Basic Oncology

Basic Applications, Tumor Markers, Genes

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Financial Disclosures

I have no real or apparent conflict of interest with the information presented in this lecture

Cancer Statistics

Leading Sites of New Cancer Cases and Deaths – 2016 Estimates

Estimated New Cases		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 180,890 (21%)	Breast 246,660 (29%)	Lung & bronchus 85,920 (27%)	Lung & bronchus 72,160 (26%)
Lung & bronchus 117,920 (14%)	Lung & bronchus 106,470 (13%)	Prostate 26,120 (8%)	Breast 40,450 (14%)
Colon & rectum 70,820 (8%)	Colon & rectum 63,670 (8%)	Colon & rectum 26,020 (8%)	Colon & rectum 23,170 (8%)
Urinary bladder 58,950 (7%)	Uterine corpus 60,050 (7%)	Pancreas 21,450 (7%)	Pancreas 20,330 (7%)
Melanoma of the skin 46,870 (6%)	Thyroid 49,350 (6%)	Liver & intrahepatic bile duct 18,280 (6%)	Ovary 14,240 (5%)
Non-Hodgkin lymphoma 40,170 (5%)	Non-Hodgkin lymphoma 32,410 (4%)	Leukemia 14,130 (4%)	Uterine corpus 10,470 (4%)
Kidney & renal pelvis 39,650 (5%)	Melanoma of the skin 29,510 (3%)	Esophagus 12,720 (4%)	Leukemia 10,270 (4%)
Oral cavity & pharynx 34,780 (4%)	Leukemia 26,050 (3%)	Urinary bladder 11,820 (4%)	Liver & intrahepatic bile duct 8,890 (3%)
Leukemia 34,090 (4%)	Pancreas 25,400 (3%)	Non-Hodgkin lymphoma 11,520 (4%)	Non-Hodgkin lymphoma 8,630 (3%)
Liver & intrahepatic bile duct 28,410 (3%)	Kidney & renal pelvis 23,050 (3%)	Brain & other nervous system 9,440 (3%)	Brain & other nervous system 6,610 (2%)
All sites 841,390 (100%)	All sites 843,820 (100%)	All sites 314,290 (100%)	All sites 281,400 (100%)

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

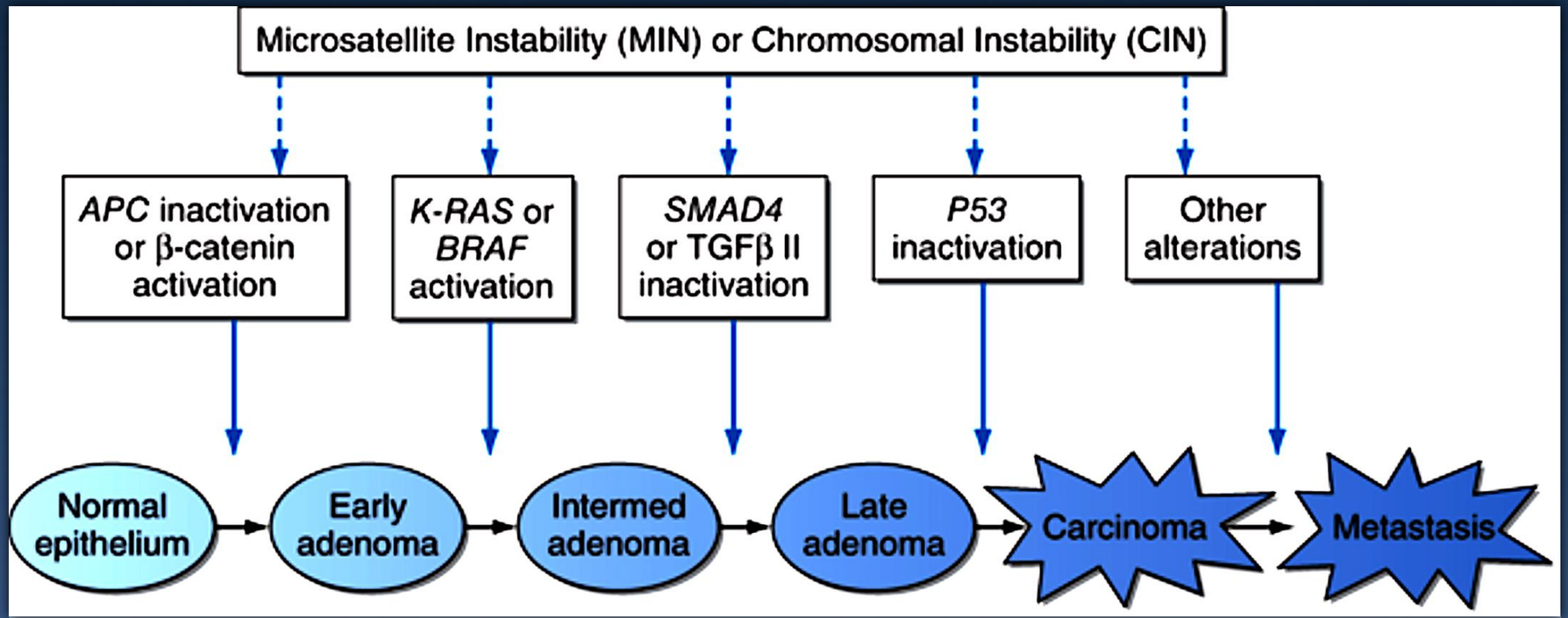
Definition—What is Cancer?

- Cancer is best defined by…
  - Clonality - arises from a single cell; multiple cumulative mutations are needed
  - Autonomy - loss of normal control over cell division
  - Anaplasia - lacks normal differentiation
  - Metastasis - spread to distant sites
- The process by which a normal cell exhibits these characteristics is termed *malignant transformation*

Cancer Clonality

- The multi-hit theory of cancer genesis
- Multiple genetic mutations are required

Harrison's Principles of Internal Medicine, 19e, 2015



Progressive somatic mutational steps in the development of colon carcinoma. The accumulation of alterations in a number of different genes results in the progression from normal epithelium through adenoma to full-blown carcinoma. Genetic instability (microsatellite or chromosomal) accelerates the progression by increasing the likelihood of mutation at each step. Patients with familial polyposis are already one step into this pathway, because they inherit a germline alteration of the APC gene. TGF, transforming growth factor.

Two Types of Cancer Genes

- Oncogenes
- Tumor suppressor genes
  - “Caretaker” genes - control genomic integrity

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”

How Do Oncogenes Work?

- Point Mutation - results in gain or loss of functional activity
- DNA Amplification - leads to over expression of the gene product
- Chromosomal Rearrangement - translocations of genetic material resulting in a new fusion gene; term also used for gain or loss of chromosomal material

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

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)

Tumor Suppressor Genes (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

How Do Tumor Suppressor Genes Fail?

- Two major components…
  - Point mutations - lead to truncated proteins or to no functional product at all
  - Large deletions - lead to loss of functional product; may also lead to loss of heterozygosity in tumor DNA
- Also…epigenetic change can lead to gene silencing

Epigenetic change: change in the genome, heritable by cell progeny, that does not involve a change in the DNA sequence. In normal DNA, the switching off of one X chromosome is an example.

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 due to mutation of *TP53* gene 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 due to germline mutations in the adenomatous polyposis coli (*APC*) tumor-suppressor gene on chromosome 5
  - 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

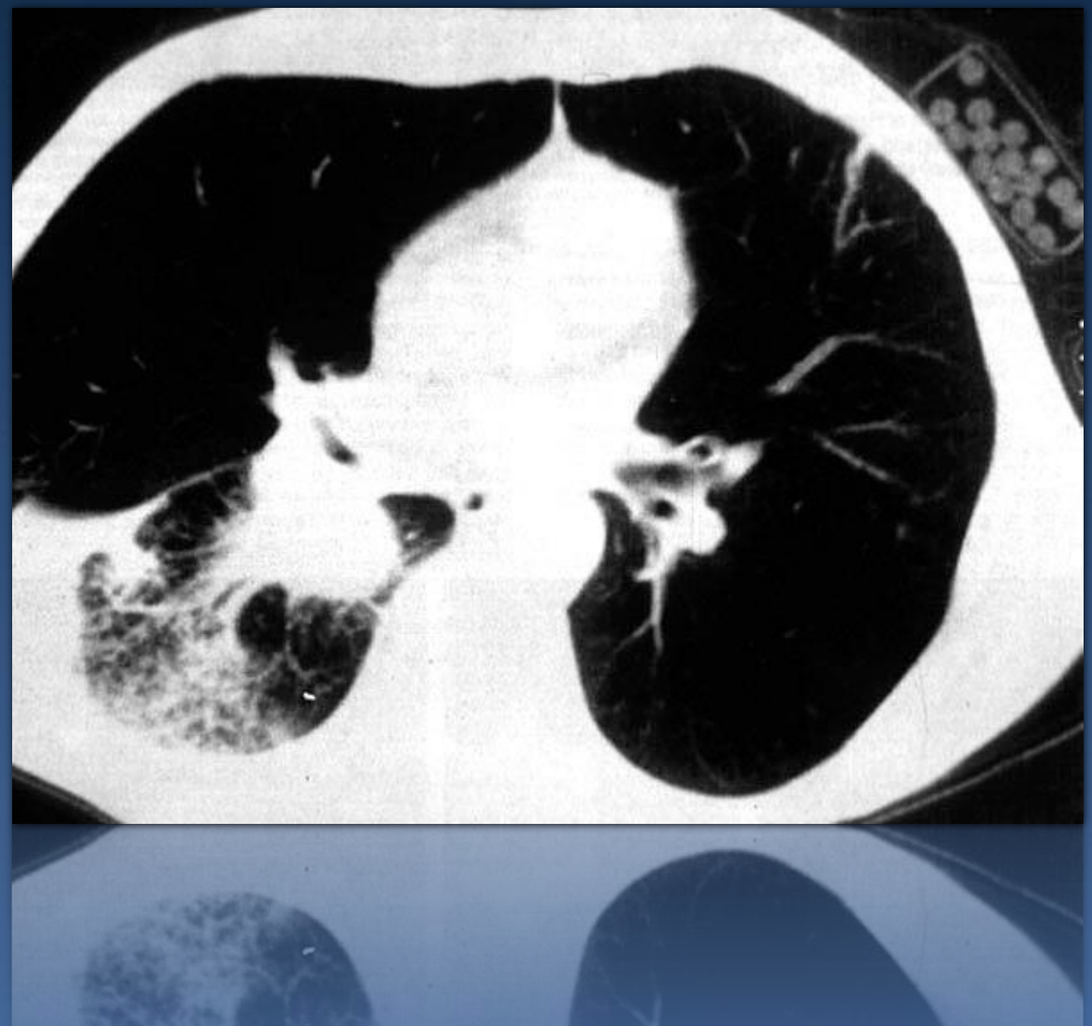
- The carcinogenic effect of solar irradiation is spectral range of 290 to 320 nm. This range of wavelengths correlates with the action spectrum for UV-induced damage to DNA
- Risk for melanoma is cumulative with continued sun exposure, and increases dramatically for those who have a history of 3 or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

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

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. Viral genome inserts near (and may activate) the *c-myc* protooncogene
  - Chronic active hepatitis due to HBV might predispose to carcinogenesis. There may be a variety of contributing factors, including malaria, malnutrition, and 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!

Tumor Markers in General Use

Tumor markers are neither sensitive nor specific for diagnosis. They are only helpful in certain screening applications and for monitoring response to therapy!

Marker	Disorder
PSA	Prostate cancer; BPH
AFP	HCC; Testis (non-seminoma)
HCG	Testis (non-seminoma)
CA 15-3	Breast
CA 27.29	Breast

Marker	Disorder
Thyroglobulin	Thyroid cancer
CEA	Lung, GI (esophagus, stomach, small intestine, colorectal)
CA 19-9	GI (pancreas, biliary)
β_2-microglobulin	Myeloma, CLL, NHL
CA 125	Ovarian, Endometrial
Immunoglobulin	Plasma Cell Disorders