The concept of preneoplastic lesions
This concept is only available in tumours derived from epithelium

Squamous epithelium
lining:
- skin, oesophagus, anal canal, pharynx, larynx, uterine cervix, vagina...

Glandular epithelium
lining:
- stomach, intestine, biliary tract, pancreas, lung, liver, bladder, breast...
Natural history of carcinomas/adenocarcinomas

- A lengthy (several years) and sequential process
- Can be divided in several steps:
  - transformation of a normal cell into a tumour cell
  - clonal proliferation of this tumour cell during the pre-invasion step
  - growth of the tumour until clinically becoming detectable and local invasion through the basal membrane
  - the metastatic step: spread of the tumour away from the primary site
• Tumour progression (or carcinogenesis) is correlated to a genetic instability of tumour cells: example of colon carcinogenesis.

Cancer Tends to Involve Multiple Mutations

Benign tumor cells grow only locally and cannot spread by invasion or metastasis.

Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites.


p53, MLH1, KRAS
The first steps of carcinogenesis in carcinoma/adenocarcinoma: the preneoplastic lesions

- Correspond to the steps **before invasion of surrounding tissue**, before disruption of the basal membrane

- Correspond to the **intra-epithelial step** of carcinogenesis

- **Dysplasia** correspond to the **morphological features** of the intra-epithelial steps of carcinogenesis
  - > the first microscopically detectable changes in the neoplastic process
Dysplasia : definition - characteristics

• **Dysplasia** : histologically unequivocal neoplastic epithelium without evidence of tissue invasion

  > **microscopic** term
  > used only in **epithelia** (digestif tract, breast, lung, uterine cervix, urinary tract, pancreas....)
  > corresponds to an excessive and uncontroled cell proliferation
  > results from the acquisition of genetic abnormalities that alter cell proliferation and differentiation
  > **occasionally** they gradually **become malignant (invading surrounding tissue)** by acquisition of other genetic abnormalities
  > no invasion of surrounding tissue +++ (integrity of the basal membrane)
  > because of their potential malignant transformation, areas of dysplasia should be closely **monitored and treat ++++**
Dysplasia can be observed in...

- **Inflammatory conditions**
  - chronic gastritis caused by *Helicobacter pylori*
  - Barrett’s esophagus caused by chronic reflux esophagitis
  - inflammatory bowel diseases (Crohn’s disease CD, ulcerative colitis, UC)

- **Virus infections**
  - human papilloma virus (HPV) infection in uterine cervix

- **Some benign tumours**
  - colonic adenoma

- **Others...**
The colorectal carcinogenesis: an example of a colonic adenoma progressing to a carcinoma.
The proof that some pre-neoplastic lesion can evolved to an invasive lesion: the identification of remnants of pre-neoplastic lesion (adenoma) beyond the invasive tumor (adenocarcinoma).

Colorectal adenocarcinoma developed from an adenoma.
Microscopic criteria of dysplasia

- Diagnosed by cytological (pap smear) or histological (biopsy or surgical resection) examination
- 2 main criteria:

<table>
<thead>
<tr>
<th>Architectural</th>
<th>Cytological</th>
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<tbody>
<tr>
<td>Increased number of cells</td>
<td>Increased number of mitosis (dividing cells)</td>
</tr>
<tr>
<td>Loss of cell differentiation</td>
<td>Increased nuclear/cytoplasmic ratio</td>
</tr>
<tr>
<td>Loss of normal epithelium organization</td>
<td>Anisocytosis (cell of irregular size)</td>
</tr>
<tr>
<td>Loss of cell polarity</td>
<td>Anisokaryosis (nuclei of irregular size)</td>
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Normal stratified squamous epithelium of the uterine cervix

Dysplastic squamous epithelium
Grade of dysplasia

- Refers to the intensity, the severity of architectural and cytological abnormalities

- Two or 3 grades depending on the organ:
  - low/high (colon)
  - cervical intra-epithelial neoplasia (CIN) I, II, III (cervix)

- The more high grade dysplasia, the more high risk of progression to cancer: the grade is a prognostic factor

- High grade dysplasia is synonymous with in situ carcinoma in most organs
Colon adenoma with low grade dysplasia
- atypical elongated cell and nuclei, loss of differentiation (loss of goblet cells)
- preserved cell polarity (nuclei are located at the basal pole of cell)

Colon adenoma with high grade dysplasia
- loss of cell polarity +++
  (nuclear stratifications: nuclei reach the luminal surface)
- enlarged irregular nuclei
- increased mitosis+++
Benefits of screening of preneoplastic lesions

• Prevents invasive cancer
  > removal of preneoplastic lesions prevents invasive cancer

• Improves survival
  > early detection markedly improves chance of long term survival
Cervical cytology: an appropriate tool for the screening of cervical intra epithelial neoplasia

Simple, safe and non-invasive method of detecting preneoplastic changes in the cervix

Normal pap smear

Dysplastic cells
HEMOCULT TEST: a fecal occult blood test to detect invisible amounts of blood in the feces
Conclusion

• A pre-neoplastic (pre-malignant) lesion is a microscopically non-invasive tissue abnormality at a given site, composed of dysplastic cells

• Dysplastic lesions:
  - represent potentially curable early stages of cancer
  - represent lesions that can be screened in populations in an attempt to reduce (and prevent) cancer
  - provide evidence in support of multi-step carcinogenesis.