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**
- **By the year 2035 the WHO expects that the numbers of cancer cases and deaths worldwide will increase to 24 million**

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.

It's relate to the exposure to some carcinogen that are present in food consumed in Japan

- **The death rate for stomach carcinoma in men and women is about 7 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.**

Due to improperly stored grains which allow the growth of fungus that produces alpha toxins (alpha feto protein) which is carcinogenic
Which occur largely in young age group in contrast to liver cancer in western country which is related to the exposure of alcohol

Incidence rate of stomach cancer started decreasing by Changing the type of food consumed, it's started to be more western , food was consumed by native Japanese was rich in carcinogens (smoked fish and meat which are believed to have high concentrations of nitrosamine)

Carcinogens determine development and age of development

- **The most important environmental exposures linked to cancer include the following:** (ك)

1. Diet. Exposure linked mainly to diet

Certain features of diet have been implicated as predisposing influences.

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.

One of the pro types of carcinogen is exposure of smoking
There is types of lung cancer which occur only in smokers

3. Alcohol consumption.

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

An independent risk factor is something that increases the risk of developing a disease on its own, regardless of the presence of other risk factors. This means that even if other risks are absent, the factor alone can still raise the likelihood of the disease.

- **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.

Exposure to estrogen is associated with the development of endometrial hyperplasia, which can progress to endometrial carcinoma if there is continuous estrogen stimulation without opposing progesterone. Additionally, prolonged estrogen exposure has been linked to an increased risk of breast cancer

"Opposing progesterone" means the presence of progesterone counteracts or balances the effects of estrogen. In the context of endometrial health:

- **Estrogen** stimulates the growth of the endometrial lining.
- **Progesterone** stabilizes the lining and prevents overgrowth by opposing estrogen's proliferative effect.

So, **"lack of opposing progesterone"** means there's no progesterone to balance estrogen, leading to continuous endometrial stimulation, which can result in hyperplasia or even cancer.

5. Infectious agents

Including both viruses and bacteria

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

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 Is increased with age

2. The decline in immune competence that accompanies aging

This weakens the immune system's ability to eliminate abnormal cells, increasing the risk of their survival. As a result, these abnormal cells can grow, multiply, and potentially develop into masses with cancerous behavior

Cancers that develop early in life in children and young adults are related to some genetic factors

- **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**

Believed to be related to some genetic mutations which leads to development of tumors early in life

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.**

Familial cancers refer to cancers that occur more frequently within a family than would be expected by chance alone. They arise due to a combination of genetic, environmental, and lifestyle factors shared among family members.

- **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.

Patients who develop cancers that typically occur in adults or older age groups should be suspected of having a familial predisposition. Typically, individuals with familial cancers present at an early age (when they are young) and have a family history of multiple cancers in more than one family member. These cancers often appear as bilateral or multifocal tumors

So if we have person with young developing colonic adenocarcinoma we should think about the possibility of being a familial cancer

- **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.**

Patients with familial cancer have a two to three times increased risk of developing cancer in their relatives compared to the affected population

Further exploration for better understanding

In *familial adenomatous polyposis (FAP)*, people develop many small growths in the colon called *polyps*. These polyps are not cancer at first, but over time, some can turn into cancer.

In *familial colonic cancers* like *Lynch syndrome*, cancer starts directly in the colon tissue **without forming polyps first**. This happens because of inherited gene problems that cause the colon cells to become cancerous quickly, skipping the polyp stage.

So, FAP = polyps first, then cancer.
Familial colonic cancer = cancer starts directly.

- **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**

  Leading to increase in development of cancer

Acquired Cancer Predisposing Conditions

Include:

1. **Disorders associated with chronic inflammation**
2. **Immunodeficiency states**
3. **Precursor lesions**

It’s well known that the presence of these acquired conditions is associated with increased malignancy and disordered can be related to inflammation

extra

1. **Carcinomas**: From **epithelial cells** (e.g., skin, lungs, breast). Common due to frequent cell turnover.
2. **Mesotheliomas**: From **mesothelial cells** (lining body cavities). Linked to asbestos exposure.
3. **Lymphomas**: From **lymphocytes** (immune cells). Caused by chronic infections or immune activation.

Each comes from different cell types and has unique triggers.

- **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

All these conditions wether inflammatory or bengin condition increase risk of malignancy by continuous stimulation of cells division or because they have genetic mutations that can lead to genetic abnormalities associated with development of 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, germ line 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

Interactions Between Environmental and Genetic Factors

- **Inherited trait versus Acquired factors**

(Development of genetic mutations)
It's believed that carcinogen that are presented in environment around us are very important in development of cancer

Cancer can be divided into two major parts
1) gene mutation (I heard it teen but I believe it's gene)
2);exposure to environmental agents

Causes of cancer should be considered as an interaction between inherited gene mutations and acquired environmental factors

Some of gene mutations that are well known to be associated with cancer

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

Gens involved in development of cancer

- **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**

Wether acquired to inherited , these genes mutations are required for the development of cancer, however if these genes are inherited in cells the rapidity of development of cancer is increased and cancer will present early in life

Functional classes of cancer genes

3 types.

1. Oncogenes

- **Are genes that induce a transformed phenotype when expressed in cells by promoting increased cell growth.**

These oncogenes in their normal status are called pre-oncogene or protooncogene

- **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.**

By inducing signaling in cell division

Normally drive cell growth , however once they are mutated , this drive of cell replication will be continuous leading to rapid cell division and accumulation of transformed cells leading to cancer development

Genes that control cell survival leading to increase of life span of cells leading to accumulation of abnormal cells leading to cancer development

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

Normally they inhabits negative control on cell growth , their mutations are associated with removal of this control affect leading to continuous cell replication

- **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"** Preventing growth of cells or entering cell cycle .

that act as important brakes on cellular proliferation

- **2. "Guardians"** Any abnormal cell (abnormal DNA) should be prevented from proliferating by guardians

that are responsible for sensing genomic damage

When these tumor suppressor genes are mutated, the chick points or the control effect of these genes is elevated leading to continuous cell division and production of abnormal cells

Tumor suppresser genes controls cell division it self , because after the removal of growth signaling, cells will leave cell cycle and go into dominant status

- **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.**

Further explanation for better understanding

- **Governors (Gatekeepers)**: Control cell growth and division directly. Mutations cause unchecked cell proliferation. Example: *TP53*.
- **Guardians (Caretakers)**: Repair DNA damage and maintain genome stability. Mutations increase mutation rates. Example: *BRCA1*.

In short: Governors control the cell cycle; guardians protect DNA integrity.

- **3. Genes that regulate apoptosis**

Mutations of genes that regulates apoptosis can enhance survival of-abnormal cells (muted)

- **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

Recognition the type of mutations helps in diagnosis type of 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**

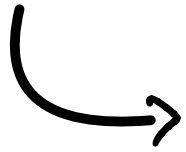
Further explanation

- **Driver mutations** cause cancer.
- **Passenger mutations** are just random changes that happen as the cancer grows, but they don't affect the cancer's ability to grow. بالمحصلة :

So, driver mutations are the key to cancer, while passenger mutations are just byproducts that don't change the cancer's behavior.

- **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** Allowing transformed cells to divide to produce abnormal cells

- Passenger mutations are acquired mutations
- Do not affect cellular behavior
- They occur at random
- Passenger mutations are sprinkled throughout the genome Their site of occurrence might be different from type to type
- Passenger mutations related to cancers caused by carcinogen exposure, such as melanoma and smoking-related lung cancer



acquired due to exposure to ultraviolet (UV) radiation

Types of gene mutations in cancer

5 types.

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** Regarding cell growth
- **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**

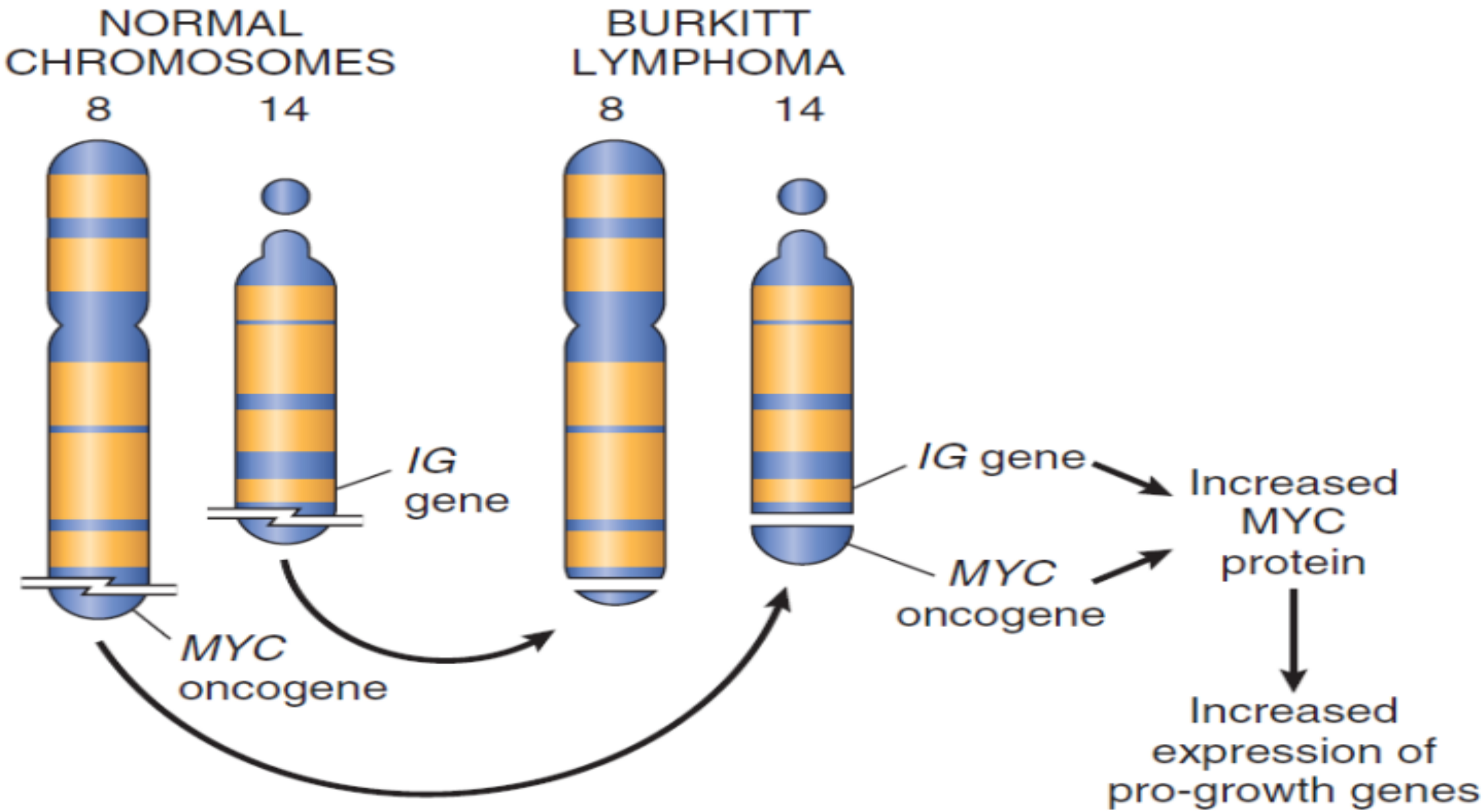
- **Gene rearrangements can activate proto-oncogenes in two ways:**

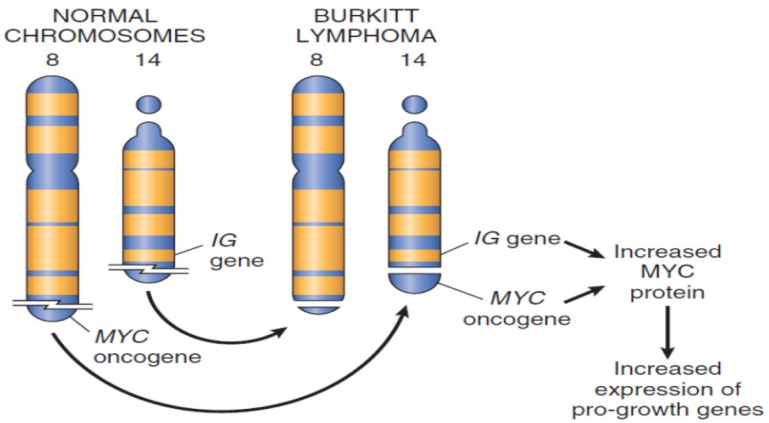
1. **Some gene rearrangements result in overexpression of proto-oncogenes by removing them from their normal regulatory elements and placing them under control of an inappropriate, highly active promoter or enhancer**

   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**

The over expression of this antiapoptic gene is associated with prevention of cell death leading to accumulation of lymphoma cells and development of follicular lymphoma


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



Explanation of this pic , since dr's explanation wasn't clear

This picture shows a **chromosomal translocation** that occurs in **Burkitt Lymphoma**:

1. Normally, the **MYC oncogene** is on chromosome **8** and the **immunoglobulin (IG) gene** is on chromosome **14**.
2. In Burkitt Lymphoma, part of chromosome **8** (containing MYC) swaps places with part of chromosome **14** (where IG gene is located).
3. This translocation places the **MYC oncogene** under the control of the active **IG gene** promoter.
4. As a result, MYC protein production increases, leading to **overexpression of pro-growth genes** that drive uncontrolled cell proliferation.

In short: Chromosomal translocation causes overactivation of the **MYC oncogene**, driving cancer growth.

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

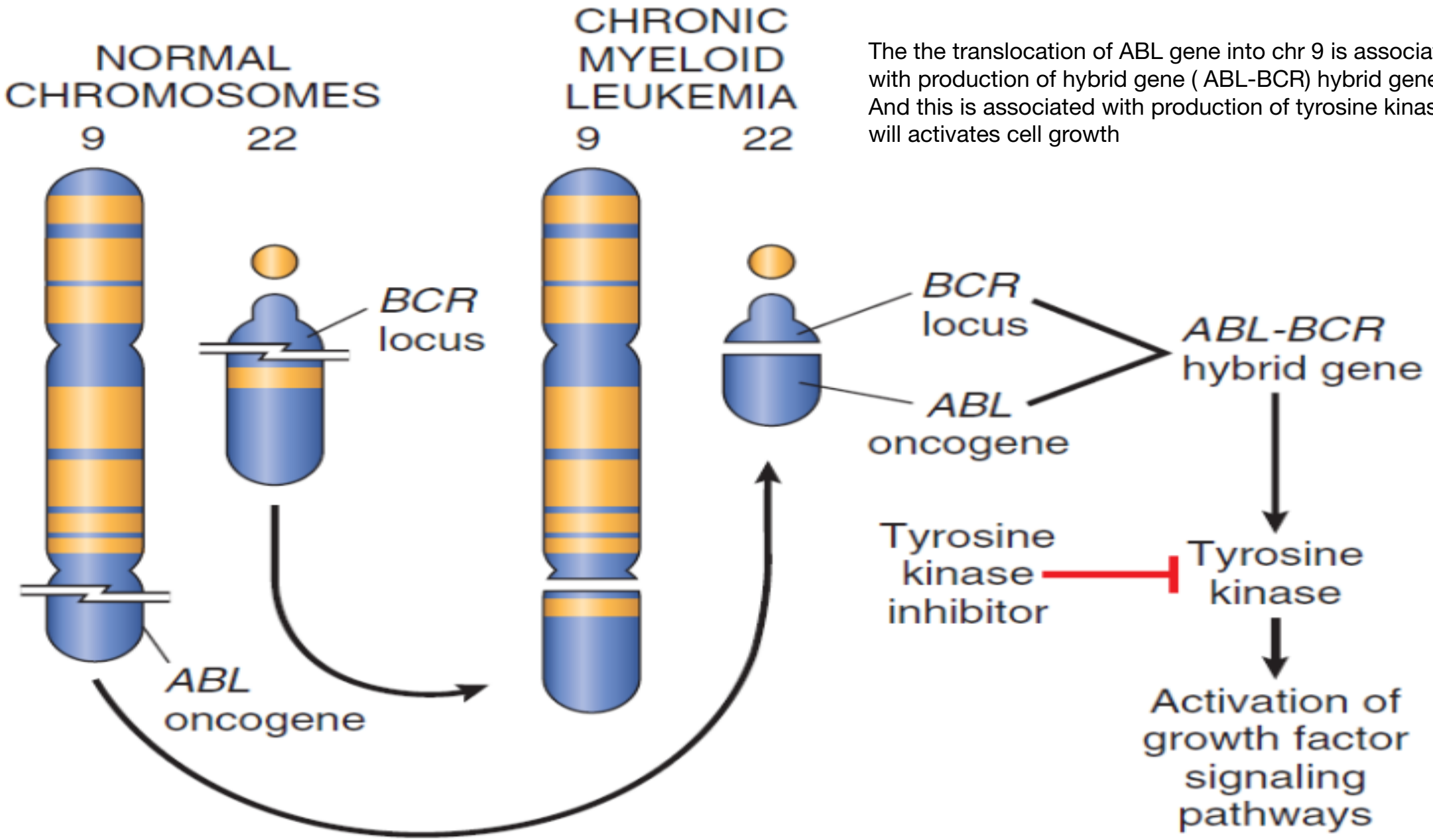
This protein can be associated with increased signals for growth and division

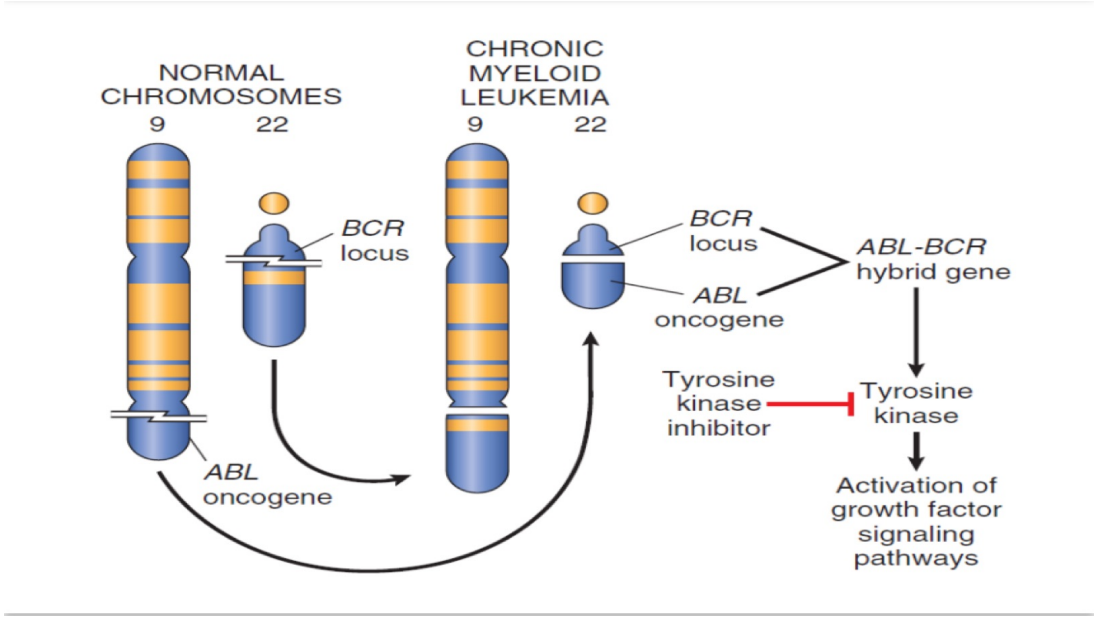
Example

- **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**

Producing accumulation of abnormal cells

The the translocation of ABL gene into chr 9 is associated with production of hybrid gene (ABL-BCR) hybrid gene
And this is associated with production of tyrosine kinase that will activates cell growth





Explanation of this pic

This image explains the **chromosomal translocation** seen in **Chronic Myeloid Leukemia (CML):**

1. Normally, the **ABL oncogene** is on chromosome **9** and the **BCR gene** is on chromosome **22**.
2. In CML, part of chromosome 9 (ABL) fuses with part of chromosome 22 (BCR), forming the **BCR-ABL hybrid gene**.
3. The **BCR-ABL hybrid gene** produces a **tyrosine kinase** enzyme, which **overactivates growth factor signaling pathways**, leading to uncontrolled cell growth.
4. **Tyrosine kinase inhibitors** (like Imatinib) block this activity to treat CML effectively.

In short: BCR-ABL fusion causes uncontrolled growth; inhibitors target this abnormal tyrosine kinase.

3. Deletions

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

Retinoblastoma

1. ***RB* gene deletions are associated with retinoblastoma**

Malignant tumor arising in retina

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.** Not multiple of normal pair of 23 chromosome
- **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.** Increasing cell division without the presence of tumor suppressor cells control
- **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 lost in tumor cells

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