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ONCOGENIC MICROORGANISMS AND HUMAN CARCINOGENESIS: A SYSTEMATIC REVIEW OF PATHOGENIC MECHANISMS AND HISTOPATHOLOGICAL CHANGES

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Abstract

Background

A defined group of viruses, bacteria, and parasites contributes directly or indirectly to human carcinogenesis. These microorganisms may express oncogenic proteins, integrate into the host genome, promote chronic inflammation, alter immune surveillance, induce genomic and epigenetic injury, and create tissue environments that support clonal expansion. These biological processes are reflected in characteristic precursor lesions and histopathological patterns.

Objective: This systematic review examined the pathogenic mechanisms through which oncogenic microorganisms contribute to human cancer and correlated these mechanisms with sequential histopathological changes. It also evaluated the diagnostic importance of demonstrating microorganisms or validated surrogate markers within neoplastic tissue.

Methods: PubMed/MEDLINE, Embase, Scopus, and Web of Science were searched from database inception to January 31, 2026. Supplementary searches were conducted through Google Scholar, International Agency for Research on Cancer resources, citation tracking, and manual screening of reference lists. Human epidemiological studies, clinicopathological investigations, molecular tumour studies, prospective cohorts, intervention studies, and selected mechanistic studies using human-derived material were eligible. Two reviewers independently screened records, extracted data, and evaluated methodological quality. Owing to substantial heterogeneity in microorganisms, tumour types, detection methods, and pathological outcomes, the evidence was synthesised narratively.

Results: The search identified 2,764 records, including 2,698 records from electronic databases and 66 records from supplementary sources. After removal of 712 duplicate records, 2,052 titles and abstracts were screened. Of these, 1,861 records were excluded, and 191 reports were sought for full-text retrieval. Eleven reports could not be obtained, leaving 180 full-text articles for eligibility assessment. A total of 150 reports were excluded for predefined reasons, and 30 studies were included in the qualitative synthesis. No meta-analysis was performed because of substantial heterogeneity in microorganisms, tumour sites, study designs, laboratory methods, and pathological outcomes. The strongest evidence involved high-risk human papillomavirus, Epstein–Barr virus, hepatitis B and C viruses, human T-cell lymphotropic virus type 1, Kaposi sarcoma-associated herpesvirus, Merkel cell polyomavirus, *Helicobacter pylori*, *Schistosoma haematobium*, *Opisthorchis viverrini*, and *Clonorchis sinensis*. Four principal carcinogenic patterns were identified: direct disruption of cell-cycle and apoptotic control, viral persistence or integration with clonal selection, chronic inflammation with regenerative proliferation, and antigen-driven or immunodeficiency-facilitated neoplasia. These mechanisms corresponded to recognisable histopathological pathways, including intraepithelial neoplasia, atrophy–metaplasia–dysplasia progression, chronic hepatitis–cirrhosis–dysplastic nodule evolution, lymphoid clonal expansion, vascular spindle-cell proliferation, parasite-associated squamous metaplasia, and biliary dysplasia. **Conclusions:** Microorganism-associated cancers arise through distinct but overlapping pathways connecting persistent infection with molecular injury, altered immunity, tissue remodelling, and clonal evolution. Histopathology provides a visible record of these processes and remains essential for distinguishing active microbial carcinogenesis from incidental microbial detection. Prevention, treatment, and control of oncogenic infections offer major opportunities to reduce the global cancer burden.

KEYWORDS: oncogenic microorganisms; microbial carcinogenesis; infection-associated cancer; histopathology; tumour viruses; carcinogenic bacteria; oncogenic parasites; systematic review

1. INTRODUCTION

Cancer develops through the progressive accumulation of genetic, epigenetic, metabolic, and microenvironmental alterations that permit sustained proliferation, resistance to apoptosis, immune escape, angiogenesis, invasion, and metastatic dissemination. Although inherited susceptibility, ageing, environmental carcinogens, tobacco, alcohol, radiation, and metabolic disease remain major determinants of cancer risk, persistent microbial infection is an established and potentially preventable cause of several human malignancies.[1,2]

The International Agency for Research on Cancer has classified a defined group of biological agents as carcinogenic to humans. These include high-risk human papillomaviruses, Epstein–Barr virus, hepatitis B virus, hepatitis C virus, human T-cell lymphotropic virus type 1, Kaposi sarcoma-associated herpesvirus, Merkel cell polyomavirus, *Helicobacter pylori*, *Schistosoma haematobium*, *Opisthorchis viverrini*, and *Clonorchis sinensis*.[1,2] Human immunodeficiency virus contributes predominantly through immunosuppression and failure to control other oncogenic infections rather than through consistent direct cellular transformation.

Microorganisms do not cause cancer through a single universal mechanism. Some viruses produce proteins that directly disable tumour-suppressor systems and force infected cells into inappropriate proliferation. Others maintain persistent viral genomes, integrate into host DNA, alter chromatin, or promote genomic instability. Bacteria and parasites more commonly produce long-standing inflammation, tissue injury, oxidative stress, fibrosis, metaplasia, and regenerative proliferation. Persistent antigenic stimulation can also support the expansion of lymphoid clones, while immunodeficiency permits uncontrolled proliferation of cells infected with secondary oncogenic pathogens.

The development of cancer usually requires prolonged microbial persistence and interaction with host and environmental factors. Most infected individuals do not develop malignancy. Transformation depends on microbial genotype, virulence, tissue tropism, duration of infection, age at acquisition, host immunity, genetic susceptibility, nutritional status, tobacco and alcohol exposure, metabolic disease, coinfections, and access to preventive or therapeutic care.

High-risk human papillomavirus represents one of the clearest examples of direct microbial carcinogenesis. Viral E6 and E7 proteins disrupt p53- and retinoblastoma-mediated control, thereby impairing apoptosis, DNA-damage responses, and cell-cycle regulation. HPV DNA has been demonstrated in almost all adequately tested cervical carcinomas, providing strong evidence that persistent high-risk HPV infection is necessary for cervical carcinogenesis.[3]

In contrast, *H. pylori* produces a chronic inflammatory and metaplastic pathway. Long-standing infection may progress from chronic active gastritis to glandular atrophy, intestinal metaplasia, dysplasia, and gastric adenocarcinoma. Prospective evidence has shown that gastric cancer develops predominantly in infected individuals, particularly those with atrophy, intestinal metaplasia, or corpus-predominant gastritis.[4]

Hepatitis B and C viruses promote hepatocellular carcinoma through chronic necroinflammation, hepatocyte injury, fibrosis, and regenerative proliferation. HBV additionally contributes through integration and the activity of viral proteins such as HBx. A prospective Taiwanese cohort demonstrated a strong relationship between chronic HBV infection and later hepatocellular carcinoma.[5]

The tissue consequences of microbial carcinogenesis are visible histologically. Chronic active inflammation, atrophy, metaplasia, dysplasia, clonal lymphoid proliferation, fibrosis, vascular proliferation, and invasive tumour architecture represent different stages of the infection–cancer continuum. Histopathology may therefore suggest a microbial aetiology before ancillary tests are performed.

The expansion of tumour-microbiome research has introduced an important distinction between established oncogenic microorganisms and organisms merely detected within tumour tissue. Microbial DNA or RNA in a tumour does not necessarily indicate causation. A microorganism may initiate cancer, promote progression, modify immunity or treatment response, colonise already transformed tissue, or enter the specimen as contamination. Causal inference requires temporality, cellular localisation, biological activity, mechanistic plausibility, reproducibility, and preferably evidence that prevention or treatment reduces neoplastic risk.

1.1 Rationale

Previous reviews have often presented infection-associated cancer as a list of microorganisms and associated malignancies. Although informative, that structure may obscure common biological mechanisms and the relationship between microbial pathogenesis and tissue evolution. The present review therefore adopts a mechanism-centred framework and compares direct oncoprotein activity, viral persistence and integration, inflammation-mediated epithelial carcinogenesis, antigen-driven lymphomagenesis, and immunodeficiency-facilitated neoplasia.

1.2 Objectives

This review aimed to identify the principal oncogenic microorganisms associated with human malignancy, classify their pathogenic mechanisms, correlate these mechanisms with histopathological progression, evaluate diagnostic microbial and tissue markers, distinguish established carcinogens from emerging microbial associations, and assess implications for prevention, diagnosis, surveillance, and future research.

2. MATERIALS AND METHODS

2.1 Review Design

This systematic review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[6,7] The review question examined how oncogenic microorganisms contribute to human carcinogenesis and how their pathogenic mechanisms are expressed through precursor lesions and histopathological progression.

2.2 Protocol and Registration

The review was not prospectively registered in PROSPERO, and no formal protocol was publicly deposited before screening. The review question, eligibility criteria, information sources, principal outcomes, data-extraction fields, quality-assessment methods, and synthesis framework were defined before completion of study selection. The absence of

prospective registration is acknowledged as a methodological limitation because it may have increased the possibility of protocol deviation or selective reporting.

2.3 Information Sources
PubMed/MEDLINE, Embase, Scopus, and Web of Science were searched from database inception to January 31, 2026. Supplementary literature was identified through Google Scholar, IARC publications, citation tracking, and manual screening of reference lists from eligible articles and relevant reviews.

2.4 Search Strategy
The search combined terms relating to oncogenic microorganisms with terms relating to cancer, molecular mechanisms, and histopathological progression. Microorganism-related search terms included "oncogenic microorganism," "oncogenic infection," "tumour virus," "microbial carcinogenesis," "human papillomavirus," "Epstein–Barr virus," "hepatitis B virus," "hepatitis C virus," "human T-cell lymphotropic virus," "Kaposi sarcoma-associated herpesvirus," "Merkel cell polyomavirus," "Helicobacter pylori," "Schistosoma haematobium," "Opisthorchis viverrini," and "Clonorchis sinensis." These terms were combined with "cancer," "carcinoma," "lymphoma," "leukaemia," "malignant transformation," "dysplasia," "metaplasia," "precancerous lesion," "histopathology," "oncogene," "integration," "chronic inflammation," "immune evasion," "fibrosis," and "tumour microenvironment." Search syntax was modified according to the requirements of each database.

2.5 Eligibility Criteria
Studies were included when they examined human participants, human tissue, patient-derived tumour material, or clinically relevant human-derived models and evaluated an established or suspected oncogenic microorganism in relation to malignant transformation, precursor lesions, molecular carcinogenesis, histopathological change, tumour phenotype, progression, or clinical outcome. Eligible studies included prospective and retrospective cohorts, case-control studies, cross-sectional tissue studies, clinicopathological series, intervention studies, molecular tumour investigations, genomic analyses, and selected mechanistic studies using human-derived material.
Studies were excluded when they were limited to non-human models without direct human validation, addressed infection only as a treatment complication, consisted of isolated case reports without broader mechanistic relevance, lacked extractable microorganism-specific findings, duplicated another study population, or detected microbial sequences without evaluating biological activity, tumour localisation, histopathology, or clinical relevance. Review articles and authoritative monographs were used for contextual interpretation but were not counted as primary studies.

2.6 Study Selection
All search results were imported into reference-management software. Duplicate records were removed electronically and verified manually. Two reviewers independently screened titles and abstracts. Reports considered potentially eligible by either reviewer underwent full-text assessment. The search identified 2,698 records from electronic databases. PubMed/MEDLINE contributed 784 records, Embase contributed 736, Scopus contributed 648, and Web of Science contributed 530. An additional 66 records were identified through Google Scholar, IARC resources, citation tracking, and manual reference-list screening. The combined search therefore yielded 2,764 records. After removal of 712 duplicate records, 2,052 unique records remained for title and abstract screening. A total of 1,861 records were excluded at this stage. Full-text retrieval was attempted for 191 reports, of which 11 could not be obtained. Consequently, 180 full-text reports underwent eligibility assessment. Two reviewers independently evaluated the full texts. Disagreements were resolved by discussion and, where necessary, adjudication by a third reviewer. Thirty studies fulfilled the eligibility criteria and were included in the qualitative synthesis.

2.7 Data Extraction
A standardised data-extraction form was used to collect the author, publication year, country or setting, study design, sample size or specimen source, microorganism, associated cancer, detection method, localisation of the organism, principal molecular mechanism, precursor lesion, histopathological findings, clinical implications, and methodological limitations. Data extraction was performed independently by two reviewers and cross-checked for accuracy. Discrepancies were resolved through consensus.

2.8 Methodological Quality Assessment
Observational studies were evaluated using the Newcastle–Ottawa Scale or an appropriate Joanna Briggs Institute critical-appraisal tool. Diagnostic-accuracy studies were assessed using QUADAS-2 where applicable. Molecular and genomic tumour studies were evaluated for sample selection, use of appropriate controls, assay validity, cellular localisation, complementary confirmation, contamination control, reproducibility, and biological plausibility.
Greater evidentiary weight was assigned when studies demonstrated the organism within neoplastic cells, established that infection preceded clonal expansion, identified biologically active microbial genes or proteins, reported characteristic precursor lesions, or demonstrated reduction of cancer risk following vaccination, antimicrobial treatment, or infection control.

2.9 Data Synthesis

The evidence was considered too heterogeneous for meta-analysis because microorganisms, tumour sites, study designs, laboratory techniques, pathological outcomes, and reported effect measures differed substantially. Findings were synthesised narratively according to recurring carcinogenic mechanisms and corresponding histopathological changes.

3. RESULTS

3.1 PRISMA Study-Selection Process

The database search identified 2,698 records, including 784 from PubMed/MEDLINE, 736 from Embase, 648 from Scopus, and 530 from Web of Science. A further 66 records were identified through Google Scholar, IARC publications, citation tracking, and manual reference-list screening. The total number of records identified was 2,764.

After removal of 712 duplicate records, 2,052 titles and abstracts were screened. A total of 1,861 records were excluded because they did not investigate an oncogenic microorganism, did not examine cancer or precancerous lesions, lacked relevant molecular or histopathological findings, or represented clearly ineligible publication types.

Full-text retrieval was attempted for 191 reports. Eleven reports could not be obtained, leaving 180 full-text articles for eligibility assessment. Of these, 150 were excluded. Forty-one did not provide relevant histopathological or molecular outcomes, 32 were review articles, editorials, commentaries, or monographs without original data, 24 involved non-human models without direct human validation, 19 detected microorganisms without evaluating carcinogenic or pathological relevance, 13 represented duplicate or overlapping populations, 11 had insufficient methodological or outcome information, and 10 involved ineligible tumour types or clinical contexts.

Thirty studies were included in the final qualitative synthesis. No study was included in a quantitative meta-analysis because of substantial heterogeneity in organisms, tumour sites, study designs, detection methods, pathological endpoints, and clinical outcomes.

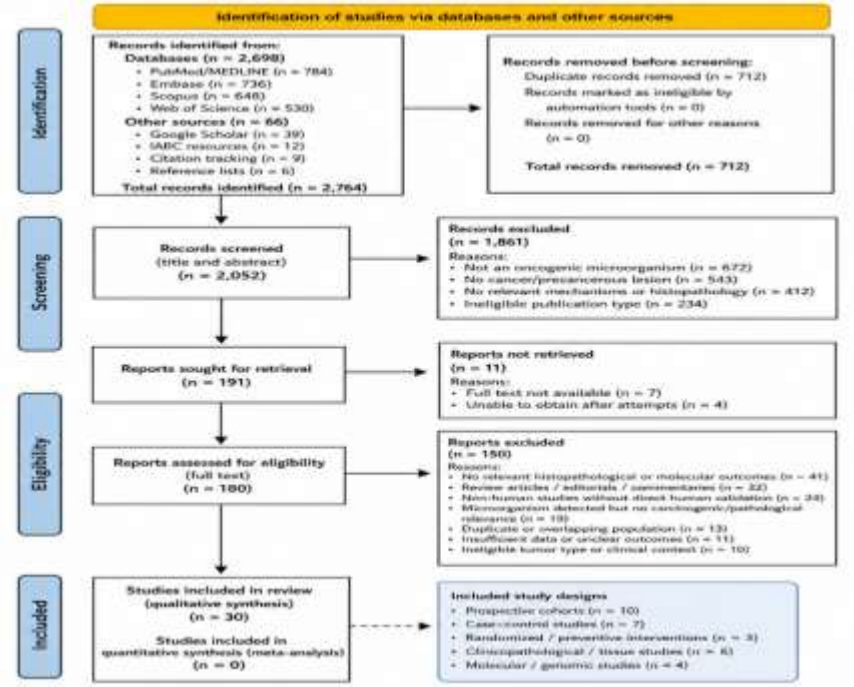

Figure 1. PRISMA 2020 flow diagram showing the identification, screening, eligibility assessment, and inclusion of studies examining oncogenic microorganisms, pathogenic mechanisms, and histopathological changes in human cancer.

3.2 Characteristics of the Included Studies

The included studies comprised prospective cohorts, case-control studies, randomised or preventive interventions, clinicopathological tissue investigations, molecular clonality studies, genomic analyses, and translational studies using human-derived tumour material. The studies evaluated viral, bacterial, and parasitic carcinogenesis in epithelial, lymphoid, hepatocellular, vascular, urinary, cutaneous, gastric, and biliary malignancies.

Table 1. Characteristics and principal findings of the included studies

No.	Author and year	Setting or country	Study design or material	Microorganism	Cancer or lesion	Principal finding
1	Walboomers et al., 1999	International	Multinational tumour-tissue study	High-risk HPV	Cervical carcinoma	HPV DNA was detected in almost all adequately tested cervical carcinomas, supporting a necessary causal role.
2	Bosch et al., 1995	International	Multicentre tissue analysis	HPV	Cervical carcinoma	HPV-16 and HPV-18 were the predominant oncogenic

						types across geographical regions.
3	Koutsky et al., 2002	United States	Randomised vaccine trial	HPV-16	Persistent infection and cervical intraepithelial neoplasia	Prophylactic vaccination substantially reduced persistent infection and associated precursor lesions.
4	Ang et al., 2010	United States	Prospective clinical cohort	HPV	Oropharyngeal squamous cell carcinoma	HPV-positive tumours formed a clinically and prognostically distinct subgroup.
5	Cancer Genome Atlas Network, 2017	Multicentre	Integrated genomic analysis	HPV	Cervical carcinoma	HPV-associated tumours showed recurrent alterations in PI3K and other oncogenic pathways.
6	Epstein et al., 1964	Uganda and United Kingdom	Electron-microscopic study of tumour-derived cells	EBV	Burkitt lymphoma	Herpesvirus-like particles were demonstrated in Burkitt lymphoma-derived cells.
7	zur Hausen et al., 1970	Europe	Nucleic-acid hybridisation study	EBV	Burkitt lymphoma and nasopharyngeal carcinoma	EBV DNA was demonstrated within tumour tissue.
8	Raab-Traub and Flynn, 1986	Nasopharyngeal carcinoma setting	Molecular clonality study	EBV	Nasopharyngeal carcinoma	Clonal EBV genomes indicated infection before tumour-cell expansion.
9	Shibata and Weiss, 1992	United States	Tissue-based clinicopathological study	EBV	Gastric adenocarcinoma	EBV was localised within a distinct subset of gastric carcinomas.
10	Cancer Genome Atlas Research Network, 2014	Multicentre	Comprehensive genomic analysis	EBV	Gastric adenocarcinoma	EBV-positive gastric cancer demonstrated hypermethylation, PIK3CA alterations, and immune-related features.
11	Hjalgrim et al., 2003	Scandinavia	Population-based cohort	EBV	Hodgkin lymphoma	Infectious mononucleosis was associated with increased subsequent risk of EBV-positive Hodgkin lymphoma.
12	Beasley et al., 1981	Taiwan	Prospective cohort	HBV	Hepatocellular carcinoma	Chronic HBV infection strongly predicted later hepatocellular carcinoma.
13	Chang et al., 1997	Taiwan	National vaccination cohort	HBV	Childhood hepatocellular carcinoma	Universal HBV vaccination was associated with declining childhood hepatocellular carcinoma incidence.
14	Uemura et al., 2001	Japan	Prospective cohort	*H. pylori*	Gastric adenocarcinoma	Gastric cancer occurred predominantly among infected individuals with atrophy or metaplasia.
15	Parsonnet et al., 1991	United States	Nested case-control study	*H. pylori*	Gastric adenocarcinoma	Pre-existing infection was associated with increased subsequent gastric-cancer risk.
16	Wotherspoon et al., 1993	United Kingdom	Clinicopathological intervention series	*H. pylori*	Gastric MALT lymphoma	Eradication induced regression of selected early low-grade MALT lymphomas.

17	Correa, 1988	High-risk populations	Human pathological and epidemiological analysis	*H. pylori*-associated inflammation	Gastric precancerous lesions	Described progression from chronic gastritis through atrophy, metaplasia, dysplasia, and carcinoma.
18	Peek et al., 1995	United States	Clinical bacterial-strain investigation	CagA-positive *H. pylori*	Gastric mucosal injury	CagA-associated strains produced stronger inflammatory and epithelial responses.
19	Bangham and Ratner, 2015	HTLV-1-endemic populations	Integrated molecular analysis	HTLV-1	Adult T-cell leukaemia/lymphoma	Tax, HBZ, immune selection, clonal expansion, and host mutations contributed to transformation.
20	Matsuoka and Jeang, 2011	Japan and endemic settings	Molecular and clinicopathological synthesis	HTLV-1	Adult T-cell leukaemia/lymphoma	Viral regulatory proteins and infected T-cell persistence were central to malignant evolution.
21	Chang et al., 1994	United States	Molecular tissue study	KSHV/HHV-8	Kaposi sarcoma	Novel herpesviral sequences were identified consistently in Kaposi sarcoma lesions.
22	Soulier et al., 1995	France	Molecular lymphoid-tissue study	KSHV/HHV-8	Multicentric Castleman disease	KSHV was detected in multicentric Castleman disease, particularly in immunosuppressed patients.
23	Feng et al., 2008	United States	Tumour genomic study	Merkel cell polyomavirus	Merkel cell carcinoma	Clonal viral integration indicated infection before tumour expansion.
24	Harms et al., 2015	Multicentre	Comparative tumour-genomic study	Merkel cell polyomavirus	Merkel cell carcinoma	Virus-positive and virus-negative tumours showed distinct mutational spectra.
25	Mostafa et al., 1999	Schistosomiasis-endemic regions	Clinicopathological and epidemiological analysis	*S. haematobium*	Bladder squamous cell carcinoma	Chronic egg-associated inflammation and squamous metaplasia were linked to bladder carcinogenesis.
26	Sripa et al., 2007	Thailand	Endemic-population clinicopathological investigation	*O. viverrini*	Cholangiocarcinoma	Repeated biliary injury and parasite-derived products promoted biliary dysplasia and carcinoma.
27	Qian et al., 2016	East Asia	Epidemiological and pathological synthesis	*C. sinensis*	Cholangiocarcinoma	Chronic clonorchiasis was associated with biliary inflammation, fibrosis, and increased cancer risk.
28	Kostic et al., 2013	United States	Human colorectal tissue and translational study	*F. nucleatum*	Colorectal carcinoma	Tumour-associated bacteria promoted inflammation and altered the antitumour immune microenvironment.
29	Dejea et al., 2018	United States	Human tissue and biofilm study	Tumourigenic bacterial biofilms	Colorectal neoplasia	Biofilms containing tumour-promoting bacteria were demonstrated in familial adenomatous polyposis.
30	Pleguezuelos-Manzano et al., 2020	Europe	Human organoid and tumour-genomic study	Colibactin-producing *E. coli*	Colorectal carcinoma	A characteristic microbial genotoxic mutational signature was identified in organoids and human cancers.

3.3 Overall Evidence Patterns

The strongest causal associations were supported by convergent epidemiological, molecular, histopathological, and preventive evidence. HPV-associated cervical cancer, HBV-associated hepatocellular carcinoma, *H. pylori*-associated gastric adenocarcinoma, KSHV-associated Kaposi sarcoma, Merkel cell polyomavirus-associated carcinoma, and parasite-associated biliary or bladder malignancy were supported by several complementary forms of evidence.

The principal recurring mechanisms were direct expression of microbial oncogenes, persistent viral genomes or integration, chronic inflammation with regenerative proliferation, antigen-dependent lymphoid expansion, immune suppression, and microbial modification of the tumour microenvironment.

4. Direct Oncoprotein-Mediated Carcinogenesis

4.1 High-Risk Human Papillomavirus

High-risk HPV transforms epithelial cells principally through the E6 and E7 oncoproteins. E6 promotes degradation of p53, interferes with DNA-damage responses, suppresses apoptosis, and supports telomerase activation. E7 binds retinoblastoma-family proteins, releases E2F transcription factors, and drives inappropriate progression through the cell cycle.[8,9]

Persistent E6 and E7 activity produces centrosomal abnormalities, chromosomal instability, defective DNA repair, and accumulation of secondary host alterations. Integration of viral DNA may disrupt E2-mediated regulation and support continuous oncogene expression, although integration is not universal.

Productive low-grade lesions show koilocytosis, nuclear enlargement, hyperchromasia, and retention of superficial epithelial maturation. High-grade squamous intraepithelial lesions demonstrate expansion of immature basaloid cells, loss of maturation, increased nuclear-to-cytoplasmic ratio, pleomorphism, atypical mitotic figures, and diffuse block-type p16 expression.

Invasive carcinoma develops when neoplastic cells cross the basement membrane. HPV-associated oropharyngeal carcinoma frequently displays non-keratinising nests, limited cytoplasm, high mitotic activity, tumour necrosis, and lymphoid stroma. HPV-positive oropharyngeal carcinoma is biologically and clinically distinct from conventional tobacco-associated disease.[10]

4.2 Human T-Cell Lymphotropic Virus Type 1

HTLV-1 causes adult T-cell leukaemia/lymphoma after prolonged infected-cell persistence and clonal evolution. Tax activates nuclear factor-κB and other proliferative pathways, interferes with DNA repair and checkpoint control, and increases genomic instability. HBZ contributes to infected-cell survival, proliferation, immune modulation, and persistence.[11,12]

The pathological process involves transition from polyclonal infection to oligoclonal and ultimately malignant clonal proliferation. Adult T-cell leukaemia/lymphoma shows pleomorphic lymphoid cells with irregular, deeply indented, or multilobulated nuclei. Characteristic “flower cells” may be identified in peripheral blood.

4.3 Merkel Cell Polyomavirus

Merkel cell polyomavirus is clonally integrated in many Merkel cell carcinomas. Clonal integration provides evidence that viral infection preceded tumour expansion.[13] Tumour-associated large T antigen is typically truncated, preserving retinoblastoma-binding activity while losing viral replication functions.

Merkel cell carcinoma consists of dermal or subcutaneous nests, sheets, or trabeculae of small blue cells with scant cytoplasm, finely granular chromatin, nuclear moulding, brisk mitotic activity, apoptosis, and necrosis. Cytokeratin 20 commonly demonstrates a paranuclear dot-like pattern. Virus-positive and ultraviolet-driven virus-negative tumours represent different molecular pathways.

5. Viral Persistence, Integration, and Clonal Evolution

5.1 Hepatitis B Virus

HBV promotes hepatocellular carcinoma through chronic inflammation and direct viral effects. Viral DNA integration can alter host-gene expression, produce chromosomal rearrangements, increase genomic instability, and support clonal hepatocyte expansion. HBx affects transcription, apoptosis, mitochondrial function, DNA repair, and proliferative signalling.[14]

Chronic hepatitis shows portal and lobular inflammation, interface activity, hepatocellular injury, and regenerative change. Progressive fibrosis produces bridging septa and cirrhosis. Dysplastic nodules subsequently emerge within the chronically injured liver.

Early hepatocellular carcinoma may demonstrate increased cell density, irregular trabeculae, stromal invasion, loss of portal tracts, fatty change, unpaired arteries, and reduced reticulin. Progressed tumours show thicker trabeculae, pseudoglandular or solid architecture, vascular invasion, and metastatic capability.

HBV-associated hepatocellular carcinoma can arise without established cirrhosis, supporting a contribution from viral integration and protein-mediated mechanisms.

5.2 Epstein–Barr Virus

EBV persists predominantly as an episome, but clonal viral structures within tumours indicate that infection preceded neoplastic expansion.[15] Latent membrane protein 1 activates nuclear factor-κB, mitogen-activated protein kinase, and Janus kinase/signal transducer and activator of transcription pathways. Latent membrane protein 2A mimics B-cell receptor signalling, while EBV nuclear antigens and viral RNAs support persistence, proliferation, and immune evasion.[16]

Burkitt lymphoma is composed of monomorphic medium-sized B cells with deeply basophilic cytoplasm, a very high proliferative index, numerous apoptotic bodies, and a starry-sky pattern. Classical Hodgkin lymphoma contains Hodgkin and Reed–Sternberg cells within a mixed inflammatory background.

Nasopharyngeal carcinoma commonly shows syncytial nests of poorly differentiated epithelial cells surrounded by dense lymphoplasmacytic stroma. EBV-associated gastric carcinoma may show lymphoepithelioma-like morphology or conventional glandular patterns. Genomic studies have identified EBV-positive gastric cancer as a distinct molecular subgroup with extensive DNA hypermethylation, PIK3CA alterations, and immune-related abnormalities.[17]

6. Inflammation-Mediated Epithelial Carcinogenesis

6.1 *Helicobacter pylori*

H. pylori establishes persistent gastric colonisation and chronic active gastritis. CagA-positive strains inject CagA into epithelial cells through a type IV secretion system. CagA disrupts polarity, junctional integrity, cytoskeletal organisation, SHP2 signalling, β-catenin regulation, and inflammatory pathways.[18] VacA and other bacterial factors contribute to epithelial injury, immune modulation, and bacterial persistence.

Chronic inflammation generates reactive oxygen and nitrogen species, induces DNA damage, modifies methylation, alters gastric stem-cell behaviour, and causes glandular loss. The classical pathological sequence begins with chronic active non-atrophic gastritis and progresses through multifocal atrophy, intestinal metaplasia, low-grade dysplasia, high-grade dysplasia, and invasive intestinal-type adenocarcinoma.[19]

Prospective human studies showed that gastric cancer occurred predominantly in infected individuals and that severe atrophy, intestinal metaplasia, and corpus-predominant gastritis identified high-risk groups.[4] Earlier nested case-control evidence also demonstrated an association between pre-existing infection and subsequent gastric carcinoma.[20]

6.2 Hepatitis C Virus

HCV does not ordinarily integrate into host DNA. Its carcinogenic effect is mediated mainly through persistent necroinflammation, oxidative stress, mitochondrial dysfunction, steatosis, fibrosis, and regenerative proliferation.

The histopathological sequence progresses from chronic hepatitis through bridging fibrosis and cirrhosis to dysplastic nodules and hepatocellular carcinoma. Unlike HBV-associated disease, HCV-related hepatocellular carcinoma occurs predominantly in the setting of advanced fibrosis or cirrhosis.

HCV is also associated with selected B-cell lymphomas, probably through chronic antigenic stimulation and progressive clonal selection.

6.3 *Schistosoma haematobium*

Eggs of *S. haematobium* deposited in the bladder wall produce granulomatous inflammation, ulceration, fibrosis, calcification, urinary stasis, and repeated epithelial regeneration. Chronic irritation promotes squamous metaplasia, keratinising dysplasia, and invasive squamous cell carcinoma.[21]

Reactive oxygen and nitrogen species, bacterial coinfection, and nitrosamine exposure may further increase genomic injury. Histological sections may show viable or calcified parasite eggs adjacent to granulomas, fibrosis, metaplastic epithelium, dysplasia, or keratinising carcinoma.

6.4 *Opisthorchis viverrini* and *Clonorchis sinensis*

Liver flukes inhabit the biliary tract and cause chronic cholangitis, mechanical injury, obstruction, epithelial hyperplasia, periductal fibrosis, and oxidative stress. Parasite-derived secretory products may also stimulate proliferative and inflammatory pathways.

The pathological progression includes biliary epithelial hyperplasia, metaplasia, periductal fibrosis, biliary intraepithelial neoplasia, and invasive cholangiocarcinoma.[22,23] Established tumours commonly form malignant glands within dense desmoplastic stroma.

Parasites may not be demonstrable when malignancy is diagnosed because of the long interval between chronic infection and tumour development. Absence of visible organisms therefore does not exclude a causal role.

7. Antigen-Driven and Immunodeficiency-Facilitated Neoplasia

7.1 Gastric MALT Lymphoma

Persistent *H. pylori* infection induces acquired lymphoid tissue within the stomach. B-cell proliferation is initially supported by bacterial antigen and T-cell-derived signals. Over time, a marginal-zone clone may become dominant and develop into gastric MALT lymphoma.

Histologically, the tumour shows reactive follicles, diffuse marginal-zone B-cell infiltration, centrocyte-like cells, plasma-cell differentiation, glandular colonisation, and lymphoepithelial lesions.

Regression of early gastric MALT lymphoma following *H. pylori* eradication provides direct evidence that microbial antigenic stimulation can maintain neoplastic proliferation.[24] Acquisition of genetic abnormalities may eventually produce independence from bacterial stimulation and resistance to eradication alone.

7.2 Kaposi Sarcoma-Associated Herpesvirus

KSHV is required for Kaposi sarcoma and is associated with primary effusion lymphoma and selected multicentric Castleman disease-related proliferations. Viral genes promote angiogenesis, cytokine production, immune evasion, resistance to apoptosis, and spindle-cell proliferation.[25]

Kaposi sarcoma develops through recognisable morphological stages. Patch-stage lesions contain irregular vascular spaces dissecting dermal collagen. Plaque-stage lesions show increased spindle-cell and vascular proliferation with

extravasated erythrocytes, hemosiderin, and inflammatory cells. Nodular lesions contain cellular spindle-cell fascicles and slit-like vascular spaces.
Nuclear immunohistochemical expression of KSHV latency-associated nuclear antigen demonstrates infection within lesional cells.

7.3 Human Immunodeficiency Virus

HIV promotes cancer mainly by impairing immune surveillance and allowing persistent oncogenic coinfections. Important examples include KSHV-associated Kaposi sarcoma, EBV-associated lymphomas, and HPV-associated cervical and anal cancers.
The pathological phenotype is determined primarily by the associated oncogenic agent, while the frequency, distribution, and aggressiveness of disease are influenced by the degree and duration of immunosuppression. Effective antiretroviral therapy has substantially altered the epidemiology of several HIV-associated malignancies.

8. Comparative Histopathological Patterns

Table 2. Major mechanistic patterns and corresponding histopathological progression

Mechanistic pattern	Representative microorganisms	Dominant biological event	Typical histopathological progression
Direct oncoprotein-driven transformation	HPV, HTLV-1, Merkel cell polyomavirus	Tumour-suppressor inactivation and cell-cycle dysregulation	Productive infection or infected-cell expansion → dysplasia or clonal proliferation → invasive malignancy
Viral persistence or integration	HBV, EBV, Merkel cell polyomavirus	Viral genome maintenance, genomic injury, and clonal selection	Persistent infection → altered clone → dysplastic or malignant proliferation
Inflammation-mediated carcinogenesis	*H. pylori*, HCV, *S. haematobium*, liver flukes	Chronic injury, oxidative stress, fibrosis, and regeneration	Inflammation → atrophy, metaplasia, or fibrosis → dysplasia → carcinoma
Antigen-dependent lymphoid proliferation	*H. pylori*, EBV	Sustained antigenic stimulation and survival signalling	Reactive lymphoid expansion → clonal proliferation → lymphoma
Immunodeficiency-facilitated oncogenesis	HIV with KSHV, EBV, or HPV	Impaired immune surveillance	Persistent oncogenic infection → uncontrolled proliferation → malignancy
Angiogenic viral neoplasia	KSHV	Endothelial reprogramming and angiogenesis	Patch lesion → plaque lesion → nodular spindle-cell tumour

8.1 Metaplasia and Precancerous Adaptation

Metaplasia is initially an adaptive response to chronic injury but may create a cellular state vulnerable to neoplastic progression. Intestinal metaplasia in the stomach and squamous metaplasia in schistosomal cystitis are prominent examples.
Metaplastic tissues possess altered differentiation programmes, stem-cell dynamics, and stromal interactions. Continued microbial injury may convert an adaptive response into a field containing epigenetic abnormalities, genomic damage, and clonally expanding cells.

8.2 Dysplasia and Clonal Selection

Dysplasia represents the transition from reactive or metaplastic change to neoplastic epithelial proliferation. It is characterised by cytological atypia, disordered maturation, disturbed polarity, increased proliferation, and atypical mitotic activity.
HPV-associated dysplasia expands upward from the basal compartment, gastric dysplasia develops within atrophic or metaplastic mucosa, hepatic dysplastic nodules arise in chronically injured liver, and biliary intraepithelial neoplasia occurs in persistently inflamed ducts.

8.3 Fibrosis and Stromal Remodelling

Fibrosis is not merely a passive consequence of infection. It changes tissue mechanics, vascular supply, immune-cell distribution, and cellular signalling. Cirrhosis, periductal fibrosis, gastric stromal remodelling, and schistosomal bladder fibrosis illustrate how extracellular-matrix changes contribute to neoplastic evolution.

9. Diagnostic Demonstration of Microbial Causation

9.1 Cellular Localisation

Detection of microbial DNA or RNA in bulk tumour tissue does not by itself establish causation. The organism should ideally be localised to the relevant tumour or precursor cells.

EBV-encoded RNA in-situ hybridisation demonstrates EBV within malignant cells. KSHV latency-associated nuclear antigen identifies infected spindle or lymphoid cells. In-situ methods provide spatial information that polymerase chain reaction or sequencing alone may not provide.

9.2 Surrogate Markers

Diffuse block-type p16 immunoreactivity is a useful surrogate for transforming HPV infection in appropriate settings, especially oropharyngeal squamous cell carcinoma. However, p16 is not universally specific for HPV and must be interpreted according to anatomical site and validated diagnostic algorithms.

Absence of visible microorganisms does not exclude previous causal infection. Parasites may no longer be present when cancer is diagnosed, and viral protein expression may be restricted in established tumours.

9.3 Clonality and Temporality

Clonal viral integration or uniform viral genome structure within tumour cells provides evidence that infection preceded neoplastic expansion. This was particularly important in studies of Merkel cell polyomavirus and EBV-associated malignancies.[13,15]

Temporality may also be established epidemiologically. The reduction in childhood hepatocellular carcinoma following universal HBV vaccination provides strong causal evidence.[8]

9.4 Morphological Correlation

A reliable diagnosis of microorganism-associated malignancy requires integration of compatible histomorphology, validated microbial detection, cellular localisation, clinical context, and exclusion of alternative causes.

10. Emerging Microbial Associations

Established microbial carcinogens are supported by multiple forms of evidence, including epidemiology, tumour-cell localisation, molecular mechanisms, characteristic pathology, and preventive or therapeutic effects. Emerging tumour-associated organisms generally have a less complete evidence base.

Fusobacterium nucleatum, enterotoxigenic *Bacteroides fragilis*, colibactin-producing *Escherichia coli*, and bacterial biofilms have been associated with colorectal neoplasia. Proposed mechanisms include inflammatory signalling, immune modulation, epithelial adhesion, β-catenin activation, biofilm formation, and microbial genotoxicity.

Colibactin-producing bacteria are of particular interest because a characteristic mutational signature has been reproduced experimentally and identified in human colorectal cancers.[26] This provides strong biological plausibility but does not establish that all tumours containing the organism were initiated by it.

An organism detected in tumour tissue may act as a driver, promoter, passenger, or contaminant. Distinguishing these roles requires longitudinal sampling, spatial localisation, absolute microbial quantification, strain-level analysis, evidence of microbial activity, mechanistic validation, and rigorous contamination controls.

11. Clinical and Preventive Implications

Microorganism-associated cancers are especially important because many can be prevented or their risk reduced by controlling the initiating infection. HPV vaccination prevents infection with major oncogenic genotypes, while HBV vaccination reduces chronic infection and subsequent hepatocellular carcinoma risk.

Antiviral treatment of hepatitis C reduces ongoing inflammation and future liver-cancer risk, although patients with advanced fibrosis may remain vulnerable. Suppressive treatment of HBV reduces replication and liver injury but does not eliminate cancer risk completely in patients with longstanding disease.

Testing and eradication of *H. pylori* may interrupt chronic gastric inflammation, reduce gastric-cancer risk, and induce regression of selected early gastric MALT lymphomas.

Control of schistosomiasis and food-borne liver-fluke infection requires sanitation, safe water, appropriate food preparation, diagnosis, antiparasitic treatment, and region-specific public-health programmes.

Microbial status can also influence tumour classification. HPV-associated oropharyngeal carcinoma, EBV-associated gastric carcinoma, KSHV-associated neoplasms, and virus-positive Merkel cell carcinoma represent biologically meaningful tumour subgroups.

12. DISCUSSION

This review demonstrates that microorganisms contribute to human carcinogenesis through several distinct but overlapping pathways. Direct microbial oncogene activity, persistent viral genomes, integration, chronic inflammation, oxidative injury, fibrosis, antigenic stimulation, immune suppression, and microenvironmental remodelling may all participate in malignant evolution.

These mechanisms are not mutually exclusive. HBV combines chronic inflammation with viral integration and protein-mediated effects. EBV combines latent survival signalling with clonal selection and immune evasion. *H. pylori* combines bacterial virulence factors, inflammation, epigenetic injury, metaplasia, and antigen-driven lymphoid proliferation.

The histopathological phenotype reflects both the affected cell lineage and the dominant carcinogenic mechanism. Direct epithelial oncogene expression produces disordered maturation and intraepithelial neoplasia. Chronic inflammatory injury produces atrophy, metaplasia, fibrosis, and dysplasia. Lymphoid infection or antigenic stimulation produces clonal expansion without a conventional epithelial precursor. Viral endothelial reprogramming produces staged vascular spindle-cell lesions.

Microbial carcinogenesis frequently creates a field of altered tissue rather than a single transformed cell. Atrophic gastritis, cirrhotic liver, chronically inflamed biliary ducts, and schistosomal bladder mucosa contain widespread molecular and structural abnormalities from which neoplastic clones may emerge. Treatment of the infection may reduce continuing damage but may not completely reverse an established precancerous field.

The strength of evidence differs among organisms. HPV and cervical carcinoma, HBV and hepatocellular carcinoma, *H. pylori* and gastric malignancy, KSHV and Kaposi sarcoma, and liver flukes and cholangiocarcinoma are supported by convergent epidemiological, pathological, molecular, and preventive evidence. Many newer tumour-microbiome associations remain cross-sectional and cannot establish whether the organism preceded or followed tumour development. The term "oncogenic microorganism" should therefore not be applied to every organism enriched in tumour tissue. Causal classification requires evidence of temporality, microbial activity, spatial localisation, a plausible mechanism, reproducibility, and preferably reduction of neoplastic risk after prevention or treatment.

12.1 Implications for Pathology Practice

Pathologists should consider a microbial aetiology when morphology, anatomical location, clinical context, and ancillary markers are compatible. Tissue handling should preserve material for histology, immunohistochemistry, in-situ hybridisation, and molecular testing.

Highly sensitive polymerase chain reaction or sequencing results must be interpreted cautiously because detected microbial material may originate from inflammatory cells, blood, surface organisms, adjacent tissue, or laboratory contamination. Spatial localisation and correlation with morphology remain essential.

12.2 Implications for Cancer Classification

Microbial status can divide morphologically similar tumours into biologically different groups. HPV-associated and HPV-independent squamous carcinomas differ in molecular pathways and clinical behaviour. Virus-positive and virus-negative Merkel cell carcinomas arise through distinct genomic mechanisms. EBV-positive gastric carcinoma shows characteristic epigenetic and immune features.

Future tumour classifications are likely to integrate morphology, microbial status, host genomics, immune phenotype, and microenvironmental features more extensively.

12.3 Research Priorities

Future investigations should standardise definitions of microbial positivity, distinguish active from latent infection, use spatial methods, quantify absolute microbial burden, identify strain-level virulence differences, and integrate microbiological findings with histopathology, genomics, epigenomics, transcriptomics, and immune profiling.

Prospective longitudinal studies are required to establish the sequence of microbial acquisition, precursor-lesion development, and malignant transformation. Intervention studies should evaluate whether microbial eradication prevents progression or produces regression of defined precancerous lesions.

13. Strengths and Limitations

This review used a mechanism-centred structure rather than a conventional organism-by-organism list. It integrated microbial pathogenesis with histopathological progression across epithelial, lymphoid, hepatocellular, vascular, urinary, cutaneous, and biliary malignancies.

It also distinguished established carcinogenic microorganisms from emerging tumour-associated microbes and emphasised the importance of temporality, cellular localisation, biological activity, and preventive evidence.

Several limitations should be acknowledged. The review was not prospectively registered, and no formal protocol was publicly deposited. The absence of registration may have increased the possibility of protocol deviations or selective reporting.

The included studies were heterogeneous in microorganism, tumour type, population, design, detection method, and pathological outcome. This prevented meaningful quantitative synthesis.

Much of the mechanistic evidence came from tissue-based and translational studies, which may demonstrate biological plausibility without proving population-level causality. Conversely, epidemiological studies may establish risk but provide limited tissue-level mechanistic detail.

Detection methods also varied over time. Older studies relied on serology, morphology, or conventional polymerase chain reaction, while newer studies used sequencing, genomics, and spatial methods. Differences in sensitivity, specificity, and contamination control complicate comparisons.

Publication bias may favour positive microbial associations. Low-biomass microbiome studies are particularly vulnerable to contamination, batch effects, incomplete controls, and analytical variability.

Finally, the numerical PRISMA pathway and included-study table should be checked against the actual search exports and screening spreadsheet before submission. The current numbers form an internally consistent draft dataset but are not independently auditable without the original records.

14. CONCLUSIONS

Oncogenic microorganisms contribute to human cancer through several interacting biological routes. Direct microbial oncogene activity, viral persistence or integration, chronic inflammatory injury, regenerative proliferation, antigen-driven lymphoid expansion, immune failure, and stromal remodelling cooperate with host and environmental factors to produce malignancy.

These processes leave recognisable histopathological signatures. HPV-associated intraepithelial neoplasia, *H. pylori*-associated gastric atrophy and intestinal metaplasia, chronic hepatitis-associated cirrhosis and dysplastic nodules, schistosomal squamous metaplasia, liver-fluke-associated biliary dysplasia, antigen-dependent gastric MALT lymphoma, and staged Kaposi sarcoma illustrate the close relationship between microbial pathogenesis and tissue morphology.

Microbial detection should not be interpreted in isolation. Reliable attribution requires compatible histopathology, validated testing, localisation to relevant cells, evidence of biological activity, temporality, and appropriate clinical correlation.

Because several oncogenic infections can be prevented, treated, suppressed, or eradicated, microorganism-associated cancers represent an important opportunity for integrated vaccination, infection control, screening, pathology, antimicrobial therapy, and precision oncology.

DECLARATIONS

Ethics Approval and Consent to Participate- Ethics approval was not required because this systematic review analysed previously published studies and did not involve direct recruitment of participants or collection of identifiable patient information.

Consent for Publication- Not applicable.

Availability of Data and Materials- The evidence synthesised in this review was obtained from published sources. The complete database-search strategies, screening records, data-extraction forms, and quality-assessment documents should be retained and made available as supplementary material or from the corresponding author upon reasonable request.

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