Basic Oncology

Basic Applications, Tumor Markers, Genes

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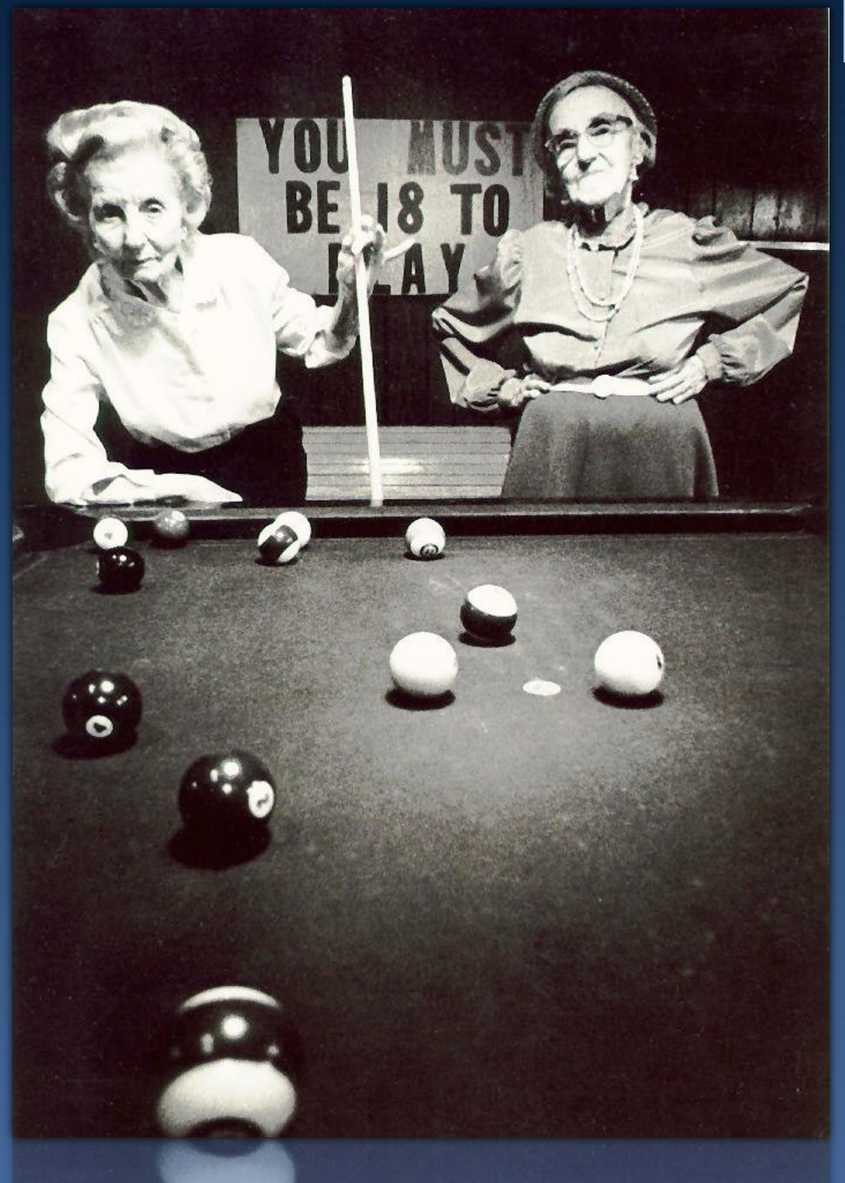
The Biology of Cancer

- Karyotypic abnormalities
  - Expression of cellular characteristics normally occurs under strict control
  - In malignancy, normal control is subverted or bypassed due to the action of a select group of genes ("oncogenes"), which regulate cellular activities
  - Loss of function of tumor suppressor genes ("anti-oncogenes") may be responsible for the development of certain tumors, such as retinoblastoma

Etiology

- Genetic Factors
- Radiation
- Tobacco
- Occupational exposure
- Medications
- Viruses
- Oncogenes and Antioncogenes

- At least 80% of cancers in Americans are caused by living habits and environmental conditions!



Genetic Factors

- For many common malignancies the incidence of cancer is higher among patients with a positive family history
  - As high as 25- to 30-fold in certain groups of patients with a familial history of breast cancer or bowel cancer
  - Inheritance patterns in these disorders are generally autosomal dominant, with varying penetrance. Half of the children of patients with these disorders will inherit the gene defect

Genetic Factors

- Preneoplastic syndromes (4 varieties)
  - Hamartomatous syndromes (phakomatoses)
    - Includes neurofibromatosis, vonHippel-Lindau syndrome, tuberous sclerosis, Cowden's syndrome, Peutz-Jeghers syndrome, and multiple exostosis syndrome
    - Benign lesions can undergo malignant transformation into sarcomas
    - May develop gliomas in the brain or optic nerve, meningiomas, acoustic neuromas, or pheochromocytomas

Genetic Factors

- Preneoplastic syndromes
  - Genodermatoses
    - Includes xeroderma pigmentosum, albinism, Werner's syndrome, epidermodysplasia verricuformis, dyskeratosis congenita, and polydysplastic epidermolysis bullosa
    - Rare autosomal recessive genetic disorders that involve skin

Genetic Factors

- Preneoplastic syndromes
  - Hereditary immune deficiency syndromes
    - Includes ataxia telangiectasia, Wiskott-Aldrich syndrome, late onset immune deficiency, and X-linked agammaglobulinemia
    - Increased incidence of neoplasia, most commonly lymphoproliferative malignancies

Genetic Factors

- Preneoplastic syndromes
  - Chromosome breakage disorders
    - Includes Bloom's syndrome and Fanconi's syndrome
    - Autosomal recessive inheritance of chromosomal instability and rearrangements of karyotypes; patients have an increased incidence of acute leukemia

Genetic Factors

- Li-Fraumeni Syndrome (or SBLA syndrome)
  - Autosomal dominant syndrome predisposing to a variety of malignancies, including soft tissue sarcomas, breast cancer, brain tumors, leukemias, lung cancer, and adrenocortical carcinomas

Genetic Factors

- Lynch Syndrome
  - Autosomal dominant disorder which predisposes to nonpolyposis carcinomas of the colorectum (Lynch I). Additionally, the association of colorectal cancer with carcinomas of the breast (Lynch II), endometrium, and ovary exists
  - Variations in DNA repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*) increase the risk of developing Lynch syndrome

Radiation

- Less than 3% of cancers result from exposure to radiation
- Exposure to the aerosol from radon daughters (uranium miners) increases the risk of malignancy in exposed tissues (lung). Radon daughters emit α-particles which can directly damage DNA. Individuals in ground-level dwellings are also at risk

Radiation

- Nearly all tissues are susceptible to tumor induction by radiation; most sensitive are the bone marrow, breast, and thyroid. The latent period is only 2-5 years for acute leukemia, and 5-10 years for solid tumors
- Higher incidence in those who have received radiation for neoplastic diseases and for ankylosing spondylitis, and of thyroid cancer in children irradiated for thymic enlargement

Radiation

- Solar radiation is the primary risk factor in skin cancer
- Occurs primarily on the parts of the body exposed to sunlight. Has a higher incidence in outdoor workers
- Patients with genetic diseases such as xeroderma pigmentosum and albinism are at high risk for developing skin cancer

Radiation

- The carcinogenic effect of solar irradiation is spectral range of 290 to 320 nm. This range of wavelengths correlates with the action spectrum for UV-induced damage to DNA
- Risk for melanoma is cumulative with continued sun exposure, and increases dramatically for those who have a history of 3 or more blistering sunburns

Tobacco

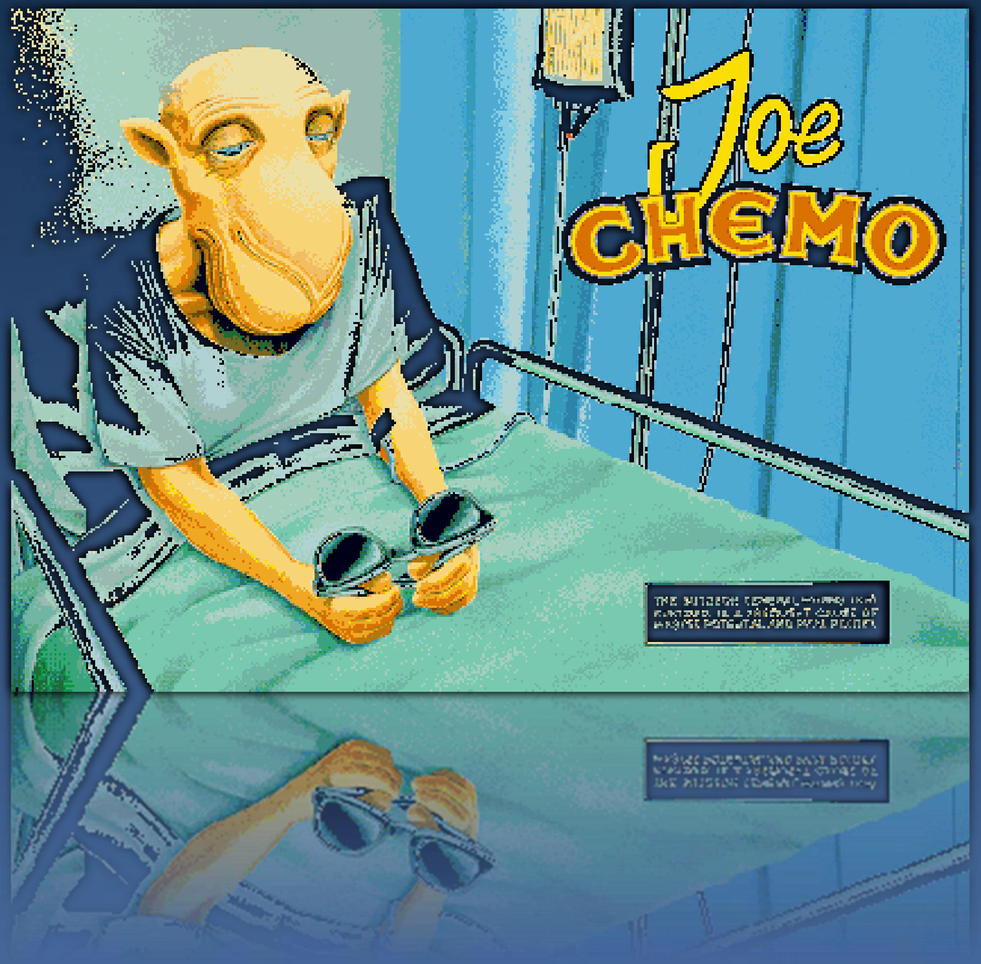
- Lung cancer incidence is 10 to 20 times higher in smokers than in nonsmokers
- Tobacco smoking is associated with cancer of the oral cavity, esophagus, kidney, bladder, and pancreas. Particulate matter known as *tar* contains polycyclic hydrocarbons, which have been shown experimentally to be contact carcinogens

Tobacco

- The metabolic activation of tobacco components such as the cyclic N-nitrosamines can produce carcinogens with the capacity to act upon the cells of internal organs
- Tobacco-related malignancies account for one-third of all male cancer deaths and for 10-20% of all female cancer deaths

Tobacco

- As a result of increased use of tobacco by women in the period since World War II, the incidence of lung cancer deaths in females has surpassed that of breast cancer
- Smoking cessation results in a gradual decrease in risk, so that after 10-15 years former smokers have nearly the same risk of lung cancer as nonsmokers



Occupational Exposure

Occupational Agent	*Related Cancer*
Arsenic	lung, skin, liver
Asbestos	mesothelioma, lung
Benzene	leukemia
Benzidine	bladder
Chromium compounds	lung
Mustard gas	lung
Polycyclic hydrocarbons	lung, skin
Vinyl chloride	angiosarcoma of liver

Air Pollution

- Lung cancer incidence is increased by smoking and by certain industrial and occupational exposures (primarily related to coal tar and combustion by-products)
- Higher incidence of lung cancer in urban dwellers above and beyond industrial and occupational exposure

Medications

- Estrogens
  - DES associated with vaginal and cervical cancer in daughters who were exposed *in utero*
  - Estrogens increase the incidence of endometrial cancer. Risk is decreased by the additional use of progesterone and a decreased estrogen dose
  - Correlation between estrogen exposure and breast cancer development

Medications

- Chemotherapeutic agents
  - Alkylating agents cause an increased incidence of acute myelocytic leukemia, bladder cancer, and probably other malignancies
  - BRAF kinase inhibitors—keratoacanthomas, SCC of skin. Managed by local therapies; does not require discontinuation of therapy
- Androgens—risk of prostate cancer
- Immunosuppressives
  - Organ transplant patients treated with immunosuppressives, such as azathioprine and prednisone, have an increased incidence of large cell lymphoma as well as a variety of solid tumors

Medications

- As cancer preventatives
  - Calcium, nonsteroidal anti-inflammatory drugs (NSAIDS), and aspirin may reduce the risk for developing colon cancer
  - Celecoxib (Celebrex®) FDA approved for treatment of familial adenomatous polyposis
  - Vitamin D supplementation?
    - Emerging data sets regarding Vitamin D deficiency and levels of 25-hydroxy Vitamin D with increased risk of cancers of breast, colon and rectum, and other sites

Medications

- As cancer preventatives
  - Tamoxifen (Nolvadex®) effective in decreasing development of breast cancer in women at high risk
  - Raloxifene (Evista®) effective in decreasing second primary breast cancer; doesn’t lower risk of developing *in situ* cancer

Diet

- Evidence strongly correlates the intake of fat with cancer at several sites, especially the breast and colon. No definitive reason, but postulated explanations include:
  - Increased adiposity=higher estrogen levels
  - Increased bile salt excretion which could alter gut flora and raise the production of carcinogenic substances

Diet

- Dietary substances are associated with cancers in the following sites:
  - Fat: breast and colon
  - High total caloric intake: breast, endometrium, prostate, colon, and gall bladder
  - Animal protein, particularly as red meats: breast, endometrium, and colon
  - Alcohol, particularly in smokers: mouth, pharynx, larynx, esophagus, and liver
  - Salt-cured, smoked, or charred foods: esophagus and stomach
  - Nitrate and nitrite additives: intestine

Diet

- No support for anticarcinogenic value of particular vitamins, minerals, or nutritional supplements in amounts greater than provided by a prudent diet
  - Analogs of Vitamin A have been shown to work as differentiating agents in leukemia and to reduce the incidence of secondary malignancies of the head and neck
  - Vitamin A analogs may also have a role in treatment of carcinomas of the cervix and vagina

Infectious Agents

- Human T cell Lymphotropic Virus type 1 (HTLV-1)
  - Retrovirus associated with T cell lymphoma, cutaneous T cell lymphoma (mycosis fungoides) and acute T cell leukemia
- Epstein-Barr virus (EBV)
  - Closely associated with African Burkitt's lymphoma and NPC

Infectious Agents

- Hepatitis B virus (HBV)
  - Strongly linked with the incidence of hepatocellular carcinoma
  - Contributing factors
    - Malaria
    - Malnutrition
    - Exposure to aflatoxin

Infectious Agents

- Hepatitis C virus (HCV)
  - Accounts for about one third of all cases of hepatocellular cancer in the US each year
  - Occurs almost exclusively in those with cirrhosis
- Herpes simplex virus (HSV)
  - There is a statistical correlation between HSV-2 viral infection, which is sexually transmitted, and the incidence of cervical cancer

Infectious Agents

- Human papilloma virus (HPV)
  - Strong correlation between HPV infection and cancers of the labia, vagina, cervix, penis, head/neck, and anus
  - Two vaccines on market - hope to decrease incidence of HPV-caused cancer at these sites
- *Helicobacter pylori*
  - Association with gastric carcinoma and low grade lymphoma
    - Antibiotic treatment in face of lymphoma has been associated with regression of malignancy!

Oncogenes

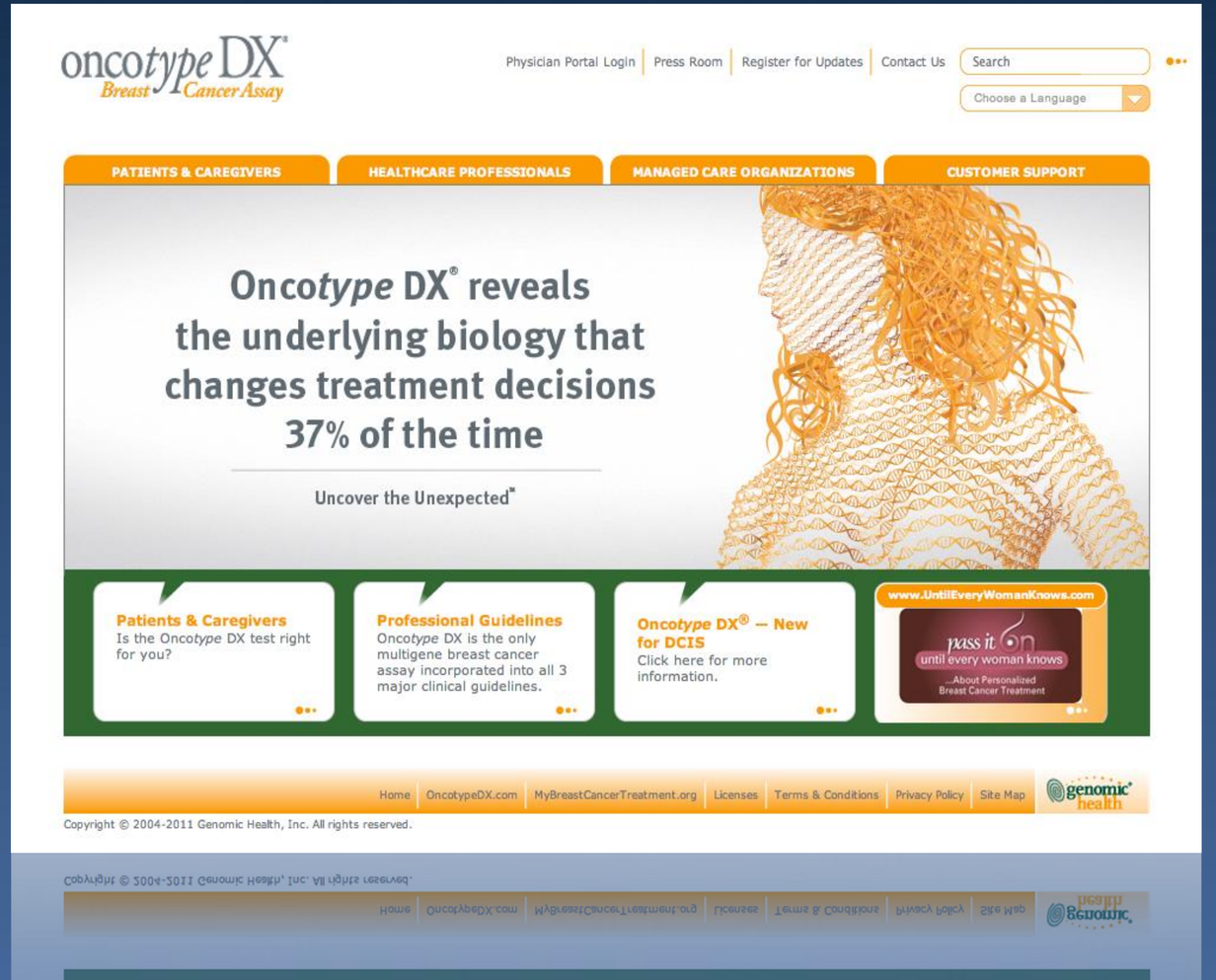
- Genetic material which, when altered, causes formation of cancer
- Definitions…
  - Protooncogene—a presumably normal gene which may be a target for carcinogenic agents. Not causative of cancer by itself in an inactive form
  - Oncogene—the active cancer gene; an “activated protooncogene”
  - Antioncogene—a gene which prevents the formation of a given malignancy. Also known as “tumor suppressor” gene

Oncogenes

Oncogene	*Tumor Association*
HER2	Breast, ovarian, gastric
RAF	Gastric, thyroid, kidney, melanoma
H-RAS	Bladder
K-RAS	Lung, colon
N-RAS	Leukemia
C-MYC	Lymphoma, various carcinomas
N-MYC	Neuroblastoma
L-MYC	Small Cell Lung Cancer
BCL-2	Lymphoma

Oncogene Applications

Genomic oncogene detection strategies can help identify patients at risk for more aggressive cancer



Oncogenes

Specific therapy exists for cancers with mutated genes…

Oncogene	*Cancer Association and Agent(s) Used*
BRAF	Melanoma (vemurafenib, dabrafenib)
MEK	Melanoma (trametinib)
ALK	NSCLC (crizotinib, ceritinib)
BCR-ABL	CML (imatinib, dasatinib, nilotinib)

Antioncogenes

- Genes that decrease the likelihood of developing a given malignancy
- Earliest example is the retinoblastoma (RB) gene. Normal cell growth and differentiation is not affected if one RB gene is inactivated; when both RB genes are inactivated, the risk of developing retinoblastoma increases dramatically