

Diet and Cancer

Environmental exposures • Carcinogenic mechanisms • Evidence appraisal

Dr Abu Suraih Sakhri

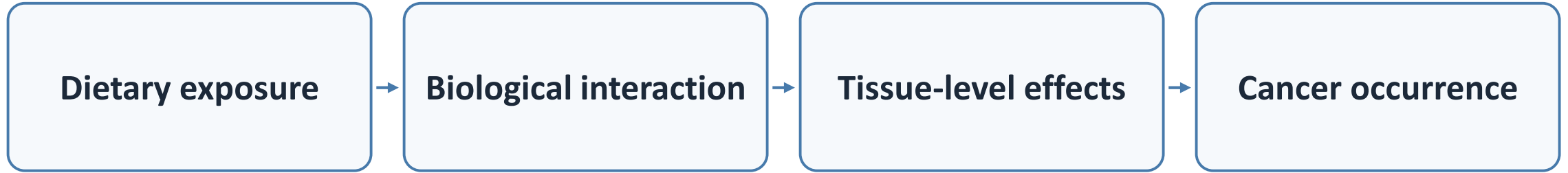
MBBS, MD (Pathology)

www.abusuraisakhri.com

Learning objectives

- Interpret geographic and migration evidence without inferring a single dietary cause.
- Distinguish exogenous carcinogens from compounds formed from dietary precursors.
- Explain proposed colorectal, gastric, and hepatocellular carcinogenic mechanisms.
- Appraise nutritional prevention claims and the obesity–cancer connection.

Diet may modify cancer risk

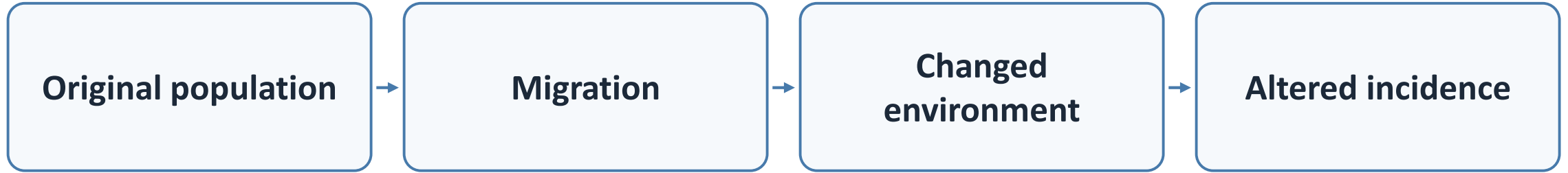


- Diet is one environmental influence among many.
- A plausible mechanism is not equivalent to demonstrated human causation.
- Unresolved links between specific diets and tumors.

Cancer incidence differs across populations

- Site-specific cancer incidence varies markedly by geographic region.
- Differences reaching as much as 100-fold.
- Variation invites examination of environmental, dietary, and other influences.
- A geographic contrast alone does not identify which exposure is causal.

Migration offers a natural comparison



- Progressively higher colon cancer occurrence among Japanese populations moving to Hawaii and then the continental United States.
- The pattern supports environmental modifiability but does not isolate diet.

Colon cancer incidence changed in Japan

- Substantial temporal increases in Japanese populations.
- An incidence pattern is not necessarily fixed by ancestry.
- Changing diet is a possible contributor within a broader environmental transition.
- Specific causal dietary components remain uncertain.

What population comparisons can establish

Supported inference

- Cancer rates are modifiable.
- Environment matters alongside inherited susceptibility.
- Diet is a reasonable exposure to investigate.

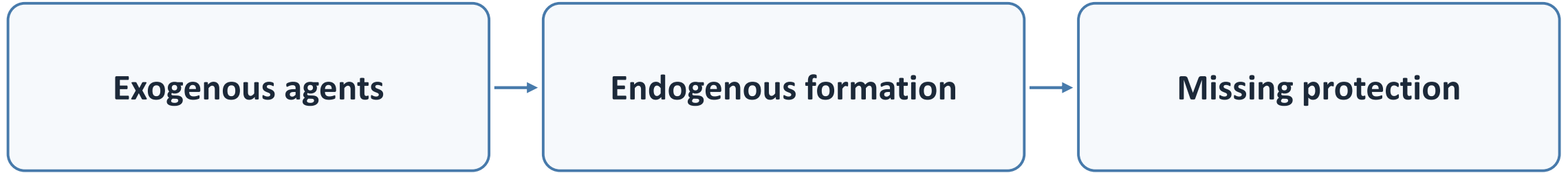
Not established

- A specific nutrient is the sole cause.
- An observed food pattern has a proven mechanism.
- A particular diet prevents cancer in an individual.

Why nutrition epidemiology is difficult

Problem	Consequence	Interpretation
Correlated exposures	Diet travels with other behaviors	Confounding can persist
Long latency	Past intake may be uncertain	Exposure timing matters
Multiple pathways	One cancer has many influences	Single-cause stories mislead
Changing populations	Incidence reflects several shifts	Temporal inference is limited

Three dietary concerns in carcinogenesis



- Carcinogens may be ingested already formed.
- Dietary constituents can yield reactive substances inside the body.
- Low intake of putative protective components may be relevant.

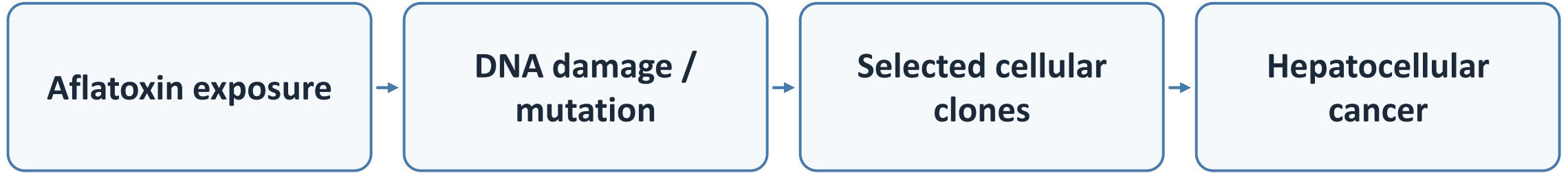
Distinguish the three exposure pathways

Category	Representative concept	Evidence caveat
External carcinogen	Aflatoxin exposure	Strong molecular association with HCC
Formed in vivo	Nitroso compounds from precursors	Animal evidence; Human relevance uncertain
Putative protection	Fiber and antioxidants	Mechanisms often inconsistent or unproven

Aflatoxin is a dietary carcinogenic exposure

- Aflatoxin is discussed by Robbins as an exogenous food-related carcinogen.
- It contributes to hepatocellular carcinoma in parts of Asia and Africa.
- The relationship is often observed together with hepatitis B virus infection.
- This example links an environmental exposure to a specific molecular change.

Aflatoxin and hepatocellular carcinoma



- The source identifies a characteristic mutation affecting TP53 codon 249.
- Mutation is a mechanistic signature, not a stand-alone clinical diagnosis.

Aflatoxin and hepatitis B: Two contributors

Aflatoxin

- Diet-associated exogenous agent
- Linked to a characteristic TP53 alteration
- Relevant to hepatocellular carcinoma

Hepatitis B virus

- Infectious carcinogenic factor
- Often coexists in implicated settings
- Shows that dietary and nondietary risks interact

Codon 249 of TP53 is a molecular clue

- A specific TP53 codon 249 mutation is associated with aflatoxin exposure.
- It as a molecular signature in relevant liver tumors.
- The alteration connects exposure biology with tumor molecular pathology.
- It should not be interpreted as a universal feature of hepatocellular carcinoma.

Exposure signature is not a screening test

What the signature supports

- A link between mutagenic exposure and tumor biology
- Mechanistic specificity in an appropriate setting
- Interpretation at the population or tumor level

What it does not prove

- That all affected tumors share the same mutation
- That a mutation alone identifies clinical exposure history
- That TP53 mutation is sufficient for cancer

Interpret chemical-additive concerns cautiously

- Debate over the carcinogenicity of food additives.
- Artificial sweeteners are included among the debated exposures.
- The textbook does not establish that these agents cause human cancers.
- Avoid conflating a theoretical concern with an established cancer risk.

Food contaminants versus dietary constituents

External agents

- Examples include aflatoxin and debated contaminants.
- The candidate carcinogen may be present before ingestion.
- Exposure definition is central.

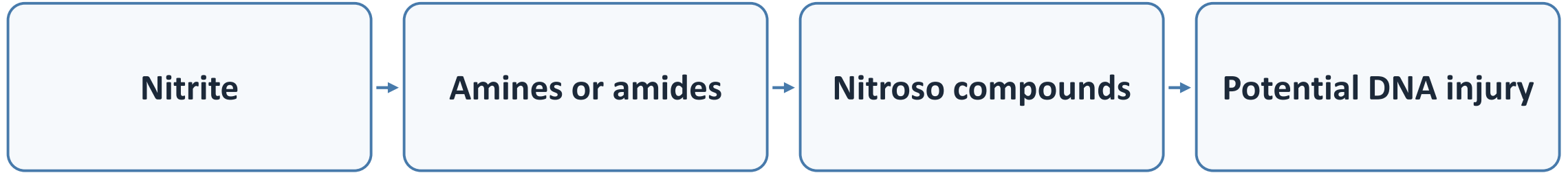
Dietary precursors

- Compounds are formed after ingestion.
- Gut chemistry and microbial activity may intervene.
- Dose, host, and context influence plausibility.

Nitroso compounds are a gastric cancer hypothesis

- Nitrosamines and nitrosamides in gastric carcinogenesis.
- Such compounds induce gastric cancer in experimental animals.
- They may arise through endogenous reactions involving dietary components.
- Animal carcinogenicity does not directly quantify human dietary risk.

Nitrosation combines different dietary precursors

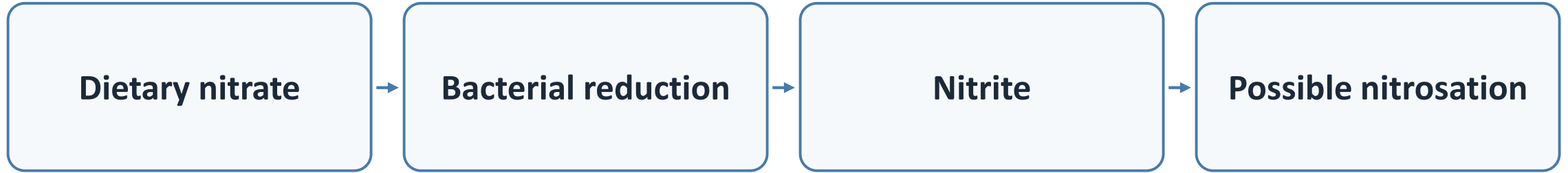


- Protein digestion supplies amine or amide precursors.
- Nitrites can participate in chemical formation of nitrosamines or nitrosamides.
- This as a potential contributor to gastric cancer.

Food preservation provides one nitrite source

- Sodium nitrite can be added to certain foods as a preservative.
- Dietary nitrite can enter the chemical pathway toward N-nitroso compounds.
- Presence of a precursor does not establish that a carcinogenic dose forms.
- Do not equate a single preserved food with a cancer diagnosis.

Dietary nitrate may become nitrite

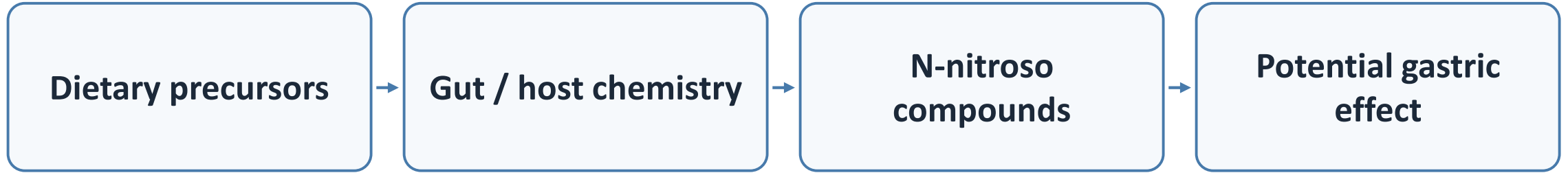


- Vegetables can contain nitrates.
- Gut bacterial flora can reduce nitrates to nitrites.
- This pathway describes chemistry, not proof that vegetables cause cancer.

Protein digestion contributes amine substrates

- Digestion can yield amines or amides from dietary proteins.
- These substrates may react with nitrite to form N-nitroso compounds.
- Both precursor availability and conditions for formation are relevant.
- Mechanistic diagrams must not imply a known cancer risk per meal.

Proposed endogenous route to gastric carcinogenesis



- The causal link is plausible because some formed compounds are carcinogenic in animals.
- Human diet–gastric cancer causation is not established by this pathway alone.

Animal experiments and human causality

Experimental finding

- Certain nitroso compounds cause gastric tumors in animals.
- Demonstrates biological carcinogenic potential.
- Controls exposure more directly.

Human uncertainty

- Real dietary precursor conversion varies.
- Dietary associations are prone to confounding.
- No individual risk estimate follows from animal results.

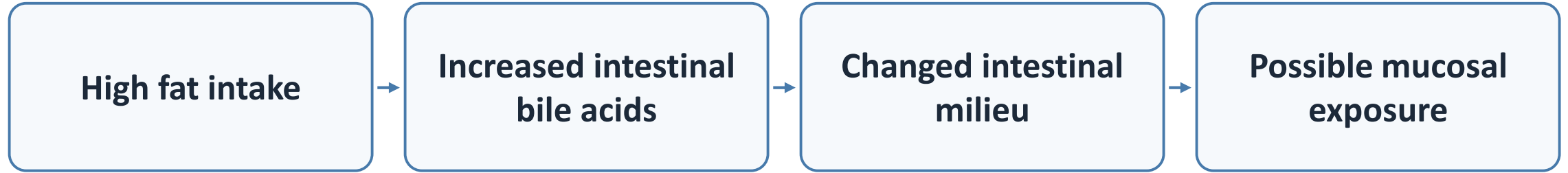
Avoid attributing gastric cancer to one compound

- Robbins frames endogenous formation as a possible contributor.
- Tumor development cannot be inferred merely from exposure to nitrates or nitrites.
- An experimentally active agent may not be generated at relevant human levels.
- The distinction between concern and demonstrated cause is essential.

Colorectal cancer: An implicated dietary pattern

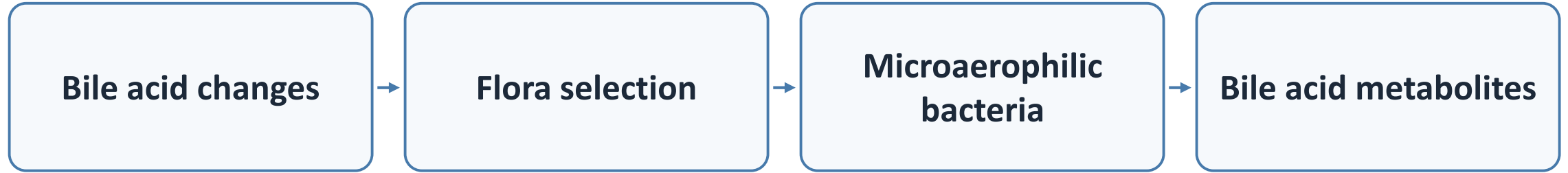
- High animal-fat intake combined with low fiber intake.
- The pattern has been implicated in colon carcinogenesis.
- Several mechanistic explanations have been proposed.
- The textbook explicitly notes inconsistent validation of these explanations.

Proposed pathway from fat intake to bile acids



- Higher bile acid levels in the gut are proposed as a link between dietary fat and colorectal cancer.
- This is an explanatory hypothesis, not a proven linear human pathway.

Bile acids may reshape intestinal flora



- Preferential growth of certain microaerophilic bacteria.
- Bacterial metabolism may generate compounds with carcinogenic potential.

Bile acid metabolites are candidate mediators

- Bacteria may transform bile acids into secondary metabolites.
- Some metabolites have been proposed to act as carcinogens.
- A microbial intermediary supplies mechanistic plausibility.
- Clinical and experimental evidence has not consistently confirmed the full chain.

Mechanism proposed; Clinical proof incomplete

Mechanistic narrative

- Fat alters intraluminal bile acid conditions.
- Bacterial composition or activity changes.
- Metabolites may affect colorectal mucosa.

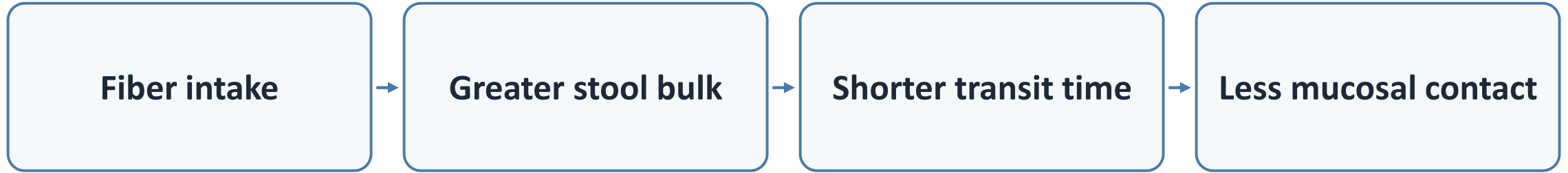
Evidentiary limitation

- The complete chain has not been consistently reproduced.
- Dietary association does not identify the mediator.
- Do not portray arrows as proven human causal estimates.

Fiber increases stool bulk

- Dietary fiber can increase fecal mass.
- More bulk may dilute potentially harmful intraluminal substances.
- The proposed protective mechanism also involves shortening transit time.
- A physical mechanism should not be mistaken for established chemoprevention.

Fiber and mucosal contact time



- Reduced duration of exposure to putative luminal carcinogens.
- The key intermediate is contact time, not a direct antitumor action.

Certain fibers might bind luminal carcinogens

- Another proposed mechanism is direct binding of carcinogens.
- Binding would reduce access of reactive molecules to colorectal mucosa.
- The effect likely depends on fiber type and chemical context.
- No consistent clinical or experimental confirmation.

Two hypothesized benefits of fiber

Bulk

- Higher fecal mass
- Potential dilution

Transit

- Reduced residence time
- Potentially less contact

Binding

- Sequestration of some molecules
- Potentially less mucosal access

Uncertainty

- Proposed mechanisms
- Not consistently validated

Evaluate the colorectal diet hypothesis

Proposed link	Possible mediator	Strength of conclusion
Animal fat → colon risk	Bile acids / microbiota	Implicated; Not firmly causal
Microbiota → mucosal injury	Bile acid metabolites	Biologically plausible
Fiber → protection	Bulk / transit / binding	Inconsistent mechanism studies
Exposure → cancer	Multiple long-term factors	Not reducible to one nutrient

Historical fiber-risk estimate needs context

- An estimate that intake near 40 g/day could halve colon cancer risk.
- This estimate is presented in a discussion of proposed protective effects.
- Robbins immediately notes inconsistent confirmation of relevant theories.
- Do not present the historical figure as an individualized or established risk reduction.

Association is not a dosing recommendation

What was reported

- An estimated effect of increasing population fiber intake.
- A proposed link between bulk, transit, and carcinogen contact.
- A topic warranting investigation.

What remains unresolved

- Causal magnitude in humans
- Applicability to different populations and fibers
- A universal therapeutic target for cancer prevention

Antioxidants are a prevention hypothesis

- Reactive oxidant injury provides a rationale for antioxidant protection.
- Vitamins C and E, β -carotene, and selenium.
- Their antioxidant properties motivated chemoprevention hypotheses.
- Biological plausibility alone is insufficient to establish benefit.

Putative antioxidant micronutrients

Vitamin C

- Antioxidant activity
- Not proven as chemopreventive

Vitamin E

- Antioxidant activity
- Not proven as chemopreventive

β-Carotene

- Antioxidant-associated rationale
- No convincing preventive evidence here

Selenium

- Antioxidant-associated rationale
- No convincing preventive evidence here

Nutritional adequacy versus supplementation

Nutritional concept

- Micronutrients have physiological functions.
- Dietary adequacy and cancer prevention are different questions.
- Associations can prompt research.

Chemoprevention claim

- Requires evidence that intake reduces cancer incidence.
- Antioxidant action is not sufficient evidence.
- Robbins finds no convincing prevention benefit.

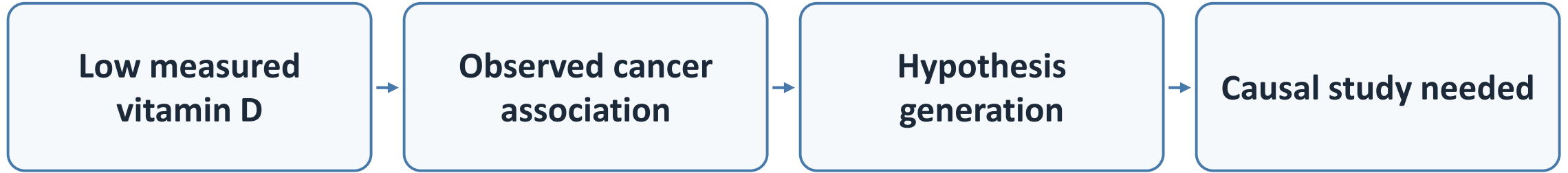
Antioxidant chemoprevention is unproven

- Robbins does not find convincing evidence for preventive effects.
- A proposed anticarcinogenic mechanism cannot replace clinical outcomes.
- Do not imply vitamin supplementation reliably prevents malignancy.
- Treatment indications elsewhere cannot validate a prevention claim.

Retinoids in acute promyelocytic leukemia

- The efficacy of retinoids in treating acute promyelocytic leukemia.
- This is a therapeutic oncology application.
- It does not establish that dietary antioxidant supplements prevent cancer.
- Treatment of an established neoplasm and primary prevention are distinct endpoints.

Vitamin D: Observation is not intervention



- Associations with cancers of the colon, prostate, and breast.
- The text does not establish that vitamin D supplementation prevents these tumors.

Vitamin D associations: Two possible readings

Association observed

- Low vitamin D levels occur with some cancers.
- A potential biological relationship can be studied.
- This observation has no necessary intervention effect.

Other explanations

- Confounding by behaviors or disease states
- Reverse causality or correlated risk factors
- Other unmeasured determinants

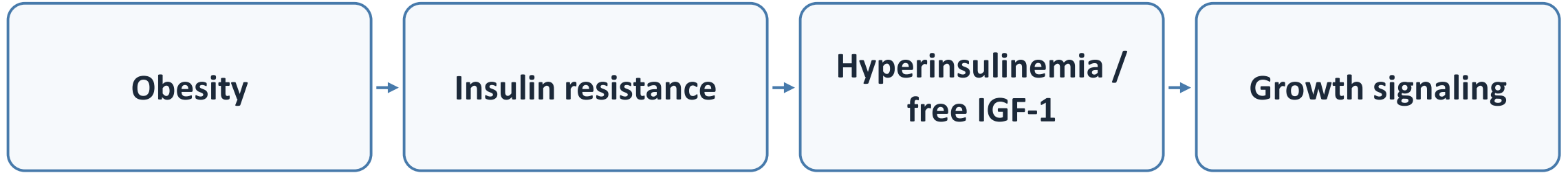
Diet and obesity are related but not identical

- Dietary composition and body adiposity are distinct exposures.
- Obesity-associated cancer immediately before this section.
- Obesity may alter hormones, metabolism, and inflammatory signaling.
- Benefits of a healthy dietary pattern should not be equated with proven effects of a single food.

Cancer sites linked to obesity

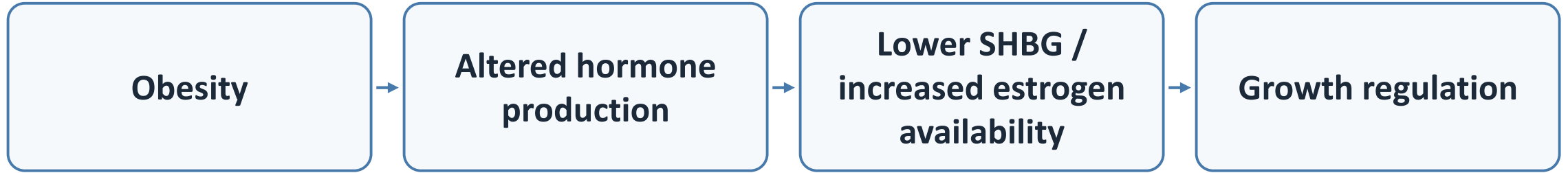
Gastrointestinal	Hormone-responsive	Additional sites
Esophagus / upper stomach	Endometrium	Kidney
Colon / rectum	Breast	Meningioma
Gallbladder / liver	Ovary	Multiple myeloma
Pancreas	—	—

Insulin resistance can increase growth signaling



- IGF-1 receptor signaling to RAS and PI3K/AKT pathways.
- This is one proposed contributor, not a sole explanation for obesity-associated cancers.

Adiposity alters sex-steroid availability

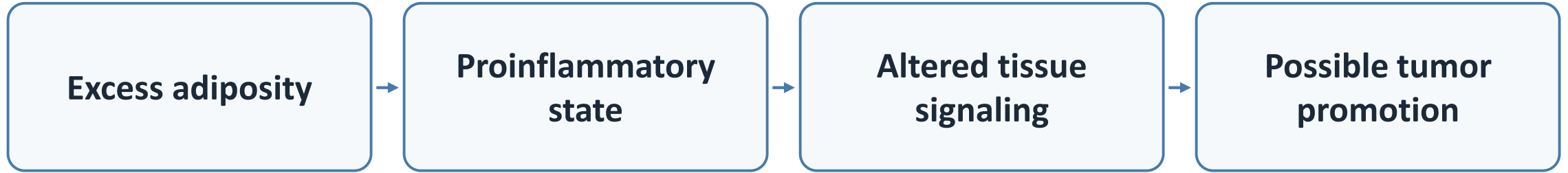


- Estrogen synthesis from androgen precursors and lower hepatic SHBG.
- These changes are relevant to hormone-responsive tissues.

Adiponectin: A proposed protective signal

- Adiponectin secretion decreases in obesity.
- Antiproliferative and pro-apoptotic actions.
- The proposed links include promotion of p53 and p21 activity.
- Reduced signaling could weaken antineoplastic influences.

Chronic inflammation is another candidate link



- Obesity-associated inflammation as a possible carcinogenic mechanism.
- The cancer relationship is likely multifactorial.

No single obesity–cancer mechanism explains all sites

Systemic mediators

- Insulin / IGF-1 signaling
- Steroid-hormone changes
- Adiponectin reduction

Local and contextual effects

- Chronic inflammation
- Cancer-site differences
- Long duration and degree of adiposity

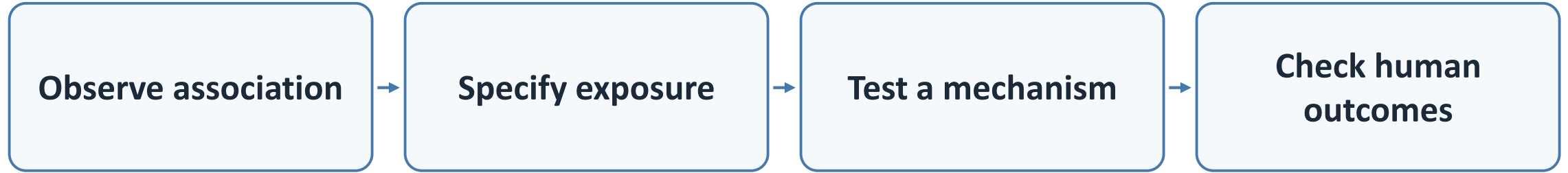
Weight-loss drugs: An open cancer question

- GLP-1 agonists as an area of interest for future research.
- Their possible effects on obesity-associated cancer incidence remain to be determined in this source.
- Weight reduction is not equivalent to established pharmacologic cancer prevention.
- Do not claim a protective cancer outcome from a question still under study.

Rank the strength of textbook claims

Claim	What the source supports	Avoid saying
Aflatoxin → HCC	Recognized contributor; TP53 signature	Every HCC has that mutation
Nitroso compounds → gastric cancer	Animal carcinogenicity; Possible human route	Processed food uniquely causes gastric cancer
Fiber → reduced colon cancer	Proposed protective mechanisms	Specific fiber dose reliably halves risk
Antioxidants → prevention	Plausibility; No convincing prevention proof	Supplements prevent cancer

How to appraise a diet–cancer claim



- Distinguish correlation, biological plausibility, and intervention effects.
- Ask whether cancer incidence—not merely a biomarker—was assessed.
- Keep uncertainty visible in conclusions.

Applied interpretation: An HCC mutation

Clinical / reasoning prompt

An HCC contains a TP53 alteration at codon 249. The clinical team asks whether this establishes aflatoxin exposure.

Interpretation

- This mutation is a molecular signature associated with aflatoxin.
- It supports etiologic interpretation in context, but is not a complete exposure history.
- Consider viral and other carcinogenic influences.

Applied interpretation: Gastric carcinogens

Clinical / reasoning prompt

A proposed preventive message states: “All nitrate-containing vegetables cause gastric cancer.”
How should the evidence be assessed?

Interpretation

- Reject the conclusion: Nitrate can be converted to nitrite, which may form nitroso compounds.
- The pathway does not demonstrate that eating vegetables causes gastric cancer.
- Distinguish precursor chemistry from human causal effects.

Applied interpretation: Colorectal fiber

Clinical / reasoning prompt

A patient reads that increasing fiber to 40 g/day will cut personal colon cancer risk by 50%. What is the defensible response?

Interpretation

- The number is a historical estimate cited, not an individual prognostic calculation.
- Proposed benefits involve stool bulk, transit, or binding.
- Mechanistic studies have produced inconsistent results.

Applied interpretation: Vitamin supplementation

Clinical / reasoning prompt

A person asks whether antioxidant supplements reliably prevent cancer. Another asks about low vitamin D levels and malignancy.

Interpretation

- Robbins finds no convincing chemopreventive evidence for named antioxidants.
- Low vitamin D–cancer associations do not demonstrate prevention by supplementation.
- Do not conflate anticancer therapy with nutritional prevention.

Prevention message: Proportionate to evidence

- Avoid certainty that a particular diet alone causes or prevents cancer.
- A healthy diet that helps prevent obesity is a reasonable general-health strategy.
- Be explicit when discussing speculative chemical or microbial mechanisms.
- Keep the cancer-prevention claim separate from other health benefits.

Integrated diet–cancer mechanism map

Domain	Main exemplar	Inference boundary
External exposure	Aflatoxin / TP53 codon 249	Molecular signature in HCC
Internal synthesis	Nitrosamines / nitrosamides	Gastric hypothesis; Animal evidence
Local intestinal milieu	Fat–bile acids–microbiota	Proposed CRC mediator
Missing protective factor	Fiber / antioxidants	Inconsistent or nonconvincing human evidence
Energy regulation	Obesity-associated pathways	Multifactorial cancer association

Final synthesis

- Diet enters carcinogenesis through exposures, chemical formation, and putative protection.
- Aflatoxin provides a relatively specific exposure–mutation–tumor example.
- Nitrosation, bile-acid conversion, and fiber protection remain mechanistically plausible but incompletely demonstrated.
- Nutrient supplementation should not be recommended as proven anticancer chemoprevention.

Selected reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026)

Chapter 9: Environmental and Nutritional Diseases

“Diet and Cancer,” p. 409; related “Obesity and Cancer,” pp. 408–409.