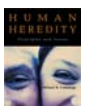
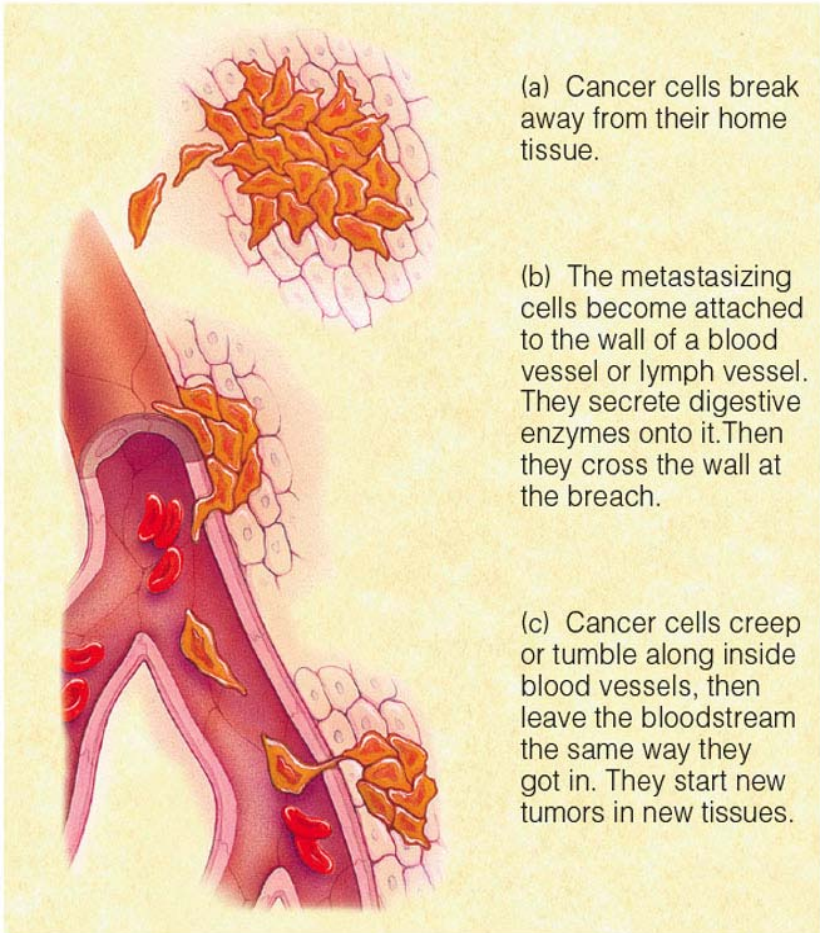
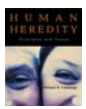
Genes and Cancer



Cancer

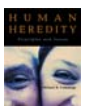
- It is a phenotype produced by the environment and the genotype
- It can affects somatic cells and tissues in the body or germ cells which well then pass these mutations on to the next generation
- Cell division is out of control
- It can **metastasize** or spread to other sites





Cancer Is Most Often a Sporadic Event

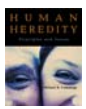
- Cancer can be an inherited susceptibility or a sporadic event
- Sporadic cases are the **most** common
- In some inherited cancers, individuals carrying the mutant allele causing a predisposition to cancer have a 100,000 fold increased risk



Cancer Is a Genetic Disorder

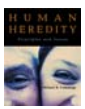
Evidence that cancer has a genetic origin

- >50 forms of cancer have some degree of inherited predisposition
- Most carcinogens are also mutagens
- Some viruses carry mutant genes **(oncogenes)** that promote and maintain the growth of a tumor
- Specific chromosomal changes are found in some cancers



Cancer Begins with a Single Cell

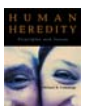
- All cells in the tumor are descended from a single cell. Not all tumors are cancerous.
- Most cancers develop after a cell accumulates a number of specific mutations over a long period of time
- Once formed cancer cells divide continuously
- Cancer cells are invasive



Inherited Susceptibilities

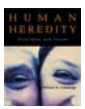
Table 12.1 Heritable Predispositions to Cancer

Disorder	Chromosome	OMIM Number
Early-onset familial breast cancer	17q	113705
Familial adenomatous polyposis	5q	175100
Hereditary nonpolyposis colorectal cancer	2p	120435
Li-Fraumeni syndrome	17p	151623
Multiple endocrine neoplasia type 1	11q	131100
Multiple endocrine neoplasia type 2	10	171400
Neurofibromatous type 1	17q	162200
Neurofibromatous type 2	22q	101000
Retinoblastoma	13	180200
Von Hippel-Lindau disease	3p	193300
Wilms tumor	11p	194070



Sporadic Cancer Is Caused by Mutations

- Most common cause of cancer
- May be caused by a single dominant mutation or a number of recessive mutations in a somatic cell
- Certain number of mutations may be required
- Age is the leading risk factor for many cancers because cancer causing mutation accumulate over time



Several Independent Mutations May Cause Cancer

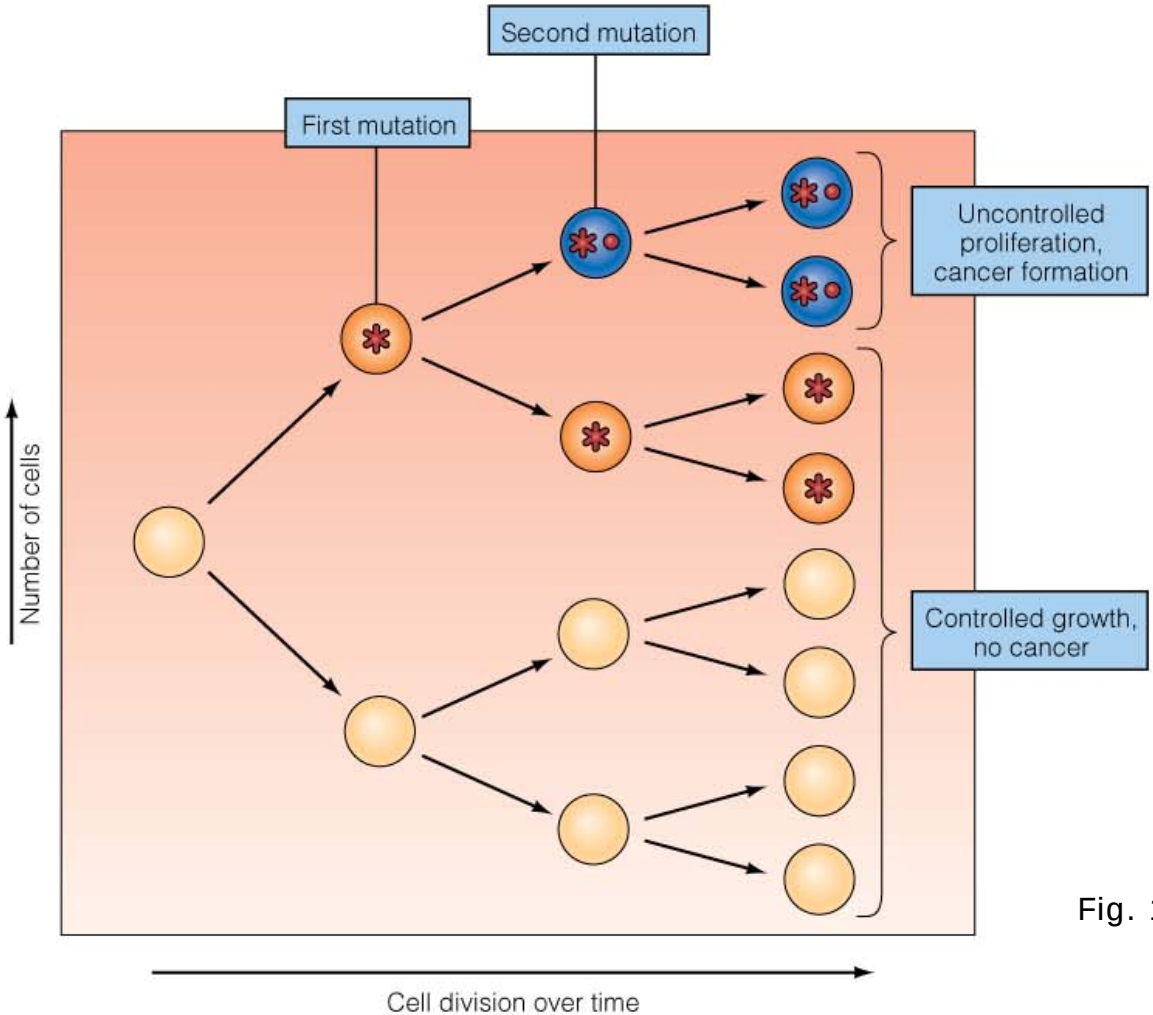
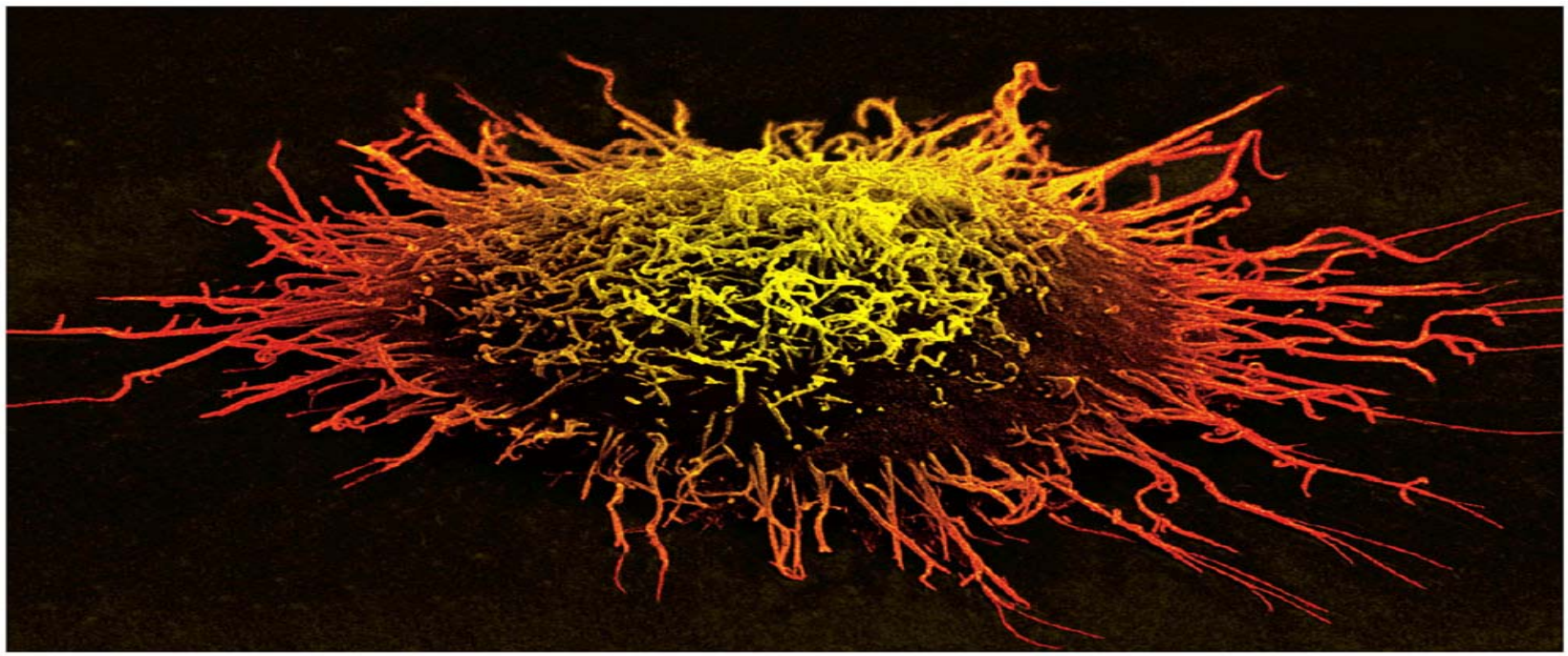


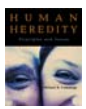
Fig. 12.3

Cell Cycle Out of Control

- Cancer cells show uncontrolled cell division
- They have abnormal shapes
- Bypass checkpoints in the cell cycle



(a) Cervical cancer cell



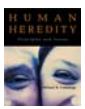
Two Types of Genes Involved with Cancer

Gatekeeper genes

- Regulate cell growth and passage through cell cycle
  - Example tumor suppressor genes and some oncogenes

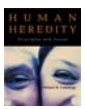
Caretaker genes

- Help maintain the integrity of the genome
  - Example DNA repair genes



Proto-Oncogenes to Oncogenes

- **Proto-oncogenes** when turn on or off cell division
- Mutant forms permanently switch on cell division and are called **oncogenes**
- Many different types of mutations have been identified
- Example: *ras* proto-oncogene receives and transfers signal needed for cell divsion



Checkpoint Genes

- **Tumor suppressor genes**
  - Suppress cell division
  - Act at either G1/S or G2/M control points
- **Proto-oncogenes**
  - Promote cell division if mutation
- **Onocogenes**
  - Mutant forms of proto-oncogenes induce or continue uncontrolled cell division

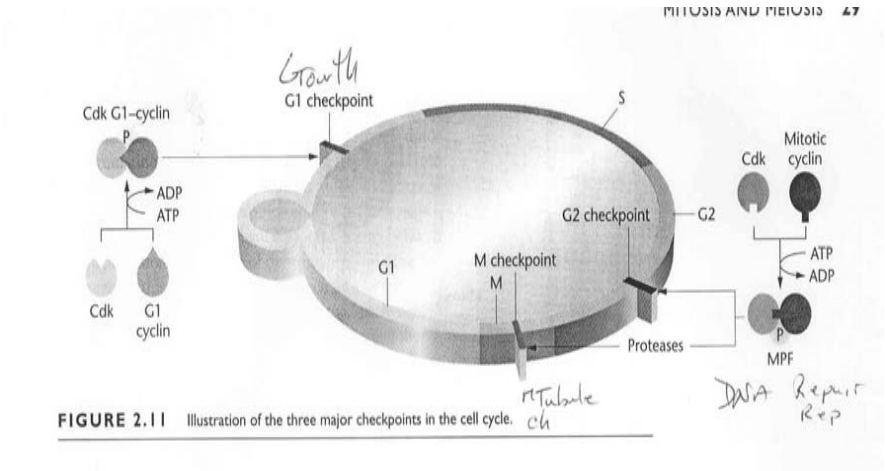


FIGURE 2.11 Illustration of the three major checkpoints in the cell cycle.

Retinoblastoma

- Cancer of the retina
- Diagnosed between 1–3 years of age
- 40% of all cases are due to an autosomal dominant trait
- 60% are sporadic cases
- Tumor suppressor gene

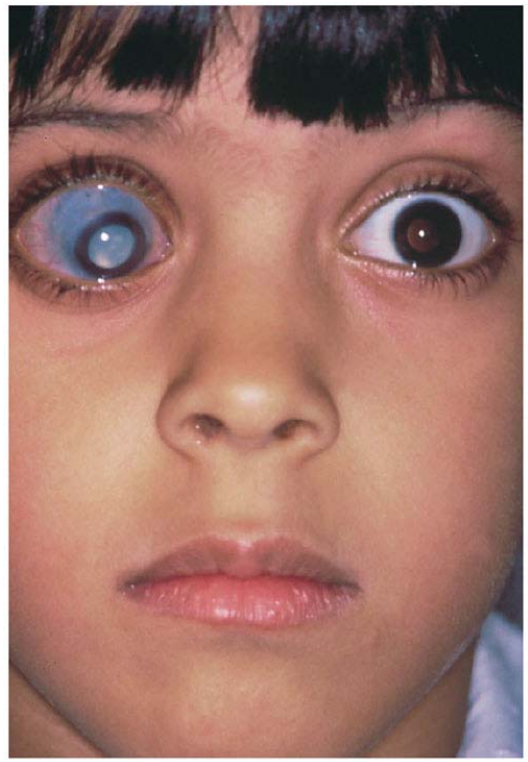
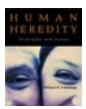
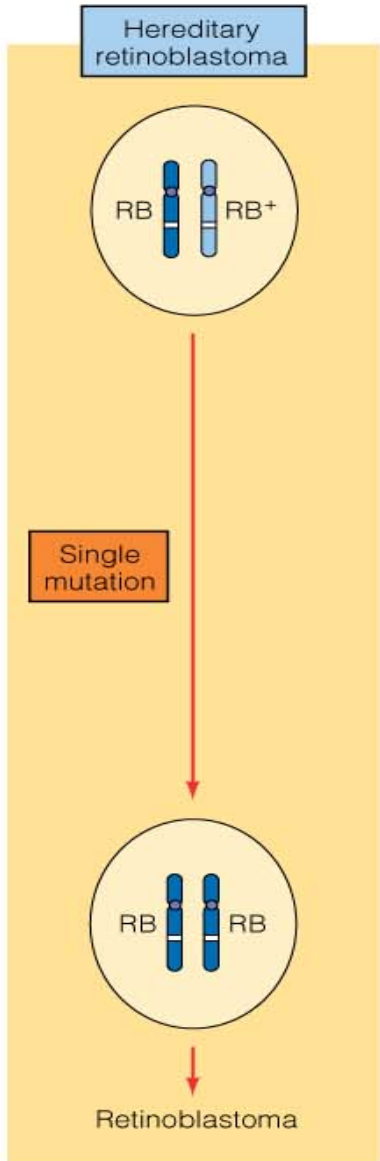


Fig. 12.6

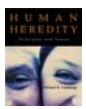


Hereditary Retinoblastoma

- Autosomal dominant
- Individuals with the allele, *RB* have a 90% chance of developing retinoblastoma
- Usually in both eyes
- High risk for other cancers especially osteosacroma and fibrosacroma

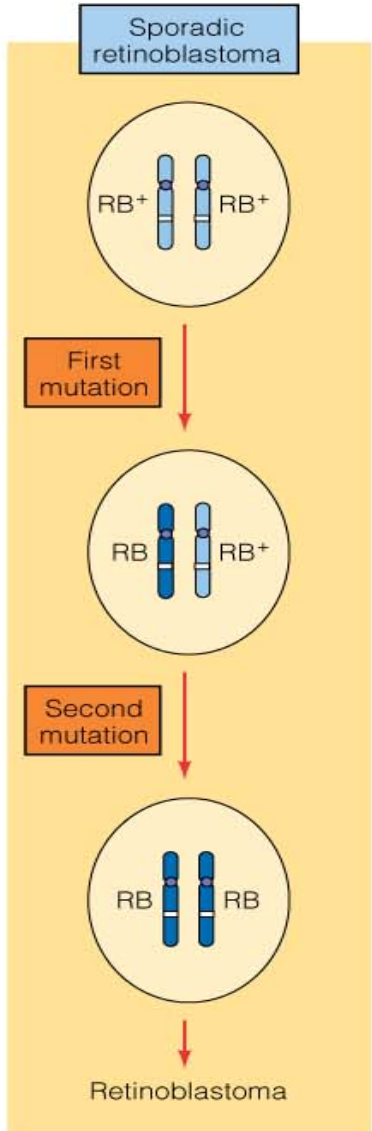


(a) Fig. 12.7



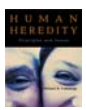
Sporadic Form of Retinoblastoma

- Mutations occur in both copies of the *RB1* gene at 13q14
- Tumors form generally in only one eye
- No increased risk of other cancers



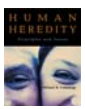
(b)

Fig. 12.7



Knudson Two-Step Model

- Disease develops when two mutant copies of *RB1* are present in the cell
- With inherited retinoblastoma, a child inherits one mutant allele and if the normal copy becomes mutated the develops retinoblastoma
- In the sporadic form, both copies must become mutated to develop the disease, generally only in one eye and later in childhood



RB1 gene

- Located at 13q14 and encodes for protein pRB
- pRB regulates the cell cycle
  - It is present in most cells
  - Activated pRB prevents the cell from moving from G1 to S
- If both copies of the *RB1* gene are deleted or mutated the cell divides in an uncontrolled manner

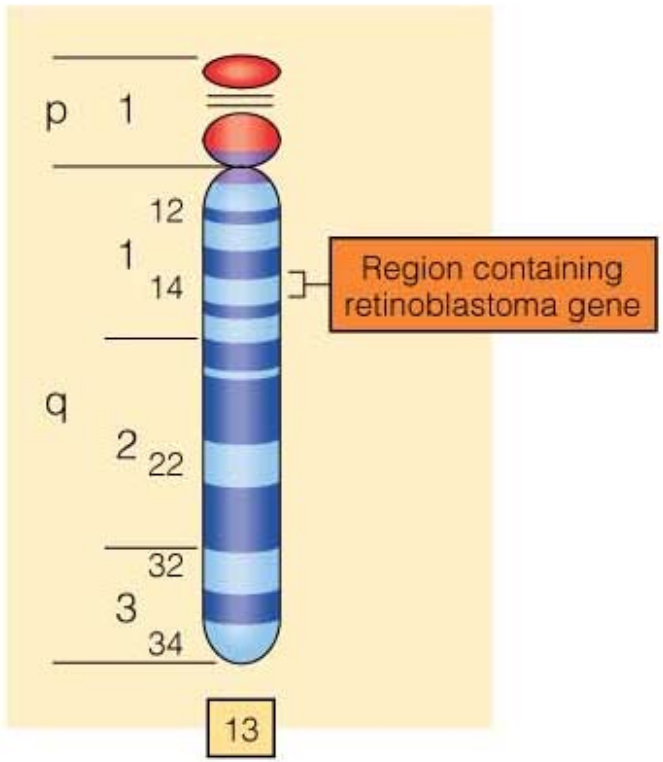
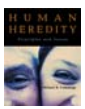


Fig. 12.8

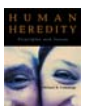
Breast Cancer

- Most common form of cancer in US women, but may also be found in men
- 40,000 deaths/year; 180,000 new cases
- Most cases are sporadic but approximately 5% are the result of a mutation of the ***BRCA1* gene**
- About 1/200 women inherit the allele; of these, approximately 90% will develop breast cancer



BRCA1 Gene

- Mary-Claire King's research began in the 1970s
- In 1990, using recombinant DNA technology found linkage with a variable–number tandem repeat (VNTR) on the 183rd marker tested
- Marker also is linked to ovarian cancer
- The autosomal dominant *BRCA1* gene was identified in 1994



BRCA1 and *BRCA2*

- *BRCA1* maps to chromosome 17
- Another autosomal dominant gene, *BRCA2* is mapped to chromosome 13
- Together *BRCA1* and *BRCA2* account for 10–15% of breast cancer
- Allele frequencies of theses genes vary between population

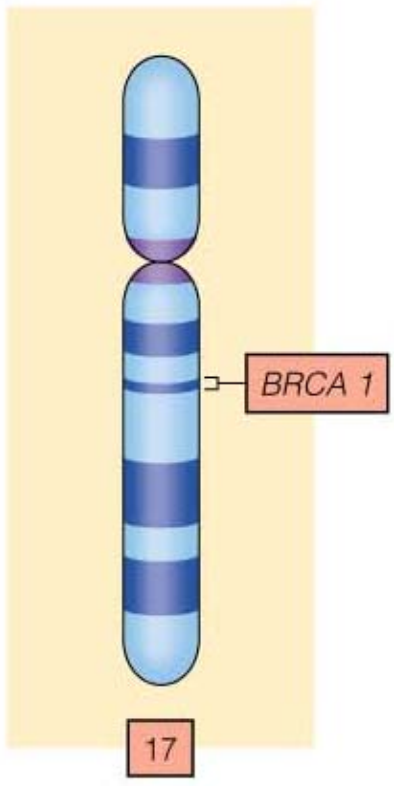
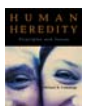
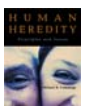


Fig. 12.10



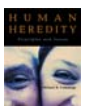
BRCA1 and *BRCA2* Are DNA Repair Genes

- Expression is highest at the G1/S boundary and S phase of the cell cycle
- BRC1 protein is activated when DNA is damaged
- Involved with repair of double stranded breaks in the DNA
- BRCA2 protein has similar function
- Regarded as tumor suppressor genes



Colon Cancer

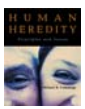
- Common form of cancer, approximately 84% sporadic forms
- Multiple mutations are required to initiate formation of cancer cell
- Two forms of genetic predisposition
  - Familial adenomatous polypoisis (FAP) accounts for 1% of all cases
  - Hereditary nonpolyposis colon cancer (HNPCC) accounts for 15% of all cases



Colon and Rectal Cancer

Table 12.2 Colon and Rectal Cancer in the United States

Estimated new cases, 2004	
Colon	106,370
Rectum	40,570
Total	146,940
Mortality (estimated deaths, 2004)	
Colon and rectum	56,730
	(16% of cancer deaths)
5-year survival rate (early detection)	
Colon	90%
Rectum	85%



Familial Adenomatous Polyposis

- Autosomal dominant trait
- Mutation of the APC gene
- Frequency in general population 3/1,000
- Results in development of polyps and benign growths in the colon
- Polyps often become malignant

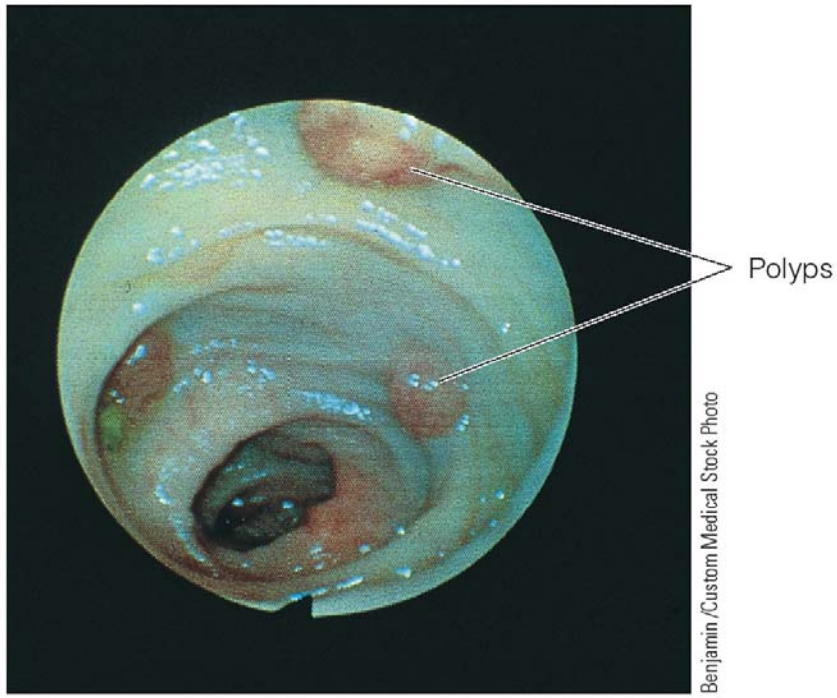
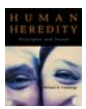


Fig. 12.11



Model for Colon Cancer

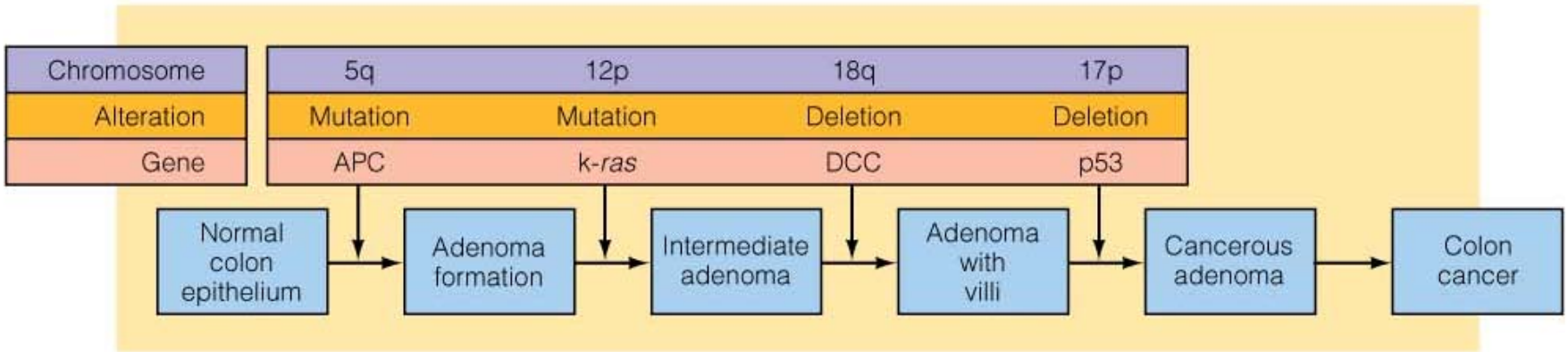
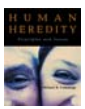


Fig. 12.12

Mutations and Cancer

Table 12.3 Number of Mutations Associated with Specific Forms of Cancer

Cancer	Chromosomal Sites of Mutations	Minimal Number of Mutations Required
Retinoblastoma	13q14	2
Wilms tumor	11p13	2
Colon cancer	5q, 12p, 17p, 18q	5 to 7
Small-cell lung cancer	3p, 11p, 13q, 17p	10 to 15



Chromosome Instability and Cancer Susceptibility

Table 12.4 Human Genetic Disorders Associated with Chromosome Instability and Cancer Susceptibility

Disorder	Inheritance	Chromosome Damage	Cancer Susceptibility	Hypersensitivity
Ataxia telangiectasia	Autosomal recessive	Translocations on 7, 14	Lymphoid, others	X-rays
Bloom syndrome	Autosomal recessive	Breaks, translocations	Lymphoid, others	Sunlight
Fanconi anemia	Autosomal recessive	Breaks, translocations	Leukemia	X-rays
Xeroderma pigmentosum	Autosomal recessive	Breaks	Skin	Sunlight

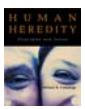
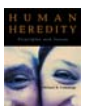


Table 12.5 Chromosomal Translocation Associated with Human Cancers

Chromosomal Translocation	Cancer
t(9;22)	Chronic myelogenous leukemia (Philadelphia chromosome)
t(15;17)	Acute promyelocytic leukemia
t(11;19)	Acute monocytic leukemia, acute myelomonocytic leukemia
t(1;9)	Pre-B-cell leukemia
t(8;14),t(8;22),t(2;8)	Burkitt's lymphoma, acute lymphocytic leukemia of the B-cell type
t(8;21)	Acute myelogenous leukemia, acute myeloblastic leukemia
t(11;14)	Chronic lymphocytic leukemia, diffuse lymphoma, multiple myeloma
t(4;18)	Follicular lymphoma
t(4;11)	Acute lymphocytic leukemia
t(11;14)(p13;q13)	Acute lymphocytic leukemia



Philadelphia Chromosome

- Abnormal chromosome produced by a translocation between long arms chromosome 9 and chromosome 22
- Linked to chronic myelogenous leukemia (CML)

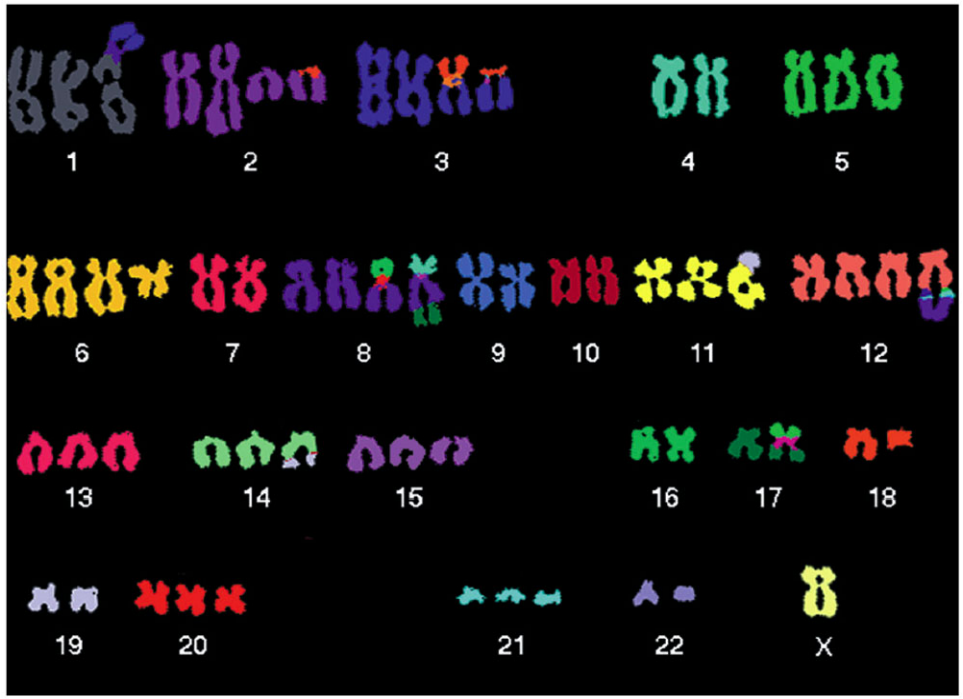
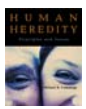


Fig. 12.13



Cancer Drugs

- Traditional therapy, chemo and radiation therapy, targets all rapidly dividing cells and creates serious side effects
- New drug, Gleevec, targets the specific hybrid protein

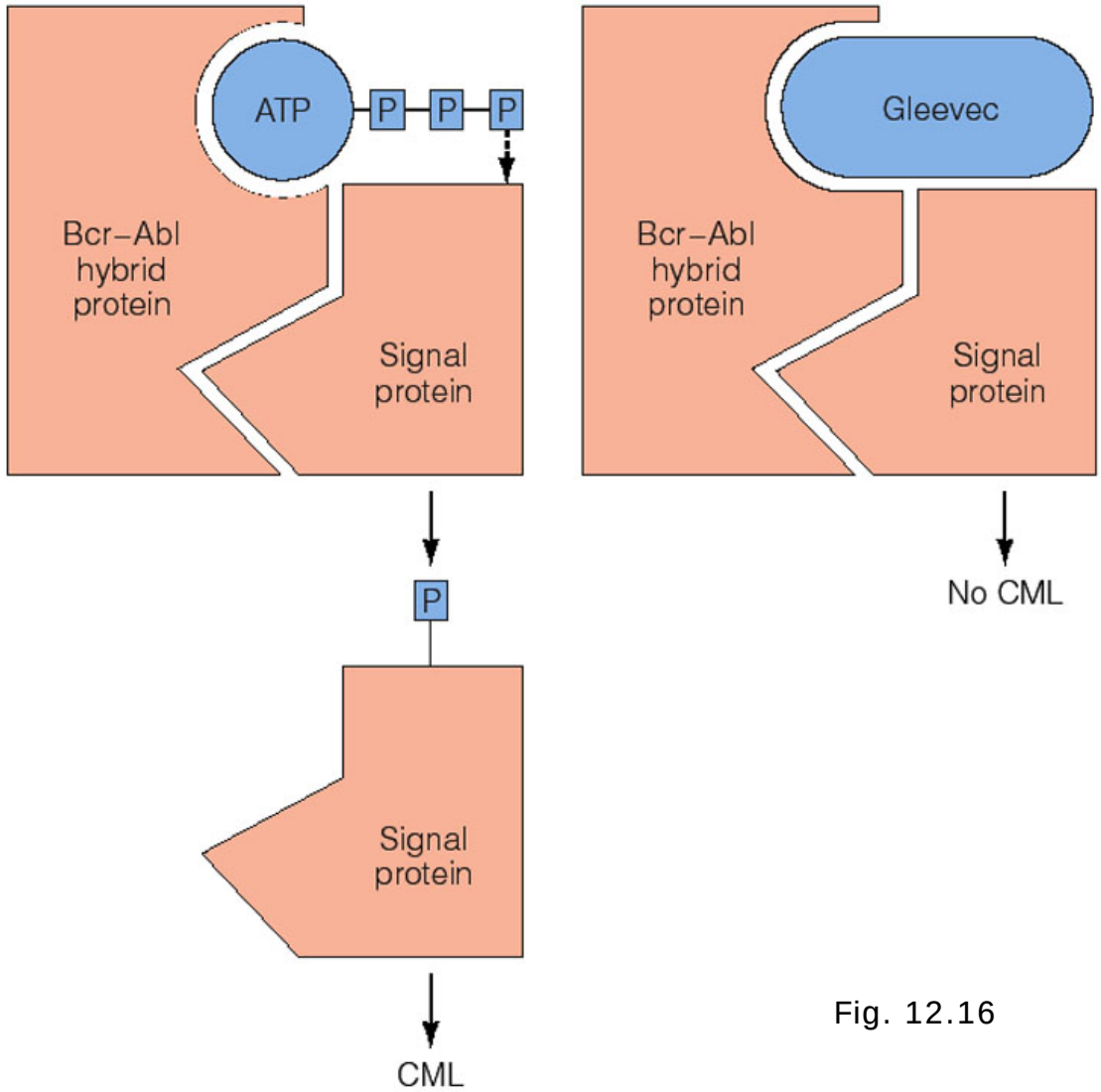


Fig. 12.16

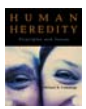
Cancer and the Environment

- Epidemiological studies can identify variation in cancer deaths between populations and help identify environmental factors

Table 12.6 Age-Adjusted Cancer Death Rates per 100,000 Population

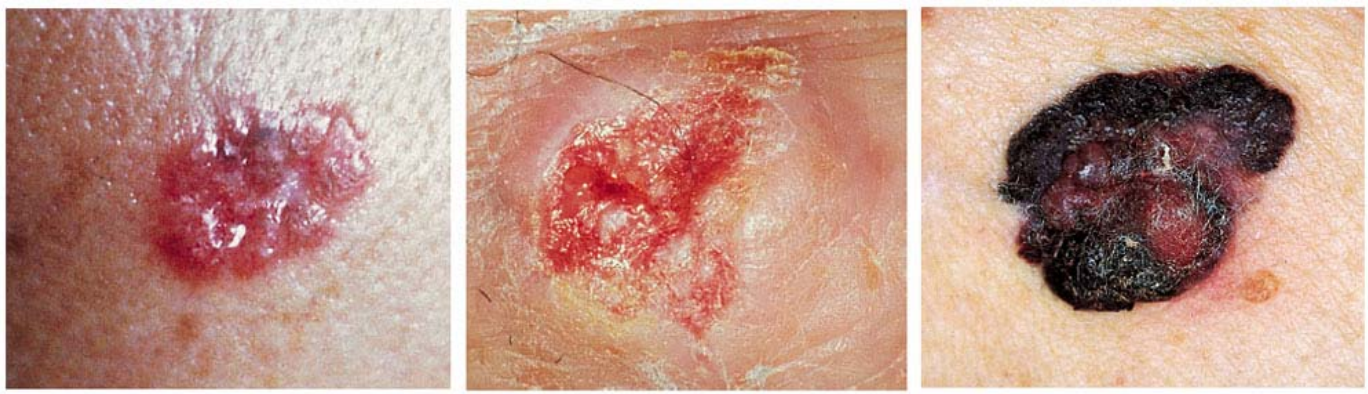
	All Sites	
Country	**Male**	**Female**
United States	165.3 (27)*	111.1 (18)
Australia	158.5 (28)	100.2 (20)
Austria	171.6 (20)	105.6 (16)
Denmark	178.7 (17)	138.1 (1)
Germany	177.3 (18)	108.2 (11)
Hungary	258.7 (1)	135.2 (2)
Japan	149.8 (32)	75.2 (43)
Latvia	206.1 (6)	98.7 (23)
Mauritius	85.4 (47)	63.8 (46)
Mexico	81.6 (48)	77.6 (41)
Poland	204.2 (8)	107.6 (13)
Romania	140.2 (36)	84.5 (38)
Slovenia	203.9 (9)	108.0 (12)
Switzerland	167.2 (24)	96.5 (26)
Trinidad, Tobago	120.0 (42)	91.4 (31)
United Kingdom	179.1 (16)	124.6 (5)

* Number in parentheses refers to rank order.



Skin Cancer Epidemic

- Most common form of cancer
- Americans have 1/5 lifetime risk
- Why is the risk increasing?
- What factors increase your risk?
- What can you do to protect yourself?



(b) basal cell carcinoma | squamous cell carcinoma | malignant melanoma

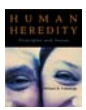


Fig. 12.4