CANCER = Malignant Tumor = Malignant Neoplasm

A tissue growth:

• Not necessary for body’s development or repair
• Invading healthy tissues
• Spreading to other sites of the body (metastasizing)
• Lethal because of its invasion, metabolism, and complications
Tissues

Four types of tissue

Connective tissue

Epithelial tissue

Muscle tissue

Nervous tissue
# Cancer Terms to Know

<table>
<thead>
<tr>
<th>Origin</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium (lining tissue)</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Glands</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Bones</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Muscles</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Brain tissue (glial cells)</td>
<td>Glioma</td>
</tr>
<tr>
<td>Lymphatic glands, spleen</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Blood cells</td>
<td>Leukemia</td>
</tr>
</tbody>
</table>

E. MORAN - 2018
Benign tumors do not invade surrounding healthy tissues
Benign tumors do not spread out
Benign tumors may cause complications due to their presence which may obstruct natural conduits [bronchi (airways), intestine]
Terms: Adenoma, lipoma, osteoma
A highly regulated and controlled cell death. It results in changes that include, cell shrinkage, nuclear breakage, chromatin and chromosomal breakage, and global messenger RNA decay.

Defective apoptotic processes have been implicated in a wide variety of diseases. An insufficient amount results in uncontrolled cell proliferation, such as cancer.

Between 50 and 70 billion cells die each day due to apoptosis in the average human adult.
What Causes Cancer?

- Some viruses or bacteria
- Some chemicals
- Radiation
- Heredity
- Diet
- Hormones
Oncogenes

Normal cell

Normal genes regulate cell growth

Cancer cell

Oncogenes accelerate cell growth and division

Mutated/damaged oncogene

E. Moran - 2018
p53 Tumor Suppressor Protein Triggers Cell Suicide

Normal cell

Excessive DNA damage

Cell suicide (Apoptosis)
Chances of Genomic Instability

Human Body Cells $\sim 10^{14}$

Lifetime Cell Divisions $\sim 10^{16}$

Chances of Mutation $\sim 10^{124}$
Cancer Risk and Aging

Number of CANCER Cases (per 100,000 people)
Population - Based Studies

Regions of Highest Incidence

U.K.: Lung cancer

CHINA: Liver cancer

JAPAN: Stomach cancer

U.S.: Colon cancer

AUSTRALIA: Skin cancer

CANADA: Leukemia

BRAZIL: Cervical cancer

CHINA: Liver cancer

AUSTRALIA: Skin cancer

JAPAN: Stomach cancer

U.S.: Colon cancer

CANADA: Leukemia

BRAZIL: Cervical cancer

Heredity? Behavior? “Acculturation”?

**Colon Cancer**
(Number of new cases per 100,000 people)

- Japan: 70
- Japanese families in U.S.: 50
- U.S.: 100

**Stomach Cancer**
(Number of new cases per 100,000 people)

- Japan: 7
- Japanese families in U.S.: 5
- U.S.: 0

Sources:
- N. C. I.
THE DAWN OF MOLECULAR EPIDEMIOLOGY OF HUMAN CANCER

"NO ONE SUPPOSES THAT ALL THE INDIVIDUALS OF THE SAME SPECIES ARE CAST IN THE VERY SAME MOLD"

C. Darwin, 1859
Tumors (Neoplasms)
Invasion and Metastasis

1. Cancer cells invade surrounding tissues and blood vessels
2. Cancer cells are transported by the circulatory system to distant sites
3. Cancer cells reinvade and grow at new location
Malignant versus Benign Tumors

Benign (not cancer) tumor cells grow only locally and cannot spread by invasion or metastasis.

Malignant (cancer) cells invade neighboring tissues, enter blood vessels, and metastasize to different sites.

Time
Development of a Malignant Tumor

Figure 1. Development of a tumor.
LECTURE #2
TUMOR EMBOLUS
CANCER INVASION

A  In situ cancer

B  Invasion of the tumor border

C  Lymphatic spread

D  Intraversion of the circulatory system
   survival, transport

E  Arrest extraversion

F  Solitary dormant cells
   occult micrometastases

G  Progressive colonization
   angiogenesis

Source: Brunner FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB,
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LYMPHATIC SYSTEM

Lymph Capillaries in the Tissue Spaces

- Lymph capillary
- Arteriole
- Tissue fluid
- Tissue spaces
- Tissue cells
- Venule
- Lymphatic vessel
Lymph Node Structure - Schema

afferent lymph vessels

lymph follicle

medullary sinusoids

intermediary sinusoids

subcapsular sinusoids

efferent lymph vessels

capsule

trabecula
Left cervical lymphadenopathy
(Enlarged lymph nodes)
Right Cervical (Neck) Enlarged Lymph Nodes
Swollen glands
Enlarged Glands (Lymphadenopathy)

Subjective: Tender or painless (?)

Objective: Acute or chronic
  Local or general
  Isolated or matted glands

Differential diagnosis: Chronic infections
  Cancer

Diagnosis: Biopsy and pathologic examination
  No needle biopsy
Preferential Sites of Cancer Spread

LUNGS ⇒ Lymph nodes, adrenal glands, bones, Liver, Brain

BREAST ⇒ Lymph nodes, lungs, liver, bones, brain

PROSTATE ⇒ Lymph nodes, spine, bones, lungs

COLON ⇒ Lymph nodes, liver, lungs

BRAIN - Rarely to lymph nodes of the neck
ENVIRONMENT and CANCER
## Environmental Factors of Air Pollution

<table>
<thead>
<tr>
<th>Factor</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combustion</td>
<td>- Polycyclic hydrocarbons</td>
</tr>
<tr>
<td>Smoking</td>
<td>- Passive smoking</td>
</tr>
<tr>
<td></td>
<td>- Indoor air pollution</td>
</tr>
<tr>
<td>Radon Gas</td>
<td>- Miners</td>
</tr>
<tr>
<td>Asbestos</td>
<td>- Zeolite fibers</td>
</tr>
<tr>
<td></td>
<td>- Chrysotile vs. Amphibole</td>
</tr>
<tr>
<td>Arsenic</td>
<td>- Smelters</td>
</tr>
<tr>
<td>Oil Vapors</td>
<td>- Wok cooking</td>
</tr>
</tbody>
</table>
COMBUSTION OF FOSSIL FUELS

Industry, motor vehicle traffic
50% increase in lung cancer
Si and C particles
\downarrow
Inflammatory response
\downarrow
cytokines + free radicals
\downarrow
mutagenic effects
AIR POLLUTION BY COMBUSTION
Epidemiologic Studies

Silesia (Poland) → PAH → genotoxic effects

Yunan (China) - lung cancer in women

Shanghai - lung cancer in non-smoking women
CAUTIONS
Against the immoderate Use of
SNUFF.
Founded on the known Qualities of the
TOBACCO PLANT;
And the Effects it must produce when this
Way taken into the Body:
AND
Enforced by Instances of Persons who have
perished miserably of Diseases, occasioned,
or rendered incurable by its Use.

By Dr. J. HILL.

*****************
THE SECOND EDITION.
*****************

LONDON:
Printed for R. BALDWIN in Pater-nooster Row,
and J. JACKSON in St. James’s-street.
MDCCLXI.
[Price One Shilling.]
TOBACCO SMOKING

Dr. John Hill’s warning (1761)

Exponential increase with number of cigarettes smoked/day

Genetic Predisposition:
- Mutation of p53 tumor suppressor gene
- Activation of ras oncogene
- Deletion of chromosome 3p14-23
- Deregulated expression of myc family genes
- Autocrine stimulation by growth factors
TOBACCO AND LUNG CANCER
Genetic Predisposition

Hydroxylation of PAH

Aryl hydrocarbon hydroxylase inducibility

Debrisoquine 4-hydroxylation
PASSIVE TOBACCO SMOKING

• 20-90% increase in lung cancer in non-smoking spouses of smokers

• Increased levels of carcinogens in plasma of non-smoking spouses

• Banning of tobacco smoking from public places
LUNG CANCER
RISK FACTORS

- Active tobacco smoking (87%)
- Passive smoking
- Environmental factors (asbestos, metals)
Lag Time

20-Year Lag Time Between Smoking and Lung Cancer

Cigarette consumption (men)

Lung cancer (men)

Lung Cancer Deaths (per 100,000 people)

Year

1900 1920 1940 1960 1980

100 150

50

1000 2000 3000 4000

Cigarettes Smoked
Person per Year

E. MORAN - 2018
INTERMISSION
ASBESTOS

Natural soil deposits

Contamination from mining

↑ Underground water table

↑ Gastric, esophageal, and pancreatic cancer (California)

↑ Gastric, pancreas, and lung (Quebec)
ASBESTOS

Serpentine (chrysotile) - Quebec, S. Africa, N. Italy, Russia

Amphiboles (crocidolite, amosite, tremolite, actinolite)

Domestic - Cappadocia dwellings - zeolite

Industry - Occupational exposure - high friction devices - insulation
ASBESTOS (cont’d)
Non-Occupational Exposure:

Malignant mesothelioma & lung cancer = 22% of asbestosis cases

Tobacco smoking = co-carcinogen

Genetic susceptibility = defect in gap junctional intercellular communication capacity

Department of Veterans Affairs
SOLAR RADIATION

SOLAR RADIATION (290-320 nm)

- Skin Cancer
- Melanoma
Low-Strength Radiation

Skin Cancer Incidence

Annual Sunshine (UV radiation)

Least

Low

High

Most

Dallas

Pittsburgh

Detroit

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NUCLEAR POWER

THREE MILE ISLAND (1979):
SOLID DECAY PRODUCTS CONTAINED
1 cancer death / 2 Mil. people

CHERNOBYL (1986):
SOLID DECAY PRODUCTS RELEASED
2% - 3% increase in cancer deaths
High-Strength Radiation

Leukemia Incidence

X-ray Dose (atomic radiation)

High

Low

Least

Most

N. C. I.
WATER POLLUTION AND CANCER

- Organic compounds
- Inorganic solutes
- Radionuclides
- Particulate matter
- Microorganisms
INDUSTRIAL POLLUTION

Contamination of ground water

Dieldrin in rivers - lymphoma

Chlorophenols (sawmills - Finland) - sarcoma & lymphoma

Toxic waste disposal - lung, bladder, stomach, colorectal, esophagus, breast

Chromosomal aberrations
Sister chromatid exchanges
AGRICULTURAL POLLUTION

Chemical Fertilizers (> 150 tons/yr.)

- ↓ soil microorganisms and small mammals
- ↓ insects and organic matter
Phosphates → algal growth in water
Nitrates → toxic, carcinogenic

Pesticides: Arsenic compounds

- Plant parts
- Petroleum products ("dirty dozen")
- ↑ Breast cancer (Hawaii)
CHLORINATION BY-PRODUCTS

Chlorine + natural organic substances present in untreated water ➔ Trihalomethanes (THM’s)

THM are organohalogen compounds derivatives of methane

Ecological studies: Bladder, colon, rectal, lung, brain cancer
RADIONUCLIDES

Naturally occurring in water

From industry

From nuclear power generation

Radium-226, Radium-228, Radon-222

$^{222}\text{Rn} = 1\text{pCi/L} \rightarrow \text{cancer probability} = 1 \times 10^{-6}$

Increased incidence of childhood leukemia, bone sarcoma, lung and bladder cancer
Bacteria and Cancer

- *Helicobacter pylori* → Stomach cancer

- *Chlamydia trachomatis* → greater risk of cervical cancer
Bacteria and Stomach Cancer

Patient’s tissue sample

H. pylori
**STOMACH CANCER**

**H. pylori** - 2/3 of world’s population harbors the bacterium
- Second cause of cancer deaths worldwide

**H. pylori** → inflammation → reactive O\(^{•}\) species →
cytokines → mutations → cancer - 6-8 fold increase
compared to non-infected individuals

**H. pylori** → reduced risk of gastroesophageal (cardia)
cancer → less acidity.
### Human Viruses and Cancer

<table>
<thead>
<tr>
<th>Virus</th>
<th>Human Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B and C</td>
<td>Liver, pancreas, breast cancer</td>
</tr>
<tr>
<td>Herpes virus</td>
<td>Nasopharyngeal carcinoma, Lymphomas</td>
</tr>
<tr>
<td>Human Papilloma Virus</td>
<td>Cervical cancer, skin cancer</td>
</tr>
</tbody>
</table>
Avoid Cancer Viruses

HPV Infection Increases Risk for Cervical Cancer

Cervical Cancer Risk

High

Low

Noninfected women

Women infected with HPV

N. C. I.
CANCER PREVENTION
Disease Prevention

- Primary: Prevent onset of the disease
  - e.g. immunizations, chemoprevention
- Secondary: Prevent preclinical disease
  - cancer screening
- Tertiary: Prevent complications
  - cholesterol reduction in CAD

(US Preventive Service Task Force)
CANCER PREVENTION

WEIGHT

DIET

PHYSICAL ACTIVITY

aim to be a healthy weight throughout life
be physically active every day in any way for 30 minutes or more
choose mostly plant foods, limit red and processed meat

NUTRITION and CANCER

• Overnutrition
  - Colon, breast, and prostate cancer

• Undernutrition
  - Esophagus, stomach, and liver cancer
Limit Alcohol and Tobacco

Combination of Alcohol and Cigarettes Increases Risk for **Cancer of the Esophagus**

- **Risk Increase**
  - 40x
  - 30x
  - 20x
  - 10x

- **Alcoholic Drinks Consumed per Day**
  - 0
  - 4+
  - 0
  - 4+

- **Packs of Cigarettes Consumed per Day**
  - 0
  - 0
  - 2+
  - 2+


E. Moran - 2018
Diet: Limit Fats and Calories

Correlation Between Meat Consumption and Colon Cancer Rates in Different Countries

Number of cancer cases (per 100,000 people)

Grams (per person per day)
Cancer Death Rates of Obese Compared to that of Individuals with Normal Body Weight (BMI < 25)

- Men: 52%
- Women: 62%

- 30.0-34.9: 10%
- 35.0-39.9: 20%
- 40 or more: 62%
OBESITY and CANCER
New Findings

- ~30% of US adults are obese (BMI > 30)
- ~35% of US adults are overweight (BMI 25 - 30)

- Women: Uterine cancer 6-fold
  Kidney cancer x 5-fold

- Men: Liver cancer 6-fold
  Colorectal cancer ~1.75-fold
Recommendations for Cancer Prevention

1. Be as lean as possible within the normal range of body weight.
2. Be **physically active** as part of everyday life.
3. **Do not smoke**.
4. Limit consumption of energy-dense foods; **avoid sugary drinks**.
5. **Eat mostly foods of plant origin**.
6. **Limit intake of red meat**; avoid processed meat.
7. **Limit alcoholic drinks**.
8. **Limit consumption of salt**; avoid moldy cereals (grains) or pulses (legumes).
3. Aim to meet nutritional needs through **diet alone**.
Diet: Consume Fruits and Vegetables
Nutrition – Cancer Relationship
The Evidence

Cancer Causing Agents Found in Food

• Chemicals produced during:
  – Cooking meat: at high temperature, over direct flame
  – Preserving meat: smoked, salt-, nitrate- or nitrite- cured
  – Digesting red meat

• Alcohol

• Aflatoxins
Nutrition – Cancer Relationship
The Evidence

Cancer Protective Agents

- Fruits
- Vegetables
- Foods with:
  - Lycopene
  - Selenium
  - Folate
  - Fiber
Cancer Prevention

WCRF & AICR Recommendations

1. Be as lean as possible (normal weight range).

2. Be physically active every day.

3. Limit foods that promote weight gain:
   - Limit intake of processed, energy dense foods.
   - Avoid sugary drinks.
   - Consume fast foods sparingly, if at all.
Cancer Prevention

WCRF & AICR Recommendations

4. Eat mostly plant foods.
   - At least 5 servings of a variety of non-starchy vegetables and of fruits every day.
   - Eat unprocessed grains and/or legumes with every meal.
   - Limit refined starchy foods.
Cancer Prevention
WCRF & AICR Recommendations

5. Limit intake of red meat, and avoid processed meat.

Red Meat:
Consume less than 18 oz/week.

Processed meat:
Smoked, cured, salted, chemically preserved
Cancer Prevention

WCRF & AICR Recommendations

6. Limit alcohol intake to
   Not more than:
   - 2 drinks per day for men.
   - 1 drink per day for women.

1 drink = 1 ½ oz liquor, 5 oz wine, or 12 oz beer
Cancer Prevention

WCRF & AICR Recommendations

Preserved/Processed Food

7. Limit salt intake.
   - Avoid salt-preserved, salted or salty foods.
   - Limit intake of processed foods with added salt.

Avoid moldy grains or legumes.
   - Stored a long time in warm temperatures.
Cancer Prevention

WCRF & AICR Recommendations

8. Aim to meet nutritional needs through diet.
   - Dietary supplements are not recommended for cancer prevention.

Food is!
CANCER CHEMOPREVENTION
### CHEMOPREVENTIVE SUBSTANCES IN FOOD (I)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavonoids</td>
<td>Green plants, fruits, vegetables, tea, coffee, wine</td>
</tr>
<tr>
<td>Indoles</td>
<td>Cruciferous vegetables</td>
</tr>
<tr>
<td>Organic Isothiocyanates</td>
<td>Cruciferous vegetables</td>
</tr>
<tr>
<td>Monoterpenes</td>
<td>Citrus fruits</td>
</tr>
<tr>
<td>Phenolic Acids</td>
<td>Fruits, vegetables, nuts, coffee, tea</td>
</tr>
<tr>
<td>Phytic Acid</td>
<td>Legumes, cereals</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td>Seeds, grains, legumes</td>
</tr>
</tbody>
</table>
CHEMOPREVENTIVE SUBSTANCES IN FOOD (II)

Carotenoids - Fruits, cereals, vegetables

Chlorophyllin - Leafy vegetables

Coumarins - Vegetables, citrus fruits, nuts, beans, grains

Diallyl Sulphides - Garlic, onions

Dietary Fiber - Grains, seeds, berries, fruit skin, legumes,
## NUTRITIVE CHEMOPREVENTIVE AGENTS (III)

<table>
<thead>
<tr>
<th>Agents</th>
<th>Major Food Source</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Vegetables, fruits</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Fruits (citrus), vegetables</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Vegetable oils</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Selenium</td>
<td>Meat, eggs, dairy products</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Calcium</td>
<td>Dairy products</td>
<td>Binds bile and fatty acids</td>
</tr>
</tbody>
</table>
“The doctor of the future will give no drugs, but will interest his patients in the care of the human frame, in diet, and in the cause and prevention of human disease.”

- Thomas A. Edison