Unit IV – Problem 11 – Biochemistry: Cancer Genetics and Tumor Markers

- **Frank malignancy requires the presence of one billion malignant cells (10^9).**

Characteristics of human neoplasia	Characteristics of precursor lesions
• Abnormal growth and cell proliferation. • Invasiveness	• Abnormal cell proliferation (known as metaplasia). • No invasiveness. • Examples: ✓ Colon polyps (preceding colon cancer). ✓ Skin dysplastic navi (preceding melanoma).

- **Steps of tumorigenesis:**
  - **Initiation:**
    - ✓ Tumors usually arise from a single cell or clone.
    - ✓ Initiation event (mutation):
      - ❖ Gain of function of oncogens (amplification).
      - ❖ Loss of function of tumor-suppressor genes (deletions).
  - **Promotion:**
    - ✓ Represented by subsequent events after the initiation event (accumulation of additional mutations).
  - **Progression:**
    - ✓ Benign lesions → in situ tumors → invasive cancers!
- **Genetic alterations in neoplasia:**
  - **Genetic mutations.**
  - **Epigenetic changes**: hyper-methylation in the promoter region leading to gene silencing:
    - ✓ Influence gene expression and cell behavior.
    - ✓ Transmitted to daughter cells (inherited).
  - **A particular genetic alteration is linked to a certain cancer type (molecular marker), target for:**
    - ✓ Drug development.
    - ✓ Molecular profiling (classification).
- **Ideal tumor markers:**
  - **What are tumor markers?**
    - ✓ They are biological substances synthesized and released by cancer cells or produced by the host in response to the presence of the tumor.
  - **Characteristics:**
    - ✓ In healthy individuals: low concentrations.
    - ✓ Being specific to the tumor.
    - ✓ Levels should change in response to tumor size.
    - ✓ Predict recurrences before they are clinically detectable.
  - **Tumor markers are detected in:**
    - ✓ Solid tumor.
    - ✓ Circulating tumor cells in blood.
    - ✓ Lymph nodes.
    - ✓ Bone marrow.
    - ✓ Body fluids (e.g. urine, stool, ascites).
  - **Types of tumor markers:**
    - ✓ Tumor specific proteins:
      - ❖ They are expressed only in tumor cells.
      - ❖ They are products of mutated oncogenes and tumor suppressor genes.
    - ✓ Cell-specific proteins over-expressed in malignant cells:
      - ❖ *Example*: Prostate-Specific Antigen (PSA) expressed in prostate cancer.

- ✓ Non-specific proteins or markers related to malignant cells:
  - ❖ *Oncofetal proteins*: expressed by cells as they de-differentiate and take on embryonic characteristics:
    - ➢ α-FP (alpha Fetoprotein): hepatocellular carcinoma; testicular of ovarian cancer.
    - ➢ CEA (Carcino-Embryonic Antigen):
      - Detect early relapse of colorectal cancer.
      - Found in 30-50% of breast cancer and small cell lung cancer.
      - Normal pre-therapy CEA indicates lower metastasis incidence while high initial CEA indicates higher metastasis incidence.
      - CEA can also be elevated in patient with COPD and those who smoke.

- **Uses of tumor markers:**
  - ✓ Population screening:
    - ❖ *Screening tests:*
      - ➢ Cancer must be common.
      - ➢ Natural history of the cancer should be understood.
      - ➢ Effective treatments must be available.
      - ➢ The test must be acceptable to both patients and physicians.
      - ➢ The test must be safe and relatively inexpensive.
  - ✓ Diagnosis.
  - ✓ Establishing prognosis and staging.
  - ✓ Post-operative evaluation.
  - ✓ Monitor treatment response.
  - ✓ Surveillance for recurrence.
  - ✓ Targets for therapeutic intervention.
- **Breast cancer markers:**
  - ✓ HER-2-neu (Human epidermal growth factor receptor 2): it is an oncogen. If it is overexpressed in breast cancer, this indicates poor prognosis.
  - ✓ BRCA-1 (Breast cancer type 1) gene on chromosome 17 indicates familial breast-ovarian cancer syndrome.
- **Estrogen Receptor (ER):**
  - ✓ They are implicated in: breasts, ovaries, endometrium, prostate, colon and cancers.
  - ✓ There are two isoforms:
    - ❖ *ERa*: better prognosis; predictor of relapse.
    - ❖ *ERb*: correlates with low-grade tumor and negative involvement of axillary lymph nodes.
- **Cervical squamous cell carcinoma:**
  - ✓ Suqamous cell carcinoma antigen (SCC):
    - ❖ Not sensitive enough for screening early-stage carcinoma.
    - ❖ Used for prognosis and monitoring.
- **Cancer Antigen 19-9 (CA 19-9):**
  - ✓ It is not recommended for screening, diagnosis, surveillance or monitoring of therapy for colon or pancreatic cancers!! (JUST A USELESS EXTRA INFO BECAUSE YOU ARE A MEDICAL STUDENT ☺!)