

# Acquired Predisposing Conditions

Chronic inflammation · Precursor lesions · Immunodeficiency

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# Learning outcomes

- Classify acquired states that increase susceptibility to neoplasia.
- Connect chronic tissue injury with proliferation, DNA damage, and cell survival.
- Distinguish hyperplasia, metaplasia, dysplasia, and carcinoma in situ.
- Relate impaired T-cell immunity to virus-associated malignancies.
- Use representative clinicopathologic associations without assuming inevitable progression.

# Predisposition modifies risk—not diagnosis

## Predisposing condition

- Increases susceptibility to malignancy
- May act over a prolonged period
- Can exist without cancer

## Malignant neoplasm

- A transformed clone has emerged
- Requires additional biologic changes
- Must be diagnosed on its own evidence

**A risk state and an established cancer are not interchangeable diagnoses.**

# Three acquired categories

## Chronic inflammatory disorders

- Persistent damage and repair
- DNA-damaging reactive species
- Growth and survival signals

## Precursor lesions

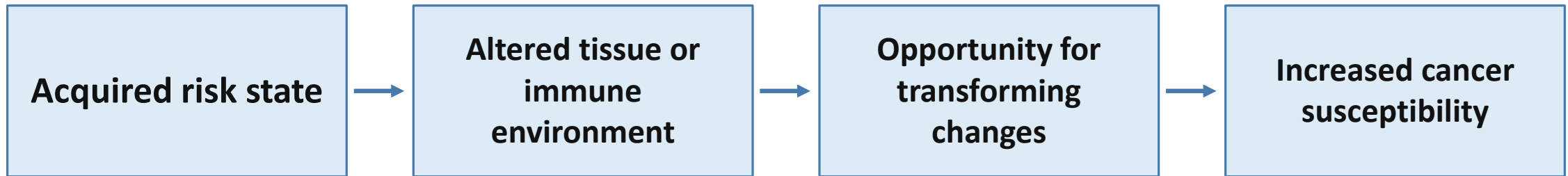
- Localized epithelial changes
- Hyperplasia, metaplasia, dysplasia
- Variable chance of progression

## Immunodeficiency

- Defective antiviral immune control
- Especially T-cell deficiency
- Virus-associated cancers prominent

# Different routes converge on neoplastic risk

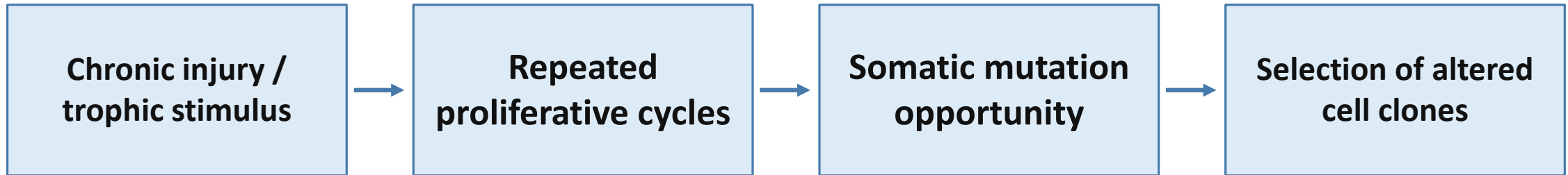
Schematic — risk pathway



- Inflammation and precursor lesions often increase epithelial replication.
- Immunodeficiency predominantly alters control of infected or abnormal cells.

# Cell replication creates a susceptible field

Schematic — risk pathway



- Proliferating cells as particularly vulnerable to oncogenic mutation.
- Proliferation alone is not sufficient to diagnose transformation.

# A useful distinction: Field versus clone

## At-risk field

- Tissue-wide regenerative or precursor change
- May be reversible or stable
- Cannot be equated with invasive cancer

## Tumor clone

- An altered precursor cell expands
- Later changes may generate malignancy
- Morphologic assessment remains decisive

# Virchow's inflammation–cancer connection

- Rudolf Virchow proposed a link between chronic inflammation and cancer in 1863.
- The association now extends across many infectious and noninfectious disorders.
- Causal pathways differ among inflammatory conditions and tissues.
- The association is clinically useful because some upstream causes are preventable.

# Inflammation has infectious and noninfectious causes

## Infectious

- H. Pylori gastritis
- Chronic viral hepatitis
- Schistosomal cystitis

## Noninfectious

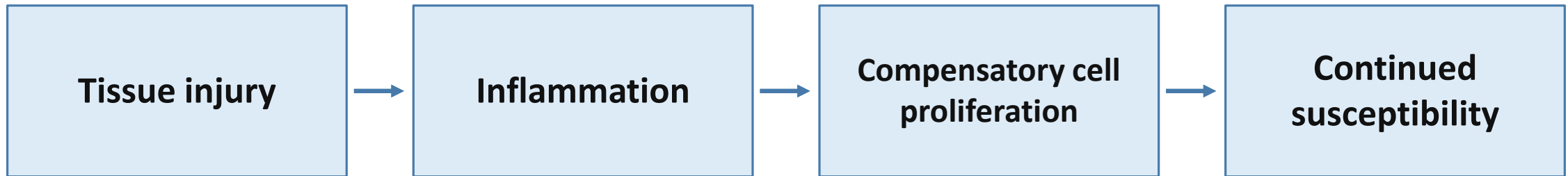
- Inflammatory bowel disease
- Chronic reflux injury
- Autoimmune gland inflammation

## Physical / irritant injury

- Asbestos-related injury
- Chronic gallstone-associated inflammation
- Long-standing draining sinuses

# Persistent injury drives repeated repair

Schematic — risk pathway



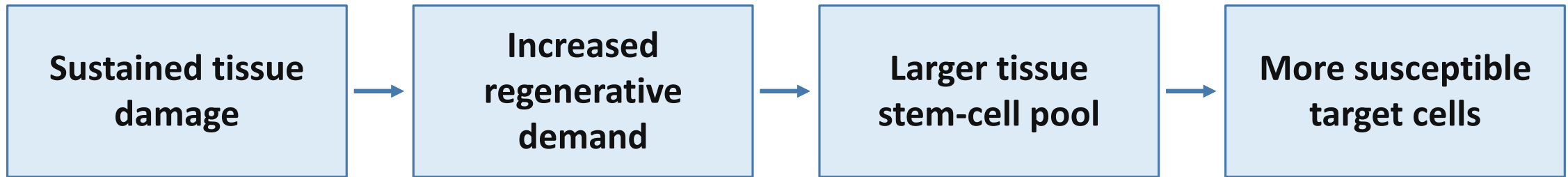
- The regenerative response is normally reparative.
- Persistent insult creates repeated cycles of tissue damage and cell replacement.

# Proliferation is one mechanistic route

- Regeneration expands the population of cycling cells after injury.
- Repeated cell division increases opportunities for heritable somatic changes.
- A proliferative environment is permissive—not itself proof of neoplasia.
- Additional alterations are needed for malignant transformation.

# Inflammation may expand stem-cell pools

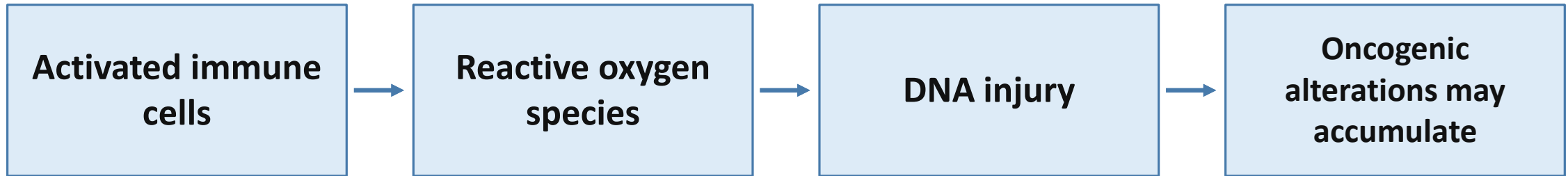
Schematic — risk pathway



- Stem-cell expansion as a possible mechanism in some settings.
- This is a proposed contributor rather than a universal feature of all inflammation.

# Reactive oxygen species can damage DNA

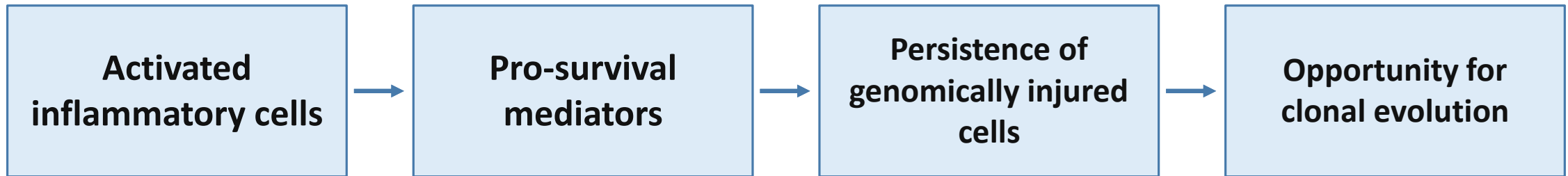
Schematic — risk pathway



- Inflammatory oxidative injury acts alongside the proliferative response.
- DNA damage does not mean that every affected cell becomes malignant.

# Inflammatory mediators may sustain damaged cells

Schematic — risk pathway



- Survival even in the presence of genomic damage.
- This route complements rather than replaces mutation-generating mechanisms.

# Mechanisms act together, not in isolation

## Proliferation

- More rounds of replication
- More opportunities for somatic change

## Damage

- Oxidative products injure DNA
- Regeneration follows ongoing injury

## Survival

- Inflammatory signals prolong viability
- Damaged cells may persist

Repeated injury, mutation opportunity, and survival signals can reinforce one another.

# Which tumor classes arise in inflamed tissues?

## Most frequent pattern

- Carcinomas are prominent
- Frequently arise in chronically injured epithelia

## Important exceptions

- Mesothelioma is included
- Several lymphomas occur in inflammatory settings

**An inflammation-related neoplasm need not be a carcinoma.**

# Chronic inflammatory associations: Digestive tract

| Inflammatory condition                 | Associated neoplasm   |
|----------------------------------------|-----------------------|
| Inflammatory bowel disease             | Colorectal carcinoma  |
| Reflux esophagitis / Barrett esophagus | Esophageal carcinoma  |
| Chronic cholecystitis                  | Gallbladder carcinoma |
| Pancreatitis                           | Pancreatic carcinoma  |

**Associations identify risk contexts; They do not establish that every case progresses.**

# Chronic inflammatory associations: Infection

| Chronic condition / agent           | Associated neoplasm                           |
|-------------------------------------|-----------------------------------------------|
| H. pylori gastritis / ulcers        | Gastric adenocarcinoma; gastric MALT lymphoma |
| Hepatitis B or C infection          | Hepatocellular carcinoma                      |
| Schistosomiasis-associated cystitis | Bladder carcinoma                             |
| Opisthorchis-associated cholangitis | Cholangiocarcinoma                            |

**Infectious causes can act through different combinations of inflammation and pathogen-specific effects.**

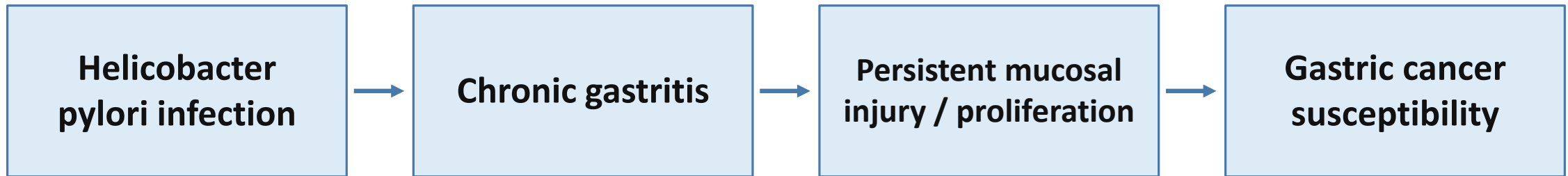
## Chronic inflammatory associations: Other sites

| Condition                                      | Associated malignancy                           |
|------------------------------------------------|-------------------------------------------------|
| Lichen sclerosus                               | Vulvar squamous cell carcinoma                  |
| Sjögren syndrome; Hashimoto thyroiditis        | Extranodal marginal zone (MALT) lymphoma        |
| Long-standing osteomyelitis / draining sinus   | Carcinoma in draining sinus                     |
| Asbestos-related / silicosis-associated injury | Lung carcinoma; mesothelioma linked to asbestos |

**The type of at-risk tissue helps determine the expected tumor phenotype.**

# H. Pylori: Sustained gastric injury

Schematic — risk pathway



- Chronic infection to gastric carcinoma and gastric MALT lymphoma.
- The presence of infection does not itself establish a neoplastic diagnosis.

## H. Pylori has two key neoplastic associations

### Gastric adenocarcinoma

- Epithelial malignancy
- Associated with chronic gastritis

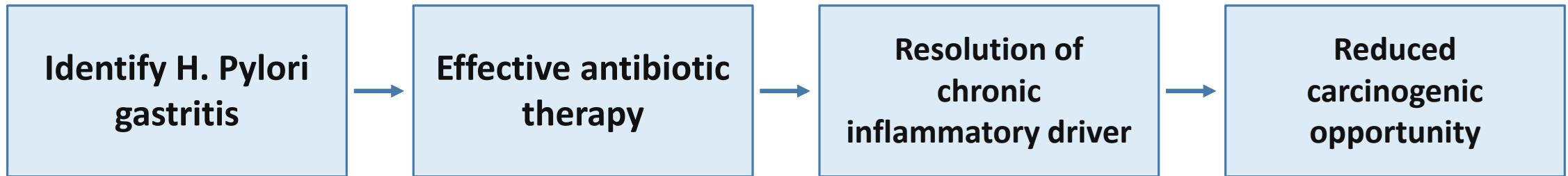
### Gastric MALT lymphoma

- Lymphoid malignancy
- Also associated with persistent H. Pylori gastritis

One inflammatory setting may be linked to different tumor lineages.

# Removing H. Pylori targets an upstream risk state

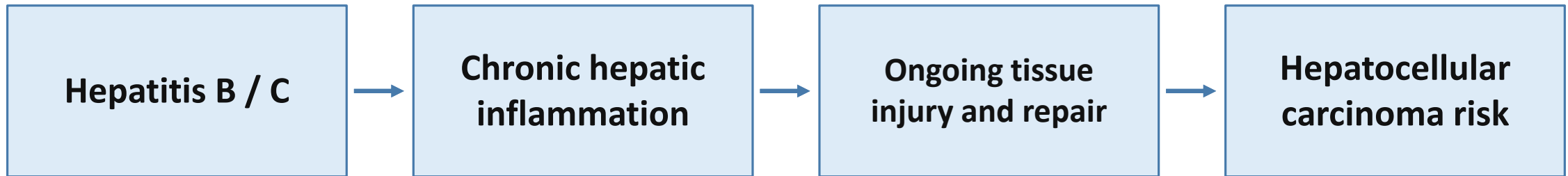
Schematic — risk pathway



- The textbook uses eradication as a prevention example.
- Treatment of inflammation is not treatment of an already established malignancy.

# Chronic viral hepatitis predisposes to liver cancer

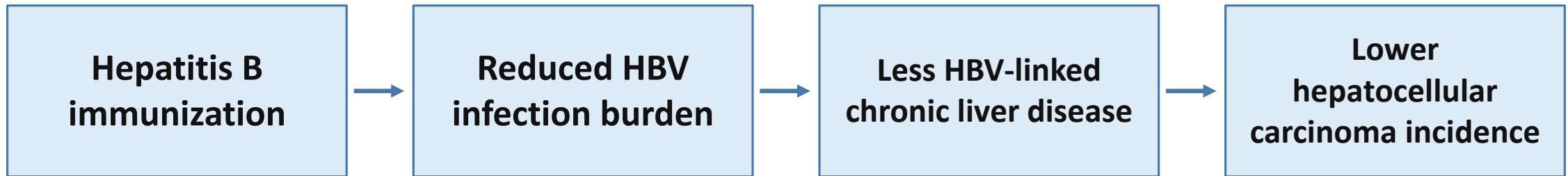
Schematic — risk pathway



- The source table links chronic hepatitis with hepatocellular carcinoma.
- Other pathogen-specific pathways are outside the source excerpt's scope.

# Hepatitis B vaccination is cancer prevention

Schematic — risk pathway



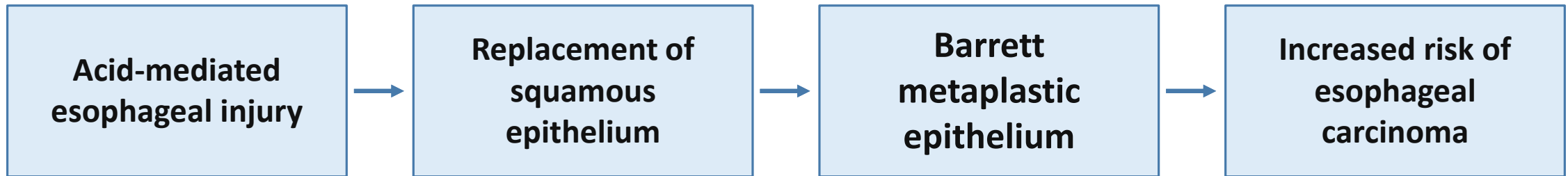
- Robbins explicitly reports a significant decrease in hepatocellular carcinoma following HBV vaccination.
- Preventing the causative infection interrupts an upstream carcinogenic route.

# Inflammatory bowel disease and colorectal cancer

- Inflammatory bowel disease is associated with colorectal carcinoma.
- The relevant pathology is persistent intestinal mucosal inflammation.
- Repeated epithelial injury and regeneration help explain the association.
- A cancer-risk association does not imply that every patient develops carcinoma.

# Reflux injury and Barrett esophagus

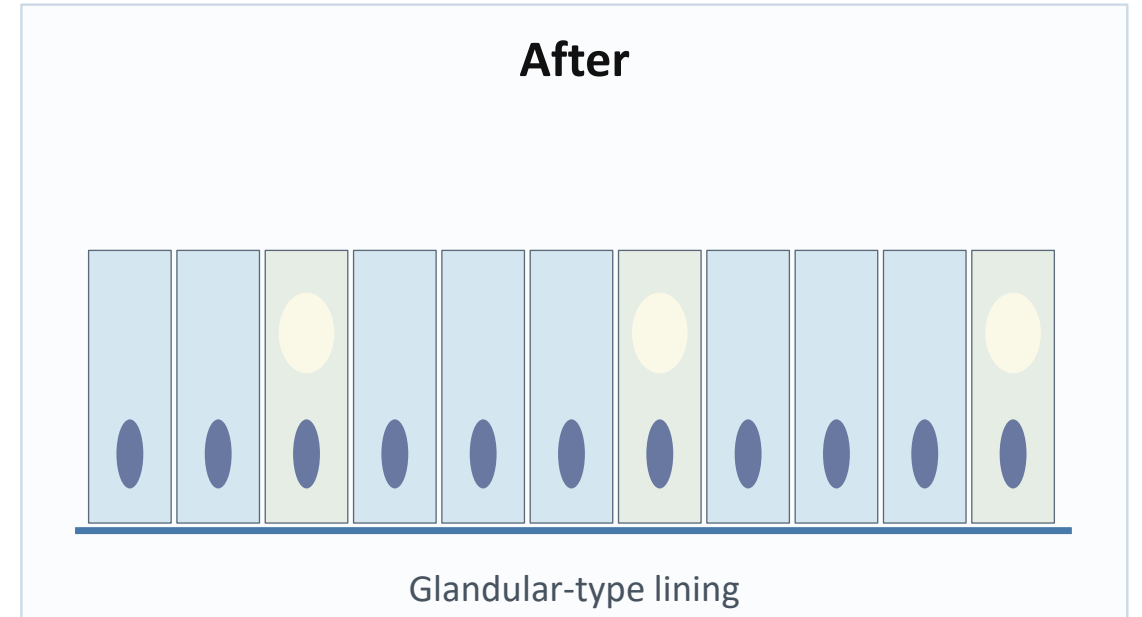
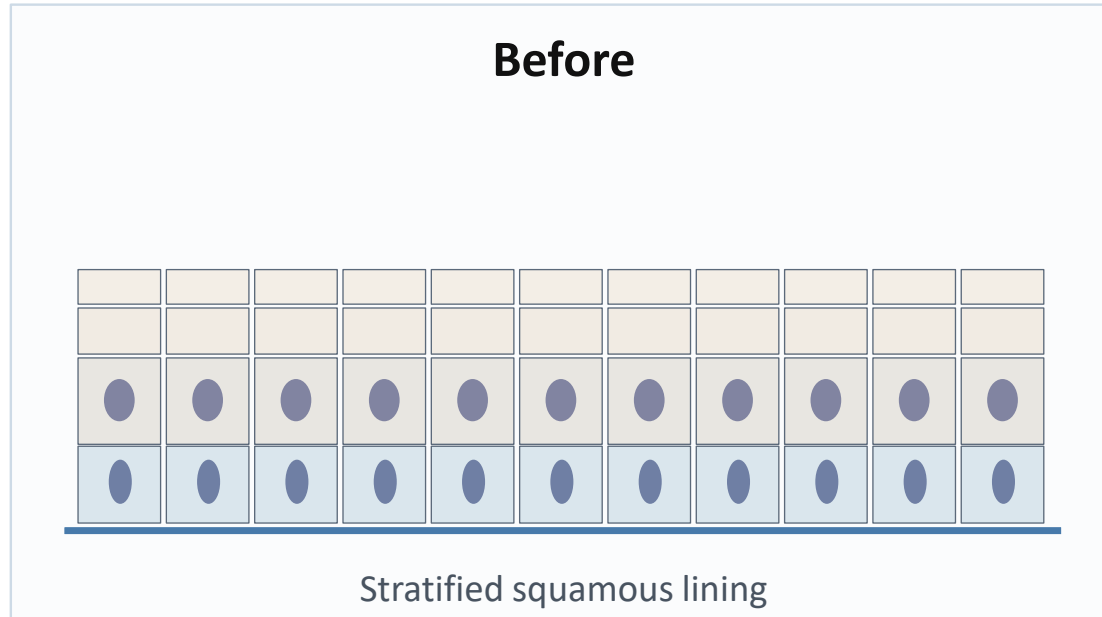
Schematic — risk pathway



- Barrett esophagus illustrates an overlap between inflammation and a precursor lesion.
- The metaplastic change is adaptive but occurs within an at-risk clinical setting.

# Barrett change is an epithelial substitution

Schematic — not a histologic specimen



- Esophageal stratified squamous cells are replaced by glandular epithelium.
- The new lining is better suited to chronic acid exposure.
- Metaplasia itself does not prove dysplasia.

# Autoimmune inflammation may precede lymphoma

## Sjögren syndrome

- Chronic autoimmune salivary-gland inflammation
- Associated extranodal marginal zone lymphoma

## Hashimoto thyroiditis

- Chronic autoimmune thyroid inflammation
- Associated extranodal marginal zone lymphoma

The MALT lymphoma association is different from the epithelial carcinoma pattern.

# Pancreas and gallbladder: Persistent injury

## Pancreatitis

- Chronic pancreatic inflammatory disease
- Associated pancreatic carcinoma

## Chronic cholecystitis

- Persistent gallbladder inflammation
- Associated gallbladder carcinoma

**The two organs illustrate inflammation-associated epithelial malignancy.**

# Chronic vulvar and draining-sinus disease

## Lichen sclerosis

- Chronic inflammatory vulvar dermatosis
- Associated vulvar squamous carcinoma

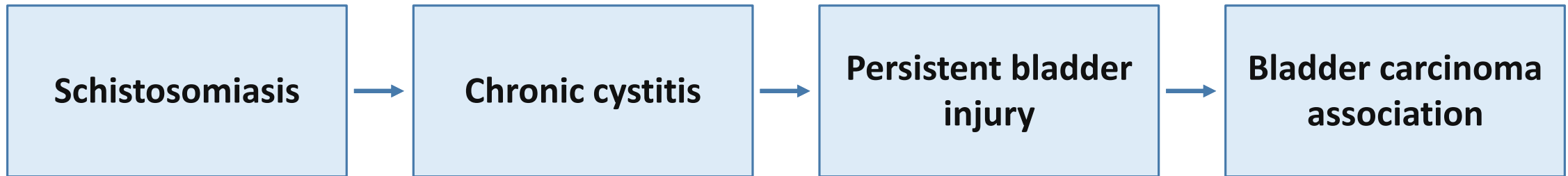
## Chronic osteomyelitis

- Long-standing draining sinus tract
- Carcinoma may arise in the draining tract

Site-specific chronic injury can create a local cancer-predisposing environment.

# Parasitic infection and urinary tract cancer

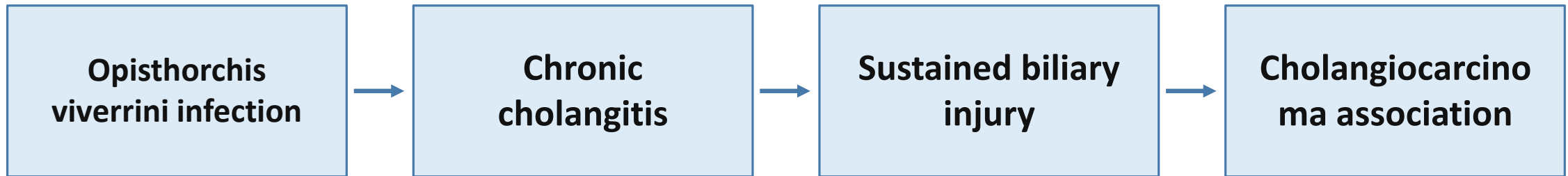
Schematic — risk pathway



- The source classifies this as a chronic inflammatory state associated with cancer.
- The table does not specify histologic subtype; Avoid assuming one here.

# Liver flukes and biliary tract malignancy

Schematic — risk pathway



- The relevant at-risk epithelium is the biliary lining.
- The source table links liver fluke–associated cholangitis to cholangiocarcinoma.

# Mineral particles: Distinguish associations

## Asbestos exposure

- Associated lung carcinoma
- Strong association with mesothelioma

## Silica-associated injury

- Silicosis linked to chronic lung injury
- Table groups silicosis with lung malignancy

**Do not infer that silica causes mesothelioma simply because a printed table groups particle injuries.**

# Inflammation-related associations are heterogeneous

## Epithelial sites

- Colon, stomach, esophagus
- Liver, pancreas, gallbladder
- Vulva and bladder

## Lymphoid sites

- Gastric MALT lymphoma
- Autoimmune-associated MALT lymphoma

## Other tumor tissue

- Mesothelioma in asbestos-associated settings
- Carcinoma from chronic draining sinus

# Interpret inflammatory associations carefully

- An epidemiologic association is not a diagnosis of neoplasia.
- Not every implicated exposure acts through inflammation alone.
- Underlying infections, repair, immune responses, and direct carcinogenic effects may coexist.
- Use source-specific rather than universal causal language.

# What defines a precursor lesion?

- Localized morphologic change identifies an epithelial field at increased risk.
- Hyperplasia, metaplasia, and dysplasia among the patterns.
- Some precursor lesions are benign neoplasms with nontrivial progression risk.
- A precursor designation is distinct from a diagnosis of invasive malignancy.

# Hyperplasia, metaplasia, and dysplasia

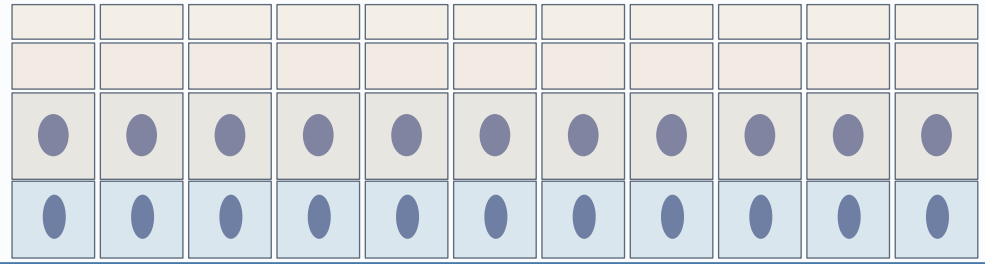
| Change      | Core morphologic idea                      | Interpretation                       |
|-------------|--------------------------------------------|--------------------------------------|
| Hyperplasia | Increase in epithelial cell number         | May reflect persistent trophic drive |
| Metaplasia  | One mature cell type replaced by another   | Adaptation to chronic injury         |
| Dysplasia   | Atypical cells and disordered architecture | Premalignant change                  |

**These are different tissue responses—not interchangeable diagnostic terms.**

# An at-risk field is defined morphologically

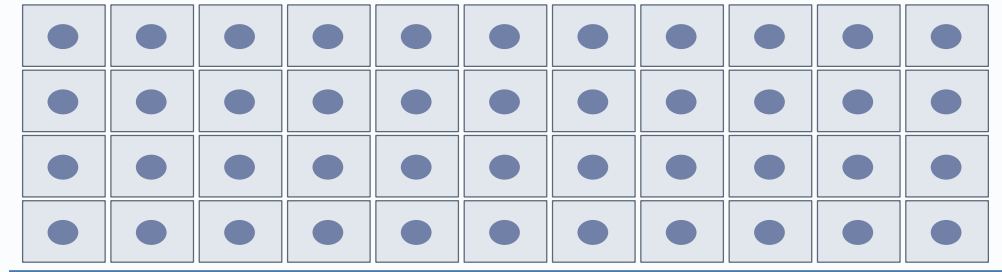
Schematic — not a histologic specimen

**Before**



Reference epithelium

**After**

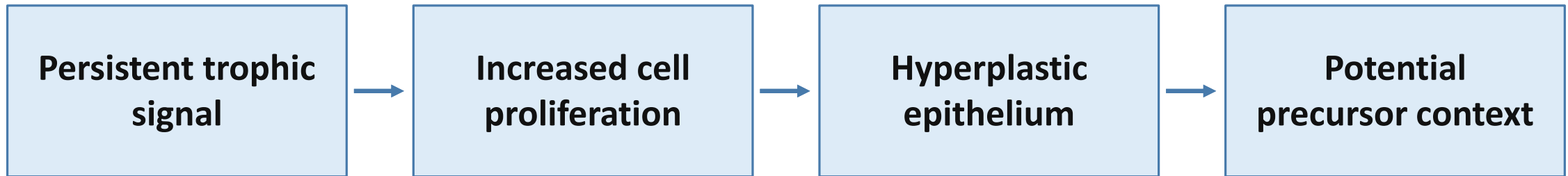


Expanded epithelial field

- The precursor change can involve a localized sheet of epithelium.
- Microscopic assessment identifies the change and its distribution.
- The field may persist without developing invasive carcinoma.

# Hyperplasia may follow sustained trophic stimulation

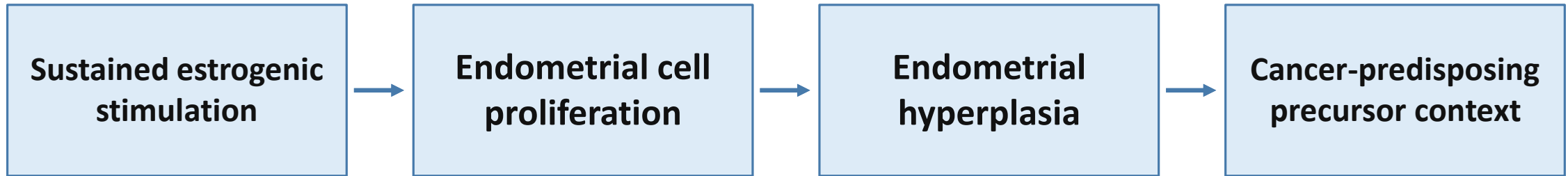
Schematic — risk pathway



- The source highlights prolonged growth stimulation as one cause of hyperplastic precursors.
- “Hyperplasia” by itself does not mean a premalignant lesion at every anatomic site.

# Endometrial hyperplasia illustrates hormonal drive

Schematic — risk pathway



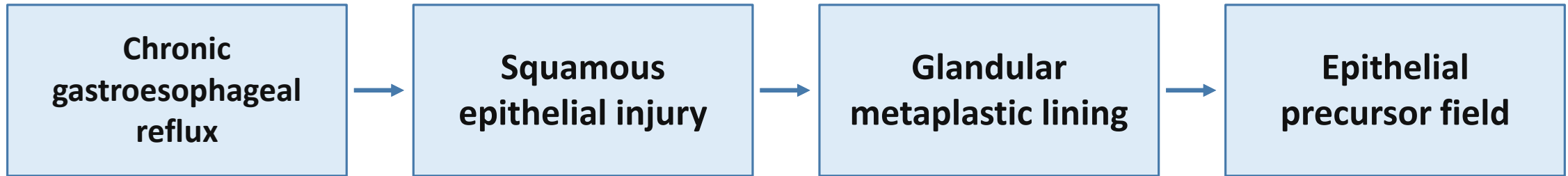
- This as a common hyperplastic precursor example.
- The source excerpt does not provide a histologic subclassification or numerical progression rates.

# Metaplasia is an adaptive substitution

- A differentiated epithelial cell type is replaced by another type.
- This generally occurs with ongoing damage, repair, and regeneration.
- The replacement lining can better withstand the chronic insult.
- Adaptation does not automatically imply dysplasia or carcinoma.

# Barrett esophagus connects adaptation and risk

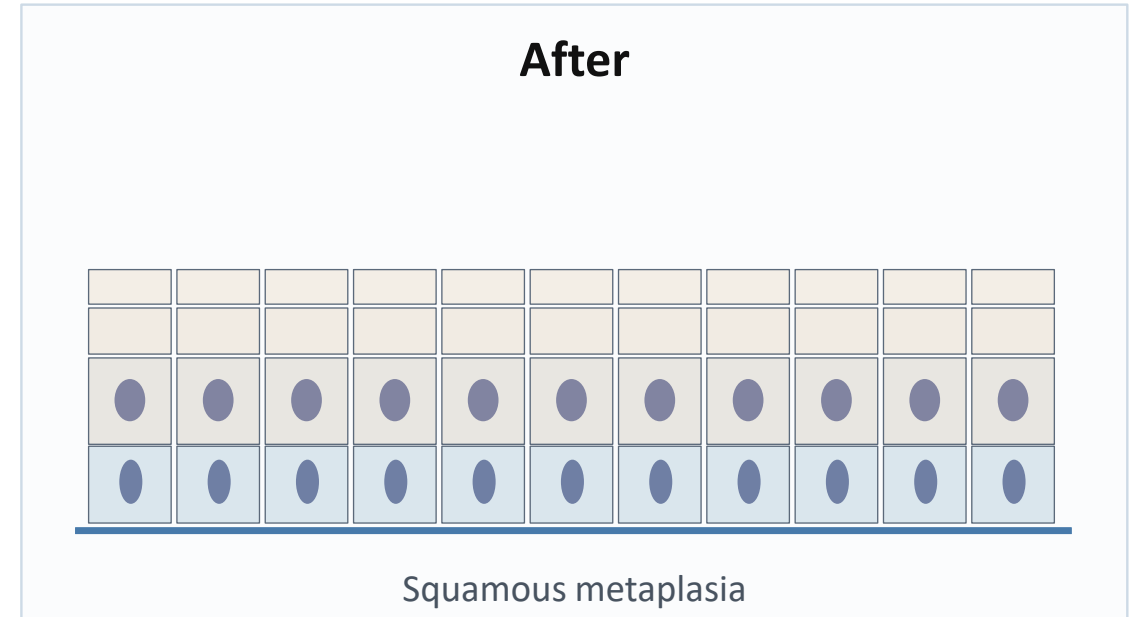
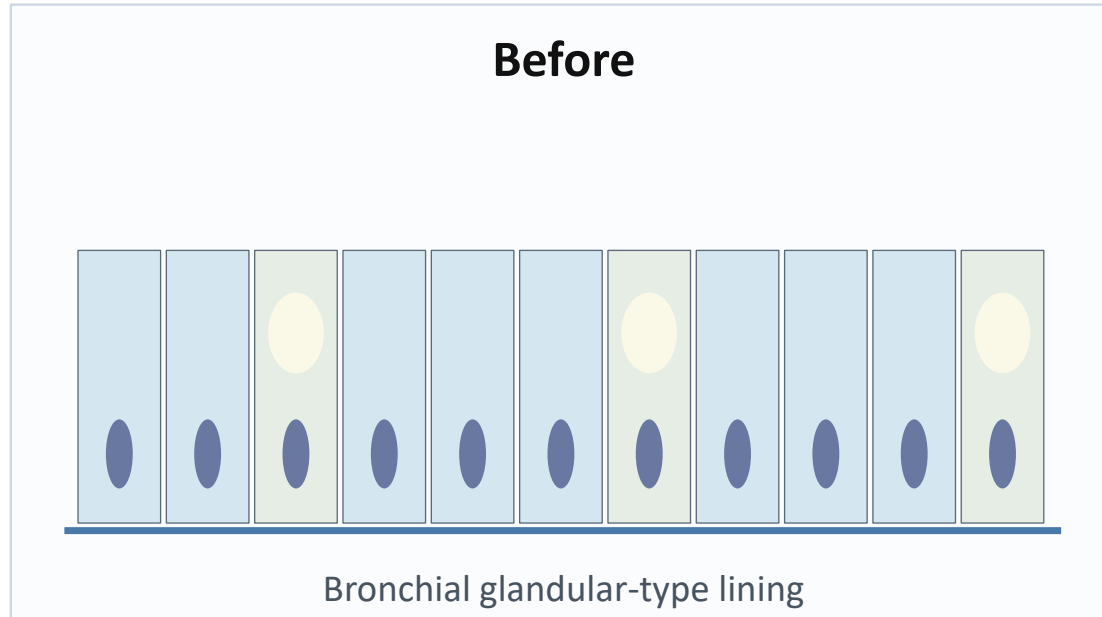
Schematic — risk pathway



- Glandular replacement of the normal squamous lining.
- Barrett esophagus is listed with reflux esophagitis among cancer-associated conditions.

# Bronchial squamous metaplasia: A second example

Schematic — not a histologic specimen



- Chronic tobacco smoke irritates bronchial glandular epithelium.
- The injured lining can be replaced by squamous epithelium.
- Morphologic adaptation need not be dysplastic.

# Metaplasia and dysplasia must not be conflated

## Metaplasia

- Changed epithelial differentiation
- Often adaptive to injury
- May lack cytologic atypia

## Dysplasia

- Loss of orderly maturation
- Nuclear atypia and disorganization
- Premalignant morphologic pattern

**Not all metaplastic epithelium is dysplastic.**

# Dysplasia: Cellular atypia

- Cellular pleomorphism is common.
- Nuclei may be enlarged and hyperchromatic.
- The nuclear-to-cytoplasmic ratio is increased.
- Mitotic activity may be greater than in normal epithelium.

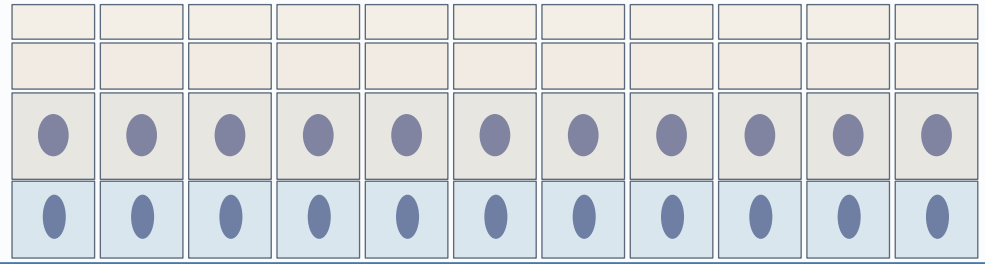
# Dysplasia: Disruption of tissue architecture

- Orderly maturation from basal to superficial epithelial layers is impaired.
- Basal-like atypical cells may extend toward the epithelial surface.
- Mitotic figures may occur outside the usual basal proliferative compartment.
- Cytologic changes should be integrated with architecture.

# Normal maturation versus epithelial dysplasia

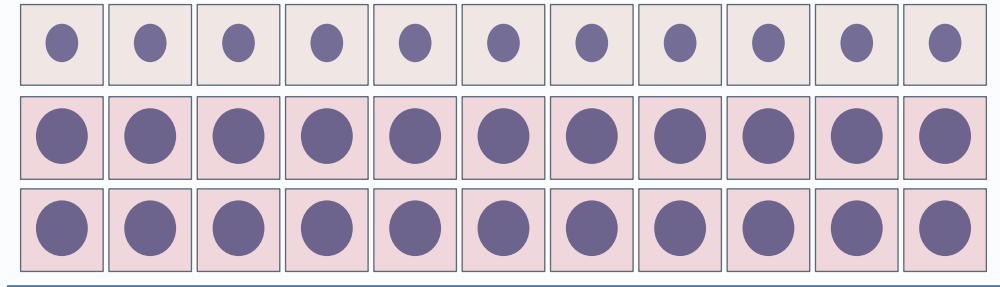
Schematic — not a histologic specimen

## Normal maturation



Basement membrane intact

## Epithelial dysplasia



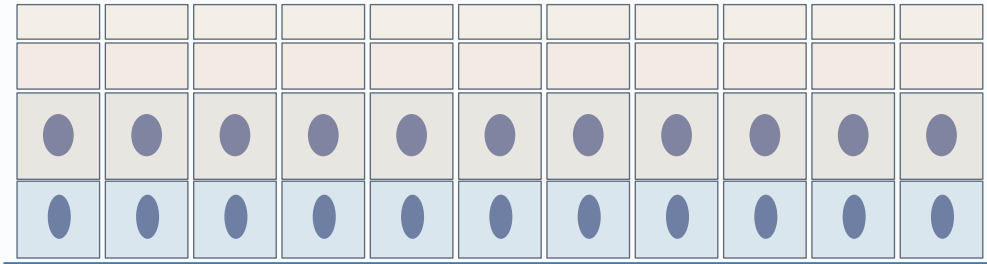
Basement membrane intact

- Normal squamous epithelium matures from basal cells toward the surface.
- Dysplasia loses this orderly gradient.
- Basement membrane integrity separates intraepithelial atypia from invasion.

# Carcinoma in situ has an intact basement membrane

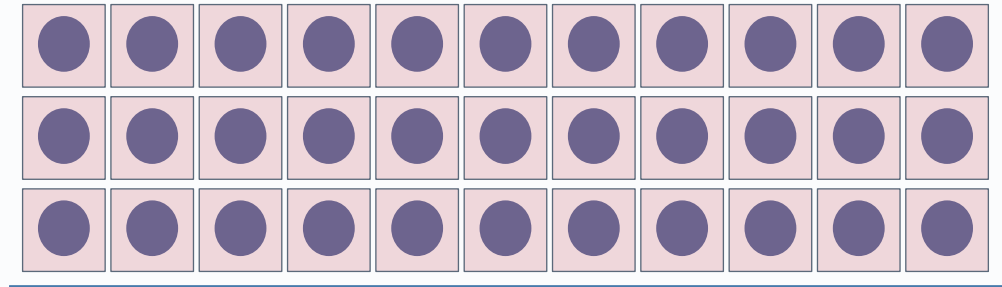
Schematic — not a histologic specimen

## Normal maturation



Basement membrane intact

## Carcinoma in situ

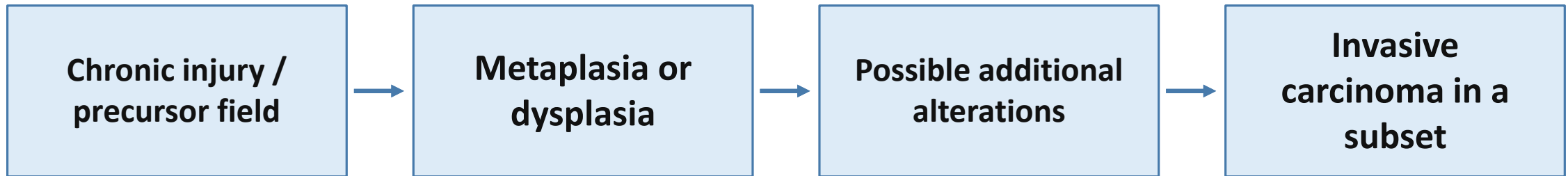


Basement membrane intact

- Severe dysplasia involves the full thickness of the epithelium.
- Atypical cells remain above an intact basement membrane.
- Stromal invasion is absent by definition.

# Morphologic progression is not inevitable

Schematic — risk pathway



- Dysplasia can precede invasive cancer, but progression is not assured.
- Some dysplastic changes regress after removal of inciting causes.

# Dysplasia may regress after removing the cause

## Possible regression

- Elimination of inciting injury
- Restoration of more normal architecture
- Moderately severe dysplasia may reverse

## Possible persistence / progression

- Abnormal clone may persist
- Additional changes can accumulate
- Carcinoma in situ may remain noninvasive for years

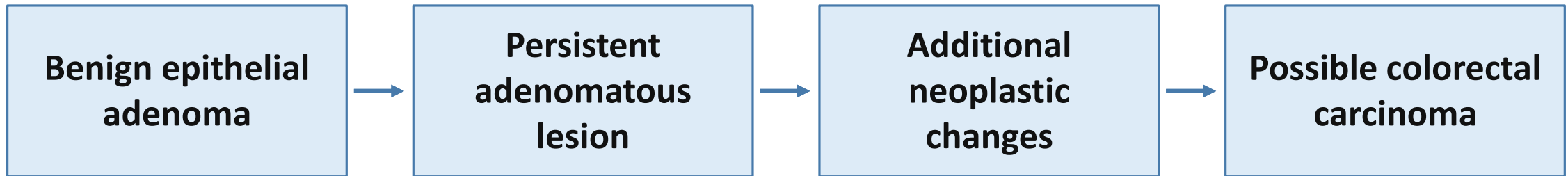
**Natural history depends on context; A single observation cannot predict every outcome.**

# Benign neoplasms are not uniformly precancerous

- Some benign tumors are clinically important cancer precursors.
- Most benign tumors undergo malignant transformation rarely.
- Some, such as lipomas, are not described as transforming into malignancy.
- Risk depends on the specific lesion, not just the word “benign.”

# Colonic villous adenoma: A recognized precursor

Schematic — risk pathway



- The colonic villous adenoma as a classic precursor.
- Adenoma is a neoplasm; It is not synonymous with invasive carcinoma.

## The textbook's villous-adenoma risk estimate

- About 50% of untreated colonic villous adenomas progress to cancer.
- The statement is specific to the example and its untreated context.
- Do not apply the percentage to all adenomas or all benign neoplasms.
- The source excerpt gives no follow-up duration or risk stratification.

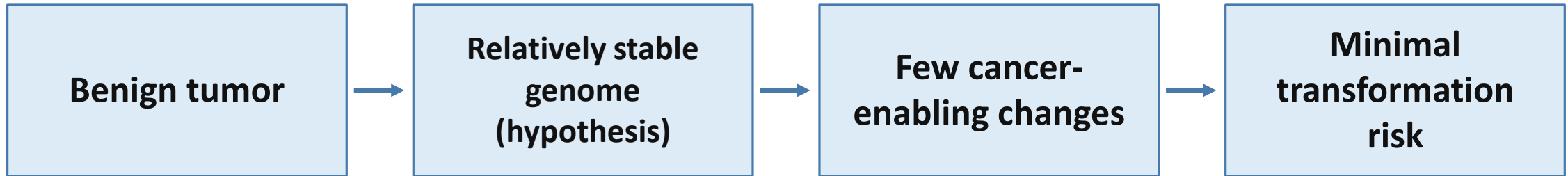
# Low transformation risk: Contrasting tumors

| Benign lesion           | How Robbins characterizes transformation         |
|-------------------------|--------------------------------------------------|
| Colonic villous adenoma | Substantial risk if untreated (specific example) |
| Uterine leiomyoma       | Malignant transformation rare                    |
| Pleomorphic adenoma     | Malignant transformation rare                    |
| Lipoma                  | No malignant transformation described            |

**“Benign” alone is inadequate to estimate future malignant potential.**

# Why do most benign tumors remain benign?

Schematic — risk pathway



- Robbins explicitly calls the explanation unresolved.
- Lack of genomic instability is offered as a possibility—not an established universal rule.

# Precursor lesion versus established malignancy

| Feature           | Precursor field / lesion                               | Invasive carcinoma                      |
|-------------------|--------------------------------------------------------|-----------------------------------------|
| Morphology        | Hyperplasia, metaplasia, dysplasia or selected adenoma | Invasive malignant neoplasm             |
| Basement membrane | Not invaded by a precursor in situ process             | May be penetrated in invasive carcinoma |
| Outcome           | Progression may not occur                              | Cancer is already present               |

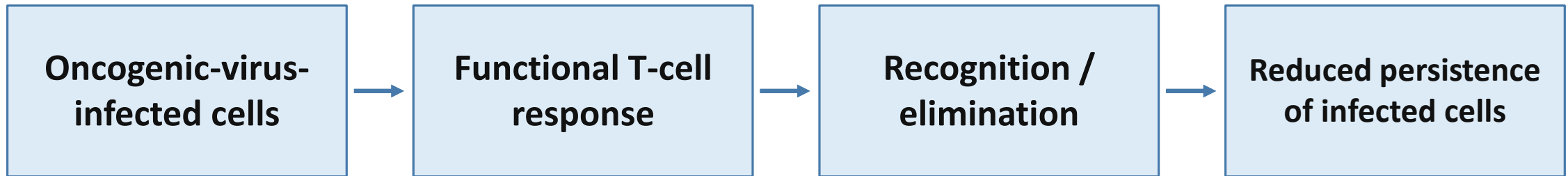
**Risk assessment and detection of an invasive tumor answer different clinical questions.**

# Immunodeficiency is a distinct risk mechanism

- Cancer risk is increased in immunodeficient patients.
- Deficient T-cell immunity is particularly implicated.
- Weak immune responses may fail to eliminate virus-infected cells.
- Immunodeficiency predisposes especially to oncogenic-virus-related tumors.

# T-cell surveillance limits virus-infected cells

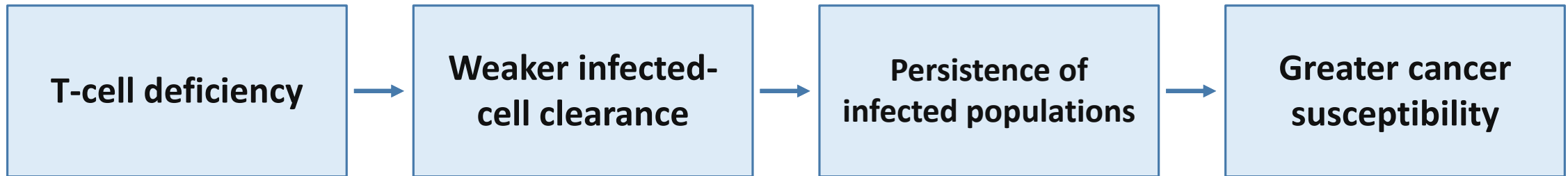
Schematic — risk pathway



- The protective mechanism is expressed in the source as a presumed explanation.
- Failure of this control makes virus-associated neoplasms more likely.

# What changes when immune control is lost?

Schematic — risk pathway



- The pathway concerns host surveillance rather than only epithelial proliferation.
- Exact viruses and named tumor subtypes are discussed elsewhere.

# Cancer phenotypes in immunodeficiency

## Lymphomas

- Prominent virus-associated tumor category
- Can arise during weakened immune surveillance

## Carcinomas

- Some carcinomas become more frequent
- Risk depends on oncogenic context

## Sarcomas / proliferations

- Some sarcomas and sarcoma-like lesions
- Not all are epithelial tumors

# Inflammation and immunodeficiency act differently

| Mechanism              | Inflammatory state              | Immunodeficiency                          |
|------------------------|---------------------------------|-------------------------------------------|
| Primary setting        | Repeated injury and repair      | Reduced antiviral immune control          |
| Cellular emphasis      | Proliferating injured tissue    | Persisting virus-infected cells           |
| Characteristic outcome | Many carcinomas; some lymphomas | Virus-linked tumors, especially lymphomas |

**Both increase susceptibility, but they should not be taught as one identical pathway.**

# Application: Immune-suppressed host

Teaching vignette — hypothetical

A patient with marked T-cell immune dysfunction develops a new lymphoid mass. No diagnosis has yet been established.

**Which acquired cancer-predisposing mechanism best explains the increased concern?**

Interpretation

Impaired control of oncogenic-virus-infected cells; A lymphoma is a relevant tumor category. Tissue diagnosis remains necessary.

# Acquired and inherited susceptibility interact

## Acquired background

- Inflammation and exposures
- Infectious or chemical effects

## Inherited background

- Germline susceptibility variants
- May modify response to exposure

## Observed cancer risk

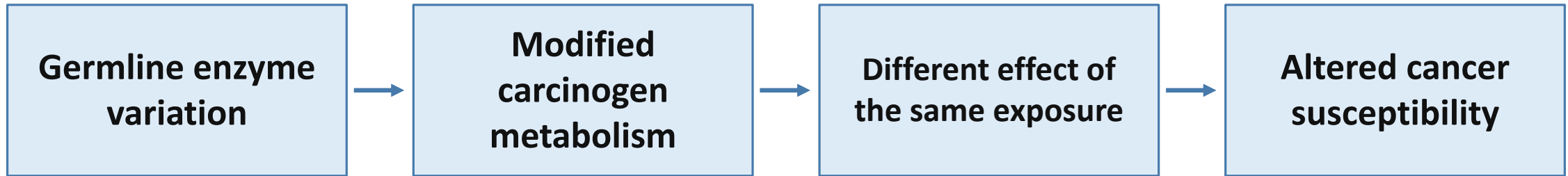
- Reflects both classes of influence
- Often cannot be neatly partitioned

# A negative family history does not exclude heredity

- Most cancers are sporadic rather than familial.
- Absence of a family history does not exclude inherited contributions.
- Germline susceptibility and acquired risk conditions can coexist.
- Complex traits are difficult to allocate to one causal category.

# Genetic context changes exposure-related risk

Schematic — risk pathway



- Cytochrome P-450 variation as an example.
- A P-450 variant is discussed in relation to smoking-induced lung cancer.

## BRCA susceptibility also depends on context

- Inherited BRCA1/BRCA2 alterations convey an important genetic susceptibility.
- Historical birth-cohort differences in breast cancer risk among carriers.
- Changing reproductive histories are suggested as one explanation.
- This illustrates environmental modification of inherited risk rather than a universal numerical estimate.

## Risk assessment should identify the pathway

| History / lesion            | Predisposing pathway                        | Illustrative cancer concern       |
|-----------------------------|---------------------------------------------|-----------------------------------|
| Chronic H. pylori gastritis | Infectious chronic inflammation             | Gastric carcinoma / MALT lymphoma |
| Barrett metaplasia          | Inflammation and epithelial precursor field | Esophageal carcinoma              |
| Endometrial hyperplasia     | Sustained trophic stimulation               | Endometrial neoplasia risk        |
| T-cell deficiency           | Reduced immune surveillance                 | Virus-related tumors              |

**The mechanism, tissue, and morphology should be specified—not simply “high cancer risk.”**

# Prevention targets an upstream risk mechanism

## Treat infection

- H. Pylori antibiotic eradication
- Removes persistent gastric inflammatory stimulus

## Prevent infection

- Hepatitis B vaccination
- Reduces downstream hepatocellular carcinoma

## Remove injury

- End inciting source where feasible
- Some dysplastic changes may regress

# Application: Two pathways in one patient

Teaching vignette — hypothetical

A patient with chronic gastroesophageal reflux develops a glandular lining in the distal esophagus; No atypia is identified.

**What is the morphologic response, and why does the setting matter?**

Interpretation

Barrett-type metaplasia: An adaptive epithelial substitution within an inflammation-associated cancer-risk setting; Dysplasia cannot be assumed.

# Application: Precursor $\neq$ carcinoma

Teaching vignette — hypothetical

A colonic biopsy contains adenomatous epithelium, with no evidence of stromal invasion in the submitted sample.

**Does the lesion represent cancer, a precursor, or neither?**

Interpretation

A benign epithelial neoplasm that can serve as a cancer precursor. The biopsy does not establish invasive carcinoma.

# Integrating the three major mechanisms

## Chronic inflammation

- Repeated tissue repair
- ROS-related DNA injury
- Pro-survival signaling

## Precursor lesions

- Recognizable epithelial fields
- Variable natural history
- Some reversible changes

## Immunodeficiency

- Impaired T-cell surveillance
- Virus-infected cells may persist
- Lymphomas and other cancers

## Five distinctions to retain

- Increased cancer risk is not equivalent to cancer.
- Inflammation may act through regeneration, DNA injury, and cell survival.
- Metaplasia is not the same lesion as dysplasia.
- An intact basement membrane excludes invasion in carcinoma in situ.
- Immune deficiency promotes malignancy through deficient host surveillance.

# Primary reference

## Primary source

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition.
- Neoplasia: acquired predisposing conditions; precursor-lesion morphology; cancer epidemiology.