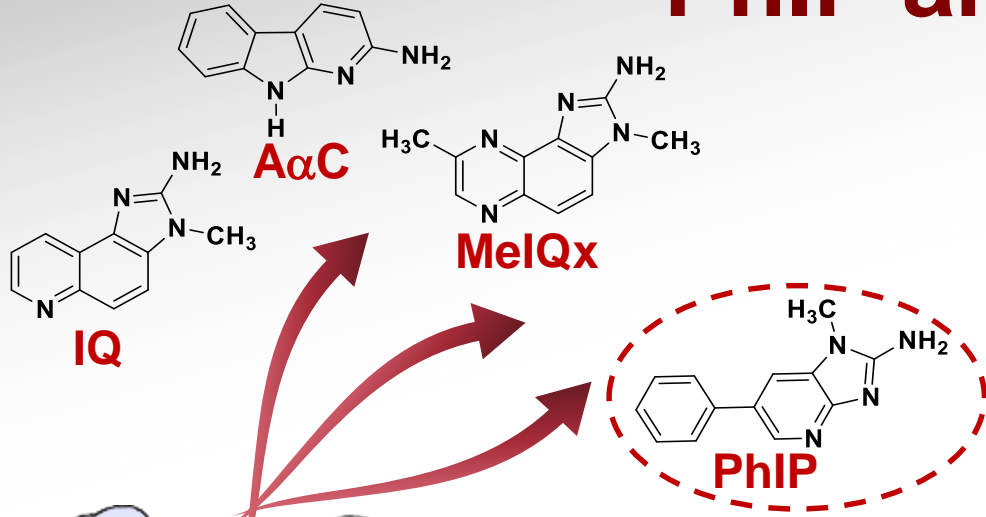
Updated 5:03 PM ET, Wed November 23, 2011



"This is another piece of evidence for the notion that ... grilled meat, contains carcinogens," Ronald D. Ennis says.

- 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**

PhIP and human cancer

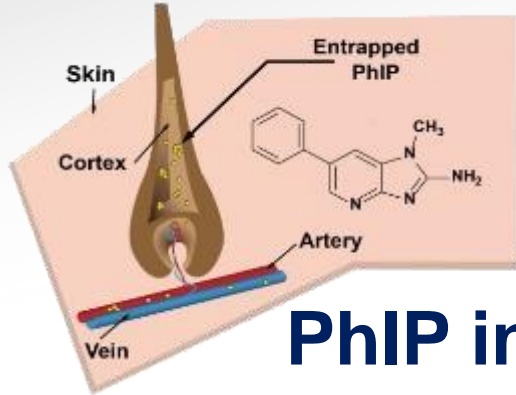


Hair from Prostate cancer patients



- **PhIP** is formed in well-done cooked red meats
- 1/4 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 and a simple test change a man's treatment plan?
- Can early aggressive treatment – *directed by this biomarker screen* **SAVE LIVES?**

Hair as a Biomarker for the Exposure of PhIP from Cooked Meat



PhIP in hair

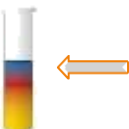


Hair Collection



Hair Digestion

Solid-phase Extraction



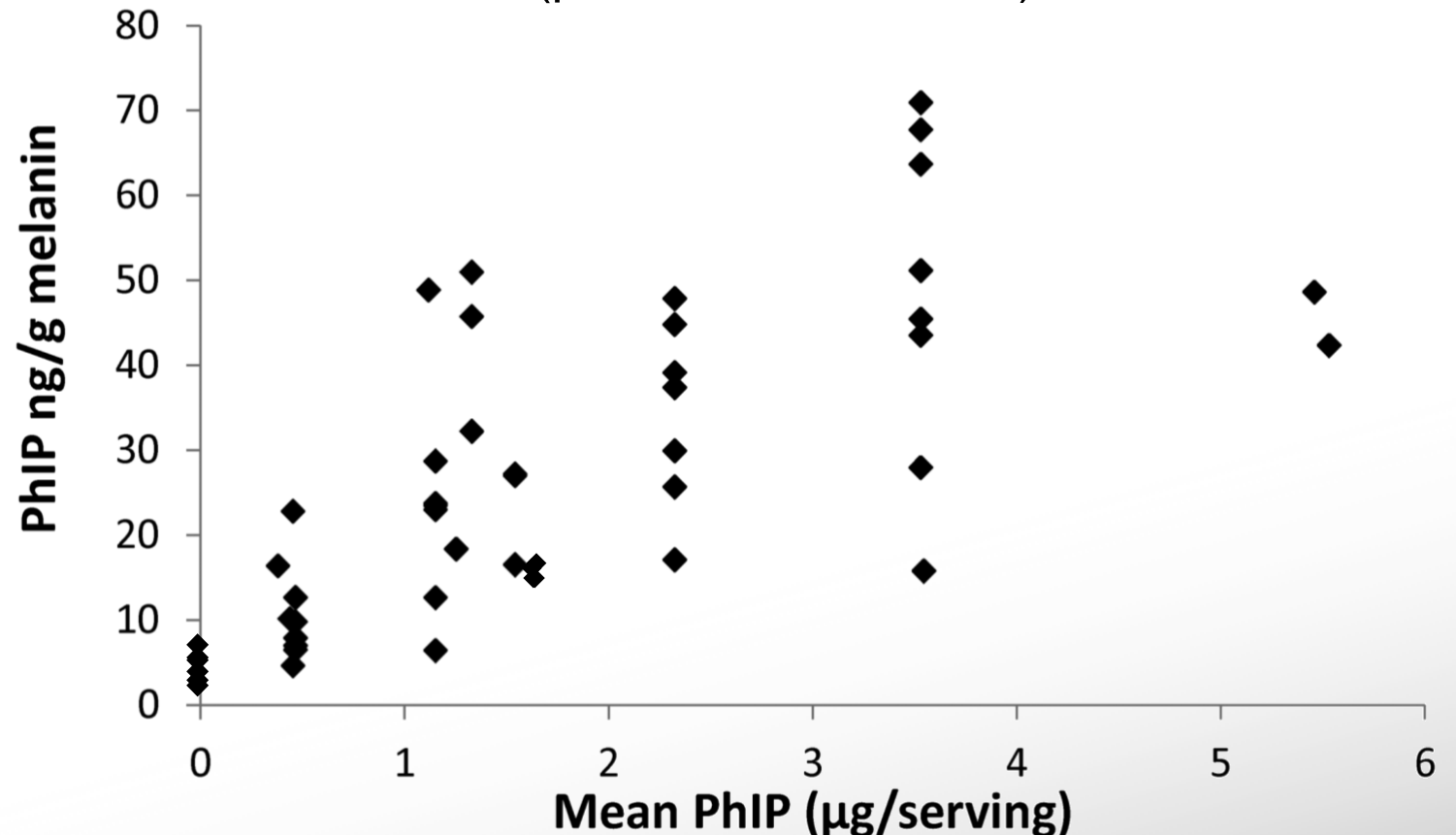
Liquid-liquid Extraction

HPLC-QqQ-MS

LOQ: 2 pg PhIP/50 mg hair

Dose-dependent increase in hair PhIP levels

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



Turesky et al., *CEBP*, 2013

Le Marchand, et al., *Carcinogenesis*, 2016

Yvorne, Switzerland: The Wine Chateau Maison Blanche, Suisse Bernese Mountain Dog, Chateau Chillon in Montreux



Biomonitoring a Carcinogenic Heterocyclic

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



Does kibble containing PhIP contribute to canine cancer?

Public Concern and Controversy about the Safety of Pet Foods

Home > Lifestyle

Poison in jerky treats from China is fatal to some pets; FDA asks pet owners and vets for help

Article by: SUE MANNING , Associated Press | Updated: October 24, 2013 - 4:59 PM



<http://www.startribune.com/lifestyle/229046281.html>

Blogs on Dog Food and Cancer Risk

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Dog Food: Is There A Cancer Risk?

by DEMIAN DRESSLER, DVM



- 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.



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Story at-a-glance

- » [Dr. Becker interviews Dr. Robert Turesky](#), a research scientist for the Division of Environmental Health Sciences at the New York State Department of Health, on his study of hair analysis to detect the presence of specific carcinogens in cooked meat.
- » As a test, Dr. Turesky analyzed the fur of his own dogs and much to his surprise, discovered the presence of one of the carcinogens he is researching. Since his dogs don't eat grilled steaks or burgers, it seemed clear they were being exposed through their own processed pet food diet.
- » Dr. Becker discovered that including Dr. Turesky's published study, there appear to be

Dr. Becker Interviews Dr. Turesky



<https://healthypets.mercola.com/sites/healthypets/archive/2013/05/27/cooked-meat-carcinogens.aspx>

How much meat can I eat?



How bad is eating meat?
The World Health Organization has determined that eating processed

Is bacon really as bad as tobacco?



Bacon's Cancer Risk

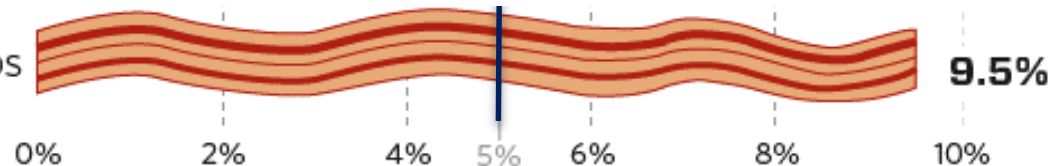
How much bacon you have to eat to raise your risk of colorectal cancer

Strips of bacon
(per day)



Smoking a pack of cigarettes for 40 years increases your risk of developing lung cancer by ~30-fold

10 strips



Baseline risk

Percent risk of colorectal cancer

Kaitlyn Kelly / Vocativ
Source: World Health Organization/IARC

Safe Cooking and Handling of Barbeque Grills

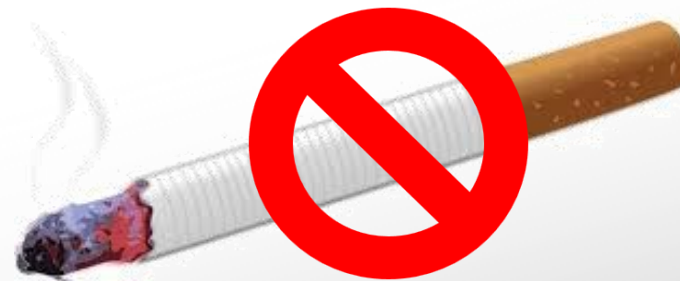


- Avoid exposure to the smoke generated from cooked meats as they can contain mutagens and potential carcinogens
- Don't over-cook meat!! Avoid eating well-done, charred meat
- Flip meat samples often and use marinades to minimize formation of carcinogens
- Use gloves when removing charred residues on grilled surface - burnt residues may contain carcinogens too!

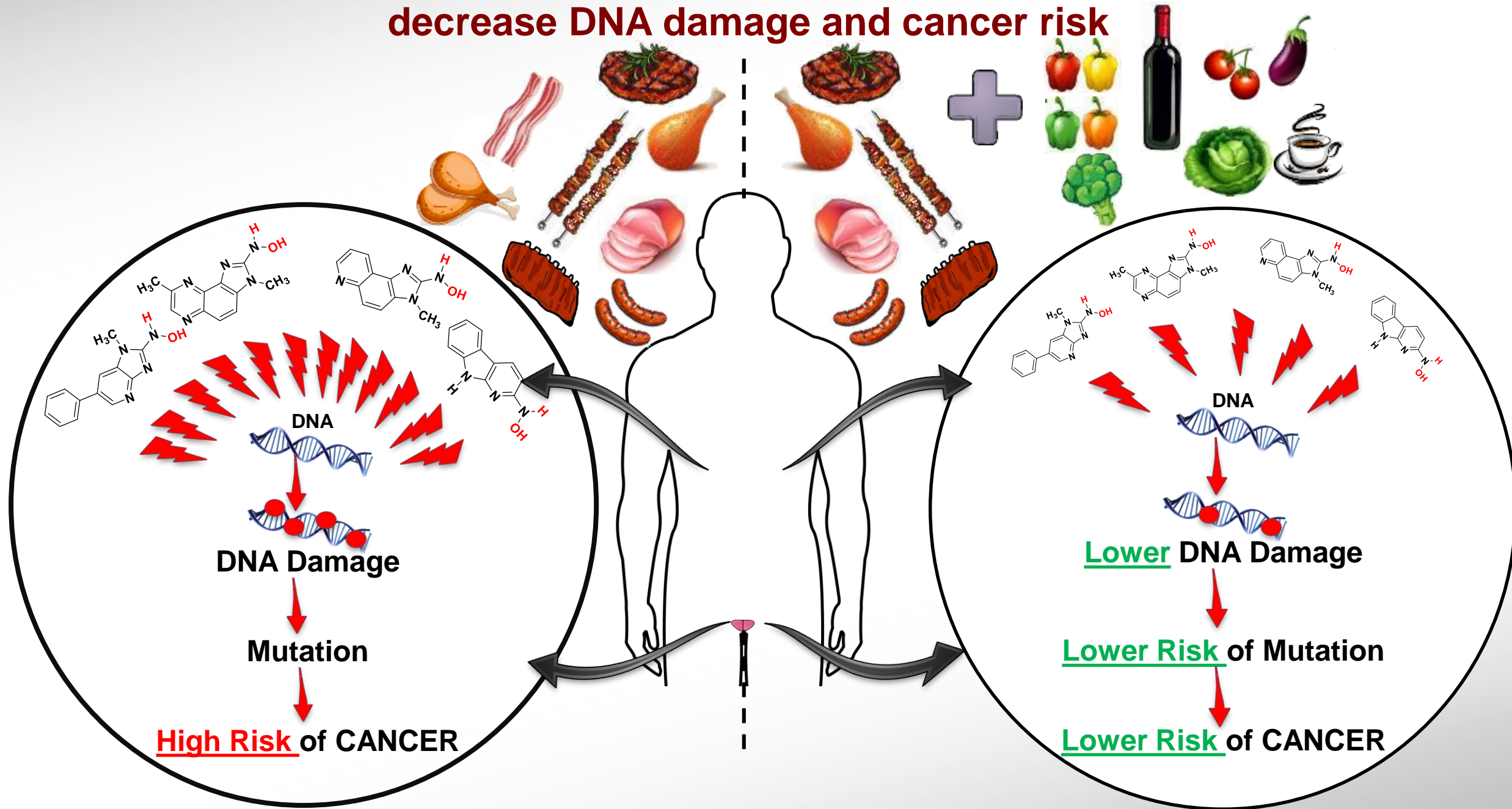
Not everything we eat or drink is going to kill us!

There are many beneficial foods – some are anti-carcinogenic

Preventive (Anti-carcinogenic) Foods



Goal: **FIND AND USE** Chemicals in food or precision medicines to decrease DNA damage and cancer risk



Summary

- The diet contains essential nutrients for health and sustenance. There are many beneficial chemicals in food that can protect against DNA damage and may decrease cancer risk
- **Minimize alcohol intake**: AIRC 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 many foods that protect against DNA damage and cancer.
- 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!**

Take Home Messages

- Environmental and lifestyle-factors can induce DNA damage.
- Environmental and lifestyle-factors can induce cancer.
- In some cases an association is clear, but in most cases it is not.
- There are many beneficial foods and beverages that may protect against cancer.
- Understanding these associations is crucial to identify opportunities for intervention and for prevention!

Ten Recommendation for cancer prevention



<http://www.aicr.org/reduce-your-cancer-risk/recommendations-for-cancer-prevention/>

Acknowledgements

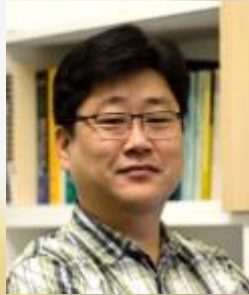


Robert J. Turesky Ph. D.

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- Dr. G. Scelo, IARC, Lyon ,France
- The **Patients!!**



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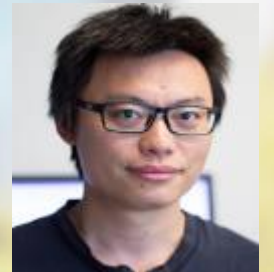


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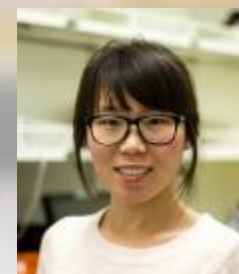
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