

Obesity and Cancer

Epidemiologic associations · Endocrine mechanisms · Metabolic inflammation

Pathogenesis and clinicopathologic interpretation

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Learning objectives

By the end of this lecture, learners should be able to:

- Identify cancer sites associated with excess body weight.
- Trace the insulin–IGF-1, sex-steroid, adiponectin, and inflammatory mechanisms.
- Distinguish an epidemiologic association from a demonstrated causal pathway.
- Apply the pathway model to clinicopathologic examples without overinterpretation.

The central observation

Excess adiposity is associated with increased incidence of selected malignancies.

- The relationship is site-specific, not a uniform elevation across all tumors.
- Individual relative-risk increments may be modest, yet population impact can be substantial.
- The underlying mechanisms are multiple and incompletely established.

Association does not demonstrate a particular initiating oncogenic event.

Cancer sites: Gastrointestinal tract

Anatomic group	Associated malignancy	Teaching distinction
Upper gastrointestinal	Esophageal carcinoma; Upper gastric carcinoma	An association is reported; Subtype-specific inference is not supplied.
Large intestine	Colon and rectal carcinoma	May reflect several interacting metabolic pathways.

Use site-specific cancer risk, not “all GI cancers.”

Cancer sites: Hepatopancreatobiliary

Organ	Associated malignancy	Interpretation
Gallbladder	Gallbladder carcinoma	Included in the obesity-associated sites listed.
Liver	Liver carcinoma	Obesity association is stated; A unique pathway is not established here.
Pancreas	Pancreatic carcinoma	Metabolic and inflammatory mechanisms are candidates.

Anatomic association ≠ verified organ-specific molecular mechanism.

Cancer sites: Hormone-sensitive and other

Organ / tissue	Cancer associated with overweight or obesity
Breast / endometrium	Breast carcinoma; Endometrial carcinoma
Ovary / kidney	Ovarian carcinoma; Renal carcinoma
Meninges / plasma cells	Meningioma; Multiple myeloma

Cancer associations span epithelial, meningeal, and hematologic neoplasms.

A risk gradient across exposure

Obesity-related exposure

Higher BMI

Greater adiposity

Longer duration

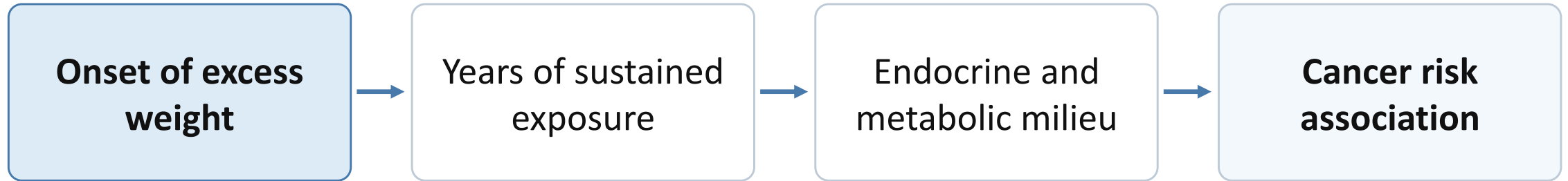
Prolonged exposure

Earlier onset

More lifetime exposure

Each dimension of excess weight is associated with higher observed cancer risk.

Duration of adiposity matters



- Longer time spent overweight or obese correlates with greater risk.
- Duration is a population-level determinant, not a time-to-cancer calculator.

Interpret as duration-associated risk, not a deterministic sequence.

Individual risk versus population burden

Individual perspective

- The association for any one person may be relatively modest.
- Risk varies by cancer type and individual context.

Population perspective

- Obesity is common across populations.
- Even moderate associations may contribute materially to aggregate cancer burden.

The textbook's "at least 40% associated" statement is not an attributable-fraction estimate.

Interpreting the United States estimate

Obesity as associated with at least 40% of US cancers.

- This is the phrasing of the textbook, not a claim that obesity caused 40% of tumors.
- Association and attributable proportion have different epidemiologic meanings.
- The source reports a somewhat greater association in females than in males.
- Do not apply this population estimate to an individual patient.

Do not equate “associated with” and “caused by.”

Association is not mechanistic proof

Observational observation

- Excess adiposity correlates with incidence of some cancers.
- Magnitude and duration of exposure matter.

Biologic explanation

- Insulin/IGF-1, steroids, adiponectin and inflammation are plausible mediators.
- Relative contributions to particular cancer sites remain uncertain.

A proposed biologic mechanism strengthens plausibility but does not settle causality.

Central obesity: The metabolic context

Central adiposity is a major correlate of metabolic dysfunction.

- Central obesity in mortality and metabolic syndrome.
- Cancer-related effects involve adipose signaling, not only passive energy storage.
- BMI is a population exposure marker; It does not directly assay tissue signaling.

The pathway model starts with metabolic and endocrine consequences of adiposity.

Metabolic syndrome as a pathway hub

Central adiposity

**Glucose
intolerance**

Insulin resistance

Dyslipidemia

Lipid excess

Hypertension

Cardiometabolic effect

Inflammation

Proinflammatory state

These features occur together; None alone diagnoses obesity-mediated cancer.

White adipose tissue is an endocrine organ

Secreted metabolic mediators

- Leptin and adiponectin participate in systemic energy metabolism.
- Adiponectin is reduced in obesity.

Immune and steroid mediators

- TNF, IL-1, IL-6, IL-18 and chemokines are produced.
- Adipose tissue also participates in steroid-hormone regulation.

Secreted products link adiposity with distant tissue behavior.

Four complementary candidate pathways

Excess adiposity

Insulin/IGF-1 Mitogenic signal

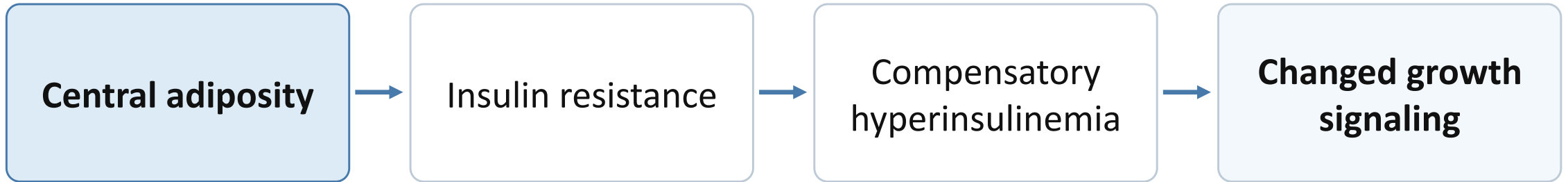
Sex steroids Hormone availability

Adiponectin ↓ Less growth restraint

Inflammation Pro-tumor milieu

Pathways interact; They are not competing explanations.

Insulin resistance begins the mitogenic axis



- Insulin resistance and hyperinsulinemia are common in obesity.
- Chronic excess insulin can alter endocrine and mitogenic signaling.

Insulin resistance initiates the proposed insulin–IGF axis.

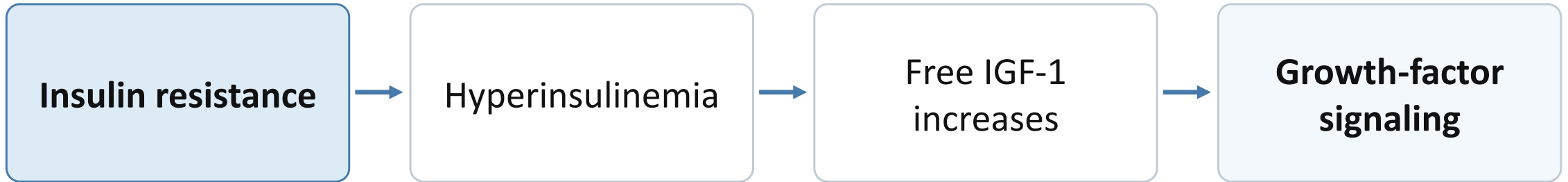
Hyperinsulinemia is more than hyperglycemia

Elevated insulin as a candidate cancer-promoting mechanism.

- Persistent high insulin arises in the setting of insulin resistance.
- Insulin-related effects can be direct or mediated through other signaling systems.
- Obesity-associated cancer cannot be inferred from insulin level alone.

The relevant hypothesis concerns sustained growth signaling, not a diagnostic cutoff.

From insulin to free IGF-1



- Elevated free insulin-like growth factor-1 (IGF-1).
- The figure also identifies IGF-binding proteins as part of this axis.

Free IGF-1, not simply total IGF-1, is emphasized in the source.

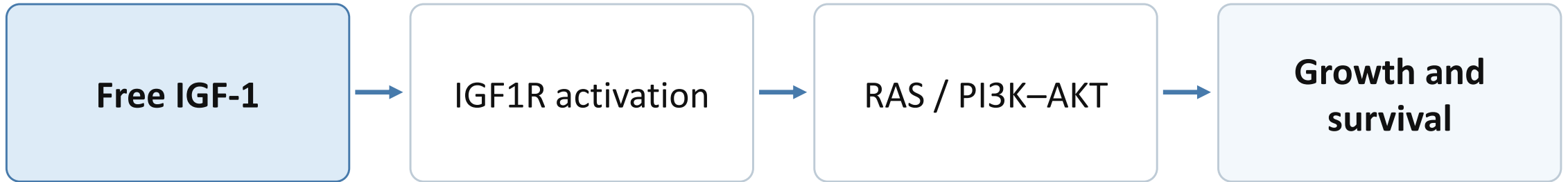
IGF-1 is a mitogen

Mitogenic hormones can increase cell division in susceptible tissues.

- IGF-1 acts through the IGF-1 receptor (IGF1R).
- The receptor is highly expressed in many human cancers.
- Receptor activation engages RAS and PI3K–AKT downstream pathways.

Mitogenic stimulation may promote growth of pre-existing neoplastic cells.

IGF-1 receptor signaling



- These are downstream signaling branches, not separate endocrine exposures.
- The same pathways function in normal as well as neoplastic cells.

Shared signaling machinery explains why a mitogen is not cancer-specific.

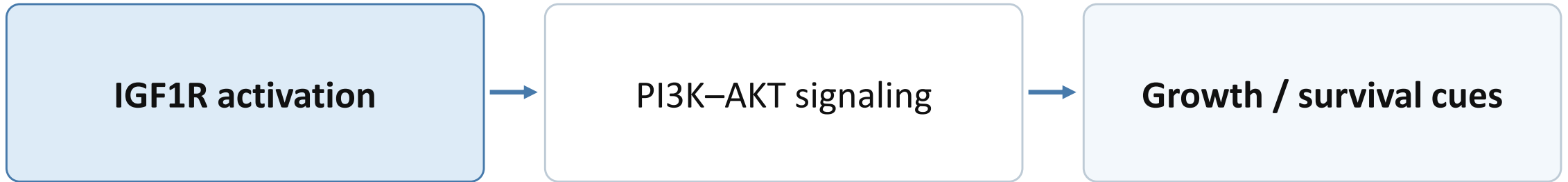
The RAS branch: Growth signaling



- IGF1R activation to RAS signaling.
- The relevant tumor-promoting effect is increased cellular growth.
- Receptor signaling is not evidence of a somatic RAS mutation.

Do not confuse activation of a pathway with mutation of the pathway gene.

The PI3K–AKT branch: Growth and survival



- IGF1R signaling activates the PI3K–AKT pathway.
- The insulin–IGF axis to proliferation and reduced apoptosis.
- The effect is context-dependent, not a histologic diagnosis.

Increased proliferation and reduced cell loss jointly favor expansion.

Proliferation and apoptosis are complementary

More cells entering the pool

- Mitogenic cues promote cellular proliferation.
- Sustained signaling can enlarge a responsive cell population.

Fewer cells leaving the pool

- Pro-survival cues oppose programmed cell death.
- An imbalance may favor persistence of abnormal clones.

The figure links insulin/IGF signaling to both processes.

Complete insulin–IGF causal hypothesis



- This is a proposed tumor-promotion model.
- No single step establishes that a malignant mutation will occur.

A proposed tumor-promotion model, not proof of a specific tumor origin.

Receptor expression is not a cancer diagnosis

IGF1R expression has mechanistic relevance, not standalone diagnostic specificity.

- Many normal cells also use growth-factor signaling pathways.
- Receptor abundance does not establish obesity as the cause of an individual tumor.
- The source does not provide an IGF1R clinical testing algorithm or cutoff.

Mechanistic biomarkers and validated diagnostic biomarkers are different categories.

Limits of the insulin–IGF model

What the textbook supports

- Insulin resistance → hyperinsulinemia.
- Free IGF-1 and IGF1R can stimulate mitogenic pathways.

What remains unproved here

- Which pathway dominates at each associated cancer site.
- What fraction of excess incidence is mediated through IGF signaling.

Treat this pathway as one member of a multifactorial model.

Obesity changes steroid-hormone biology

Sex-steroid milieu

Aromatization ↑

Androgens → estrogens

Androgen production ↑

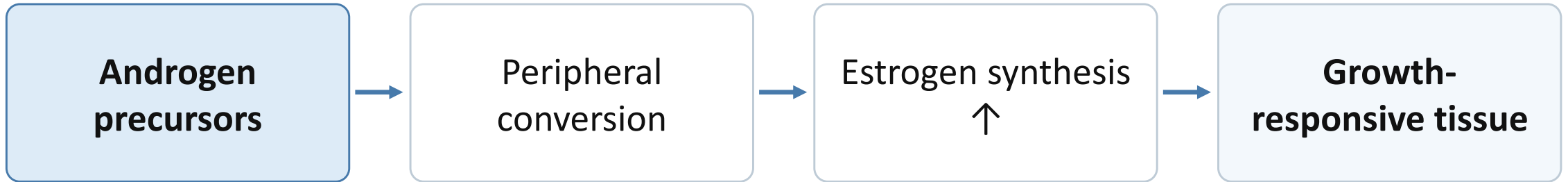
Ovaries / adrenals

Hepatic SHBG ↓

Availability ↑

Altered exposure influences growth and differentiation in responsive tissues.

Peripheral aromatization: Estrogen synthesis



- Greater synthesis of estrogens from androgen precursors.
- This provides a biologic link between adiposity and hormone-sensitive tissues.

This diagram represents a hormone-production effect, not a cancer-specific mutation.

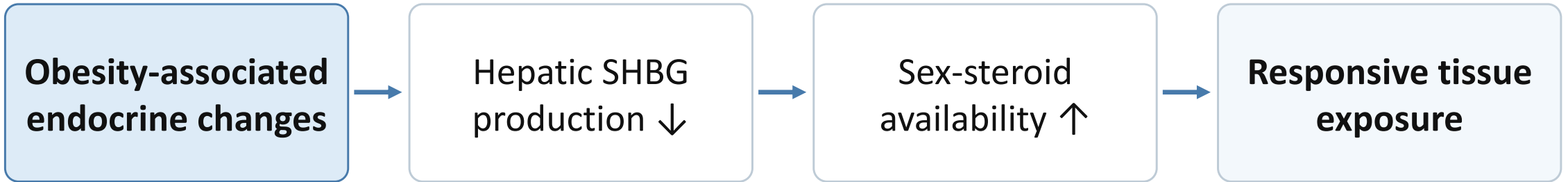
Ovarian and adrenal androgen synthesis

Obesity also affects the supply of steroid precursors.

- The text describes increased androgen synthesis in ovaries and adrenal glands.
- Androgens may enter the wider sex-steroid metabolic network.
- Downstream effects depend on tissue biology and hormonal context.

The contribution of each organ and steroid is not quantified in the source.

Reduced SHBG increases bioavailability



- SHBG means sex hormone–binding globulin.
- Inhibited hepatic SHBG production as an obesity effect.

Hormone concentration and biologically available hormone are not equivalent.

Estrogen abundance has two components

Greater production

- Enhanced conversion of androgen precursors into estrogen.
- Increased production of androgen precursors.

Greater availability

- Reduced hepatic synthesis of SHBG.
- Increased biologically available circulating sex steroids.

Synthesis and binding are separate levers in the same endocrine axis.

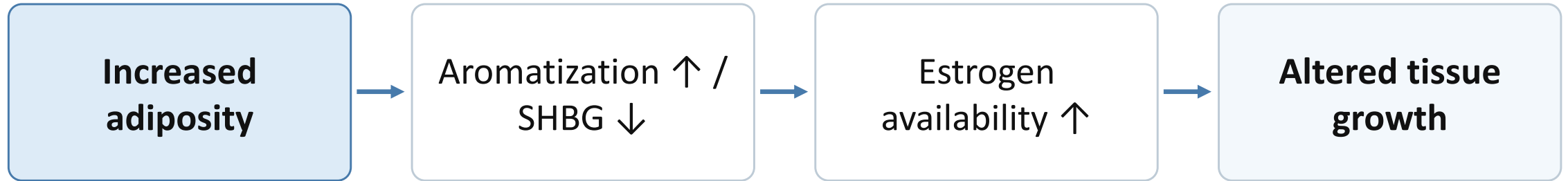
Breast and uterine tissue are hormone-responsive

Steroid hormones regulate growth and differentiation in some tissues.

- Robbins explicitly highlights breast and uterus as examples.
- Breast and endometrial carcinoma are in the obesity-associated cancer list.
- The source does not establish an identical hormonal mechanism for every subtype.

Avoid extrapolating the hormonal pathway to all breast or gynecologic tumors.

Integrated sex-steroid hypothesis



- Changes in steroid synthesis and availability occur together.
- The endpoint is a plausible effect on growth or differentiation, not guaranteed transformation.

Original synthesis of the insulin–sex hormone axis.

Risk sites differ in pathway plausibility

Hormone-responsive examples

- Breast and endometrium are explicitly named as hormone-regulated tissues.
- An endocrine mechanism is biologically plausible.

Do not overgeneralize

- Ovary appears on the associated-site list.
- The source does not attribute every ovarian malignancy to estrogen availability.

Distinguish the cancer-site list from demonstrated tissue-specific causal pathways.

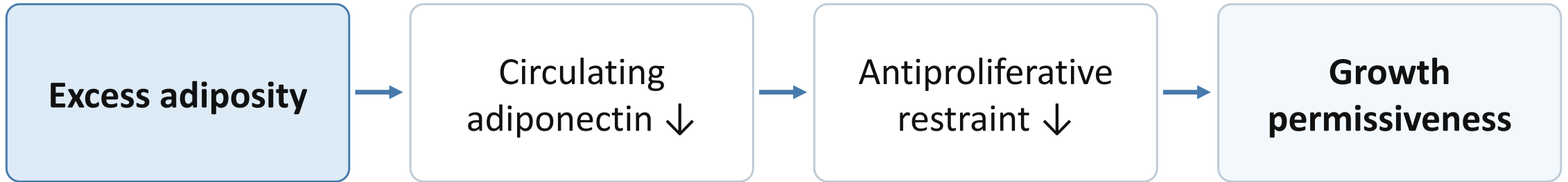
Adiponectin is a protective adipokine

Adiponectin is secreted by adipose tissue and has metabolic actions.

- It promotes fatty-acid oxidation and enhances insulin sensitivity.
- Anti-inflammatory and antiproliferative properties.
- Its serum levels are lower in obesity than in lean individuals.

The anticancer axis begins with loss of a restraining signal.

Obesity reduces adiponectin signaling



- A reduced protective factor differs from an increased mitogenic stimulus.
- The pathway is plausible and does not quantify individual cancer risk.

Loss of restraint may combine with insulin-driven growth signals.

Adiponectin and the p53 pathway

Adiponectin promotes actions of p53 and p21.

- P53 participates in control of cell-cycle responses to cellular stress.
- model, adiponectin supports a less proliferative state.
- Reduced adiponectin may compromise this antineoplastic signaling.

A decrease in adiponectin does not establish TP53 mutation.

P21 links signaling with growth restraint

P21 is a cell-cycle inhibitory effector in the source model.

- Adiponectin promotes p21-related antineoplastic effects.
- Cell-cycle restraint limits unnecessary proliferation.
- Reduced adiponectin may weaken the protective milieu.

Pathway activity should not be confused with measured p21 expression in a tumor.

Adiponectin: Two antineoplastic effects

Proliferation

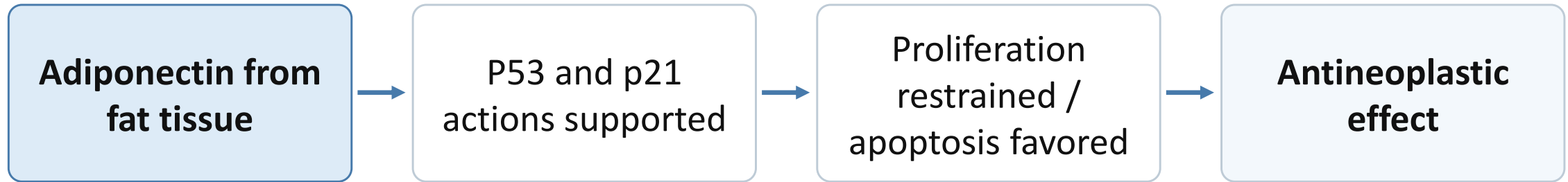
- Adiponectin is described as suppressing cell proliferation.
- Lower adiponectin may reduce this restraint.

Apoptosis

- Adiponectin promotes apoptosis model.
- Lower adiponectin may impair this safeguard.

Reduced proliferation and enhanced apoptosis normally work together.

Adiponectin–p53/p21 hypothesis



- In obesity adiponectin declines, potentially weakening this sequence.
- The relationship is a candidate mechanism, not a validated test.

The source gives qualitative effects without diagnostic thresholds.

Metabolic and antineoplastic roles intersect

Metabolic function

- Fatty-acid oxidation is increased.
- Insulin sensitivity is improved.

Antineoplastic function

- Cell proliferation is suppressed.
- Apoptosis is promoted in the described model.

One adipokine can affect both systemic metabolism and growth regulation.

Obesity-associated inflammation is systemic

White adipose tissue produces cytokines and chemokines.

- TNF, IL-6, IL-1 and IL-18 among adipose mediators.
- Higher mediator production contributes to chronic proinflammatory activity.
- Increased circulating C-reactive protein is described as a feature.

Inflammation is an endocrine-systemic consequence, not merely a local fat-tissue finding.

Adipose inflammatory signaling

Mediator / compartment	Role
TNF; IL-6; IL-1; IL-18	Examples of cytokines produced by white adipose tissue
Chemokines	Recruitment/communication signals in inflammatory networks
Tissue macrophages and T cells	Immune cells implicated in regulating adipocyte function
Circulating CRP	Systemic marker of the chronic proinflammatory state

The presence of inflammation does not identify a specific cancer pathway.

Adipocyte–immune-cell reciprocity

Adipose to immune cells

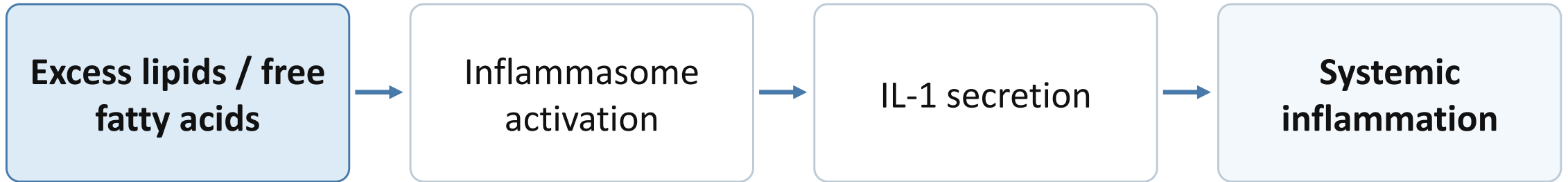
- Adipocyte cytokines and chemokines contribute to inflammatory signaling.
- Immune cells respond within adipose tissue.

Immune cells to adipocytes

- Macrophages and some T cells regulate adipocyte function.
- The source describes communication as bidirectional.

Reciprocal interactions can maintain a chronic inflammatory environment.

Lipid excess can activate the inflammasome



- The obesity section places IL-1 within the metabolic-syndrome inflammatory state.
- This is a proposed link between lipid excess and chronic inflammation.

Lipid excess is one route to chronic systemic inflammation.

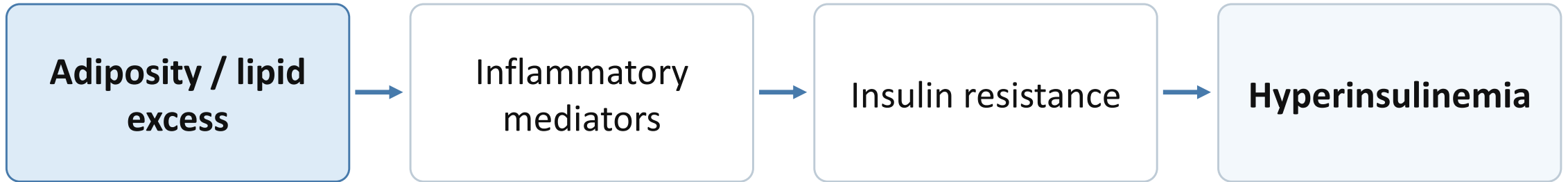
IL-1 is part of a metabolic inflammatory loop

Inflammation contributes to insulin resistance account.

- Excess lipids activate inflammatory signaling.
- IL-1 and other factors are implicated in insulin resistance.
- Insulin resistance sustains the hyperinsulinemic hormonal state.

Inflammatory and insulin-growth axes can reinforce one another.

Metabolic inflammation links to insulin signaling



- These steps explain why mechanisms need not be independent.
- The major components but does not quantify feedback strength.

This is an integrative conceptual diagram; It is not a measured kinetic model.

CRP identifies inflammation, not cancer causation

A raised inflammatory marker has limited etiologic specificity.

- The textbook uses CRP as a feature of obesity-related inflammation.
- It does not provide a CRP threshold predicting obesity-associated cancer.
- Inflammation is one candidate mediator among several pathways.

Do not treat an inflammatory marker as proof of a carcinogenic mechanism.

Why inflammation could be tumor-promoting

Established source claim

- Obesity is accompanied by a proinflammatory state.
- Inflammation itself may be carcinogenic.

Critical qualification

- The mechanism is referred to the neoplasia chapter rather than detailed here.
- Cancer-site-specific inflammatory mediators are not established in this excerpt.

Use “may contribute” rather than “necessarily causes.”

The axes converge on cell-fate regulation

Tumor-permissive milieu

IGF axis

Proliferation ↑

Steroids

Growth regulation altered

Adiponectin ↓

Apoptotic support ↓

Inflammation

Chronic stress signals

This is a conceptual integration; The source does not assign percentages to axes.

Why no single mechanism is sufficient

Shared systemic environment

- Metabolic and endocrine changes can affect many organs.
- Several signals influence proliferation and apoptosis.

Cancer remains heterogeneous

- Each site has distinct cell biology and pre-existing susceptibility.
- Robbins calls the mechanisms incompletely understood and multiple.

A systemic risk factor does not imply one histologic phenotype.

Keep evidence categories separate

Question	Supported answer	Not justified
Where is risk associated?	Named cancer sites	Every cancer type or histologic subtype
What pathways are plausible?	Insulin/IGF-1; Steroids; Adiponectin; Inflammation	Exclusive or quantitatively ranked causation
What can be diagnosed?	A malignancy by its usual diagnostic criteria	Obesity as proof of tumor origin

Epidemiology, mechanisms, and patient-level attribution are different tasks.

An obesity history does not diagnose cancer

A risk factor changes prior risk; It is not a pathological criterion.

- No characteristic “obesity-induced morphology” is defined in this section.
- Histology, immunophenotype and molecular studies address tumor classification as appropriate.
- Patient adiposity does not establish etiology for any single tumor.

Risk-factor attribution must not replace standard tissue diagnosis.

Proposed pathway components are not routine cancer tests

The excerpt provides a mechanistic framework rather than a test panel.

- IGF1R expression is not a source-defined diagnostic cutoff.
- Adiponectin and CRP are not validated here to classify obesity-associated neoplasms.
- P53/p21 pathway discussion is biologic; No IHC criteria are supplied.

Do not convert a signaling diagram into an unsupported clinical algorithm.

Three dimensions of exposure to ask about

Obesity history

Severity

BMI magnitude

Timing

Age of onset

Duration

Years of excess weight

These are epidemiologic correlates of risk, not specific tumor biomarkers.

Prevention: Avoid overclaiming the outcome

Robbins favors prevention of obesity as a general health measure.

- A healthy diet can support preventing excessive weight gain.
- The source does not prove that a single named diet prevents a particular cancer.
- Weight-related prevention is broader than the management of a single neoplasm.

Keep prevention messages proportional to the strength of evidence.

Obesity is not synonymous with a specific diet

Adiposity exposure

- The lecture focuses on metabolic, hormonal and inflammatory consequences.
- Body-weight history influences the epidemiologic association.

Dietary carcinogen exposure

- Diet may involve exogenous or endogenously produced carcinogens.
- Robbins addresses these separately under “Diet and Cancer.”

Do not transfer a diet-specific carcinogen mechanism into this obesity lecture.

GLP-1 medicines: A research question

The textbook explicitly calls for studying cancer incidence after effective weight loss.

- GLP-1 agonists and GLP-1/GIP co-agonists are discussed as obesity treatments.
- The source does not claim that these drugs prevent obesity-associated cancers.
- Mechanistic plausibility is not evidence of a reduced cancer-incidence endpoint.

No drug-specific cancer-prevention effect is asserted.

Application case: Metabolic axis

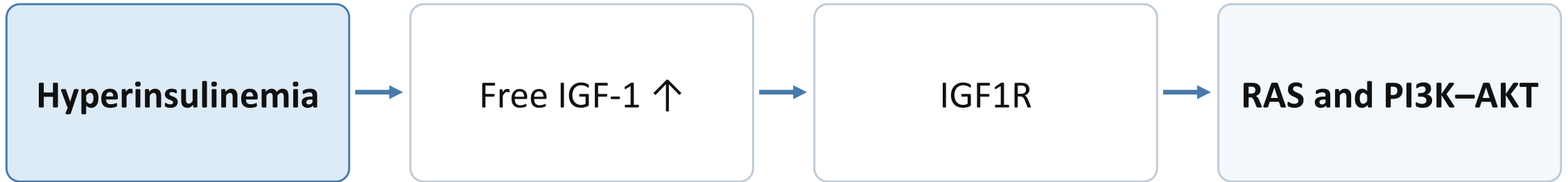
Illustrative case: An adult with long-standing central obesity develops a malignancy. The history includes insulin resistance and hyperinsulinemia.

Relevant clues

- Exposure: Prolonged central adiposity
- Metabolic finding: Insulin resistance
- Possible mediator: Increased free IGF-1

Which receptor and two signaling pathways are implicated by the textbook model?

Case interpretation: Insulin–IGF axis



- The proposed effect is increased growth and impaired apoptosis.
- Neither the obesity history nor pathway plausibility proves the tumor was caused by obesity.

Answer: IGF1R, RAS, and PI3K–AKT.

Application case: Endocrine axis

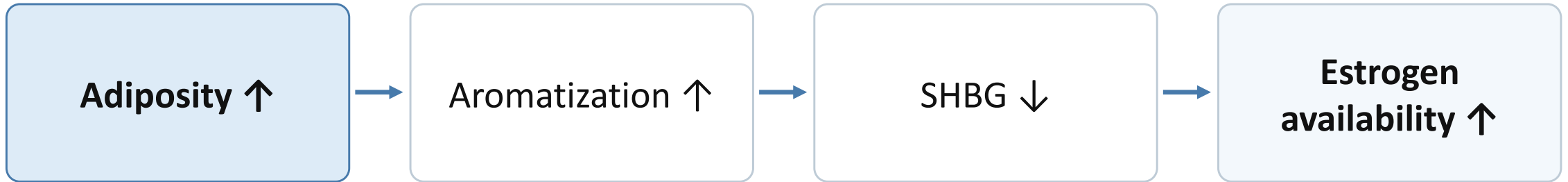
Illustrative case: An adult with obesity is diagnosed with an endometrial carcinoma. The clinical question is why adiposity may alter hormone exposure.

Relevant clues

- Reported obesity association: Endometrial carcinoma
- Potential mechanism: Greater peripheral estrogen synthesis
- Additional effect: Reduced SHBG production

Explain why estrogen availability may increase through two separate routes.

Case interpretation: Sex-steroid axis



- Greater estrogen synthesis and reduced binding capacity are distinct effects.
- The mechanism is plausible, but the case does not demonstrate direct causation.

Answer: Increased synthesis plus reduced binding.

Application case: Inflammatory axis

Illustrative case: An adult with central obesity has features of metabolic syndrome and chronically elevated inflammatory markers.

Relevant clues

- Adipose secretion of inflammatory cytokines
- Lipid excess may activate the inflammasome
- IL-1 and other mediators may aggravate insulin resistance

Which observation is evidence of inflammation, and which statement remains a cancer hypothesis?

Case interpretation: Evidence and hypothesis

Supported metabolic observations

- Obesity produces systemic inflammatory signaling.
- CRP may be elevated; Insulin resistance may coexist.

Cancer hypothesis

- Chronic inflammation may contribute to carcinogenesis.
- CRP does not diagnose or attribute an individual malignancy.

An inflammatory state is not the same as established cancer causality.

Integrative synthesis

Excess adiposity

Incidence

Selected sites ↑

Endocrine

IGF-1 / steroids

Cell restraint

Adiponectin ↓

Immunity

Inflammation ↑

Duration, severity and early onset are important epidemiologic modifiers.

Four conclusions to retain

Risk and scope

- Increased risk is associated with selected cancers.
- BMI, exposure duration and earlier onset track with greater risk.

Pathway interpretation

- Insulin–IGF-1, steroids, adiponectin and inflammation interact.
- Cancer-site causation remains incompletely resolved.

Do not confuse an association with proof about a particular patient's tumor.

Principal source and scope

Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). The sections on obesity-associated cancers, adipose physiology, and metabolic consequences form the basis of this lecture.

Diagram provenance

All teaching diagrams are original native, editable PowerPoint schematics based on the textbook discussion. They are explanatory models, not experimental data or reproduced source figures.