

Smoking and Lung Cancer

Carcinogenic exposures • molecular injury • tumor evolution • clinicopathologic correlation

Pathology teaching lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Link tobacco exposure to lung carcinogenesis through metabolic activation, DNA adducts and acquired mutations.
- Explain exposure–response relationships, susceptibility, co-exposures and the residual risk after cessation.
- Compare tobacco-associated lung-carcinoma phenotypes and their major precursor lesions.
- Apply pathological reasoning to clinical scenarios without confusing exposure with a tumor diagnosis.

Two complementary Robbins perspectives

CONTEXT A

- Tobacco as an environmental carcinogen
- Smoke chemistry, exposure intensity and DNA injury
- Exposure interactions with occupational carcinogens

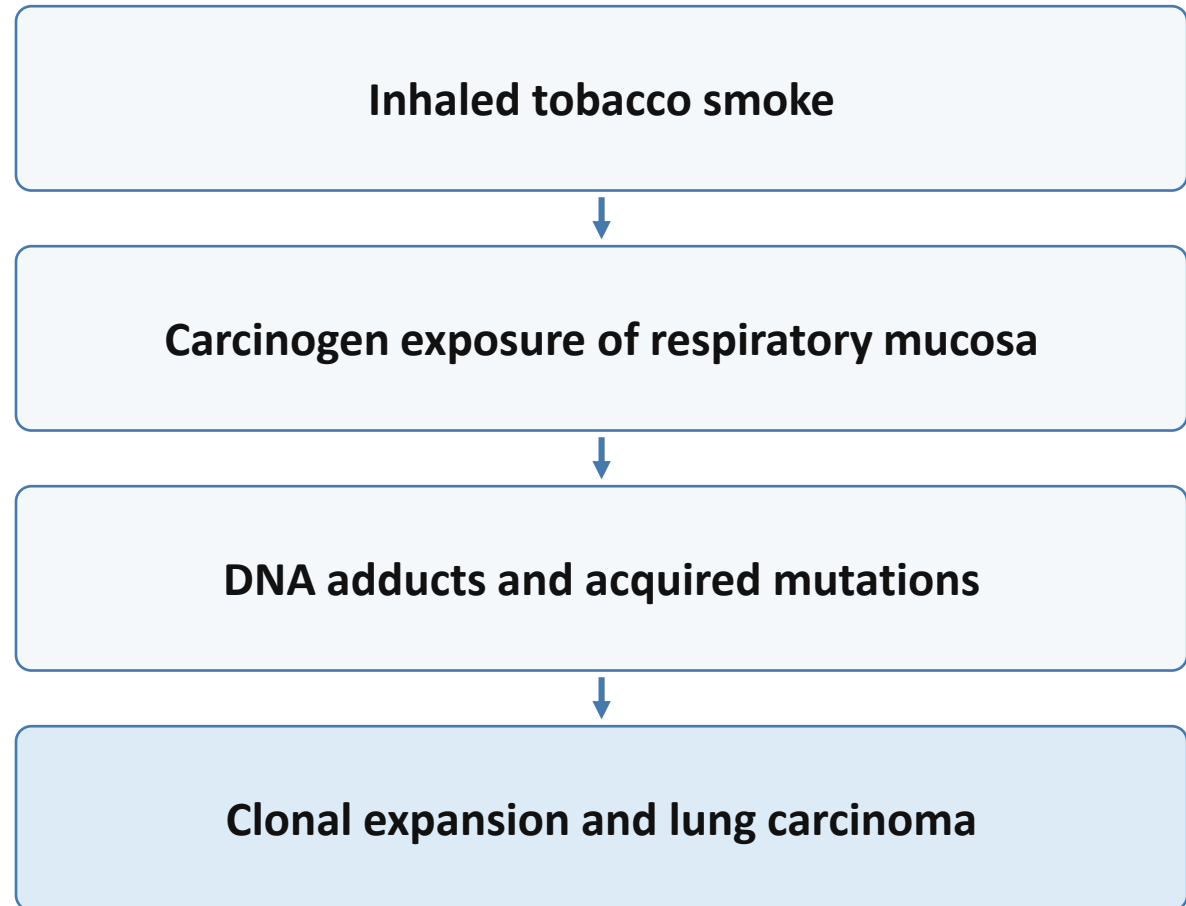
CONTEXT B

- Lung carcinoma as the clinical outcome
- Acquired driver alterations and precursor lesions
- Histologic categories, morphology and consequences

A mechanistic argument for causation

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.



Schematic — The sequence is a conceptual path; Cancer is not inevitable after any particular exposure.

Tobacco smoke contains many distinct hazards

- Approximately 7,000 constituents in tobacco smoke.
- More than 60 constituents are identified as carcinogens.
- Different constituents produce DNA injury, mucosal irritation, ciliary toxicity or impaired oxygen transport.
- These mechanisms must not be collapsed into a single “smoke toxin.”

Selected smoke constituents: Distinct effects

Constituent	Principal effect described in Robbins
Polycyclic aromatic hydrocarbons	Carcinogenesis
Benzo[a]pyrene	Carcinogenesis
Nitrosamines	Carcinogenesis
Phenol	Tumor promotion; mucosal irritation
Formaldehyde / nitrogen oxides	Ciliary toxicity; mucosal irritation
Carbon monoxide	Impaired oxygen transport and utilization

Airway irritation is not equivalent to cancer

CONTEXT A

- Irritant effect on tracheobronchial mucosa
- Increased mucus production
- Bronchitis and mucociliary dysfunction

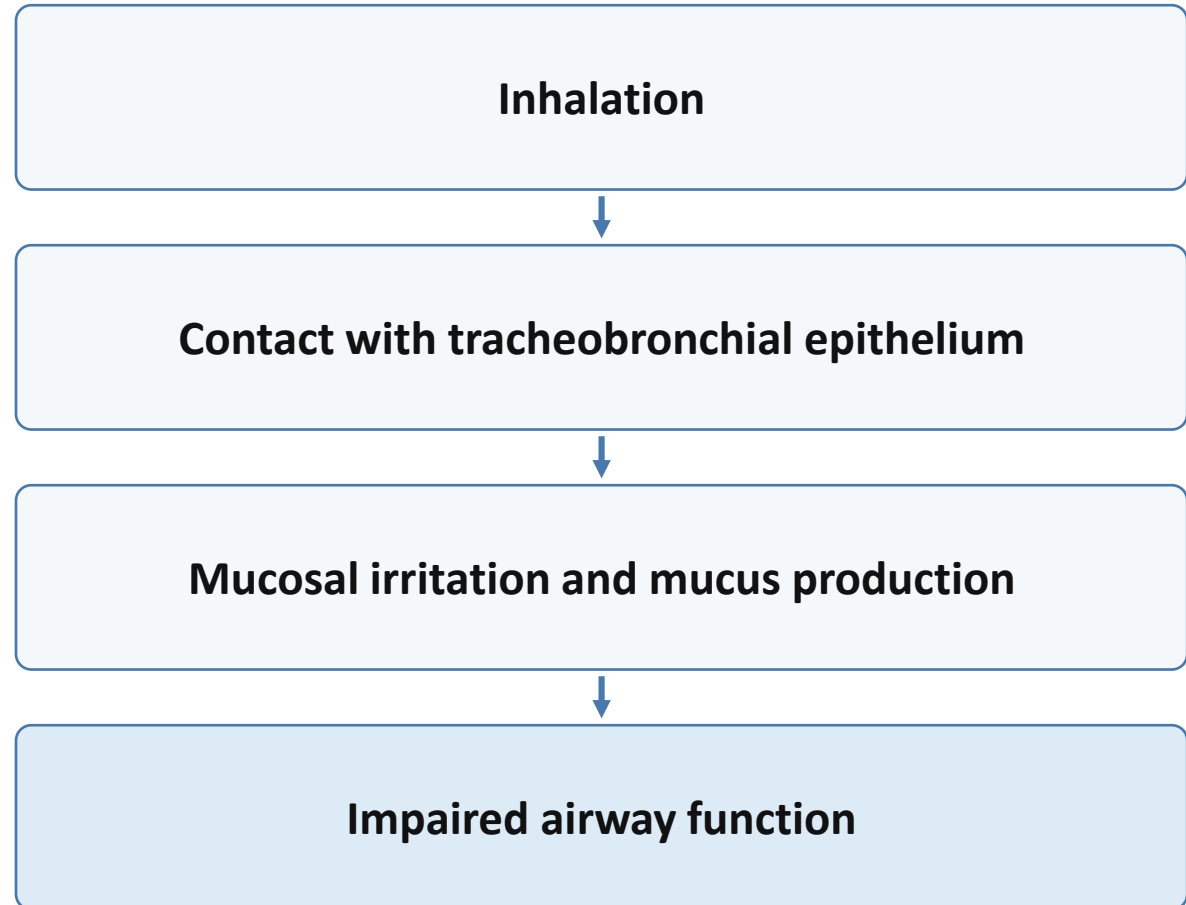
CONTEXT B

- Chemical bioactivation
- Electrophilic DNA-reactive intermediates
- Mutations that may contribute to malignant transformation

Chemical injury begins at the airway surface

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.



Schematic — Parallel to, not synonymous with, the pathway that produces oncogenic mutations.

Direct and secondhand smoke both matter

- Active smokers inhale a complex mixture of chemicals produced during tobacco combustion.
- Environmental (secondhand) smoke exposes nonsmokers to carcinogens.
- Robbins explicitly connects passive inhalation with lung cancer in nonsmokers.
- No safe secondhand-smoke exposure level is asserted in the pulmonary carcinoma discussion.

Nicotine: Dependence and promotion, not the whole causal story

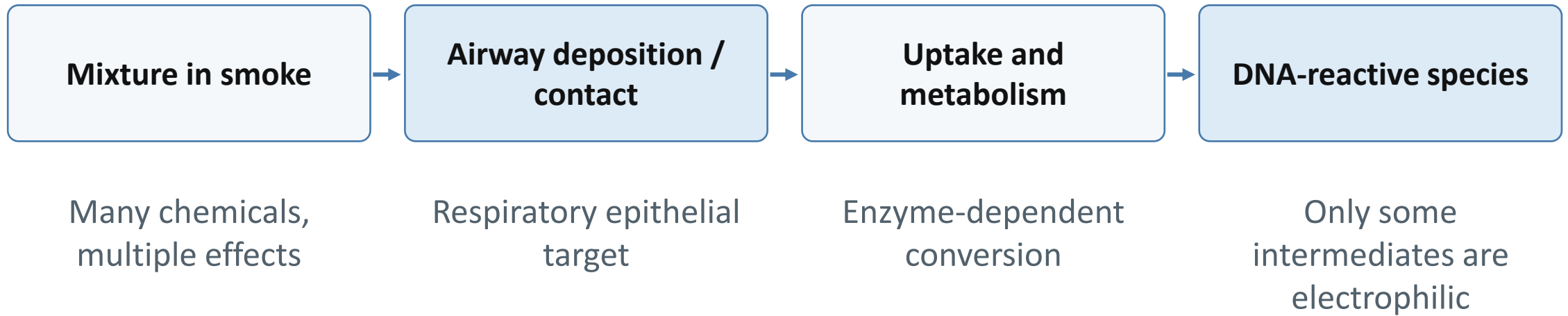
CONTEXT A

- Nicotine is strongly addictive.
- Nicotinic receptors and catecholamine release help explain acute physiological effects.
- Tumor promotion among nicotine-related effects.

CONTEXT B

- Major carcinogenic exposures include polycyclic aromatic hydrocarbons and tobacco nitrosamines.
- DNA-reactive metabolites directly explain a central mutagenic pathway.
- Nicotine exposure cannot substitute for an inventory of smoke carcinogens.

From inhaled compounds to cellular exposure



Schematic — conceptual stages, not a diagnostic specimen.

Procarcinogens require biological activation

- Some chemicals in cigarette smoke are metabolized by cytochrome P450 (CYP) enzymes.
- Metabolism can generate intermediates with greater water solubility.
- Phase II enzyme pathways contribute to the handling and excretion of xenobiotics.
- However, CYP processing can also yield electrophilic, DNA-reactive species.

Detoxification and bioactivation are competing outcomes

CONTEXT A

- Metabolic handling
- Increased water solubility
- Facilitated elimination

CONTEXT B

- Electrophilic intermediate formation
- Chemical attack on cellular DNA
- Potential fixation of mutations

The critical DNA-adduct pathway

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.

CYP-mediated conversion



Electrophilic intermediate



Covalent DNA adduct



Imperfect repair → mutation

Schematic — Specific chemical intermediates depend on the smoke constituent; This is a generalized pathway.

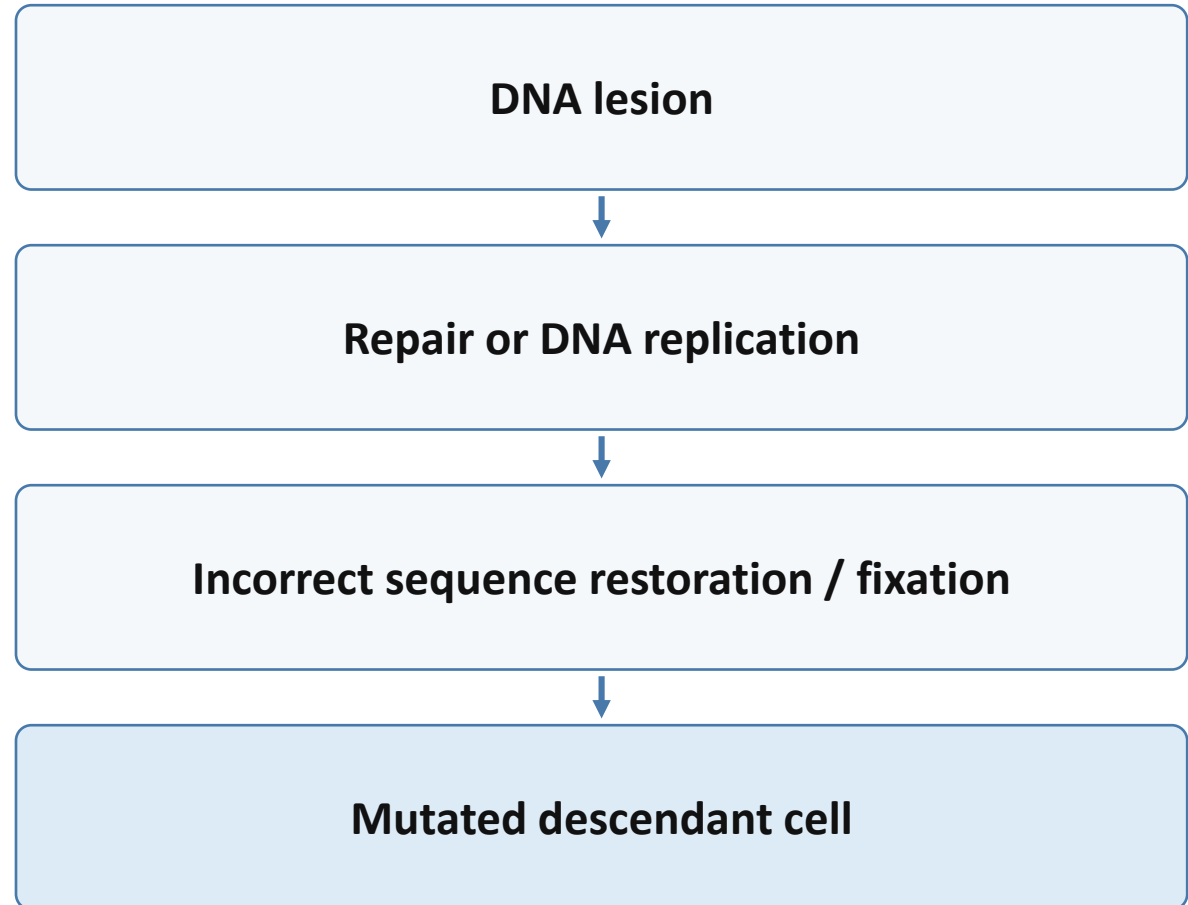
What is a DNA adduct?

- An adduct forms when a reactive chemical species covalently binds to DNA.
- The altered template can interfere with faithful copying or repair.
- Error-prone processing can convert chemical damage into a stable sequence mutation.
- Not every adduct persists or produces an oncogenic driver event.

How damage becomes a permanent mutation

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.



Schematic — The diagram shows a possible causal route; Accurate repair may prevent mutation.

DNA damage is not the same as a driver mutation

CONTEXT A

- DNA damage: Chemical lesion in a molecule
- May be repaired correctly
- May never be inherited by daughter cells

CONTEXT B

- Mutation: Persistent sequence alteration
- Can be propagated during cell division
- Only a subset promotes malignant growth

Genomic sequencing provides mechanistic corroboration

- Lung cancers arising in smokers often contain thousands of somatic mutations.
- The mutation patterns include changes linked to tobacco carcinogens in experimental models.
- This connects the chemical exposure to molecular alterations within the tumors.
- Sequencing strengthens the causal inference; It does not prove every mutation is a driver.

The mutational landscape contains passengers and drivers

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.

Many smoke-related DNA lesions



Numerous acquired mutations



Selection of advantageous driver combinations



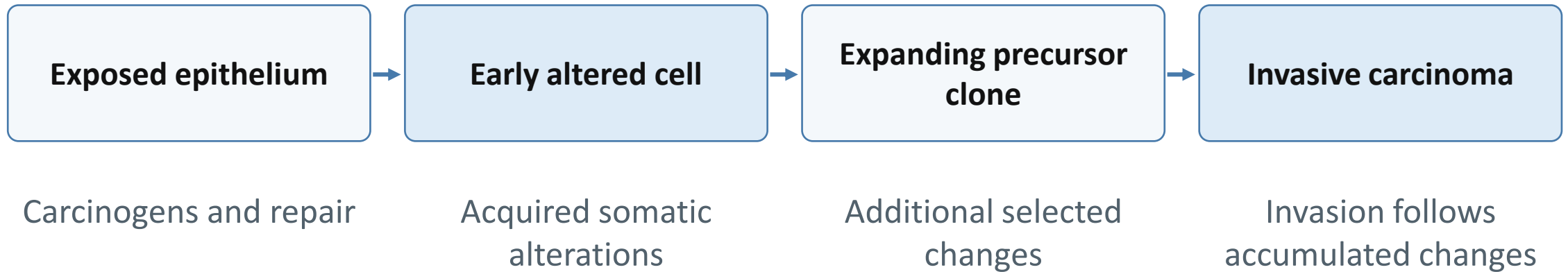
Malignant clone

Schematic — High mutation burden is not equivalent to high driver count.

Carcinogenesis requires more than one genetic event

- Stepwise accumulation of oncogenic driver alterations in lung carcinomas.
- Respiratory epithelial cells can acquire mutations before a tumor is apparent.
- Only cells with the relevant combination of functional changes acquire malignant capabilities.
- A long latency is compatible with multistep acquisition and selection.

A simplified timeline of tumor evolution



Schematic — conceptual stages, not a diagnostic specimen.

A field of altered epithelium may remain after quitting

- That genetic changes predating lung cancer may persist in bronchial epithelium for years.
- Macroscopically normal mucosa may already harbor acquired abnormalities.
- This helps explain why cancer risk decreases slowly after smoking cessation.
- Persistence of field changes does not imply that every altered cell becomes malignant.

Why do many smokers never develop lung cancer?

CONTEXT A

- Total carcinogen dose and duration differ.
- Random acquisition and survival of driver combinations differ.
- Individuals differ in chemical activation.

CONTEXT B

- DNA damage responses and repair capacity vary.
- Interactions with additional exposures vary.
- Smoking is highly causal but not deterministically sufficient.

Cytochrome P450 polymorphism modifies susceptibility

- Polymorphic P450 monooxygenase enzymes.
- Some genetic variants convert procarcinogens into active carcinogens more efficiently.
- Smokers carrying such variants may incur greater lung-cancer risk.
- These observations support gene–environment interaction, not simple Mendelian inheritance.

Gene–environment interaction in chemical activation

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.

Comparable tobacco exposure



Different CYP activation capacity



Different burden of reactive metabolites



Different probability of DNA injury

Schematic — This is a directional explanatory schematic; No numerical risks are implied.

Variation in DNA repair also modifies risk

- A mutagen-sensitivity phenotype measured by chromosomal breakage after carcinogen exposure.
- Higher sensitivity was associated with substantially increased lung-cancer risk in the cited comparisons.
- This suggests inherited variation in processes limiting the consequences of DNA injury.
- Such research phenotypes are not presented as routine clinical diagnostic tests.

Dose and duration both influence lung-cancer risk

- Lung-cancer occurrence to cumulative cigarette exposure.
- In general, higher exposure is associated with higher risk.
- Comparisons must distinguish cigarettes per day, years smoked and calculated pack-years.
- An exposure–response pattern is an important epidemiologic pillar of causal inference.

Pack-years summarize cumulative smoking exposure

$$\text{Pack-years} = \text{packs smoked per day} \times \text{years smoked}$$

1 pack/day $\times$ 20 years

20 pack-years

2 packs/day $\times$ 20 years

40 pack-years

$\frac{1}{2}$ pack/day $\times$ 40 years

20 pack-years

Same pack-years can represent different smoking histories; Cumulative dose does not encode every exposure feature.

Exposure metrics answer different questions

CONTEXT A

- Cigarettes per day: Intensity
- Duration in years: Temporal exposure
- Pack-years: Rough cumulative index

CONTEXT B

- Never versus ever smoked: Category
- Current versus former: Cessation status
- Secondhand exposure: Environmental exposure history

Heavy exposure carries a particularly high relative risk

- Robbins gives a 60-fold elevation in lung-cancer risk for habitual heavy smokers compared with nonsmokers.
- The example exposure is two packs daily for 20 years.
- This is a comparison reported by the textbook, not an individual probability.
- Absolute risk, relative risk and proportion of cases attributable to smoking are different measures.

Three common epidemiologic denominators

CONTEXT A

- Risk among exposed people: “How likely is disease?”
- Relative risk: “Compared with whom?”
- Attributable fraction: “How much disease is caused by the exposure?”

CONTEXT B

- Proportion of cases with smoking history: “Who has the disease?”
- Proportion of smokers who develop cancer: “Who becomes ill?”
- These quantities must not be interchanged.

Smoking is causal, but lung cancer is not exclusive to smokers

- Smoking is the most important environmental risk factor in the supplied Robbins sections.
- Not all exposed persons develop a malignancy.
- Some lung cancers arise in never-smokers.
- The phenotype and molecular profile of lung cancer are partly associated with exposure history.

Cessation lowers risk but does not erase prior exposure

During smoking



Ongoing contact with multiple carcinogens

After cessation



Further tobacco-smoke exposure stops

Subsequent years



Lung-cancer risk declines relative to continued smoking

Long term



Excess lung-cancer risk may persist for decades

A decline in risk is not equivalent to immediate normalization

- The tobacco section reports a fall in lung-cancer mortality after smoking cessation.
- The lung-carcinoma section emphasizes that risk may remain above never-smoker baseline.
- Persisting acquired mutations offer one biological explanation.
- Prevention and surveillance have different roles after quitting.

The synergistic context of occupational exposures

CONTEXT A

- Asbestos or uranium exposure independently increases lung-cancer risk.
- Tobacco adds another source of carcinogenic injury.
- Multiple processes can act upon the same airway or lung epithelium.

CONTEXT B

- The text reports markedly higher rates among exposed workers who smoke.
- Relative effects require a defined comparison group.
- Do not assume risks simply add or multiply without data.

Smoking and co-exposure: Comparisons

Exposure setting	Comparison described in source
Asbestos workers who never smoked	Higher lung-cancer risk than unexposed nonsmokers
Asbestos workers who smoked	Much greater elevation than asbestos exposure alone
Uranium miners who never smoked	Elevated risk relative to general population
Uranium miners who smoked	Further elevation over nonsmoking miners

The tobacco-specific lung carcinogens include several classes

- Robbins Table 9.4 identifies polycyclic aromatic hydrocarbons for lung and larynx.
- It also lists tobacco-specific nitrosamine NNK.
- Polonium-210 appears among the suspected lung carcinogens.
- “Suspected organ-specific” is the source table’s designation; The list is not exhaustive.

Mechanism-oriented exposure inventory

Source group	Biologic role
Polycyclic aromatic hydrocarbons	Chemical carcinogens; DNA injury following bioactivation
Tobacco nitrosamines (e.g., NNK)	Tobacco-associated chemical carcinogens
Polonium-210	Suspected lung carcinogen listed in Robbins
Irritants / ciliary toxicants	Airway injury; not interchangeable with DNA adduct formation

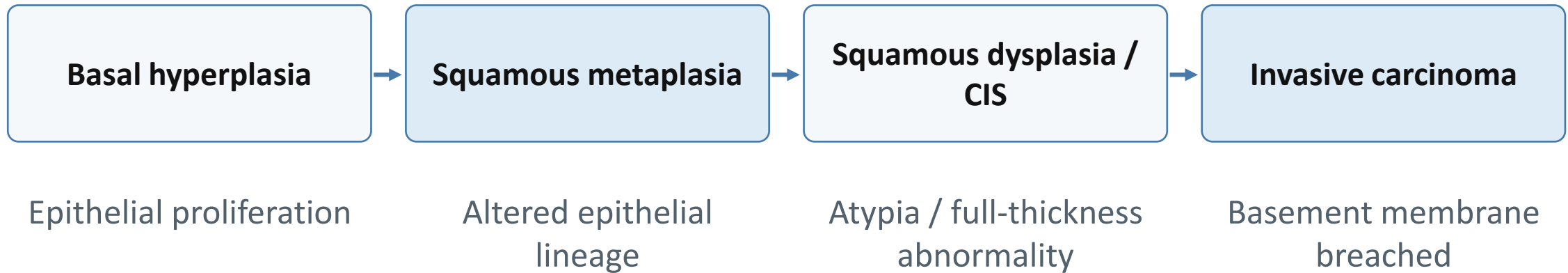
Major lung-carcinoma categories differ biologically

- Robbins groups tumors into small cell and non–small cell lung carcinomas.
- Adenocarcinoma and squamous cell carcinoma are major non–small cell subtypes.
- Small cell carcinoma has particularly strong smoking association.
- Morphology and molecular alterations are not identical across histotypes.

Histotypes: Relationship to tobacco exposure

Histologic category	Relation to smoking in supplied Robbins
Squamous cell carcinoma	Strongly associated with tobacco smoke
Small cell carcinoma	Virtually always smoking related
Adenocarcinoma	Associated with smoking, but also most common in never-smokers
Large cell carcinoma	Undifferentiated category; no single exposure-specific feature established here

Squamous carcinogenesis has recognizable precursor stages



Schematic — conceptual stages, not a diagnostic specimen.

Metaplasia and dysplasia answer different questions

CONTEXT A

- Metaplasia: A change in differentiated epithelial phenotype
- May occur during chronic mucosal injury
- Not itself a diagnosis of invasive malignancy

CONTEXT B

- Dysplasia: Cytologic and architectural abnormalities
- Loss of polarity; Nuclear atypia; Mitotic activity
- More advanced abnormalities raise concern for neoplastic progression

Carcinoma in situ versus invasion

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.

Atypical epithelium



Full-thickness epithelial atypia



Intact basement membrane = in situ



Basement membrane breach = invasion

Schematic — A conceptual transition; Not a diagnostic photomicrograph.

Squamous cell carcinoma: Morphology and setting

- A central or hilar location is characteristic, though peripheral cases occur.
- Keratinization and/or intercellular bridges support squamous differentiation.
- Keratin pearls may be prominent in well-differentiated lesions.
- Poorly differentiated tumors may require p40 immunostaining to demonstrate squamous lineage.

Why a central squamous tumor causes obstruction

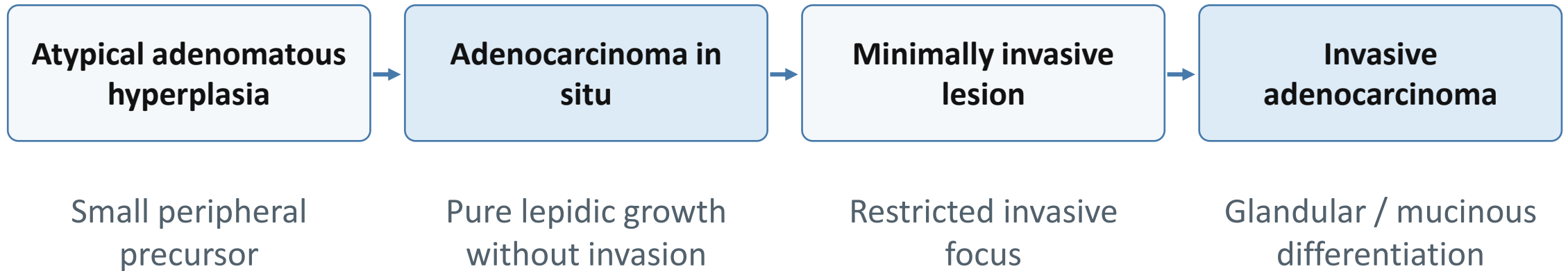
CONTEXT A

- A central mass can protrude into the bronchial lumen.
- Complete obstruction prevents distal ventilation.
- Retained secretions can predispose to infection.

CONTEXT B

- Atelectasis develops downstream of complete obstruction.
- Postobstructive pneumonia or abscess may reveal an occult tumor.
- Local effects reflect position, not only histologic grade.

Adenocarcinoma: A different precursor context



Schematic — conceptual stages, not a diagnostic specimen.

Lepidic growth is an architectural pattern

- Neoplastic cells extend along pre-existing alveolar septa.
- Pure lepidic growth without stromal invasion characterizes adenocarcinoma in situ.
- Invasive adenocarcinomas may contain a lepidic component plus invasive patterns.
- A schematic cannot substitute for authentic sections in a morphology examination.

Peripheral adenocarcinoma versus central squamous cancer

CONTEXT A

- Adenocarcinoma is often peripheral.
- Gland formation or mucin production supports differentiation.
- Many cases express TTF-1.

CONTEXT B

- Squamous carcinoma has a historical central predilection.
- Keratinization / intercellular bridges are defining clues.
- P40 can establish squamous differentiation when morphology is limited.

Adenocarcinoma spans distinct molecular backgrounds

- KRAS alterations are prominent in a subset of tumors.
- Some adenocarcinomas contain activating EGFR or other receptor kinase pathway alterations.
- The driver spectrum varies with smoking history and other factors.
- Predictive molecular testing concerns tumor biology, not proof that a particular exposure caused that cancer.

Oncogenic signaling in some adenocarcinomas

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.

Receptor kinase activation



Downstream growth signaling



Clonal proliferation / survival



Invasive adenocarcinoma phenotype

Schematic — Generic signaling schematic; Molecular drivers and effects vary by tumor.

Small cell carcinoma is especially smoking associated

- Small cell carcinoma is virtually always related to smoking.
- It has a particularly high burden of acquired mutations.
- TP53 and RB loss of function is characteristic of the subtype.
- Aggressive biology and early dissemination distinguish it clinically.

Small cell carcinoma: Diagnostic morphology

- Tumor cells are small with scant cytoplasm and finely granular chromatin.
- Nuclear molding and inconspicuous nucleoli are typical.
- Mitotic activity is high and necrosis often extensive.
- Neuroendocrine differentiation may be supported by appropriate marker expression.

Acquired alteration patterns across major histotypes

Tumor type	Illustrative genetic changes in Robbins
Squamous cell carcinoma	TP53; CDKN2A; 3p loss; sometimes FGFR1 amplification
Small cell carcinoma	Frequent TP53 and RB inactivation; MYC family amplification in some
Adenocarcinoma	KRAS, EGFR, ALK, ROS1, MET, RET, BRAF and other driver pathways

Smoking-related versus never-smoker lung cancer

CONTEXT A

- Smoking-related tumors often show high mutation burden.
- Squamous and small cell carcinomas strongly track smoking.
- Tobacco mutational patterns can be identified by sequencing.

CONTEXT B

- Adenocarcinoma commonly occurs in never-smokers.
- EGFR alterations are relatively enriched in some never-smoker groups.
- Exposure history changes prior probability—not histologic diagnosis.

Immunophenotype: A diagnostic adjunct, not exposure proof

- TTF-1 expression is frequent in pulmonary adenocarcinoma.
- P40 supports squamous differentiation in poorly differentiated carcinomas.
- Chromogranin, synaptophysin and CD56 support neuroendocrine differentiation.
- A staining pattern identifies lineage; It does not establish whether smoking caused the tumor.

Pathology reasoning: Keep the levels separate

Question	Evidence to use
Was there tobacco exposure?	Patient history and exposure assessment
Does the lesion represent carcinoma?	Histology and invasion assessment
Which lung-carcinoma phenotype?	Architecture, cytology and selective immunostains
What drives this tumor?	Tumor molecular characterization
Can smoking be assigned as an individual cause?	Exposure history plus population-level and molecular context; avoid categorical attribution

Local anatomy explains clinical presentations

- Central airway involvement may cause cough or hemoptysis.
- Bronchial blockage can lead to atelectasis and postobstructive infection.
- Extension into pleura, chest wall or mediastinum produces additional local effects.
- These findings signal tumor location or spread, not a specific carcinogen.

How a bronchial carcinoma produces secondary disease

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.

Tumor grows into bronchial lumen



Partial or complete obstruction



Impaired ventilation and secretion clearance



Atelectasis / infection / abscess

Schematic — Anatomic complication rather than a specific etiologic marker.

Dissemination makes lung cancer clinically consequential

- Lung carcinomas spread through lymphatic and hematogenous pathways.
- Adrenal glands, liver, brain and bone as frequent metastatic sites.
- Small cell carcinoma often disseminates early.
- Stage and disease distribution are distinct from the initiating tobacco exposure.

Paraneoplastic associations reflect tumor phenotype

CONTEXT A

- Small cell carcinoma: ADH-related hyponatremia may occur.
- Small cell carcinoma: Ectopic ACTH may occur.
- Other neuroendocrine/systemic manifestations are described.

CONTEXT B

- Squamous carcinoma: PTHrP-related hypercalcemia is a familiar association.
- An unexpected metabolic syndrome may precede tumor recognition.
- These associations are not diagnostic in isolation.

Prevention targets the causal exposure

- Avoiding initiation of tobacco smoking prevents a major source of lung carcinogens.
- Stopping smoking limits future delivery of DNA-damaging compounds.
- Reducing secondhand exposure protects nonsmokers.
- The persistence of residual risk does not negate the benefits of cessation.

Screening and prevention serve different purposes

- Smoking prevention reduces carcinogen exposure before cancer develops.
- The lung-carcinoma section discusses low-dose CT detection in selected high-risk people.
- Early detection may identify resectable disease but produces false-positive findings.
- No specific current screening eligibility threshold is inferred from the supplied excerpt.

Case: Cumulative exposure and a new mass

A 67-year-old patient smoked 1½ packs daily for 30 years and now has a centrally located lung mass with bronchial obstruction.

Interpretation questions

- Compute the cumulative pack-year exposure.
- Which histologic subtype is classically associated with a central mass and smoking?
- Why might downstream lung become atelectatic?

Case interpretation: Distinguish three inferences

- Exposure: $1.5 \times 30 = 45$ pack-years.
- Morphologic hypothesis: Squamous cell carcinoma is plausible, but tissue diagnosis is required.
- Obstruction prevents distal ventilation and impairs secretion clearance; Atelectasis and infection can follow.

Case: A former smoker with an interval of abstinence

A patient quit smoking many years ago. A newly detected pulmonary carcinoma is diagnosed today.

Interpretation questions

- Does cessation make tobacco causation impossible?
- Which cellular finding can persist after smoking stops?
- Is an exposure history sufficient to identify the tumor subtype?

Case interpretation: Persistent molecular effects

- No. Excess lung-cancer risk can remain elevated for decades after cessation.
- Previous somatic changes in bronchial epithelium may persist.
- No. Histologic evaluation and, when indicated, immunophenotype and molecular assays are necessary.

Case: Lung cancer in a never-smoker

A lifelong never-smoker develops a peripheral pulmonary mass composed of malignant gland-forming cells.

Interpretation questions

- Does absence of tobacco history exclude lung cancer?
- Which major histotype is most consistent with gland formation?
- What is the role of mutation testing in this setting?

Case interpretation: Morphology before attribution

- Never-smokers can develop lung carcinoma.
- Glandular differentiation supports pulmonary adenocarcinoma when the clinical context is appropriate.
- Tumor molecular analysis can identify driver pathways; It does not retrospectively prove an environmental cause.

Integrated causal model of smoking-related lung cancer

Causal interpretation

Follow the direction of the arrows; Each transition represents a plausible biological step, not a deterministic event.

Smoke chemistry + cumulative exposure



Bioactivation / DNA adduct burden



Somatic mutations + clone selection



Precursor lesion → invasive carcinoma

Schematic — Host susceptibility and non-tobacco carcinogens can modify multiple steps.

Exam-oriented distinctions

Concept	Essential distinction
Nicotine vs carcinogens	Addiction / promotion is not interchangeable with DNA mutagenesis
Damage vs mutation	Repairable lesion versus persistent sequence change
Exposure vs diagnosis	Smoking history does not specify tumor histotype
CIS vs invasion	Basement membrane intact versus breached
Quitting vs risk eradication	Reduced future exposure; possible residual risk

What the evidence supports—and what it does not

- Smoking causes a substantial burden of lung cancer through mutagenic exposure.
- Dose–response, co-exposure effects and tumor mutation patterns support causality.
- The precise initiating events of a particular patient’s cancer usually cannot be reconstructed.
- Clinical management still requires histologic classification and assessment of tumor biology.

References and directed reading

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026): Effects of Tobacco; Smoking and Lung Cancer.
- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026): The Lung — Carcinomas.
- Review the original textbook images of squamous precursor lesions, adenocarcinoma and small cell carcinoma.
- Revisit the tobacco-smoke constituent tables when interpreting different mechanisms of injury.