Drinking Water Contaminants as Biologically Plausible Drivers of Colorectal Cancer Pathogenesis

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Common drinking-water contaminants are not established causes of Colorectal Cancer (CRC), but converging epidemiologic and mechanistic evidence supports a biologically plausible pathway linking chronic exposure to genotoxic stress, inflammation, dysbiosis, and tumor-promoting signaling. The next step is a Midland County, Michigan, study linking water-system geography, CRC incidence, and screening patterns.

Introduction

Colorectal cancer (CRC) remains a major public health burden, with incidence increasing in some populations despite expanded screening.

Although improved detection may contribute to observed trends, persistent increases suggest additional environmental and lifestyle factors may influence underlying CRC risk.

Persistent CRC trends increase despite increasing screening raise the possibility that geographically patterned environmental exposures may contribute to underlying disease risk.

Drinking water is a continuous, population-wide exposure pathway; its role in CRC pathogenesis remains underexamined.

This project synthesizes the literature and frames a local exposure-incidence study in Midland County.

PRIMARY OBJECTIVES

1. Evaluate epidemiologic + mechanistic evidence linking nitrate, THMs/DBPs, metals, and microbial pollutants to colorectal carcinogenesis.
2. Identify gaps that justify a future study integrating local water quality, CRC incidence, residential geography, and screening data.

Methods

We reviewed epidemiologic, experimental, biomarker, metabolomic, and microbiome literature. We organized evidence by contaminant class, exposure metric, CRC outcome/surrogate endpoint, proposed mechanism, host susceptibility, and causal-inference limitations.

Studies were evaluated for the following criteria:

EXPOSURE
- Long-term drinking water contamination (Nitrate, THMs/ DBPs, metals, and microbial pollutants)

OUTCOME
- CRC incidence, risk, biologically relevant carcinogenic mechanisms

EVIDENCE TYPE
- Human epidemiology, mechanistic/ experimental studies, systematic reviews/ meta-analyses

METHODOLOGICAL CONSIDERATIONS
- Exposure reconstruction, residential or utility level linkage, screening/detection effects, confounding and effect modification

RESEARCH GAPS
- Fine scale geographic linkage, long-term exposure assessment, integration of screening history, and understudied contaminant mixtures

Results

EVIDENCE IS STRONGEST FOR NITRATE AND THMS; MECHANISMS CONVERGE ACROSS CONTAMINANT CLASSES

Nitrate / nitrite	Most developed epidemiology	N-nitroso compounds; DNA damage; genomic instability
THMs / DBPs	Developed epidemiology + biomarkers	Inflammation; angiogenesis; altered redox/xenobiotic metabolism
Arsenic/ Chromium/ Metals	Experimental + emerging human data	ROS generation; oxidative DNA injury; Wnt/β-catenin signaling
Microbial pollutants	Biologic plausibility; limited analytic epidemiology	Dysbiosis; barrier dysfunction; chronic mucosal inflammation

MAGNITUDE REPORTED IN SELECTED HIGH-VS-LOW EXPOSURE COMPARISONS

Nitrate
~14–15% higher CRC risk

THMs / DBPs
~15–27% higher CRC risk

Ranges reflect estimates reported across reviewed studies; they do not establish direct causality.

Converging Biological Mechanisms

DRINKING WATER EXPOSURE → **BIOLOGIC EFFECTS** → **CRC PATHOGENESIS**

- Nitrate/Nitrites → N-nitroso compounds → DNA damage
- THMs/DBPs → inflammatory cytokines + angiogenic mediators
- Arsenic/Chromium/Metals → ROS + oxidative DNA injury + Wnt/β-catenin signaling
- Microbial pollutants → dysbiosis + barrier dysfunction + chronic mucosal inflammation
- Host modifiers → red/processed meat intake, antioxidant status, genetic/epigenetic susceptibility

Shared downstream pattern: genotoxic stress + oxidative injury + chronic inflammation + angiogenesis + metabolic reprogramming + tumor-promoting microenvironment

Evidence Boundary

What the review supports: biologic plausibility and rationale for stronger local investigation.
Research does not yet prove a direct causal relationship between drinking-water contamination and local CRC burden.

Review-to-Study Bridge

Literature review → prioritized contaminants + pathways
Water-system dataset → exposure geography and violation patterns
Registry/screening data → determine whether burden reflects detection or underlying risk

Discussion

- Nitrates and THMs/DBPs have the strongest epidemiologic support in this review.
- Metals and microbial contaminants broaden the exposure model through plausible pathways involving ROS, DNA damage, dysbiosis, barrier dysfunction, and inflammation.
- Current evidence supports biologic plausibility, not direct causation; future studies need stronger exposure reconstruction and screening adjustment.
- A Midland County water-quality dataset can serve as the foundation for spatial analyses and future tissue, biospecimen, organoid, animal, and biomarker studies.

METHODOLOGIC GAPS THAT WEAKEN CAUSAL INTERPRETATION

- Exposure misclassification from utility-level or modeled estimates.
- Incomplete residential histories and long etiologic windows.
- Limited private well, bottled-water, filtration, and household-level use data.
- Limited fine-scale geographic analyses linking water systems to CRC outcomes.
- Screening history is incorporated inconsistently, making it difficult to separate detection effects from underlying risk.
- Contaminant mixtures, metals, microbes, PFAS, and biomarker translation remain underdeveloped.

Future Direction

Advance from narrative synthesis to a locally grounded analytic framework that integrates contaminant exposure, host susceptibility, inflammatory/metabolomic signatures, gut dysbiosis, and CRC outcomes.

Proposed Next Study

MIDLAND COUNTY, MICHIGAN: GEOGRAPHICALLY RESOLVED DESIGN

Build longitudinal water-system × year dataset

Assign geography by service area / residence

Link CRC incidence and registry outcomes

Account for screening patterns

Primary question: Do persistent geographic differences in drinking-water quality correspond with CRC burden after accounting for screening-related detection?

PLANNED EXPOSURE VARIABLES

TTHM | **HAA5** | **Nitrate / nitrite** | **Arsenic** | **Chromium**

PFAS | **Violation / exceedance counts** | **Aggregate exposure levels**

Implications

If a spatial exposure-incidence signal persists after accounting for screening, findings could guide targeted prevention, exposure mitigation, and mechanistic biomarker studies in high-burden communities.

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References