Neoplasia
Lecture 3

EPIDEMIOLOGY

- **Incidence of cancer is increasing**
- **For the year 2012, the World Health Organization (WHO) estimated that there were about 14.1 million new cancer cases worldwide, leading to 8.2 million deaths (approximately 22,500 deaths per day).**
- **By the year 2035 the WHO expects that the numbers of cancer cases and deaths worldwide will increase to 24 million and 14.6 million, respectively (based on current mortality rates).**

Environmental Factors

- **Environmental exposures appear to be the dominant risk factors for many**

common cancers, suggesting that a high fraction of cancers are potentially

preventable

- **The geographic variation in death rates from specific forms of cancer, which**

is thought to stem mainly from differences in environmental exposures.

- **For example**

death rates from breast cancer are about four to five times higher in the United States and Europe than in Japan.

- **The death rate for stomach carcinoma in men and women is about seven times higher in Japan than in the United States.**
- **Liver cell carcinoma is relatively infrequent in the United States but is the most lethal cancer among many African populations.**

- **<u>The most important environmental exposures linked to cancer include the following:</u>**

1. **Diet**.

Certain features of diet have been implicated as predisposing influences.

More broadly, obesity, currently is associated with a modestly increased risk for developing many different cancers.

2. Smoking.

Smoking, particularly of cigarettes, has been implicated in cancer of the mouth, pharynx, larynx, esophagus, pancreas, bladder, and, most significantly, the lung, as 90% of lung cancer deaths are related to smoking.

3. Alcohol consumption.

Alcohol abuse is an independent risk factor for cancers of the oropharynx, larynx, esophagus, and liver.

- **Alcohol and tobacco smoking synergistically increase the risk for developing cancers of the upper airways and upper digestive tract.**

4. Reproductive history.

There is strong evidence that lifelong cumulative exposure to estrogen stimulation, particularly if unopposed by progesterone, increases the risk for developing cancers of the endometrium and breast, both of which are estrogen-responsive tissues.

5. Infectious agents.

It is estimated that infectious agents cause approximately 15% of cancers worldwide

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

Age and Cancer

- **The frequency of cancer increases with age**
- **Most cancer deaths occur between 55 and 75 years of age**
- **The rate declines after 75 years of age**
- **The rising incidence with age may be explained by:**

1. The accumulation of somatic mutations that drive the emergence of malignant neoplasms

2. The decline in immune competence that accompanies aging

- **More than 10% of all deaths among children younger than 15 years of age is due to cancer**
- **The major lethal cancers in children are:**

1. Leukemias

2. Tumors of the CNS

3. Lymphomas

4. Soft-tissue

Familial cancers

- **Virtually all the common types of cancers that occur sporadically have been reported to occur in familial forms.**
- **Examples :**
- **Breast cancer.**
- **Ovarian cancer.**
- **Pancreatic cancer.**
- **Colon cancer.**

- **Features that characterize familial cancers include:**

1-Early age at onset.

2-Tumors arising in two or more close relatives of the index case.

3-Multiple or bilateral tumors.

- **Familial cancers are not associated with specific marker phenotypes.**
- **E.g**
- **in contrast to the familial adenomatous polyposis syndrome, familial colonic cancers do not arise in preexisting benign polyps.**
- **In general, siblings have a relative risk between 2-3X.**

- **The transmission pattern of familial cancers is not clear.**
- **Segregation analysis of large families usually reveals that predisposition to the tumors is dominant, but multifactorial inheritance cannot be easily ruled out.**
- **Certain familial cancers can be linked to the inheritance of mutant genes**

Acquired Cancer Predisposing Conditions

Include:

1. Disorders associated with chronic inflammation

2. Immunodeficiency states

3. Precursor lesions

- **Tumors arising in the context of chronic inflammation are mostly carcinomas but also include mesothelioma of lymphoma.**
- **Immunodeficiency states mainly predispose to virus-induced cancers including specific types of lymphoma and carcinoma and some sarcoma-like lesions**
- **Molecular analyses have shown that precursor lesions often possess some of the genetic lesions found in their associated cancers**

Examples

- **Squamous metaplasia and dysplasia of bronchial mucosa**, seen in in habitual smokers—a risk factor for lung carcinoma
- **Endometrial hyperplasia and dysplasia,** seen in women with unopposed estrogenic stimulation—a risk factor for endometrial carcinoma
- **Leukoplakia of the oral cavity, vulva, and penis**, which may progress to squamous cell carcinoma
- **Villous adenoma of the colon**, associated with a high risk for progression to colorectal carcinoma

Table 7.4 Chronic Inflammatory States and Cancer

Pathologic Condition	Associated Neoplasm(s)	Etiologic Agent(s)
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

Interactions Between Environmental and Genetic Factors

- **Inherited trait versus Acquired factors**

Table 6.4 Inherited Predisposition to Cancer

Inherited Predisposition	Gene(s)
Autosomal Dominant Cancer Syndromes	
Retinoblastoma	*RB*
Li-Fraumeni syndrome (various tumors)	*TP53*
Melanoma	*CDKN2A*
Familial adenomatous polyposis/colon cancer	*APC*
Neurofibromatosis 1 and 2	*NF1, NF2*
Breast and ovarian tumors	*BRCA1, BRCA2*
Multiple endocrine neoplasia 1 and 2	*MEN1, RET*
Hereditary nonpolyposis colon cancer	*MSH2, MLH1, MSH6*
Nevoid basal cell carcinoma syndrome	*PTCH1*
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum	Diverse genes involved in nucleotide excision repair
Ataxia-telangiectasia	*ATM*
Bloom syndrome	*BLM*
Fanconi anemia	Diverse genes involved in repair of DNA cross-links

CANCER GENES

- **Are genes that are recurrently affected by genetic aberrations in cancers presumably because they contribute directly to the malignant behavior of cancer cells.**
- **Causative mutations that give rise to cancer genes:**
- **1. may be acquired by the action of environmental agents as chemicals, radiation, or viruses**
- **2. may occur spontaneously**
- **3. may be inherited in the germ line**

Functional classes of cancer genes

1. Oncogenes

- **Are genes that induce a transformed phenotype when expressed in cells by promoting increased cell growth.**
- **Oncogenes are mutated or overexpressed versions of normal cellular genes, which are called *proto-oncogenes.***
- **Most oncogenes encode transcription factors, factors that participate in pro-growth signaling pathways, or factors that enhance cell survival.**

- **Oncogenes are considered dominant genes because a mutation involving a single allele is sufficient to produce a pro-oncogenic effect.**

- **2. Tumor suppressor genes**
- **are genes that normally prevent uncontrolled growth and, when mutated or lost from a**

Cell allow the transformed phenotype to develop.

- **both normal alleles of tumor suppressor genes must be damaged for transformation to occur (recessive genes)**
- **Tumor suppressor genes can be placed into two general groups:**
- **1. "Governors"**

that act as important brakes on cellular proliferation

- **2. "Guardians"**

that are responsible for sensing genomic damage

- **Some guardian genes initiate “damage control response” that leads to the cessation of proliferation**
- **or, if the damage is too great to be repaired, or induce apoptosis.**

- **3. Genes that regulate apoptosis**
- **They enhance cell survival of cells**
- **Genes of this class protect against apoptosis are often overexpressed**

  in cancer cells
- **Genes that promote apoptosis tend to be underexpressed or functionally inactivated by mutations in cancer cells**

GENETIC LESIONS IN CANCER

- **The genetic changes found in cancers vary from point mutations involving single nucleotides to abnormalities large enough to produce gross changes in chromosome structure.**
- **In certain neoplasms, genetic abnormalities are non random and highly characteristic.**
- **Specific chromosomal abnormalities have been identified in most leukemias and lymphomas and in an increasing number of nonhematopoietic tumors**
- **Other tumors are characterized by particular point mutations.**

Gene mutations in cancer

- **1. Driver mutations**
- **2. Passenger mutations**

- **Driver mutations are mutations that alter the function of cancer genes and thereby directly contribute to the development or progression of a given cancer.**
- **They are usually acquired but occasionally inherited**
- **Driver mutations tend to be tightly clustered within cancer genes**

- Passenger mutations are acquired mutations
- Do not affect cellular behavior
- They occur at random
- Passenger mutations are sprinkled throughout the genome
- Passenger mutations related to cancers caused by carcinogen exposure, such as melanoma and smoking-related lung cancer

Types of gene mutations in cancer

1. Point Mutations

- **Point mutations can either activate or inactivate the protein products of the affected genes**
- **Point mutations that convert proto-oncogenes into oncogenes generally produce a gainof-function**
- **A cardinal example is point mutations that convert the *RAS* gene into a cancer gene, one of the most comment events in human cancers.**

- **The tumor suppressor gene that is most commonly affected by point mutations in cancer is *TP53***

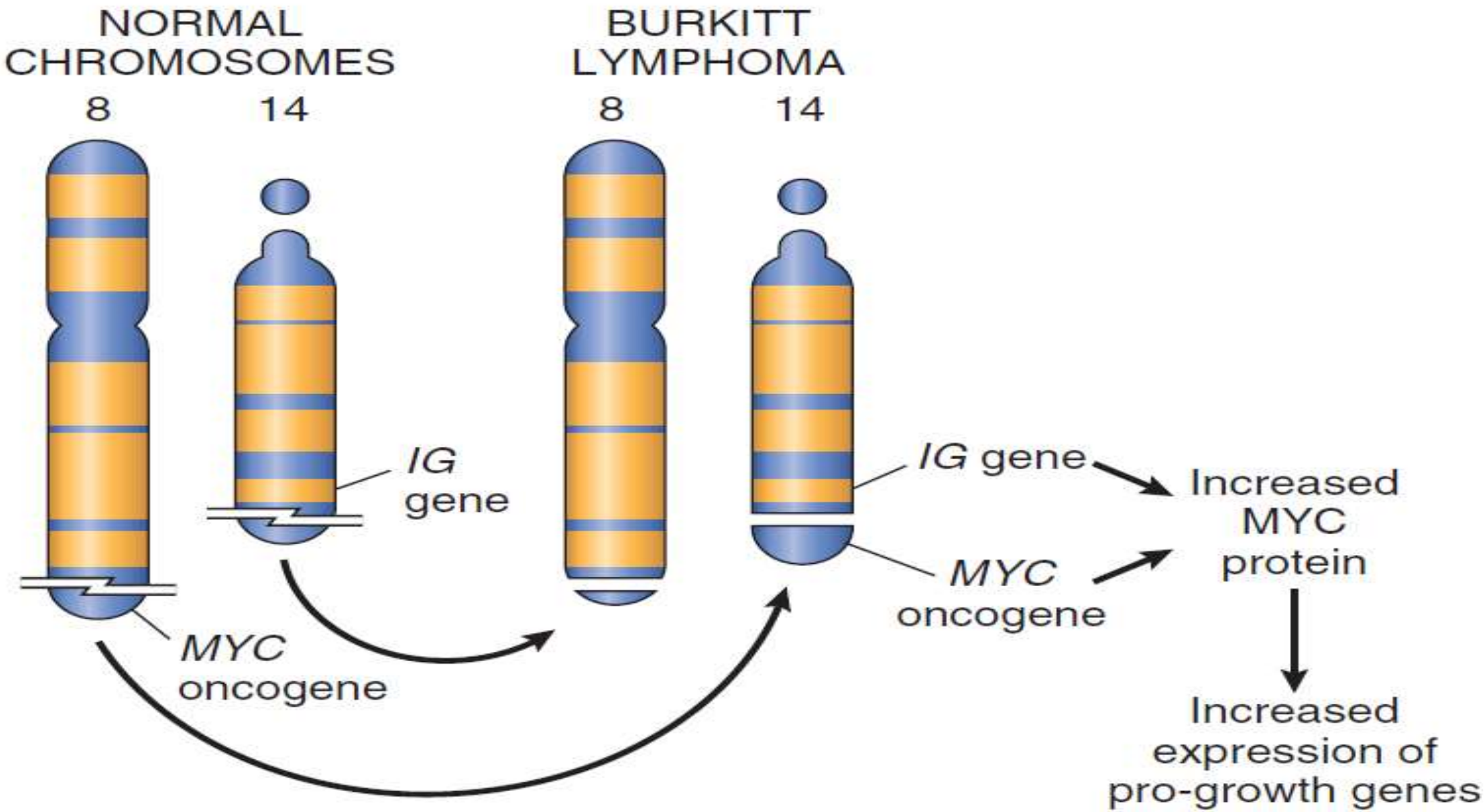
- **2. Gene Rearrangements**
- **Gene rearrangements may be produced by chromosomal translocations or inversions.**
- **Highly associated with Leeukemias and sarcomas**

- **Gene rearrangements can activate proto-oncogenes in two ways:**

1. **Some gene rearrangements result in overexpression of proto-oncogenes by removing them from their normal regulatory elements and placing them under control of an inappropriate, highly active promoter or enhancer**

   examples

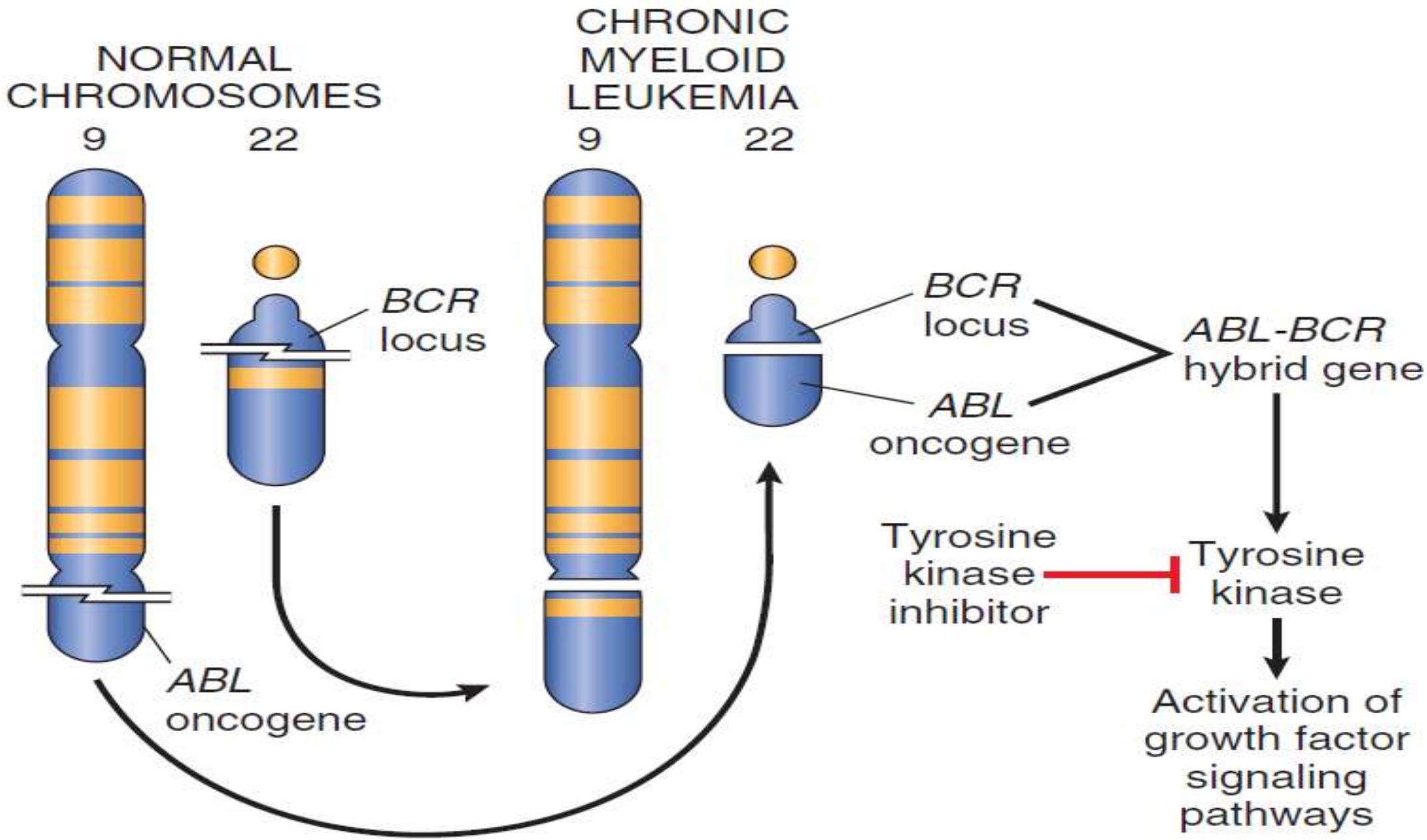
- **Burkitt lymphoma: Myc gene translocation from chr.8 to 14**
- **follicular lymphoma: a reciprocal translocation between chr.14 and 18 leads to overexpression of the anti-apoptotic gene *BCL2* on chr.18**


NORMAL CHROMOSOMES
8
14
BURKITT LYMPHOMA
8
14
IG gene
MYC oncogene
IG gene
MYC oncogene
Increased MYC protein
Increased expression of pro-growth genes

2. Oncogenic gene rearrangements create fusion genes encoding novel chimeric proteins

Example

- Philadelphia (Ph) chromosome in chronic myeloid leukemia
- Consists of balanced reciprocal translocation between chr 9 and 22 leading to fusion of ABL oncogene(chr 9) with BCR locus
- ABL-BCR hybrid gene results in activation of growth factor signaling pathways


NORMAL CHROMOSOMES
9
22
BCR locus
ABL oncogene
CHRONIC MYELOID LEUKEMIA
9
22
BCR locus
ABL oncogene
ABL-BCR hybrid gene
Tyrosine kinase inhibitor
Tyrosine kinase
Activation of growth factor signaling pathways

3. Deletions

- **Deletion of specific regions of chromosomes may result in the loss of particular tumor suppressor genes**
- **Examples**

1. *RB* gene deletions are associated with retinoblastoma

2. Deletion of 17p is associated with loss of *TP53*

4. Gene Amplifications

Proto-oncogenes may be converted to oncogenes by gene amplification with consequent overexpression and hyperactivity of otherwise normal proteins.

- **Examples**

***1. NMYC* gene amplification in 20-35% of neuroblastoma**

2. *HER2* (also known as *ERBB2*) amplification occurs in about 20% of breast cancers

5. Aneuploidy

- **It is defined as a number of chromosomes that is not a multiple of the haploid state i.e a chromosome number that is not a multiple of 23.**
- **Aneuploidy is remarkably common in carcinomas**
- **Aneuploidy tends to increase the copy number of key oncogenes and decrease the copy number of potent tumor suppressors.**
- **Examples**

1. Chr.8 carrying *MYC* oncogene is present in increased copies in tumor cells

2. Portions of chr.17 carrying *TP53* gene are often lostin tumor cells