NEOPLASIA CHEMICALS, INFECTIOUS AGENTS, RADIATION

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Risk factors

- About 15% of all cancers worldwide are believed to be caused directly or indirectly by infectious agents, with the burden of cancers linked to infections being roughly three times higher in the developing world than in the developed world.
- Smoking particularly of cigarettes, has been implicated in cancer of the mouth, pharynx, larynx, esophagus, pancreas, bladder, and most significantly, about 90% of lung cancer.

Risk factors

- Alcohol abuse alone increases the risk of carcinomas of the oropharynx (excluding lip), larynx, and esophagus and, by the development of alcoholic cirrhosis, hepatocellular carcinoma.
- Alcohol and tobacco together synergistically increase the risk of cancers in the upper airways and digestive tract.
- There is strong evidence that lifelong cumulative exposure to estrogen stimulation, particularly if unopposed by progesterone, increases the risk of cancers of the breast and endometrium.
- Excess cancer deaths of all types have been attributed to obesity

Table 7-3 Occupational Cancers

Agents or Groups of Agents	Human Cancers for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Arsenic and arsenic compounds	Lung carcinoma, skin carcinoma	By-product of metal smelting; component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, esophageal, gastric, and colon carcinoma; mesothelioma	Formerly used for many applications because of fire, heat, and friction resistance; still found in existing construction as well as fire-resistant textiles, friction materials (i.e., brake linings), underlayment and roofing papers, and floor tiles
Benzene	Acute myeloid leukemia	Principal component of light oil; despite known risk, many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents; formerly widely used as solvent and fumigant
Beryllium and beryllium compounds	Lung carcinoma	Missile fuel and space vehicles; hardener for lightweight metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate carcinoma	Uses include yellow pigments and phosphors; found in solders; used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung carcinoma	Component of metal alloys, paints, pigments, and preservatives
Nickel compounds	Lung and oropharyngeal carcinoma	Nickel plating; component of ferrous alloys, ceramics, and batteries; by-product of stainless-steel arc welding
Radon and its decay products	Lung carcinoma	From decay of minerals containing uranium; potentially serious hazard in quarries and underground mines
Vinyl chloride	Hepatic angiosarcoma	Refrigerant; monomer for vinyl polymers; adhesive for plastics; formerly inert aerosol propellant in pressurized containers

Modified from Stellman JM, Stellman SD: Cancer and workplace. CA Cancer J Clin 1996;46:70.

Age

- Most carcinomas occur in the later years of life (>55 years of age).
- Cancer is the main cause of death among women aged 40 to 79 and among men aged 60 to 79 years of age
- This may reflect both accumulation of somatic mutations as well as diminished immune surveillance

Age

- Malignancy is the cause of death in 10% of those younger than 15 years of age
- Acute leukemia and central nervous sysgtem neoplasms are responsible for approximately 60% of childhood cancer deaths.
- The common neoplasms of infancy and childhood include neuroblastoma, Wilms tumor, retinoblastoma, acute leukemias, and rhabdomyosarcomas.

Chronic inflammation

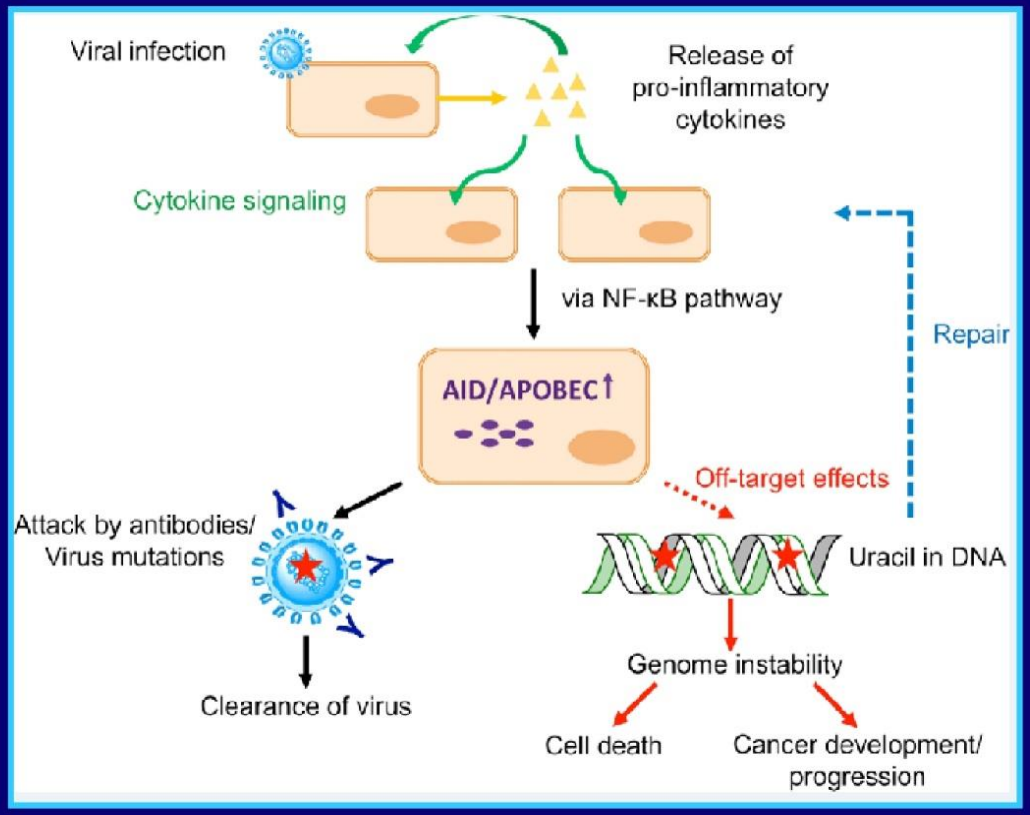
- As with any cause of tissue injury, each of these disorders is accompanied by a compensatory proliferation of cells that serves to repair the damage.
- In some cases, chronic inflammation may increase the pool of tissue stem cells, which may be particularly susceptible to transformation.
- Additionally the activated immune cells produce reactive oxygen species that are directly genotoxic.
- Inflammatory mediators may promote bystander cell survival, even in the face of genomic damage.
- Alterations may allow cells with potentially oncogenic mutations to survive

Table 7-4 Chronic Inflammatory States and Cancer

Pathologic Condition	Associated Neoplasm(s)	Etiologic Agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibers, silica particles
Inflammatory bowel disease	Colorectal carcinoma	
Lichen sclerosis	Vulvar squamous cell carcinoma	
Pancreatitis	Pancreatic carcinoma	Alcoholism, germline mutations (e.g., in the trypsinogen gene)
Chronic cholecystitis	Gallbladder cancer	Bile acids, bacteria, gallbladder stones
Reflux esophagitis, Barrett esophagus	Esophageal carcinoma	Gastric acid
Sjögren syndrome, Hashimoto thyroiditis	MALT lymphoma	
Opisthorchis, cholangitis	Cholangiocarcinoma, colon carcinoma	Liver flukes (*Opisthorchis viverrini*)
Gastritis/ulcers	Gastric adenocarcinoma, MALT lymphoma	*Helicobacter pylori*
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Osteomyelitis	Carcinoma in draining sinuses	Bacterial infection
Chronic cervicitis	Cervical carcinoma	Human papillomavirus
Chronic cystitis	Bladder carcinoma	Schistosomiasis

Adapted from Tlsty TD, Coussens LM: Tumor stroma and regulation of cancer development. Ann Rev Pathol Mech Dis 2006;1:119.

APOBEC drives mutagenesis



Surawandena SU Chem Rev 2016

Human papilloma virus oncogenesis

- In benign warts, the HPV-1 genome is maintained in a nonintegrated episomal form.
- Condyloma accumulata have low malignant potential and are associated with low-risk HPVs, predominantly HPV-6 and HPV-11.
- A large number of infected persons clear the infection through immunologic mechanisms.
- Clonal cell proliferation.

Human papilloma virus oncogenesis

- The HPV genome is integrated into the host genome in squamous cell carcinomas.
- The replication of DNA viruses is dependent on the replication machinery of the host cells
- The viral DNA is interrupted at a fairly constant site in the process of integration:
- It is almost always within the E1/E2 open reading frame of the viral genome.
- Because the E2 region of the viral DNA normally represses the transcription of the E6 and E7 early viral genes, its interruption causes over-expression of the E6 and E7 proteins.

Human papilloma virus oncogenesis

- The E6 protein binds to and mediates the degradation of p53, and also stimulates the expression of TERT.
- Human TP53 is polymorphic at codon 72, encoding either a proline or arginine residue at that position.
- The p53 Arg72 variant is much more susceptible to degradation by E6.

Human papilloma virus oncogenesis

- E7 binds to the RB protein upregulating CYCLIN E and displaces the E2F transcription factors that are normally sequestered by RB
- Promotes progression through the cell cycle.
- E7 also inactivates the CDK inhibitors p21 and p27.
- Thus, E6 and E7 block p53 and RB cell cycle suppression pathways and induce centrosome duplication as well.

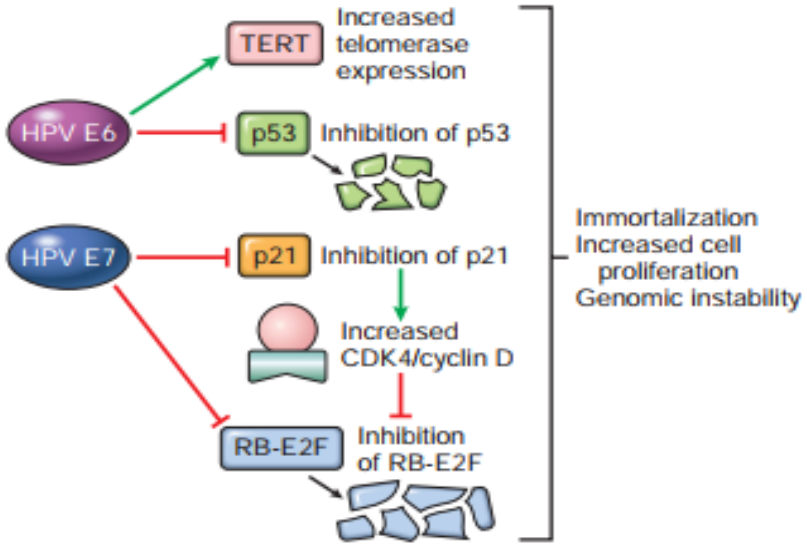


Figure 7-45 Transforming effects of HPV E6 and E7 proteins. The net effect of HPV E6 and E7 proteins is to immortalize cells and remove the restraints on cell proliferation (see Fig. 7-29). TERC, telomerase catalytic subunit. (Modified from Münger K, Howley PM: Human papillomavirus immortalization and transformation functions. Virus Res 2002;89:213-228.)

Human papilloma virus oncogenesis

- High-risk HPVs (types 16, 18, 31) have been implicated in the genesis of squamous cell carcinomas:
- Cervix
- Penis
- Anogenital region
- Head and neck
- Particularly tumors arising in the tonsillar mucosa

Adenovirus oncogenesis

- While adenovirus is not known to be oncogenic in humans, adenovirus encodes for tumor antigens.
- These are translated from early gene transcripts (E1A, E1B).
- E1A and E1B are nuclear oncogenes that down-regulate mRNA synthesis.

Adenovirus oncogenesis

- Tumor antigens from the E1A region bind to the gene product of the RB gene
- Those of E1B bind to the gene product of p53.
- One of the protein products of E1B also blocks the function of tumor necrosis factor, TNF
- The E3 transcription unit for some adenoviruses can block expression of MHC I antigens and block the actions of TNF.

Epstein-Barr virus oncogenesis

- EBV-1 is virus found in US and Europe.
- Both EBV-1 and EBV-2 are equally distributed elsewhere.
- Many people develop EBV infections as children after age 1. In very young children, symptoms are usually nonexistent or so mild that they aren’t recognized
- Generally presents with fever, swollen lymph nodes in neck and axillae, fatigue, and a sore throat
- An erythematous rash may be seen in skin or oral mucosa
- The spleen may enlarge

Epstein-Barr virus oncogenesis

- Primary target cell for EBV is the B-cell.
- Envelope glycoprotein 350/220 binds to CD21 (CR2, the C3d receptor).
- Potent B-cell mitogen.
- Leads to production of heterophile antibodies.
- Secondary target cell for EBV is the epithelial cell within the oropharynx (especially the parotid glands).
- EphrinA2 receptor
- Envelope glycoprotein 350/220 binds to α5/β1 integrin, but not efficiently.

Epstein-Barr virus oncogenesis

- The infection of B cells is latent; that is, there is no viral replication and the cells are not killed.
- However, B cells latently infected with EBV express viral proteins that result in the ability to propagate indefinitely (immortalization).
- Viral DNA circularizes in host cell genome as DNA episome and replicates in S-phase.
- EBNA-1 is essential to persistence of the genome
- Latent infection.
- Epithelial cells serve as reservoir.
- Virus shed in saliva throughout life span of host.

Epstein-Barr virus oncogenesis

- EBNA-2 activates CD23 (allowing naïve B cells to enter germinal centers, be infected, and emerge) as well as upregulates EBV genes.
- EBNA-2, encodes a nuclear protein, CBF1, that mimics a constitutively active Notch receptor.
- EBNA-2 transactivates several host genes, including cyclin D and the SRC family of proto-oncogenes.
- It is essential for immortalization of the B-cell.
- Viral DNA maybe incorporated into cell genome but cannot complete the replication cycle as viral genes essential for replication are interrupted during integration of viral DNA (abortive infection).

Epstein-Barr virus oncogenesis

- LMP-1 behaves like a constitutively active CD40 receptor
- Receives a helper T-cell signals that stimulate B-cell growth.
- LMP-1 activates the NF-κB and JAK/STAT signaling pathways and promotes B-cell survival and proliferation
- Occurs autonomously in EBV-infected B cells.
- Thus, the virus adopts B-cell activation pathways to expand the pool of latently infected cells.

Epstein-Barr virus oncogenesis

- LMP-1 also induces early protein BHRF-1 (a homologue of bcl-2) and engages TNFR, immortalizing the cell.
- LMP-1 allows the B-cell blast to become a resting memory cell.
- As it also possesses T-cell epitopes and induces expression of adherins, infected B-cells may be found in clusters with infected T-cells, evading surveillance.

Epstein-Barr virus oncogenesis

- Cells that become persistently infected and express LMP-2 lead to destruction of the host cell (lytic infection).
- LMP-2 serves as a substrate for SRC tyrosine kinases
- It also possesses T-cell epitopes.
- LMP-2 is disrupted by linearization of the genome.
- Late protein BCRF-1 is a homologue of IL-10 (vIL-10) adapted from host genome.
- This viral cytokine can prevent macrophages and monocytes from activating T cells and is required for EBV-dependent transformation of B cells

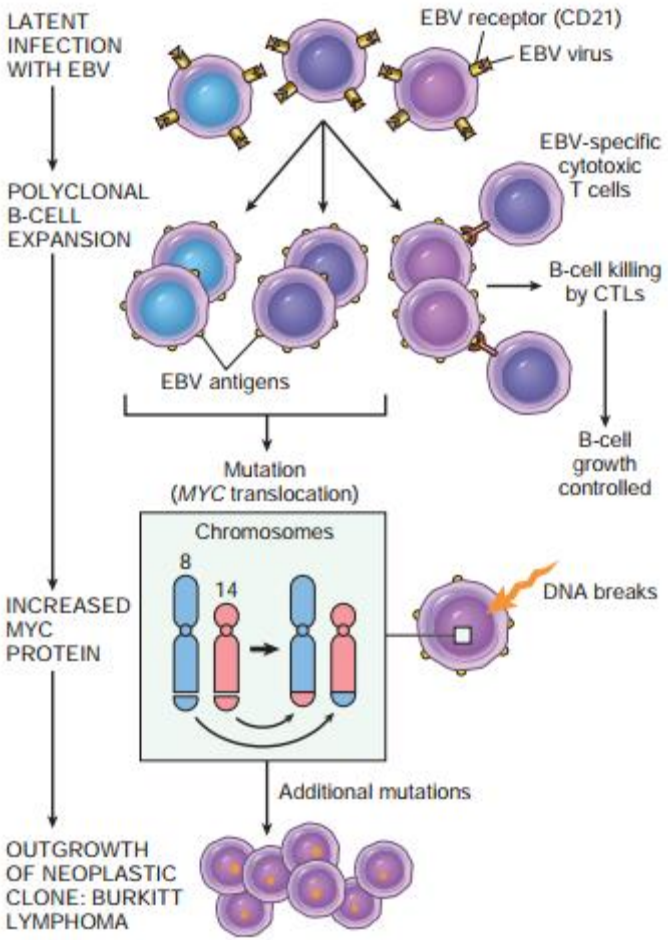


Figure 7-46 Possible evolution of EBV-induced Burkitt lymphoma.

Epstein-Barr virus oncogenesis

- Burkitt's lymphoma is a neoplasm of B lymphocytes that is endemic in central Africa and New Guinea
- Areas where it is the most common childhood tumor.
- Occurs in the jaw.
- More than 90% of African tumors carry the EBV genome; One hundred percent of the patients have elevated antibody titers against viral capsid antigens.
- Serum antibody titers against viral capsid antigens are correlated with the risk of developing the tumor.
- LMP-1 and EBVNA are not expressed

Epstein-Barr virus oncogenesis

- The EBV genome is found in only 15% to 20% of patients with Burkitt's lymphoma outside Africa.
- EBV is not directly oncogenic, but by acting as a polyclonal B-cell mitogen, it sets the stage for the acquisition of the (8;14) translocation and MYC activation that characterizes Burkitt's lymphoma.
- The B-cell tumors in immunosuppressed patients uniformly express LMP-1 and EBNA2
- They usually lack MYC translocations.

Epstein-Barr virus oncogenesis

- Lymphocyte-predominant (LP) Hodgkin's disease (HD) represents a B-cell neoplasm which is distinct from non-LP HD
- Non-LP HD constitutes a syndrome rather than a disease entity, with the existence of T-cell types and B-cell types
- Reed-Sternberg cells (and the tumor cells in anaplastic large cell lymphomas) frequently display an immature genotype in association with late activation markers compatible with previous EBV infection.

Epstein-Barr virus oncogenesis

- Nasopharyngeal carcinoma is endemic in southern China, in some parts of Africa, and in the Inuit population of the Arctic.
- 100% all nasopharyngeal carcinomas obtained from all parts of the world contain EBV.
- The structure of the viral genome is identical (clonal) in all of the tumor cells within individual tumors.
- Antibody titers to viral capsid antigens are greatly elevated
- In endemic areas patients develop IgA antibodies before the appearance of the tumor.

Epstein-Barr virus oncogenesis

- LMP-1 is expressed in nasopharyngeal carcinoma cells
- Activates the NF-κB pathway.
- NF-κB in turn upregulates the expression of factors such as VEGF, FGF-2, MMP9, and COX2

HHV-8 oncogenesis

- Human herpes virus 8 encodes a G protein-coupled receptor (vGPCR)
- May induce transformation of endothelial cells by activating NFκ-B
- AND by production of a homologue of IL-6
- Angiogenic and mitogenic effects
- AS well as a homologue of MIP-1
- Chemotactic recruitment of endogenous cytokine producing cells to amplify the response

HHV-8 oncogenesis

- HHV-8 induces genetic reprogramming of both vascular and lymphatic cells so that they more closely resemble each other as opposed to their corresponding uninfected phenotypes.
- HHV-8 is implicated in the development of Kaposi's sarcoma, Castelman's disease, and primary effusion lymphoma.

HHV-8 oncogenesis

- LANA-1, a latent nuclear antigen of HHV-8, targets RB.
- HHV-8 encodes CYCLIN K
- Inhibits the transcription of oncostatin M
- Viral interferon regulatory factor induces cellular transformation and prevents apoptosis mediated by p53 tumor suppressor
- Uncontrolled cellular proliferation.
- Viral IL-6 also blocks host production of IFN-α.

HTLV-1 oncogenesis

- HTLV-1 causes adult T-cell leukemia/lymphoma (ATLL)
- Endemic in certain parts of Japan, the Caribbean basin, South America, and Africa
- CD4+ tropism.
- Leukemia develops in only 3% to 5% of the infected individuals
- Typically after a long latent period of 40 to 60 years.
- FoxP3 expressed,
- Marker of regulatory T cells (Tregs) that act to suppress immune responses.

HTLV-1 oncogenesis

- HTLV-1 does not contain an oncogene
- No consistent integration next to a protooncogene has been discovered.
- In leukemic cells, however, viral integration shows a clonal pattern.
- The HTLV-1 genome contains the gag, pol, env, and long terminal-repeat regions typical of all retroviruses, as well as Tax.
- Tax is essential for viral replication, because it stimulates transcription of viral RNA from the 5′ long terminal repeat.

HTLV-1 oncogenesis

- Glut-1 transporter is viral receptor for HTLV-1.
- Most effective transmission is cell to cell contact.
- Infects dendritic cells via neurophilin-1.
- Tax interacts with PI3K and thereby stimulates AKT
- Tax also directly upregulates the expression of cyclin D2
- DNA polymerase and cell cycle controller p18 are repressed.
- There is also direct binding to TGF-β and cell cycle controller MOD-1.
- p53 is also affected.

HTLV-1 oncogenesis

- Tax may also cause genomic instability by interfering with DNA-repair functions and inhibiting cell cycle checkpoints activated by DNA damage.
- HTLV-1-associated leukemias tend to be highly aneuploid.
- TAX protein transcription leads to IL2, IL2R, IL15 production
- Apoptosis is blocked (BCL-X).
- Autophagy is common.
- Infection by HTLV-1 causes the expansion of a nonmalignant polyclonal cell population through stimulatory effects of Tax on cell proliferation.

HTLV-1 oncogenesis

- Body fluid transmission leads to T cell leukemia/lymphoma.
- Blood transfusion transmission leads to myelopathy
- Paraparesis.
- Patients generally die of opportunistic infections.

Hepatitis viruses

- 70% to 85% of hepatocellular carcinomas worldwide are caused by infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
- HBV is endemic in countries of the Far East and Africa
- HBV, a DNA virus, is integrated into the genome.
- The dominant effect seems to be immunologically mediated chronic inflammation and hepatocyte death leading to regeneration and, over time, genomic damage.
- The immune system may become maladaptive, promoting rather than preventing tumorigenesis.

Other oncogenic viruses

- Merkel cell carcinoma associated with polyoma virus
- Large T antigen disables RB and p53
- Virus noninfectious, thus preventing autoactivation of integrated virus replication
- Terminates in neoplasia, not cell death
- Immunosuppression and dysregulation as risk factors
- CLL, HIV, transplantation

Bacterial oncogenesis

- H. pylori infection is implicated in the genesis of both gastric adenocarcinomas and gastric lymphomas.
- In the setting of unresolved chronic inflammation, the immune response may become maladaptive, promoting rather than preventing tumorigenesis.
- Strains associated with gastric adenocarcinoma have been shown to contain a “pathogenicity island” that contains cytotoxin-associated A (CagA) gene that permits epithelial invasion.

Bacterial oncogenesis

- Strain-specific H. pylori factors, as well as host genetic factors, such as polymorphisms in the promoters of inflammatory cytokines such as IL-1β and tumor necrosis factor (TNF) are thought to lead to the appearance of H. pylori-reactive T cells
- These stimulate a polyclonal B-cell proliferation.
- Chronic infections may evolve into a monoclonal “MALToma” of stomach or small intestine that nevertheless remains dependent on T-cell stimulation of B-cell pathways that activate the transcription factor NF-κB.
- Later, such dependence is lost.

Chemical carcinogenesis

- All initiating chemical carcinogens are highly reactive electrophiles (have electron-deficient atoms) that can react with nucleophilic (electron-rich) sites in the cell.
- Their targets are DNA, RNA, and proteins
- In some cases these interactions cause cell death.
- If it inflicts nonlethal damage to the DNA that cannot be repaired, then the mutated cell passes on the DNA lesions to its daughter cells.

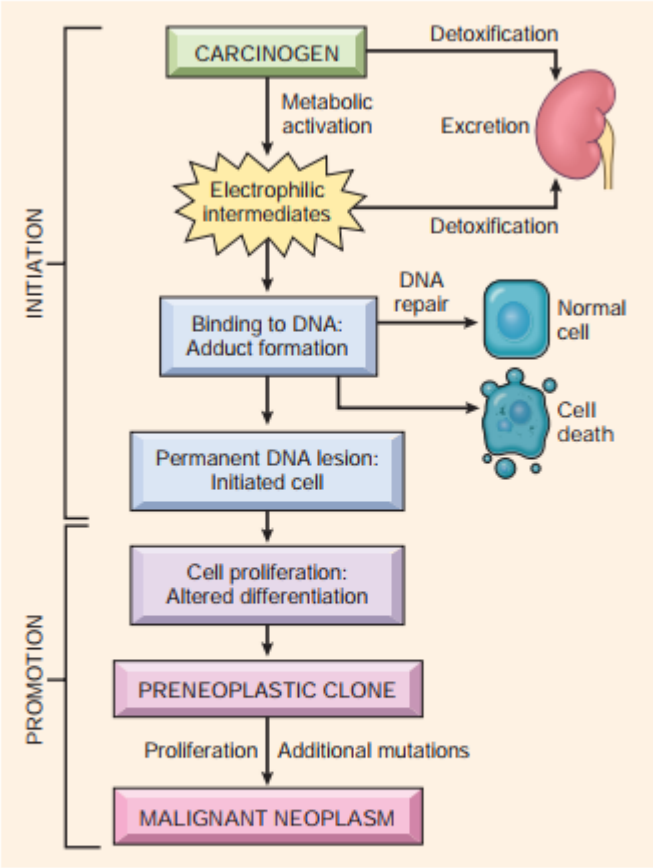


Figure 7-44 General schema of events in chemical carcinogenesis. Note that promoters cause clonal expansion of the initiated cell, thus producing a preneoplastic clone. Further proliferation induced by the promoter or other factors causes accumulation of additional mutations and emergence of a malignant tumor.

Chemical carcinogenesis

- Chemicals that can cause initiation of carcinogenesis can be classified into two categories: direct acting and indirect acting.
- Direct acting require no metabolic conversions; indirect acting require such conversion
- Phorbol esters, phenols, hormones, and drugs may promote carcinogenesis after chemical initiation

Table 7-10 Major Chemical Carcinogens

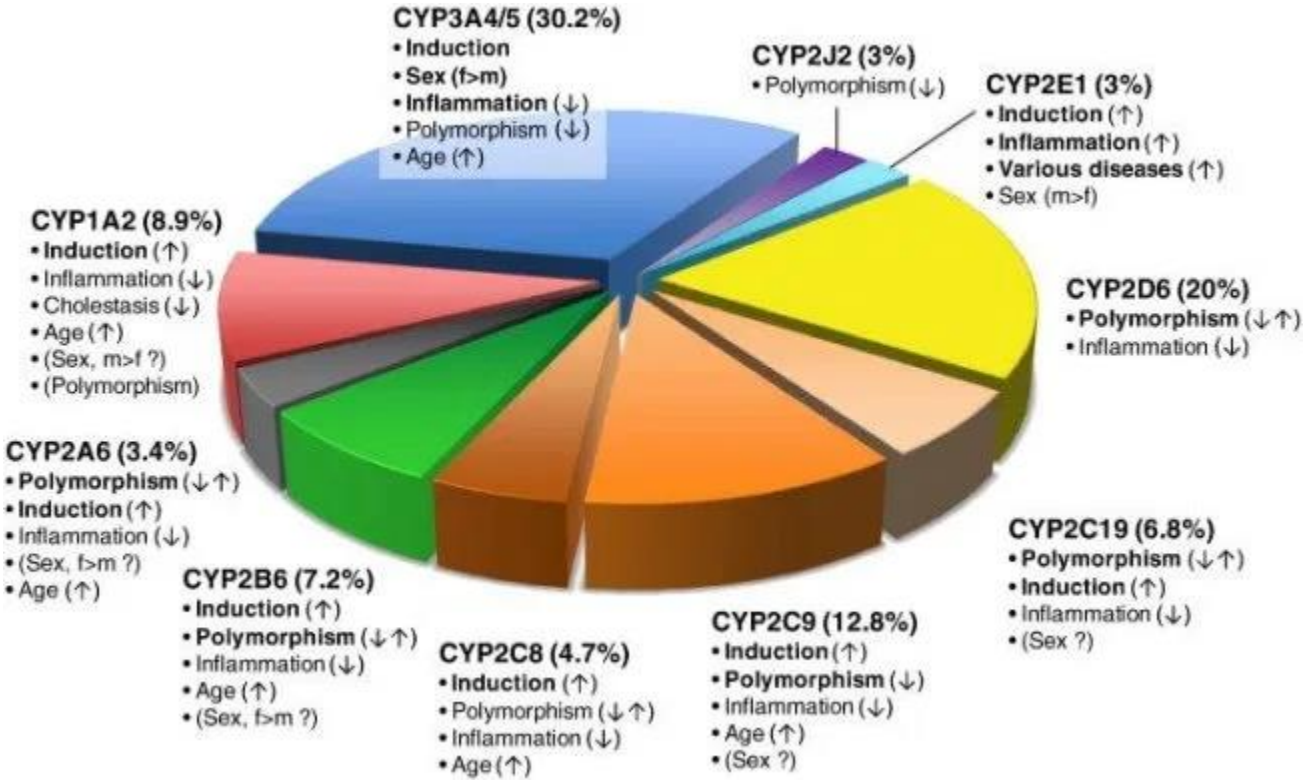
Direct-Acting Carcinogens
Alkylating Agents
β-Propiolactone
Dimethyl sulfate
Diepoxybutane
Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
Acylating Agents
1-Acetyl-imidazole
Dimethylcarbamyl chloride
Procarcinogens That Require Metabolic Activation
Polycyclic and Heterocyclic Aromatic Hydrocarbons
Benz[*a*]anthracene
Benzo[*a*]pyrene
Dibenz[*a,h*]anthracene
3-Methylcholanthrene
7,12-Dimethylbenz[*a*]anthracene
Aromatic Amines, Amides, Azo Dyes
2-Naphthylamine (β-naphthylamine)
Benzidine
2-Acetylaminofluorene
Dimethylaminoazobenzene (butter yellow)
Natural Plant and Microbial Products
Aflatoxin B_1
Griseofulvin
Cycasin
Safrole
Betel nuts
Others
Nitrosamine and amides
Vinyl chloride, nickel, chromium
Insecticides, fungicides
Polychlorinated biphenyls

Chemical carcinogenesis

- Aflatoxin B1 is a naturally occurring agent produced by some strains of Aspergillus.
- Aspergillus grows on improperly stored grains and nuts
- There is a strong correlation between the dietary level of this food contaminant and the incidence of hepatocellular carcinoma in parts of Africa and the Far East.

Chemical carcinogenesis

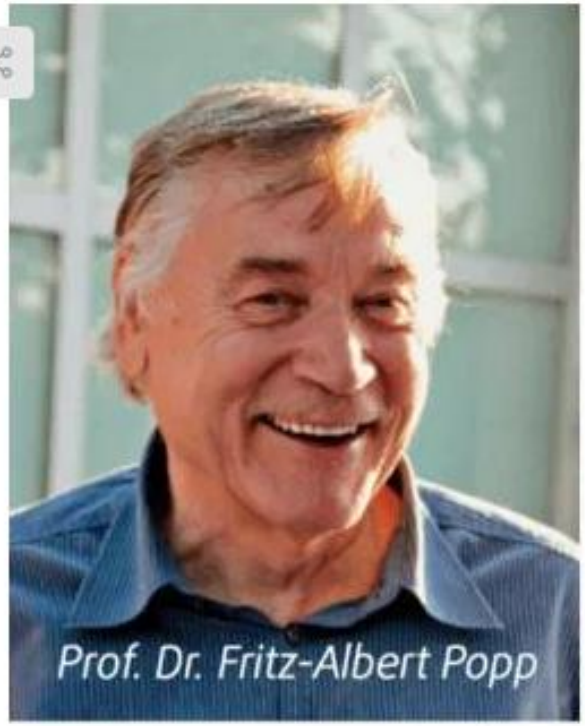
- Aflatoxin B1-associated hepatocellular carcinomas tend to have a a G:C→T:A transversion in codon 249 that produces an arginine to serine substitution in the p53 protein.
- TP53 mutations are infrequent in liver tumors from areas where aflatoxin contamination of food does not occur, and few of these mutations involve codon 249.

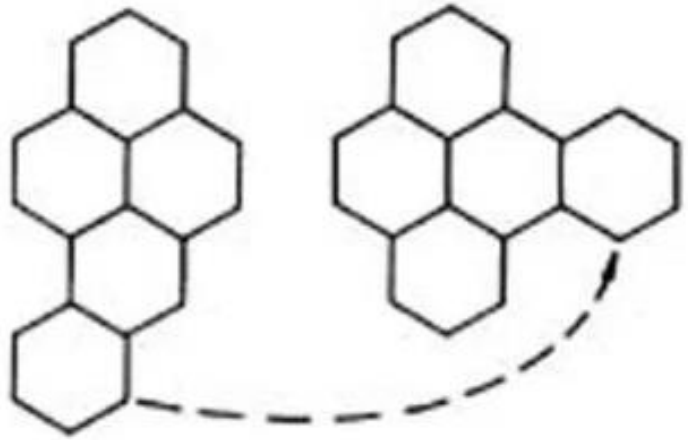


https://i1.wp.com/selfhacked.com/wp-content/uploads/2016/10/CYP-function.jpg?resize=650%2C388&ssl=1

Chemical carcinogenesis

- Carcinogens in tobacco smoke are benzo [a] pyrene (an initiator) and phenol derivatives (promoters)
- CYP1A1 is a cytochrome P450 enzyme that metabolizes polyaromatic hydrocarbons through hydroxylation of vacant position on aromatic ring
- Mediated via aryl hydrocarbon receptor
- CYP1A1 gene at 15q24.1
- 10% of whites have a highly inducible form
- Light smokers 7x more likely to develop lung cancer than those without this genotype





3,4 benzpyrene 1,2 benzpyrene

TWO FORMS OF BENZPYRENE - The 3,4 benzpyrene, which is found in coal-tar and in cigarrette smoke, is chemically very similar to 1,2 benzpyrene, which is considered harmless. The only major difference between them is that 3,4 benzpyrene has a strong absorption/emission anomaly in the ultraviolet area of the spectrum. Popp (at left) asked himself, could these optical properties of the molecule be the direct cause of its carcinogenicity? [source of image and caption: 21st Century Science and Technology]

Electromagnetic radiation

- The Sun is a charged body that spins slowly and is moving towards the constellation Vega. It continuously radiates energy to the Earth.
- Earth is a charged mass (it has poles) that spins on an axis, generating a magnetic field
- Living organisms as well generate magnetic fields (the basis of the MRI)
- Cells emit weak bursts of permanent ultraweak (1-100 photons/sec/cm2) coherent (phase-locked and/or frequency-locked) photons in the ultraviolet spectrum as they go through mitosis

Electromagnetic radiation

- These bursts originate from relaxation of electronically excited states of the constituents of living cells
- Generally associated with the presence of oxidative metabolism
- Reflects the pathophysiological state with respect to mitochondrial energy (ATP) production and the susceptibility to oxidative stress (reactive oxygen species)

Electromagnetic radiation

- The coherent emission of these weak photons is connected to energy and information transfer processes in the biological organisms
- Linked to the function of DNA and to gene regulation (synchronize activity)
- Organized in frequencies described by a Pythagorean 12-tone scale from near-UV to far-IR
- Coherent behavior coordinates cell function
- Determines protein folding
- Lack of coherence associated with dysfunction

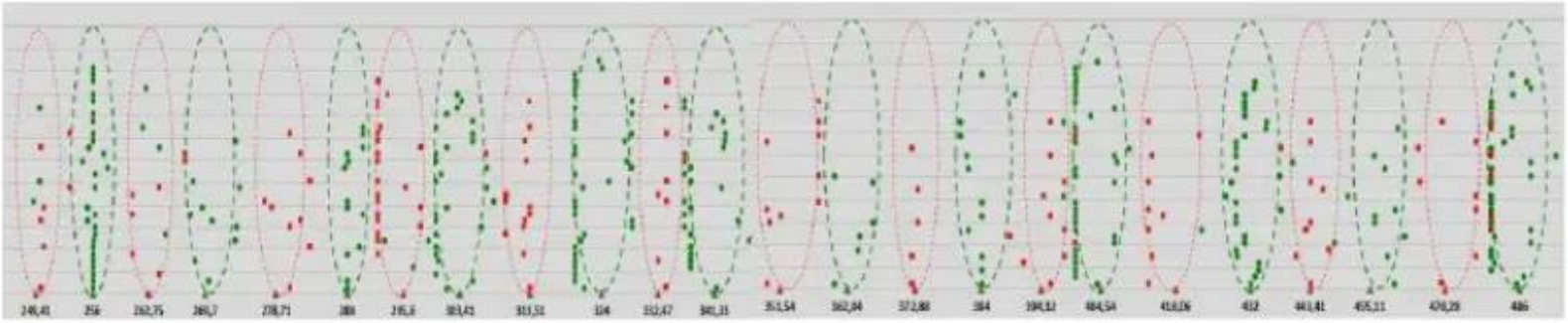


Figure 2. *Measured frequency data of living cells systems that are life-sustaining (green points) and detrimental for life (in red squares) versus calculated normalized frequencies. Biological effects measured following exposures or endogenous effects of living cells in vitro and in vivo at frequencies in the bands of Hz, kHz, MHz, GHz, THz, PHz. Green triangles plotted on a logarithmic x-axis represent calculated life-sustaining frequencies; red triangles represent calculated life-destabilizing frequencies. Each point indicated in the graph is taken from published biological data and are a typical frequency for a biological experiment(s). For clarity, points are randomly distributed along the Y-axis.*

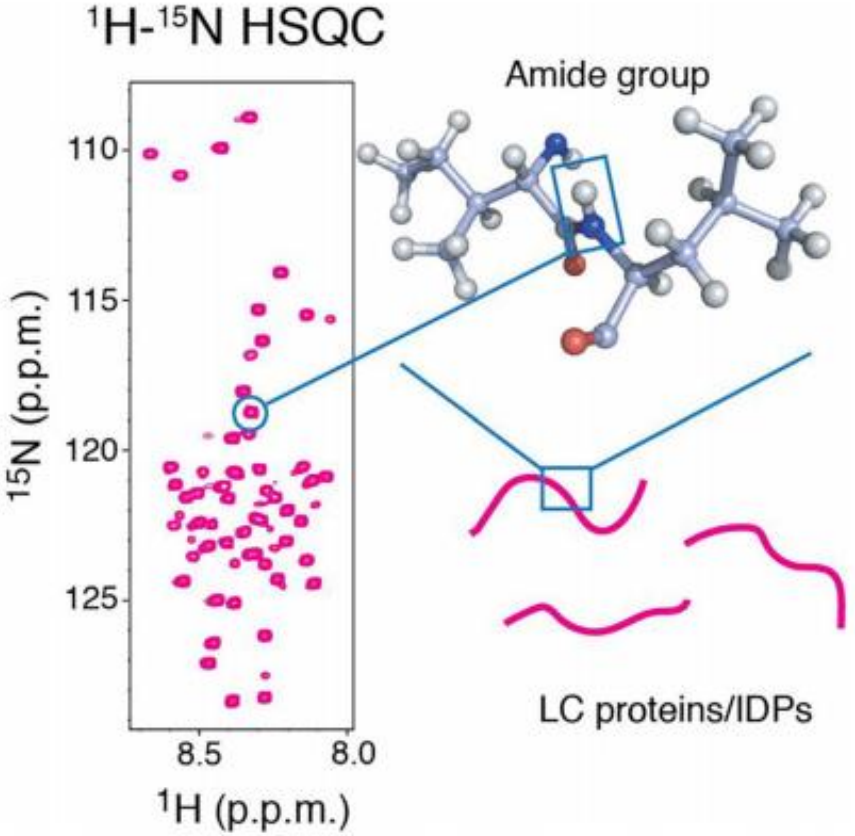


Fig. 8 ^{1}H-^{15}N Heteronuclear single quantum coherence (HSQC) spectrum of a disordered protein. In principle, one amide group gives one resonance in the spectrum. If the protein exists in multiple conformational states, each of the conformational states provides distinct sets of resonances. The spectrum of LC domain proteins/IDPs typically shows a narrow chemical shift dispersion

Biophysical Reviews (2020) 12:519–539
https://doi.org/10.1007/s12551-020-00680-x

Electromagnetic radiation

- Microtubules have a distinct polarity that is critical for their biological function.
- γ-tubulin is found principally in centrosomes and spindle cell bodies as well as cilia. Forms into a “γ-tubulin ring complex.”
- This complex acts as a nucleation center, a template for α/β-tubulin dimers to begin polymerization
- It acts as a cap of the negative end while microtubule growth continues away from this organization center in the positive direction

Electromagnetic radiation

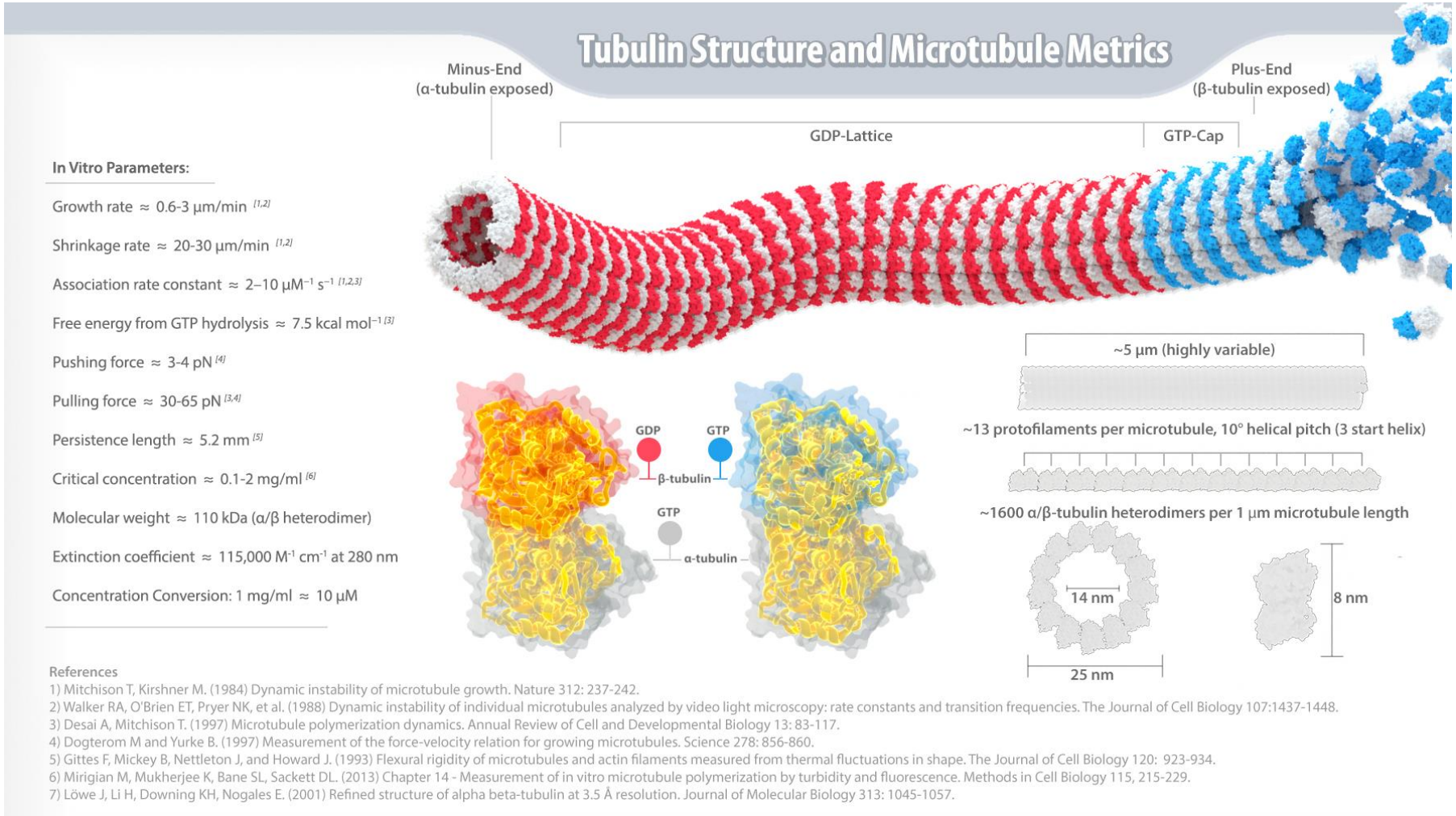
- Because nucleation from the centrosome is inherently symmetrical, Golgi-associated microtubule nucleation may allow the cell to establish asymmetry in the microtubule network
- α- and β-tubulin polymerize into dynamic microtubules.
- β-tubulin is found almost exclusively in neurons.
- δ- and ε- tubulin have been found to localize at centrioles

Electromagnetic radiation

- Tubulin adds onto the end of the microtubule in the GTP-bound state
- A cap of GTP-bound tubulin is proposed to exist at the tip of the microtubule, protecting it from disassembly.
- When hydrolysis catches up to the tip of the microtubule, it begins a rapid depolymerization and shrinkage. (catastrophe)
- GTP-bound tubulin can begin adding to the tip of the microtubule again, providing a new cap and protecting the microtubule from shrinking. (rescue)

Electromagnetic radiation

- Dimers bound to GTP tend to assemble into microtubules
- Positive ends that encounter kinetochores or sites of polarity become captured and no longer display growth or shrinkage
- Microtubules function in many processes, including structural support, dynamics of actin, intracellular transport, mitochondrial mobility and respiration, as well as DNA segregation.
- Microtubules also affect gene expression



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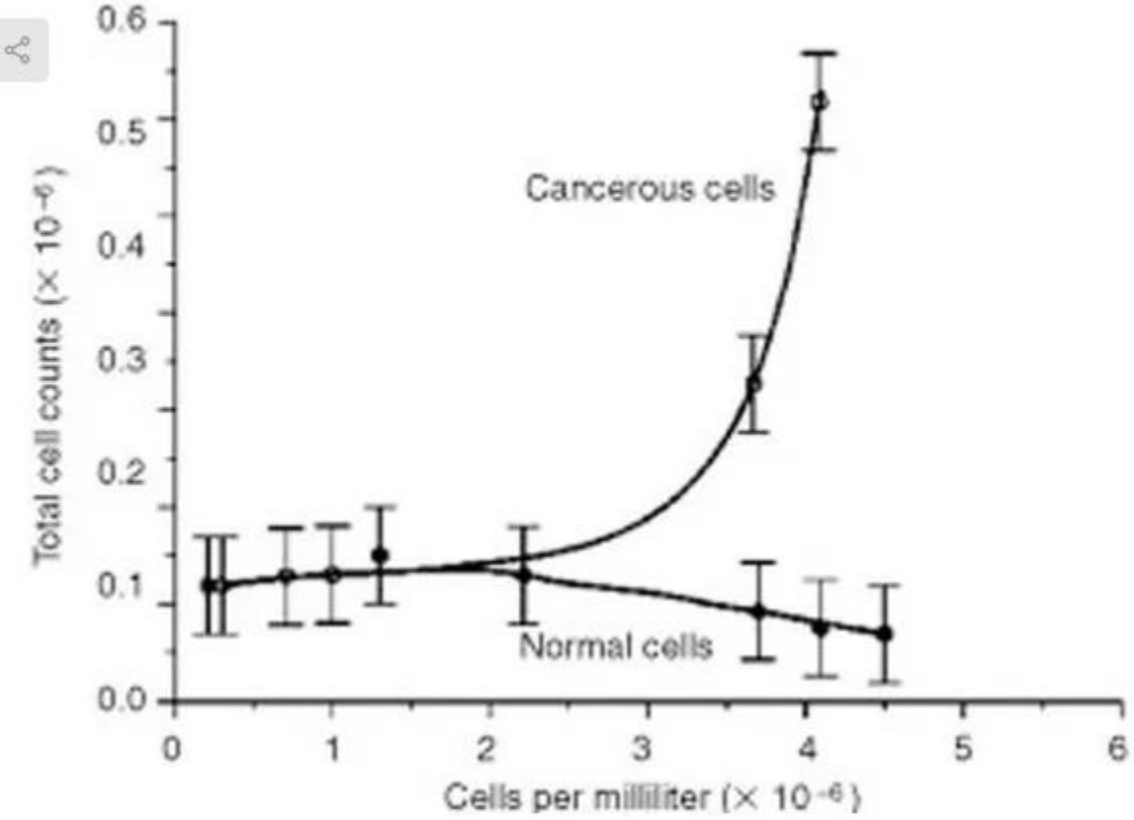

PHOTO COUNTS OF NORMAL LIVER CELLS VS CANCEROUS CELLS- Normal liver cells (lower curve) have a relatively stable or even falling level of photon counts at increasing cell density, while cancer cells of the same cell type show an increasing photon count at higher cell densities. From this, it was concluded that populations of cancer cells have lost the harmony and coherence that is typical for healthy tissue

[source of image and caption: 21st Century Science and Technology]

Ionizing radiation

- Radiant energy, in the form of the UV rays of sunlight can be carcinogenic.
- The UV portion of the solar spectrum can be divided into three wavelength ranges: UVA (320-400 nm), UVB (280-320 nm), and UVC (200-280 nm).
- Of these, UVB is believed to be responsible for the induction of cutaneous cancers.
- UVC, although a potent mutagen, is not considered significant because it is filtered out by the ozone layer surrounding the earth

Ionizing radiation

- If the energy in a photon of UV light is absorbed by DNA, the result is a covalent crosslinking of pyrimidine bases, particularly adjacent thymidine residues in the same strand of DNA.
- This distorts the DNA helix and prevents proper pairing of the dimer with bases in the opposite DNA strand.
- The capacity of the nucleotide excision repair pathway is overwhelmed
- Non-templated DNA-repair mechanisms become operative that provide for the survival of the cell. They are error prone and lead to many mutations.

Ionizing radiation

- Non-melanoma skin cancers are associated with total cumulative exposure to UVB radiation
- Melanomas are associated with intense intermittent exposure to UVB light.

Ionizing radiation

- Radiant energy as ionizing electromagnetic (x-rays, γ rays) and particulate radiation (α particles, β particles, protons, neutrons) as well as low range microwave radiation (5mm) are carcinogenic.
- Following the bombing of Hiroshima and Nagasaki there was a marked increase in the incidence of certain forms of leukemia after an average latent period of about 7 years.
- This was also seen following the use of depleted uranium in the bombing of Serbia.
- Thyroid carcinomas increased following the disaster at Chernoblyl (and occur in much higher frequency in the vicinity of nuclear power plants in general)

Ionizing radiation

- Children who get two or three CT scans have a threefold higher risk of leukemia
- Those that received five to 10 such scans have a threefold higher risk of brain tumors.
- The overall risk is very, very low, however.
- CT scan of the head is now a defensive medical practice in the emergency department for all children with suspected head injury regardless of the absence of neurological symptoms.
- CT scans are vital in following cancer therapy. The risk of a secondary malignancy from serial scans is much less than that from the treatment itself.

Ionizing radiation

- Most frequently associated with radiation exposure are myeloid leukemias
- Cancer of the thyroid follows closely but only in the young.
- In the intermediate category are cancers of the breast, lungs, and salivary glands.
- Skin, bone, and the gastrointestinal tract are relatively resistant to radiation-induced neoplasia.
- Gastrointestinal epithelial cells as well as cells of the bone marrow are vulnerable to the acute cell-killing effects of radiation
- The skin is “first in line” for all external radiation