Familial Cancer Clustering Following COVID-19 Pandemic: Evidence for Long COVID-Associated Inflammatory Carcinogenesis in Genetically Susceptible Individuals

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Abstract

This case series describes eight members of a single extended family who developed nine different cancers between 2021 and 2025, despite living 1,000 miles apart and having no prior family history of cancer. The cancers included melanoma, prostate, thyroid, hepatobiliary, squamous cell carcinoma, and myelodysplasia. The study explores possible links between these cancer cases and long COVID-related chronic inflammation, viral oncogenesis, and genetic susceptibility. The geographic separation and diversity of cancer types suggest a systemic, rather than environmental, cause. The findings raise concerns about SARS-CoV-2 potentially acting as a systemic carcinogen in genetically predisposed individuals, emphasizing the need for further research into virus-associated cancer mechanisms.

Introduction

The COVID-19 pandemic has led to not only acute illness but also long-term complications, notably long COVID, which affects at least 10% of infected individuals and involves persistent systemic inflammation [1–3,6–9]. This chronic inflammatory state, characterized by cytokine activity (e.g., IL-6, IFN-γ), has raised concerns about its potential role in cancer development [8–16].

Historically, chronic inflammation has been linked to malignancies such as lung, liver, pancreatic, and HIV-related cancers [13]. SARS-CoV-2 may act similarly to oncogenic viruses, through mechanisms like immune dysregulation, tumor suppressor disruption, and tissue damage, promoting a carcinogenic environment [17–20].

Additionally, genetic susceptibility, including syndromes like FAMMM (CDKN2A mutation), may increase vulnerability to a broader range of cancers than previously recognized [21–25]. These factors raise the possibility that COVID-19 could serve as a systemic carcinogenic trigger in predisposed individuals.

Case presentation

This case series describes eight members of a previously cancer-free extended family who developed nine distinct malignancies between 2021 and 2025, following the COVID-19 pandemic [1]. The family spans three generations, with individuals aged 37 to 80, living in two locations 1,000 miles apart, ruling out shared environmental exposures.

The index case, a 44-year-old male, was diagnosed with stage IV desmoplastic melanoma in 2021—a rare and aggressive melanoma subtype comprising <4% of cases [26]. He had no known risk factors or family cancer history.

Within four years, seven more relatives developed cancers including:

- Melanoma (3) and invasive squamous cell carcinoma (1) [dermatologic]
- Prostate adenocarcinoma (2) [genitourinary]
- Papillary thyroid carcinoma (1) [endocrine]
- Combined liver and gallbladder carcinoma (1) [hepatobiliary]
- High-risk myelodysplastic syndrome (1) [hematologic]

The temporal clustering and diverse cancer types suggest a systemic carcinogenic trigger, rather than isolated genetic or environmental causes. This pattern aligns with proposed mechanisms of COVID-19-related inflammatory carcinogenesis in genetically susceptible individuals [4,5,14–16,19,20].

Literature review and Pathophysiological framework

Long COVID and Chronic Inflammation:

Long COVID is characterized by persistent immune activation and inflammation, including complement system activation, myeloid cell inflammation, and sustained interferon gamma (IFN-γ) production [27–33]. These inflammatory signatures distinguish long COVID from full recovery and have been linked to fatigue, tissue damage, and prolonged symptomatology.

Inflammation and Carcinogenesis:

Chronic inflammation is a known driver of cancer through molecular pathways such as IL-6/STAT3/NF-κB activation, transcription factor dysregulation, and epigenetic modifications [34–40]. These changes promote tumor growth, immune evasion, and genomic instability. Inflammatory cytokines also alter the tumor microenvironment, sustaining oncogenic processes [41].

SARS-CoV-2 as a Potential Oncogenic Virus:

SARS-CoV-2 may contribute to carcinogenesis through:

- Direct effects on apoptosis, DNA repair, and cell cycle pathways [42]
- Immune dysregulation compromising tumor surveillance [43]
- Viral persistence, fueling chronic inflammation [44]
- Metabolic disruption, affecting mitochondrial and cellular energy pathways [45]

Genetic Susceptibility – CDKN2A and FAMMM:

The family's melanoma clustering suggests a role for CDKN2A mutations, which impair tumor suppressor proteins p16INK4A and p14ARF [46]. These mutations are linked to a broad cancer spectrum beyond melanoma, including neural, breast, head and neck, and soft tissue tumors [47,48]. Some CDKN2A variants may predispose to cancer without classical FAMMM features, highlighting the need for broader genetic testing criteria [49].

Age at Diagnosis	Relationship to Index	Cancer Type	Stage/Details	Year of Diagnosis	Location	Clinical Notes
44	Index case	Desmoplastic melanoma	Stage IV (bone, lung metastases)	2021	Location A	No prior sun exposure history
75	Father	Melanoma	Stage II	2024	Location B	Superficial spreading type
78	Uncle (paternal)	Melanoma + Prostate adenocarcinoma	Stage II melanoma, Gleason 7 prostate	2025	Location B	Synchronous primaries
80	Aunt (paternal)	Invasive squamous cell carcinoma (facial)	Stage II	2023	Location B	Aggressive growth pattern
76	Aunt by marriage	Hepatobiliary carcinoma	Involving liver and gallbladder	Not specified	Location B	Rare presentation
37	Wife (spouse)	Papillary thyroid carcinoma	Stage I	Not specified	Location A	Youngest affected member
78	Uncle (paternal)	Prostate adenocarcinoma	Stage II, Gleason 8	2023 (deceased)	Location B	Aggressive disease course
76	Mother	Myelodysplastic syndrome	High-risk	Not specified	Location B	Progressed rapidly

Discussion

This unprecedented familial cancer cluster, involving eight cases over four years post-COVID-19, suggests a potential link between SARS-CoV-2 infection and accelerated cancer development in genetically susceptible individuals, despite no prior family cancer history and geographic separation [50].

Key Findings and Proposed Mechanisms:

1. Inflammation-Driven Carcinogenesis:
2. COVID-19-induced cytokine storms, particularly involving IL-6, may cause chronic smoldering inflammation, a known driver of malignancy [50,51].
3. Viral Oncogenic Activation:
4. SARS-CoV-2 may disrupt cell cycle, inhibit apoptosis, and impair DNA repair, similar to oncogenic viruses, especially concerning in individuals with CDKN2A mutations [52,53].
5. Immune Surveillance Breakdown:
6. Post-COVID immune dysregulation, including reduced CD8+ T cells and NK cells, may impair cancer surveillance, allowing malignant transformation [54,55].
7. Genetic Susceptibility Amplification:
8. Inflammation may accelerate the impact of underlying genetic mutations (e.g., CDKN2A), through loss of tumor suppressor function, epigenetic silencing, and increased mutational burden [56].

Clinical Implications:

- Surveillance: Enhanced cancer screening may be warranted for COVID-19 survivors, especially those with long COVID or genetic predisposition.
- Genetic Testing: Broader testing for genes like CDKN2A, CDK4, and BAP1 should be considered in post-COVID cancer clusters.
- Anti-inflammatory Treatment: Targeting IL-6 and other pathways may offer preventive benefit in high-risk individuals.
- Population-Level Risk: If SARS-CoV-2 proves oncogenic in susceptible groups, the global cancer burden may increase significantly in coming years.

Limitations:

- Observational design limits causal inference.
- Single-family focus limits generalizability.
- Genetic and COVID exposure data are incomplete.
- Alternative explanations (e.g., undetected shared factors) cannot be fully excluded.

Future Research Priorities:

1. Epidemiological Studies:
2. Long-term tracking of cancer incidence in COVID-19 survivors, stratified by severity and genetics.
3. Mechanistic Research:
4. Laboratory models to explore viral–host interactions and oncogenic processes.
5. Genetic Investigations:
6. Germline and tumor sequencing in families with post-COVID cancer clustering.
7. Clinical Trials:
8. Testing anti-inflammatory therapies, enhanced surveillance, and lifestyle interventions to mitigate risk.

Conclusion

This unique case series of familial cancer clustering post-COVID-19 suggests a potentially groundbreaking link between SARS-CoV-2 infection and cancer development in genetically susceptible individuals. The combination of temporal proximity, geographic separation, and cancer diversity supports the theory of COVID-19-associated systemic carcinogenesis.

Proposed mechanisms include:

- Chronic inflammation (especially IL-6-driven)
- Viral activation of oncogenic pathways
- Compromised immune surveillance
- Amplified genetic susceptibility

Given the global scale of infection, this could signal a major emerging public health concern, with implications far beyond this single family.

Urgent Actions Recommended:

1. Large-scale research into post-COVID cancer incidence
2. Surveillance protocols for high-risk individuals
3. Expanded genetic testing for families with post-COVID cancer clusters
4. Clinical trials of anti-inflammatory therapies
5. Healthcare preparedness for a possible rise in cancer diagnoses

This case may be the first warning of a novel form of virus-induced cancer, highlighting the need for immediate scientific and medical investigation into the long-term oncogenic potential of SARS-CoV-2.

References

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