Long COVID and Cancer Biology: Distinguishing Mechanistic Overlap from Evidence Across Cancer-Related Outcomes

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Abstract

Long COVID is associated with persistent immune, inflammatory, vascular, and metabolic abnormalities that overlap with cancer-relevant pathways. These observations have prompted hypotheses about cancer, but de novo incidence, recurrence or progression of pre-existing disease, and treatment efficacy, toxicity, and tolerance (including treatment modification or interruption) are distinct outcomes and require separate evaluation.

This Perspective assesses those outcomes separately. Direct Long COVID-specific evidence is insufficient to determine whether de novo cancer incidence is increased, unchanged, decreased, or subgroup-specific. Experimental and observational studies after respiratory viral infection raise credible questions about dormant or established malignancy, but they are not equivalent to evidence from clinically characterized Long COVID cohorts. Evidence regarding anticancer treatment outcomes is also limited and heterogeneous.

Pandemic-era and SARS-CoV-2 infection cohorts provide context but cannot substitute for longitudinal studies comparing clinically defined Long COVID with matched recovered controls. Apparent post-pandemic cancer trends may reflect screening and diagnostic disruption; the long latency of many cancers also limits biological inference from short follow-up. Outcome-specific follow-up should specify the Long COVID definition, baseline cancer risk, latency, and cancer endpoints. Current evidence

therefore supports uncertainty about the direction or magnitude of any Long COVID-specific effect on cancer incidence, recurrence, progression, or treatment efficacy, toxicity, and tolerance.

Keywords: long COVID; cancer biology; carcinogenesis; immune dysregulation; chronic inflammation; tumor progression

1. Introduction

Long COVID is a heterogeneous post-acute condition with symptoms and diagnosable conditions arising from combinations of immune, autonomic, vascular, metabolic, and tissue-level abnormalities. [1,2] For this Perspective, Long COVID refers to a post-SARS-CoV-2 condition present for at least 3 months, consistent with the 2024 National Academies definition. [3] The World Health Organization uses a related definition in which symptoms usually begin within 3 months and last at least 2 months. [4] Long COVID is the term used throughout this Perspective. Because study definitions vary, cohorts defined by post-acute diagnoses or sequelae are not automatically equivalent to clinically defined Long COVID cohorts.

Primary Long COVID studies have identified persistent inflammatory signaling, immune dysregulation, complement abnormalities, and T-cell activation or exhaustion. [5-8] These findings intersect with cancer biology. [9] A peer-reviewed review discusses possible oncogenic or tumor-promoting effects of SARS-CoV-2-related biology, [10] whereas a recent review emphasizes mechanistic convergence and uncertainty. [11] Neither establishes a clinically defined Long COVID-specific cancer effect.

A pathway can be relevant to cancer without being carcinogenic, and a biological state can influence an existing tumor without initiating a new malignancy. This Perspective therefore evaluates three questions separately: de novo cancer incidence, recurrence or progression of pre-existing malignancy, and anticancer treatment efficacy, toxicity, and tolerance (including treatment modification or interruption).

A targeted PubMed search was updated through 17 September 2026 using combinations of Long COVID or post-COVID condition with cancer, carcinogenesis, incidence, recurrence, metastasis, treatment

response, immune dysregulation, inflammation, viral persistence, and tumor dormancy. Primary human, longitudinal, and mechanistic studies were prioritized; reviews were used for context and citation chaining. This was a narrative, nonsystematic search without protocol registration, formal risk-of-bias assessment, or formal evidence grading.

2. An outcome-specific evidence framework

Established oncogenic viruses are linked to cancer through converging epidemiologic, molecular, and tissue-specific evidence, including persistent infection, tumor associations, effects on oncogenes or tumor-suppressor pathways, genomic instability, immune suppression, and chronic inflammation. [12] For SARS-CoV-2 and Long COVID, cancer-relevant pathway activity is mechanistic context; each clinical outcome requires its own direct evidence.

Figure 1 presents an outcome-specific framework rather than a single sequential causal pathway. Shared biology and persistence may motivate hypotheses, but de novo incidence, recurrence or progression, and treatment efficacy, toxicity, and tolerance are parallel questions. De novo incidence concerns new primary cancer in people without known malignancy; recurrence or progression begins with malignant cells already present; treatment studies evaluate efficacy, toxicity, and tolerance, including treatment modification or interruption. Evidence in one branch cannot establish another.

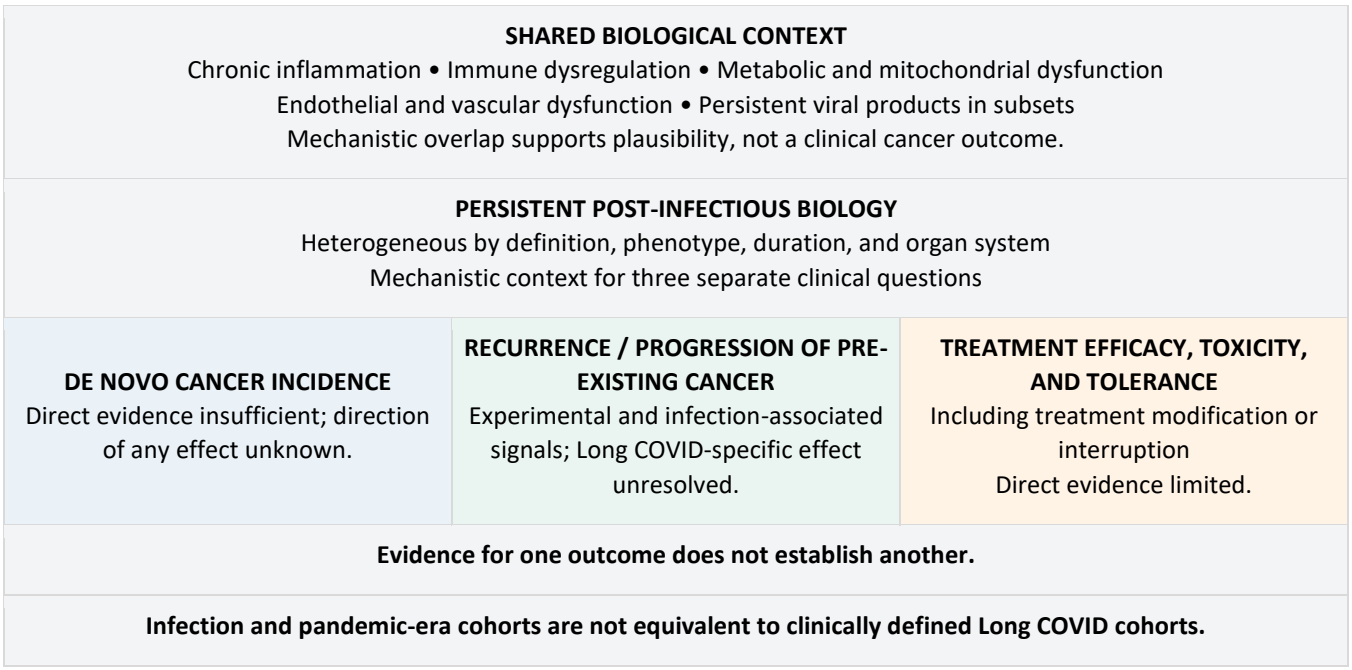

Figure 1. Outcome-specific evidence framework for Long COVID and cancer biology. Shared cancer-relevant mechanisms and heterogeneous persistent post-infectious biology provide mechanistic context for three separate clinical questions: de novo cancer incidence, recurrence or progression of pre-existing malignancy, and treatment efficacy, toxicity, and tolerance (including treatment modification or interruption). Evidence in one outcome domain does not establish another. Pandemic-era or SARS-CoV-2 infection cohorts provide contextual information but are not equivalent to clinically defined Long COVID cohorts.

Persistent viral products illustrate the issue of directness. In a blinded two-year study, circulating SARS-CoV-2 antigen was more frequent in Long COVID than in recovered participants at 6-12 months, but at 18-24 months positivity was 3.5% in Long COVID, 0% in recovered participants, and 1.5% in uninfected controls. [13] Late antigen positivity was low across all three groups, including a small proportion of uninfected controls. Other studies detected circulating spike in some participants with persistent post-acute symptoms, as defined in the study [14] and gut antigen persistence after acute COVID-19. [15] These findings support persistence in subsets but do not establish a cancer outcome.

3. Cancer-relevant biology in Long COVID: mechanistic evidence and limits

Primary Long COVID studies have identified sustained immune activation, T-cell dysregulation or exhaustion, inflammatory abnormalities, and complement-associated thromboinflammatory signals. [5-8] In cancer, inflammatory and immune states can affect tumor growth, immune escape, and the

microenvironment. [9] Whether a Long COVID immune phenotype matters for cancer therefore depends on tissue, duration, cell type, tumor context, and the outcome studied.

Metabolic and mitochondrial dysfunction provide another overlap. A skeletal-muscle study in Long COVID demonstrated reduced exercise capacity and post-exertional worsening with local and systemic metabolic abnormalities. [16] Cancer also alters cellular energetics, but reduced oxidative capacity in symptomatic muscle is not equivalent to the metabolic adaptations supporting malignant-cell survival and proliferation.

Endothelial and microvascular abnormalities, oxidative stress, senescence-associated pathways, and viral persistence have also been reported or proposed in Long COVID. [2,8,13-15] These observations broaden mechanistic plausibility but remain upstream of cancer-specific clinical endpoints.

Long COVID heterogeneity further complicates inference. Dominant phenotypes and definitions vary across studies. [1-4] Combining symptom-defined Long COVID, diagnosis-code cohorts of post-acute sequelae, and post-hospital sequelae may mix clinically and biologically different populations. Cancer studies should therefore report the operational Long COVID definition, acute infection severity, vaccination and reinfection history, duration, and relevant phenotype characteristics.

4. Clinical evidence by cancer-related outcome

4.1 De novo cancer incidence: Long COVID-specific evidence is insufficient

In this targeted, nonsystematic search, no directly relevant study was identified comparing site-specific incident cancer in a clinically defined Long COVID cohort with matched SARS-CoV-2 survivors who recovered without Long COVID. The appropriate inference is uncertainty: current evidence does not determine whether Long COVID-specific cancer incidence is increased, unchanged, decreased, or subgroup-specific.

The population and infection studies below are contextual rather than direct tests of Long COVID. A US SEER-22 analysis found that overall cancer incidence in 2021 was lower than in 2018-2019; increases

observed for nine rare cancer types were likely explained by changes in cancer reporting standards. [17] A veteran cohort found a lower observed hazard of cancer diagnosis after a positive COVID-19 test, a result vulnerable to survivor, healthcare-utilization, testing, and ascertainment biases. [18] An Italian cohort reported increased diagnoses during the pandemic while noting delayed diagnosis and screening disruption. [19] None clinically phenotyped Long COVID as the exposure.

Qian and colleagues reported an association between hospitalization for severe COVID-19 and subsequent lung cancer and showed accelerated lung tumor growth after respiratory viral infection in murine models. [20] This is an important post-infectious signal, but the human exposure was severe COVID-19 hospitalization rather than clinically characterized Long COVID, and the mechanistic work was lung-specific. It is not a Long COVID-specific incidence estimate.

These studies show why infection history, acute severity, screening behavior, healthcare utilization, and Long COVID status must be separated analytically. They do not resolve the Long COVID-specific incidence question, and not identifying a direct study in this search is not evidence for either increased or unchanged risk

4.2 Effects on pre-existing or dormant malignancy are a distinct question

The strongest experimental evidence linking respiratory viral infection with cancer biology concerns malignant cells that already exist. In mice, influenza and SARS-CoV-2 triggered interleukin-6 (IL-6)-dependent awakening and expansion of dormant disseminated breast cancer cells in the lung. In human analyses from the same study, breast-cancer patients who developed COVID-19 had an adjusted hazard ratio of 1.44 (95% CI, 1.01-2.05) for subsequent lung metastasis; after additional adjustment, the estimate was 1.41 (95% CI, 0.97-2.04) and was no longer statistically significant. [21]

These findings support the possibility that respiratory inflammation can influence dormant or established malignant cells. They do not show transformation of normal cells, and the human exposure was infection after cancer diagnosis rather than Long COVID. Long COVID-specific recurrence studies

therefore require cancer-survivor cohorts with explicit tumor type, residual-disease risk, infection severity, Long COVID definition, and follow-up.

Recurrence or metastatic progression and de novo incidence should not be combined. The former begins with known or presumed malignant cells; the latter begins without known cancer. Their cohorts, confounders, endpoints, and latency assumptions differ.

4.3 Treatment efficacy, toxicity, and tolerance (including treatment modification or interruption)

Post-acute morbidity in patients with cancer does not establish effects on treatment efficacy, toxicity, and tolerance. A 2026 cohort of 76,807 patients with cancer evaluated post-acute diagnoses and symptoms after Omicron infection. [22] These study-defined post-acute outcomes should not be assumed to identify clinically defined Long COVID. They describe illness burden, not anticancer treatment efficacy, toxicity, and tolerance.

The OnCovid registry more directly examined cancer care: among 466 patients receiving systemic anticancer therapy before COVID-19, 15.0% permanently discontinued therapy and 38.2% resumed with a dose or regimen modification; permanent discontinuation was associated with higher mortality. [23] This observational early-pandemic cohort cannot isolate a biological Long COVID effect from acute illness severity, treatment interruption, or other factors. A small lung-cancer study found immune-microenvironment changes after SARS-CoV-2 infection without impaired long-term progression-free survival on checkpoint inhibitors. [24] A review has proposed possible effects of persistent inflammation on immunotherapy response. [25] Prospective cohorts evaluating treatment efficacy, toxicity, and tolerance (including treatment modification or interruption) in clinically defined Long COVID remain needed.

The principal claims and the evidence needed to support them are summarized in **Table 1**.

Table 1. Evidence boundaries for proposed Long COVID-cancer relationships

Question	Direct Long COVID evidence and endpoint	Contextual evidence	Main uncertainty
Shared cancer-relevant biology	Biological abnormalities: primary studies document immune, inflammatory, metabolic, vascular, complement, and antigen-related abnormalities in subsets of Long COVID. These are not cancer outcomes.	Supports mechanistic overlap and biological plausibility.	Which abnormalities, if any, produce tumor-specific effects, in which tissues and phenotypes.
De novo cancer incidence	Cancer outcome: the targeted, nonsystematic search did not identify a directly relevant study of site-specific incident cancer comparing clinically defined Long COVID with matched recovered survivors.	Pandemic and infection cohorts are mixed; a 2026 severe-COVID study reported a lung-cancer signal with supporting murine mechanisms.	Whether clinically defined Long COVID changes site-specific incidence over adequate follow-up.
Recurrence or progression of pre-existing cancer	Cancer outcome: the targeted, nonsystematic search did not identify a directly relevant prospective study comparing recurrence or progression in cancer survivors with clinically defined Long COVID against comparable recovered survivors without Long COVID.	Respiratory viral infection can alter dormant or established malignant-cell behavior in experimental models; human signals are limited.	Whether Long COVID changes recurrence or progression in defined cancer-survivor populations.
Treatment efficacy, toxicity, and tolerance (including treatment modification or interruption)	Treatment outcomes: direct evidence for efficacy, toxicity, and tolerance in clinically defined Long COVID remains limited. Post-acute symptoms and biological abnormalities alone do not establish a treatment effect.	Cancer cohorts after SARS-CoV-2 infection show sequelae and treatment changes; a small immunotherapy cohort found immune changes without impaired long-term progression-free survival.	Whether Long COVID independently affects treatment efficacy, toxicity, and tolerance (including treatment modification or interruption).
Pandemic-era cancer trends	No direct Long COVID exposure: calendar-period trends do not measure a clinically defined Long COVID cohort or a Long COVID-specific cancer outcome.	Useful for identifying health-system effects, diagnostic disruption, and hypotheses.	How much temporal change reflects biology versus screening, diagnosis, healthcare utilization, registry effects, or infection severity.

Legend: Direct Long COVID biological evidence documents abnormalities in participants with Long COVID; it does not establish a cancer outcome. Direct cancer-outcome evidence requires the specific outcome to be evaluated in a clinically defined Long COVID cohort with an appropriate comparator. Statements that a study was not identified refer to the targeted, nonsystematic search updated through 17 September 2026 and do not establish that no such study exists. Contextual pandemic-era, infection, and post-acute sequelae cohorts are not treated as equivalent to clinically defined Long COVID cohorts. The table describes study design and directness without assigning formal certainty grades.

5. Interpreting post-pandemic cancer trends and latency

The pandemic complicated cancer epidemiology through interrupted screening, delayed procedures, altered diagnostic pathways, healthcare avoidance, and registry changes. These effects varied by cancer type, region, age, and health system. A rise in diagnoses after disruption can therefore reflect delayed detection of prevalent disease rather than new biological initiation. [17,19]

Latency also varies by cancer type and stage of evolution. In pancreatic cancer, genomic reconstruction estimated at least a decade between an initiating mutation and the parental nonmetastatic founder clone, followed by additional years before metastatic capability. [26] This illustrates why short follow-up cannot resolve all delayed outcomes, while early increases may reflect detection effects. Stronger inference requires individual-level infection and Long COVID phenotyping, baseline cancer-risk assessment, adequate follow-up, and recovered controls.

Temporal sequence alone does not determine causation. Attribution requires an appropriate comparator, control of confounding, a plausible latency structure, and outcome-specific evidence.

6. Research priorities for resolving the separate outcomes

Research should be organized by outcome rather than a single concept of cancer risk. For de novo incidence, the priority is a longitudinal cohort comparing well-characterized Long COVID with matched recovered SARS-CoV-2 survivors, excluding active cancer at baseline. Matching or adjustment should

include age, sex, smoking, obesity, baseline cancer risk, acute severity, vaccination, reinfection, healthcare utilization, and screening participation.

Cancer endpoints should be registry-verified and site-specific. New primary cancer, recurrence, metastatic progression, treatment efficacy, toxicity, and tolerance (including treatment modification or interruption) should remain separate outcomes. Mechanistic biomarkers are most informative when prespecified and linked to an outcome-specific intermediate or clinical endpoint rather than treated as surrogate evidence of cancer risk.

Cancer-survivor cohorts should test recurrence and dormancy while accounting for time from treatment, residual-disease risk, tumor subtype, infection severity, Long COVID definition, and inflammatory trajectories. Treatment cohorts should prospectively evaluate treatment efficacy, toxicity, and tolerance (including treatment modification or interruption). Long COVID phenotype and duration should be reported rather than inferred from a general post-COVID label.

This Perspective does not propose a Long COVID-specific cancer-screening strategy. Such a strategy cannot be inferred from mechanistic overlap or the contextual studies reviewed here. Any future surveillance recommendation would require outcome-specific evidence and evaluation within established cancer-specific guideline processes.

7. Conclusion

Long COVID and cancer biology intersect through inflammatory, immune, metabolic, vascular, and persistence-related pathways, but several clinical questions remain unresolved. Direct Long COVID-specific incidence data are insufficient to determine whether de novo cancer risk differs from matched recovered controls. Experimental and infection-associated studies support investigation of dormant or established malignancy, while treatment-related evidence remains limited and heterogeneous. These are parallel questions, not a single causal sequence.

Future studies should use explicit Long COVID definitions, recovered controls, adequate latency, baseline cancer-risk assessment, and outcome-specific endpoints. The current position is defined uncertainty rather than reassurance or alarm: mechanistic overlap and selected post-infectious signals are documented, but whether Long COVID changes specific cancer outcomes, in whom, and over what time horizon remains inadequately studied.

Abbreviations

CI, confidence interval; COVID-19, coronavirus disease 2019; IL-6, interleukin-6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Conflicts of Interest

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Availability of Data and Materials

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AI-declaration

No generative AI or AI-assisted tools were used by the author to prepare the manuscript previously submitted for editorial review. OpenAI ChatGPT (Codex) assisted with implementing the requested editorial revisions, preparing the revised schematic, and drafting the response to the editor for the present revision. The author is responsible for the accuracy and final content of the manuscript. The author did not use AI tools for the original modifications made in Microsoft Paint.

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