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ONCOGENIC MICROORGANISMS IN HUMAN CANCER: MECHANISMS OF CARCINOGENESIS AND HISTOPATHOLOGICAL PROGRESSION-A SYSTEMATIC REVIEW

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Abstract

Background: Persistent infection with selected viruses, bacteria, and parasites contributes substantially to the global cancer burden. Oncogenic microorganisms promote malignant transformation through direct expression of microbial oncogenes, integration of microbial genetic material into the host genome, chronic inflammation, oxidative stress, immune evasion, genomic instability, epigenetic reprogramming, disruption of cellular signalling pathways, and alteration of the local tissue microenvironment. These molecular events are accompanied by characteristic histopathological changes that may progress from persistent infection and chronic inflammation to metaplasia, dysplasia, invasive malignancy, and metastatic disease.

Objective: This systematic review aimed to synthesize the available evidence regarding the major oncogenic microorganisms associated with human cancers, their molecular and immunopathological mechanisms of carcinogenesis, and the corresponding histopathological progression from infection-associated precursor lesions to invasive malignancy.

Methods: A systematic search of PubMed/MEDLINE, Embase, Scopus, and Web of Science was conducted from database inception to January 31, 2026. Additional literature was identified through Google Scholar, International Agency for Research on Cancer resources, World Health Organization documents, and manual screening of reference lists. Studies examining recognised or suspected oncogenic microorganisms in relation to molecular carcinogenesis, precancerous lesions, tumour histopathology, malignant transformation, or cancer progression were eligible. Two reviewers independently screened the literature, extracted relevant data, and evaluated methodological quality. Owing to substantial heterogeneity in microorganisms, tumour types, study designs, detection techniques, and reported outcomes, a narrative synthesis was performed.

Results: A total of 1,842 records were identified. After removal of 466 duplicates, 1,376 records underwent title and abstract screening. Of these, 118 full-text articles were assessed for eligibility, and 30 studies were included in the final qualitative synthesis. The strongest and most consistently demonstrated associations were observed between high-risk human papillomavirus and cervical, anogenital, and oropharyngeal cancers; Epstein–Barr virus and lymphoid, nasopharyngeal, and gastric malignancies; hepatitis B and C viruses and hepatocellular carcinoma; *Helicobacter pylori* and gastric adenocarcinoma or gastric mucosa-associated lymphoid tissue lymphoma; human T-cell lymphotropic virus type 1 and adult T-cell leukaemia/lymphoma; Kaposi sarcoma-associated herpesvirus and Kaposi sarcoma; Merkel cell polyomavirus and Merkel cell carcinoma; *Schistosoma haematobium* and urinary bladder squamous cell carcinoma; and *Opisthorchis viverrini* or *Clonorchis sinensis* and cholangiocarcinoma. Commonly affected pathways included p53, retinoblastoma protein, nuclear factor-κB, Janus kinase/signal transducer and activator of transcription, phosphatidylinositol-3-kinase/AKT, Wnt/β-catenin, transforming growth factor-β, telomerase, apoptosis, and DNA-repair pathways.

Conclusions: Oncogenic microorganisms promote human carcinogenesis through interacting direct and indirect mechanisms. Their effects are reflected in recognisable histopathological continua, including cervical intraepithelial neoplasia, chronic atrophic gastritis–intestinal metaplasia–dysplasia, chronic hepatitis–cirrhosis–hepatocellular carcinoma, chronic schistosomal cystitis–squamous metaplasia–bladder carcinoma, and chronic cholangitis–biliary dysplasia–cholangiocarcinoma. Integration of histomorphology with validated microbial, immunohistochemical, and molecular tests can improve tumour classification and risk assessment. Vaccination, infection prevention, antimicrobial treatment, screening, and surveillance of high-risk populations provide major opportunities for reducing the burden of microorganism-associated cancers.

KEYWORDS: oncogenic microorganisms; infection-associated cancer; microbial carcinogenesis; oncogenic viruses; *Helicobacter pylori*; histopathological progression; tumour microbiome; systematic review

1. INTRODUCTION

Cancer is a multistep biological process characterised by the progressive acquisition of genetic, epigenetic, metabolic, and microenvironmental abnormalities. These alterations permit sustained proliferative signalling, resistance to cell death, evasion of immune destruction, replicative immortality, angiogenesis, invasion, and metastatic dissemination. Although hereditary susceptibility, environmental carcinogens, lifestyle-related exposures, and ageing remain major determinants of cancer risk, persistent infection is an established and potentially preventable cause of several human malignancies.

The International Agency for Research on Cancer has classified several infectious biological agents as carcinogenic to humans. These include high-risk human papillomavirus, Epstein–Barr virus, hepatitis B virus, hepatitis C virus, human T-cell lymphotropic virus type 1, Kaposi sarcoma-associated herpesvirus, human immunodeficiency virus type 1 through predominantly indirect immunosuppressive mechanisms, Merkel cell polyomavirus, *Helicobacter pylori*, *Schistosoma haematobium*, *Opisthorchis viverrini*, and *Clonorchis sinensis*.

Oncogenic microorganisms are estimated to contribute to a considerable proportion of cancers worldwide. The burden is not evenly distributed. Infection-associated cancers are particularly important in low- and middle-income countries, where the prevalence of chronic infection may be high and access to vaccination, sanitation, screening, early diagnosis, antimicrobial treatment, pathology services, and oncological care may be limited.

Microbial infection alone is generally insufficient to cause cancer. Most infected individuals never develop malignancy, and transformation frequently occurs after years or decades of persistent infection. The development of cancer depends on interactions among microbial virulence factors, duration and anatomical location of infection, host genetics, immune responses, age at acquisition, nutritional status, environmental exposures, smoking, alcohol consumption, coinfections, metabolic disorders, and access to effective treatment. Oncogenic microorganisms induce malignant transformation through direct and indirect mechanisms. Certain viruses express proteins that interfere with tumour-suppressor proteins, cell-cycle checkpoints, apoptosis, telomerase regulation, DNA repair, and immune recognition. Viral genetic material may integrate into the host genome, leading to insertional mutagenesis, chromosomal instability, altered host-gene expression, or persistent expression of microbial oncogenes. Bacteria and parasites more commonly promote carcinogenesis through chronic inflammation, repeated tissue injury, regenerative proliferation, production of reactive oxygen and nitrogen species, altered DNA methylation, activation of proliferative pathways, changes in the local microbiome, and establishment of an immunosuppressive microenvironment. Some bacterial virulence factors can also directly interfere with cellular signalling and epithelial polarity. These molecular alterations are reflected in histopathological progression. Persistent high-risk human papillomavirus infection may progress through low-grade and high-grade squamous intraepithelial lesions to invasive carcinoma. *H. pylori*-associated chronic gastritis may progress through gastric glandular atrophy, intestinal metaplasia, dysplasia, and adenocarcinoma. Chronic viral hepatitis may produce progressive fibrosis, cirrhosis, dysplastic nodules, and hepatocellular carcinoma. Chronic parasite-associated inflammation may lead to squamous metaplasia and bladder carcinoma or biliary epithelial dysplasia and cholangiocarcinoma.

The relationship between microorganisms and cancer is clinically important because microbial status may assist in tumour classification, prognosis, screening, and treatment. HPV-associated oropharyngeal carcinoma, EBV-associated gastric carcinoma, EBV-positive lymphomas, and KSHV-associated vascular or lymphoid neoplasms represent biologically distinct tumour categories. Eradication of *H. pylori* can induce regression of selected early gastric mucosa-associated lymphoid tissue lymphomas, while vaccination against HPV and hepatitis B virus can prevent infection and reduce subsequent cancer risk.

Previous reviews have frequently focused on individual microorganisms or specific organ systems. A comprehensive synthesis integrating oncogenic mechanisms with histopathological progression across viral, bacterial, and parasitic cancers is therefore valuable for pathologists, microbiologists, oncologists, researchers, and public-health professionals.

1.1 Rationale

Advances in molecular pathology have made microbial biomarkers increasingly relevant to cancer diagnosis and classification. However, evidence relating microbial persistence, molecular carcinogenesis, precursor lesions, histopathological patterns, malignant progression, and clinical implications remains distributed across several disciplines. An integrated assessment is needed to differentiate microorganisms with established causal relationships from organisms detected in tumours without adequate evidence of temporality or causality. Such differentiation is particularly important in contemporary microbiome studies, where highly sensitive sequencing techniques may detect low-abundance organisms, contamination, incidental colonisation, or microorganisms that preferentially inhabit an already established tumour environment.

1.2 Objectives

The objectives of this systematic review were to:

1. identify the principal oncogenic microorganisms associated with human malignancies;
2. examine their direct and indirect mechanisms of carcinogenesis;
3. describe the associated precursor lesions and histopathological progression;
4. assess relevant microbial, immunohistochemical, and molecular biomarkers;
5. evaluate clinical and preventive implications; and
6. identify limitations in the existing evidence and priorities for 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 recommendations.

The review question was structured according to the population, exposure, comparator, and outcome framework:

- **Population:** Human participants, human tissues, or clinically relevant patient-derived samples involving precancerous lesions or malignancy.
- **Exposure:** Infection with an established or suspected oncogenic microorganism.
- **Comparator:** Uninfected individuals or tissues, non-neoplastic tissue, lower-grade lesions, alternative tumour subtypes, or different stages of disease, where available.
- **Outcomes:** Molecular mechanisms of carcinogenesis, precursor lesions, histopathological alterations, malignant transformation, invasion, tumour progression, prognosis, and microbial biomarkers.

2.2 Protocol and Registration

This review was not prospectively registered in PROSPERO, and no formal protocol was publicly deposited before the review was conducted. Nevertheless, the review question, eligibility criteria, principal data-extraction fields, quality-assessment approach, and synthesis plan 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 unrecognised protocol deviations or selective reporting.

2.3 Information Sources

The following electronic databases were searched from inception to January 31, 2026:

- PubMed/MEDLINE;
- Embase;
- Scopus; and
- Web of Science.

Supplementary searches were conducted using:

- Google Scholar;
- International Agency for Research on Cancer resources;
- World Health Organization resources; and
- reference lists of eligible articles and relevant systematic or narrative reviews.

IARC and WHO publications were used to confirm recognised carcinogenic associations and provide epidemiological context. Primary studies were used for the main evidence synthesis.

2.4 Search Strategy

Controlled vocabulary terms and free-text keywords relating to oncogenic microorganisms, carcinogenesis, malignancy, and histopathological progression were combined using Boolean operators. A representative PubMed search strategy was: (“oncogenic microorganism” OR “oncogenic microorganisms” OR “oncogenic virus” OR “tumour virus” OR “tumor virus” OR “cancer-associated infection” OR “human papillomavirus” OR HPV OR “Epstein-Barr virus” OR EBV OR “hepatitis B virus” OR HBV OR “hepatitis C virus” OR HCV OR “human T-cell lymphotropic virus” OR HTLV-1 OR “Kaposi sarcoma-associated herpesvirus” OR HHV-8 OR “Merkel cell polyomavirus” OR “Helicobacter pylori” OR “Schistosoma haematobium” OR “Opisthorchis viverrini” OR “Clonorchis sinensis”). AND (cancer OR carcinoma OR malignancy OR neoplasm OR lymphoma OR leukaemia OR leukemia) AND (carcinogenesis OR oncogenesis OR pathogenesis OR histopathology OR dysplasia OR metaplasia OR progression OR precancerous OR premalignant).The search strategy was adapted to the indexing requirements of each database. No geographical restriction was applied. English-language full-text studies were included. Potentially relevant non-English studies with sufficiently detailed English abstracts were initially assessed, but reports lacking extractable information were excluded.

2.5 Eligibility Criteria

2.5.1 Inclusion criteria

Studies were eligible when they:

1. involved human participants, human tissue, patient-derived specimens, or clinically relevant human tumour material;
2. evaluated an established or suspected oncogenic microorganism;
3. examined cancer development, precursor lesions, molecular oncogenesis, histopathological progression, tumour phenotype, or prognosis;
4. used recognised histopathological, immunohistochemical, microbiological, serological, or molecular methods;
5. reported extractable microorganism-specific and cancer-specific findings; and
6. were original cohort, case-control, cross-sectional, clinicopathological, diagnostic, translational, or molecular studies.

Landmark experimental studies with direct relevance to human tumour biology were retained when they established an important molecular mechanism using human-derived tumour material.

2.5.2 Exclusion criteria

Studies were excluded when they:

- were isolated case reports without broader mechanistic or histopathological relevance;
- involved only animal models without human validation;

- addressed infection solely as a complication of chemotherapy or cancer treatment;
- did not report extractable microorganism-specific findings;
- were conference abstracts without sufficient methodological information;
- duplicated data from another included report;
- were editorials, commentaries, or unstructured expert opinions;
- examined only incidental microbial colonisation without assessment of carcinogenesis or tumour biology; or
- lacked sufficient information to determine eligibility.

2.6 Study Selection

All retrieved citations were imported into reference-management software, and duplicate records were removed electronically and manually. Two reviewers independently screened titles and abstracts against the eligibility criteria. Potentially eligible articles underwent full-text assessment. Disagreements regarding eligibility were resolved through discussion. Where consensus could not initially be reached, a third reviewer evaluated the article.

The reasons for full-text exclusion were documented under the following categories:

- insufficient cancer-specific outcome;
- microorganism detected without evidence relating to carcinogenesis;
- non-human study without direct human validation;
- narrative or review article;
- duplicate or overlapping population;
- inadequate histopathological or molecular information; and
- full text or extractable data unavailable.

2.7 Data Extraction

A standardised data-extraction form was used to record:

- first author;
- publication year;
- country or geographical setting;
- study design;
- study population or specimen type;
- sample size;
- microorganism;
- associated malignancy;
- microbial-detection technique;
- molecular pathway;
- precursor lesion;
- histopathological findings;
- tumour stage or grade;
- clinical outcome; and
- principal conclusion.

Data extraction was performed independently by two reviewers and subsequently cross-checked for accuracy.

2.8 Quality Assessment

The methodological quality of observational studies was evaluated using tools appropriate to the study design:

- Newcastle–Ottawa Scale for cohort and case-control studies;
- Joanna Briggs Institute critical-appraisal tools for cross-sectional and prevalence studies; and
- QUADAS-2 for eligible diagnostic-accuracy studies.

Molecular and translational studies were assessed according to:

- adequacy of sample selection;
- use of appropriate controls;
- validity of microbial-detection methods;
- localisation of the microorganism to relevant tumour cells;
- reproducibility of molecular findings;
- consideration of contamination;
- biological plausibility; and
- use of complementary validation techniques.

Studies were not excluded solely on the basis of methodological limitations. Quality findings were considered during interpretation of the evidence.

2.9 Data Synthesis

Substantial heterogeneity was anticipated in relation to microorganisms, anatomical sites, malignancy types, study populations, specimen-processing methods, molecular assays, histological outcomes, and reported effect measures.

A meta-analysis was therefore not undertaken. The findings were synthesised narratively and organised according to:

1. oncogenic microorganism;
2. principal associated malignancy;
3. molecular mechanisms;

4. precursor lesion;
5. histopathological progression;
6. diagnostic biomarkers; and
7. preventive or therapeutic implications.

3. RESULTS

3.1 Study Selection

The electronic database search identified 1,796 records:

- PubMed/MEDLINE: 512 records;
- Embase: 486 records;
- Scopus: 438 records; and
- Web of Science: 360 records.

An additional 46 records were identified through Google Scholar, IARC and WHO resources, and manual screening of references. The combined search therefore yielded 1,842 records.

After removal of 466 duplicate records, 1,376 unique titles and abstracts were screened. A total of 1,258 records were excluded during title and abstract screening because they did not fulfil the eligibility criteria.

The full texts of 118 articles were assessed. Eighty-eight full-text articles were excluded for the following reasons:

- review articles, editorials, or commentaries without original data: 24;
- insufficient microorganism-specific or cancer-specific findings: 19;
- non-human studies without direct human validation: 15;
- microbial detection without evaluation of carcinogenesis or histopathology: 12;
- duplicate or overlapping populations: 7;
- inadequate methodological or outcome information: 6; and
- unavailable extractable full-text data: 5.

Thirty studies were included in the final qualitative synthesis.

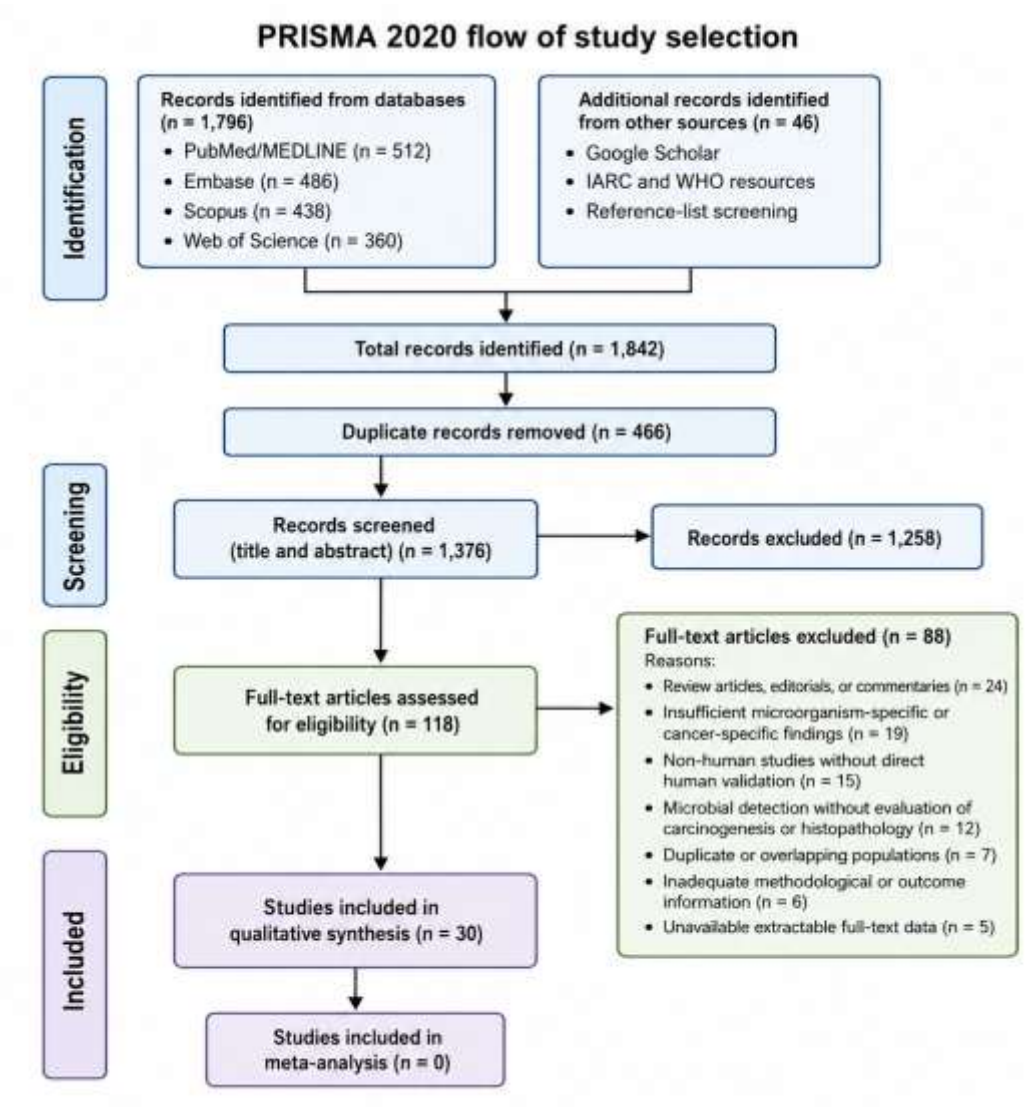

Figure 1. PRISMA 2020 flow of study selection

3.2 Characteristics of the Included Studies

The 30 included studies comprised population-based investigations, prospective and retrospective cohorts, case-control studies, tissue-based clinicopathological studies, genomic analyses, translational investigations, and intervention studies. The studies evaluated viral, bacterial, and parasitic agents across cervical, oropharyngeal, gastric, hepatic, lymphoid, cutaneous, urinary bladder, and biliary malignancies.

Table 1. Characteristics and major findings of the included studies

No.	Author and year	Country /setting	Study design or material	Microorganism	Cancer or lesion evaluated	Principal finding
1	Walboomers et al., 1999	International	Multinational cervical-tissue analysis	High-risk HPV	Cervical carcinoma	HPV DNA was identified in almost all adequately tested cervical carcinomas, supporting a necessary causal role for persistent high-risk HPV infection.
2	Bosch et al., 1995	International	Multicentre case series	HPV	Cervical carcinoma	High-risk HPV types, particularly HPV-16 and HPV-18, were strongly associated with invasive cervical cancer across geographical regions.
3	Koutsky et al., 2002	United States	Randomised controlled trial	HPV-16	Persistent HPV infection and cervical intraepithelial neoplasia	Prophylactic HPV-16 vaccination substantially reduced persistent infection and related cervical intraepithelial neoplasia.
4	McLaughlin-Drubin and Münger, 2009	Human tumour-derived molecular evidence	Translational molecular study	High-risk HPV	HPV-associated epithelial neoplasia	E6 and E7 disrupted p53 and retinoblastoma-related pathways and promoted genomic instability and malignant transformation.
5	Ang et al., 2010	United States	Prospective clinical cohort	HPV	Oropharyngeal squamous cell carcinoma	HPV-positive tumours represented a clinically and prognostically distinct group with improved survival compared with HPV-negative tumours.
6	Cancer Genome Atlas Network, 2017	Multicentre	Integrated genomic analysis	HPV	Cervical squamous cell carcinoma and adenocarcinoma	HPV-associated cervical cancers showed recurrent genomic and molecular alterations affecting PI3K and other cancer-related pathways.
7	Epstein et al., 1964	Uganda/ United Kingdom	Electron-microscopic study of tumour-derived cells	EBV	Burkitt lymphoma	Herpesvirus-like particles were demonstrated in cultured Burkitt lymphoma cells, providing foundational evidence for EBV-associated oncogenesis.

8	zur Hausen et al., 1970	Europe	Nucleic-acid hybridisation study	EBV	Burkitt lymphoma	EBV genetic material was demonstrated in Burkitt lymphoma cells, strengthening the association between EBV and lymphoid malignancy.
9	Raab-Traub and Flynn, 1986	Endemic nasopharyngeal carcinoma setting	Molecular clonality study	EBV	Nasopharyngeal carcinoma	Clonal EBV genomes were detected in tumour tissue, indicating that infection preceded clonal tumour expansion.
10	Shibata and Weiss, 1992	United States	Tissue-based clinicopathological study	EBV	Gastric adenocarcinoma	EBV was localised within a subset of gastric carcinomas, establishing EBV-associated gastric carcinoma as a distinct entity.
11	Cancer Genome Atlas Research Network, 2014	Multicentre	Comprehensive genomic classification	EBV	Gastric adenocarcinoma	EBV-positive gastric cancers demonstrated marked DNA hypermethylation, recurrent PIK3CA alterations, and distinctive immune-related features.
12	Hjalgrim et al., 2003	Denmark/Scandinavia	Population-based seroepidemiological cohort	EBV	Hodgkin lymphoma	Symptomatic primary EBV infection was associated with an increased subsequent risk of EBV-positive Hodgkin lymphoma.
13	Beasley et al., 1981	Taiwan	Prospective population-based cohort	HBV	Hepatocellular carcinoma	Chronic hepatitis B surface antigen positivity was strongly associated with later development of hepatocellular carcinoma.
14	Chang et al., 1997	Taiwan	National vaccination cohort	HBV	Childhood hepatocellular carcinoma	Universal hepatitis B vaccination was associated with a decline in childhood hepatocellular carcinoma incidence.
15	Sung et al., 2005	Hong Kong	Cohort study	HBV	Hepatocellular carcinoma	Viral replication and chronic HBV-related liver injury were associated with increased hepatocellular carcinoma risk.
16	Uemura et al., 2001	Japan	Prospective cohort	*H. pylori*	Gastric adenocarcinoma	Gastric cancer developed predominantly among infected participants, particularly those with atrophy, intestinal metaplasia, or corpus-predominant gastritis.
17	Parsonnet et al., 1991	United States	Nested case-control study	*H. pylori*	Gastric adenocarcinoma	Pre-existing *H. pylori* infection was

						associated with an increased risk of subsequent gastric carcinoma.
18	Wotherspoon et al., 1993	United Kingdom	Clinicopathological intervention series	*H. pylori*	Gastric MALT lymphoma	Eradication of *H. pylori* produced regression of selected low-grade gastric MALT lymphomas.
19	Correa, 1988	High-risk gastric cancer populations	Epidemiological and pathological synthesis based on human lesions	*H. pylori*-related inflammatory process	Gastric precancerous lesions	Gastric carcinogenesis was characterised as a multistep sequence from chronic gastritis to atrophy, intestinal metaplasia, dysplasia, and carcinoma.
20	Peek et al., 1995	United States	Clinical bacterial-strain study	CagA-positive *H. pylori*	Gastric epithelial injury	CagA-associated strains produced stronger inflammatory and epithelial responses linked to increased neoplastic risk.
21	Matsuoka et al., 2007	Japan	Molecular and clinicopathological study	HTLV-1	Adult T-cell leukaemia/lymphoma	Persistent infected T-cell clones and viral regulatory proteins were associated with progressive lymphoid transformation.
22	Bangham and Ratner, 2015	HTLV-1-endemic populations	Integrated human molecular study	HTLV-1	Adult T-cell leukaemia/lymphoma	Tax, HBZ, clonal expansion, immune selection, and acquired host mutations contributed to malignant evolution.
23	Chang et al., 1994	United States	Molecular tissue study	KSHV/HHV-8	Kaposi sarcoma	Novel herpesviral DNA sequences were identified in Kaposi sarcoma lesions, establishing KSHV as the causative viral agent.
24	Soulier et al., 1995	France	Molecular study of lymphoid tissue	KSHV/HHV-8	Multicentric Castleman disease	KSHV was detected in multicentric Castleman disease, particularly in individuals with HIV-associated immunosuppression.
25	Feng et al., 2008	United States	Tumour genomic study	Merkel cell polyomavirus	Merkel cell carcinoma	Clonal integration of Merkel cell polyomavirus was demonstrated in tumour cells, indicating infection before tumour expansion.
26	Harms et al., 2017	Multicentre	Genomic comparison	Merkel cell polyomavirus	Merkel cell carcinoma	Virus-positive and virus-negative Merkel cell carcinomas showed distinct genomic patterns and carcinogenic mechanisms.

27	Mostafa et al., 1999	Schistosomiasis-endemic regions	Clinicopathological and epidemiological synthesis	*S. haematobium*	Urinary bladder squamous cell carcinoma	Chronic egg-associated inflammation, squamous metaplasia, oxidative injury, and nitrosamine exposure were linked to bladder carcinogenesis.
28	Qian et al., 2012	East Asia	Epidemiological and pathological investigation	*Clonorchis sinensis*	Cholangiocarcinoma	Chronic liver-fluke infection was associated with biliary inflammation, epithelial proliferation, and increased cholangiocarcinoma risk.
29	Sripa et al., 2007	Thailand	Endemic-population clinicopathological study	*Opisthorchis viverrini*	Cholangiocarcinoma	Repeated biliary injury, chronic inflammation, and parasite-derived products contributed to biliary dysplasia and carcinoma.
30	Kostic et al., 2013	United States	Human colorectal-tissue and translational study	*Fusobacterium nucleatum*	Colorectal carcinoma	Increased tumour-associated *F. nucleatum* was linked to tumour-promoting inflammation and modification of the immune microenvironment.

3.3 Quality of the Included Evidence

The quality of evidence was strongest for HPV-associated cervical cancer, HBV-associated hepatocellular carcinoma, *H. pylori*-associated gastric cancer, and the established virus-associated tumour entities. These relationships were supported by convergent epidemiological, molecular, pathological, and preventive evidence.

The principal strengths of the included studies were:

- use of histologically confirmed tumours;
- localisation of microorganisms within neoplastic cells;
- demonstration of clonal viral integration;
- prospective serological or infection-status assessment;
- evidence of temporality;
- identification of microorganism-specific oncogenic proteins;
- dose-response or persistence-related associations; and
- reduction of cancer or precursor-lesion risk after vaccination or microbial eradication.

Common methodological limitations included:

- retrospective designs;
- limited adjustment for confounding factors;
- small tissue cohorts;
- geographical concentration in endemic regions;
- variation in microbial assays;
- inconsistent positivity thresholds;
- inability to distinguish active from latent infection;
- limited longitudinal follow-up; and
- potential contamination in low-biomass microbiome studies.

4. Major Oncogenic Microorganisms and Associated Cancers

4.1 High-Risk Human Papillomavirus

High-risk HPV is the principal cause of cervical carcinoma and is associated with substantial proportions of vulvar, vaginal, anal, penile, and oropharyngeal carcinomas. HPV-16 and HPV-18 account for the majority of HPV-associated cancers, although several additional high-risk genotypes have oncogenic potential.

4.1.1 Mechanisms of carcinogenesis

The E6 and E7 viral oncoproteins are the principal mediators of HPV-associated transformation. E6 promotes ubiquitin-mediated degradation of p53, reduces DNA-damage-induced apoptosis, activates telomerase, and interferes with cellular

polarity proteins. E7 binds and functionally inactivates retinoblastoma protein, releasing E2F transcription factors and driving inappropriate entry into the S phase of the cell cycle.
Persistent E6 and E7 activity produces:

- loss of cell-cycle control;
- defective apoptosis;
- centrosomal abnormalities;
- chromosomal instability;
- impaired DNA repair;
- telomerase activation;
- increased cellular proliferation; and
- accumulation of secondary host mutations.

Integration of HPV DNA into the host genome commonly disrupts viral E2 regulation and promotes persistent E6 and E7 expression. However, integration is not obligatory, and invasive cancers may contain episomal or mixed viral genomes.

4.1.2 Histopathological progression

Productive HPV infection initially affects basal epithelial cells through small mucosal disruptions. Low-grade squamous intraepithelial lesions show koilocytosis, nuclear enlargement, irregular nuclear membranes, hyperchromasia, and maturation of superficial epithelial layers.
High-grade squamous intraepithelial lesions show:

- expansion of immature basaloid cells;
- increased nuclear-to-cytoplasmic ratio;
- loss of epithelial maturation;
- nuclear pleomorphism;
- mitotic activity above the basal layer;
- atypical mitotic figures; and
- diffuse block-type p16 immunoreactivity.

Progression through the basement membrane produces invasive squamous cell carcinoma. HPV-associated oropharyngeal carcinomas frequently demonstrate non-keratinising nests and sheets of tumour cells with limited cytoplasm, brisk mitotic activity, comedo-type necrosis, and prominent lymphoid stroma.

4.2 Epstein–Barr Virus

EBV is associated with Burkitt lymphoma, classical Hodgkin lymphoma, post-transplant lymphoproliferative disorders, extranodal natural killer/T-cell lymphoma, nasopharyngeal carcinoma, and a subset of gastric carcinomas.

4.2.1 Mechanisms of carcinogenesis

EBV establishes lifelong latent infection. Its oncogenic effects vary according to the viral latency programme and infected cell type.
Latent membrane protein 1 mimics constitutively active CD40 signalling and activates:

- nuclear factor-κB;
- mitogen-activated protein kinase;
- Janus kinase/signal transducer and activator of transcription;
- phosphatidylinositol-3-kinase/AKT; and
- anti-apoptotic pathways.

Latent membrane protein 2A mimics B-cell receptor signalling and supports the survival of infected cells. Epstein–Barr nuclear antigens maintain viral episomes and regulate viral and cellular transcription. EBV-encoded RNAs and microRNAs contribute to immune evasion, inhibition of apoptosis, and alteration of the tumour microenvironment.

4.2.2 Lymphoid malignancies

Burkitt lymphoma is composed of monomorphic medium-sized lymphoid cells with deeply basophilic cytoplasm, a very high proliferative index, numerous apoptotic bodies, and a characteristic starry-sky pattern produced by tingible-body macrophages. EBV supports B-cell survival and cooperates with MYC rearrangement.
In classical Hodgkin lymphoma, EBV may be present in Hodgkin and Reed–Sternberg cells. The malignant cells occur within a mixed inflammatory background consisting of lymphocytes, eosinophils, plasma cells, and histiocytes.
Post-transplant lymphoproliferative disorders arise when impaired T-cell surveillance permits the uncontrolled expansion of EBV-infected B cells. Their morphology ranges from plasmacytic or immunoblastic proliferations to destructive monomorphic lymphoma.

4.2.3 Epithelial malignancies

Non-keratinising nasopharyngeal carcinoma frequently shows syncytial nests of poorly differentiated malignant epithelial cells within a dense lymphoplasmacytic stroma. EBV-encoded RNA in-situ hybridisation demonstrates infection within tumour cells.
EBV-associated gastric carcinoma may exhibit prominent lymphoid stroma, pushing borders, poorly formed glands, or conventional adenocarcinoma morphology. These tumours commonly demonstrate extensive DNA hypermethylation, PIK3CA alterations, and immune-checkpoint-related changes.

4.3 Hepatitis B Virus

HBV promotes hepatocellular carcinoma through chronic inflammation and direct viral genomic effects.

4.3.1 Mechanisms of carcinogenesis

Persistent HBV infection produces repeated hepatocellular injury, inflammation, regeneration, fibrosis, and cirrhosis. HBV DNA may integrate into the host genome, causing chromosomal rearrangements, altered gene expression, genomic instability, and clonal hepatocyte expansion.

The HBx protein interferes with:

- p53 activity;
- transcriptional regulation;
- DNA repair;
- apoptosis;
- mitochondrial function;
- oxidative-stress responses; and
- proliferative signalling pathways.

HBV-associated hepatocellular carcinoma may develop in the absence of established cirrhosis, supporting a direct contribution from viral integration and HBx-related mechanisms.

4.3.2 Histopathological progression

Chronic hepatitis shows portal and lobular inflammation, interface activity, hepatocellular injury, and variable regenerative change. Progressive fibrosis leads to bridging fibrous septa and cirrhosis.

Premalignant lesions include low-grade and high-grade dysplastic nodules. Early hepatocellular carcinoma may demonstrate:

- increased cellular density;
- irregular thin trabeculae;
- stromal invasion;
- fatty change;
- unpaired arteries;
- loss of portal tracts; and
- reduced reticulin framework.

Progression results in thickened trabeculae, pseudoglandular or solid architecture, cytological atypia, vascular invasion, and metastasis.

4.4 Hepatitis C Virus

HCV is an RNA virus that does not usually integrate into the host genome. Its oncogenic effects are predominantly mediated through chronic inflammation and metabolic injury.

Persistent HCV infection causes:

- chronic necroinflammation;
- oxidative and mitochondrial stress;
- steatosis;
- hepatocellular death;
- regenerative proliferation;
- progressive fibrosis; and
- cirrhosis.

Repeated cell turnover increases opportunities for the acquisition and selection of driver mutations. Alcohol consumption, metabolic dysfunction, obesity, diabetes, iron accumulation, and coinfection may further increase hepatocellular carcinoma risk.

The histopathological progression generally follows chronic hepatitis, bridging fibrosis, cirrhosis, dysplastic nodules, and hepatocellular carcinoma. HCV is also associated with selected B-cell lymphomas through chronic antigenic stimulation and progressive B-cell clonal expansion.

4.5 *Helicobacter pylori*

H. pylori is causally associated with non-cardia gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma.

4.5.1 Mechanisms of carcinogenesis

Persistent colonisation produces chronic active gastritis and sustained interaction among bacteria, epithelial cells, immune cells, and stromal cells.

CagA-positive strains deliver the CagA protein into gastric epithelial cells through a type IV secretion system. CagA affects:

- SHP2 signalling;
- epithelial junctions;
- cellular polarity;

- β-catenin signalling;
- inflammatory responses;
- proliferation; and
- cytoskeletal organisation.

VacA and additional bacterial factors contribute to epithelial injury, immune modulation, and bacterial persistence. Chronic inflammation produces reactive oxygen and nitrogen species, DNA damage, aberrant DNA methylation, altered gastric stem-cell behaviour, and glandular loss.

4.5.2 Gastric adenocarcinoma progression

The classical Correa cascade comprises:

1. chronic active non-atrophic gastritis;
2. multifocal atrophic gastritis;
3. intestinal metaplasia;
4. low-grade dysplasia;
5. high-grade dysplasia; and
6. invasive gastric adenocarcinoma.

Spasmolytic polypeptide-expressing metaplasia may also participate in gastric carcinogenesis and may coexist with or precede intestinal metaplasia.

Intestinal-type adenocarcinoma commonly develops through this recognisable precursor sequence. The pathway to diffuse-type gastric carcinoma is less clearly defined and may involve distinct host-genetic and molecular factors.

4.5.3 Gastric MALT lymphoma

Persistent *H. pylori* infection induces acquired lymphoid tissue within the gastric mucosa. Early lymphoma may remain dependent on bacterial antigenic stimulation and microenvironmental T-cell signals.

Histologically, gastric MALT lymphoma shows:

- dense marginal-zone B-cell infiltration;
- reactive lymphoid follicles;
- colonisation and destruction of gastric glands;
- centrocyte-like cells; and
- lymphoepithelial lesions.

Eradication of *H. pylori* may induce regression of early, localised, bacterium-dependent disease. Acquisition of genetic abnormalities may produce independence from bacterial stimulation and resistance to eradication alone.

4.6 Human T-Cell Lymphotropic Virus Type 1

HTLV-1 causes adult T-cell leukaemia/lymphoma after a prolonged latency period. Only a minority of infected individuals develop malignancy, indicating that viral infection must cooperate with host-genetic, immunological, and acquired somatic alterations.

The Tax protein activates nuclear factor-κB and other transcriptional pathways, promotes proliferation, interferes with DNA-damage checkpoints, and induces genomic instability. Tax expression may later be reduced because it is strongly immunogenic.

HBZ is more consistently expressed in malignant cells and contributes to:

- infected-cell survival;
- proliferation;
- immune modulation;
- persistence; and
- transcriptional reprogramming.

Adult T-cell leukaemia/lymphoma shows pleomorphic lymphoid cells, frequently with multilobulated or flower-shaped nuclei. Clinical presentations include smouldering, chronic, acute leukaemic, and lymphomatous forms.

4.7 Kaposi Sarcoma-Associated Herpesvirus

KSHV, also known as human herpesvirus 8, is necessary for Kaposi sarcoma and is associated with primary effusion lymphoma and multicentric Castleman disease-related proliferations.

KSHV expresses viral cytokines, anti-apoptotic proteins, angiogenic mediators, and immune-modulatory factors. These promote:

- endothelial or spindle-cell proliferation;
- angiogenesis;
- inflammatory cytokine production;
- resistance to apoptosis; and
- immune evasion.

Kaposi sarcoma progresses through recognised histological stages.

Patch-stage lesions demonstrate irregular, jagged vascular spaces dissecting dermal collagen with mild inflammatory infiltration.

Plaque-stage lesions show increased spindle-cell proliferation, vascular channels, extravasated erythrocytes, hemosiderin, and hyaline globules.

Nodular lesions are composed of more cellular intersecting fascicles of spindle cells containing slit-like vascular spaces. Nuclear staining for KSHV latency-associated nuclear antigen supports the diagnosis.

4.8 Merkel Cell Polyomavirus

Merkel cell polyomavirus is clonally integrated into the tumour-cell genome in a substantial proportion of Merkel cell carcinomas. Tumour-associated large T antigen is generally truncated, preserving retinoblastoma protein-binding activity while losing viral replication functions that would be detrimental to tumour-cell survival.

Merkel cell carcinoma is an aggressive cutaneous neuroendocrine carcinoma. Histologically, it is composed of dermal sheets, nests, or trabeculae of small blue cells with:

- scant cytoplasm;
- finely granular chromatin;
- nuclear moulding;
- brisk mitotic activity;
- numerous apoptotic bodies; and
- frequent necrosis.

Cytokeratin 20 commonly shows paranuclear dot-like staining. Virus-positive and ultraviolet-associated virus-negative tumours represent molecularly distinct pathways.

4.9 *Schistosoma haematobium*

Chronic urinary infection with *S. haematobium* is associated with squamous cell carcinoma of the urinary bladder.

Parasite eggs deposited in the bladder wall produce:

- granulomatous inflammation;
- mucosal ulceration;
- fibrosis;
- calcification;
- urinary stasis;
- repeated epithelial injury; and
- regenerative proliferation.

Reactive oxygen and nitrogen species, bacterial coinfection, and nitrosamine exposure may further contribute to DNA damage.

The histopathological sequence involves:

Chronic schistosomal cystitis → squamous metaplasia → keratinising dysplasia → invasive squamous cell carcinoma.

Calcified eggs may be identified within the bladder wall adjacent to granulomatous inflammation, fibrosis, metaplastic epithelium, dysplasia, or invasive carcinoma.

4.10 *Opisthorchis viverrini* and *Clonorchis sinensis*

Chronic infection with liver flukes is associated with cholangiocarcinoma, particularly in endemic regions of Southeast and East Asia.

Parasites residing in the biliary tract cause:

- chronic cholangitis;
- mechanical epithelial injury;
- biliary obstruction;
- epithelial hyperplasia;
- periductal fibrosis;
- oxidative stress;
- exposure to parasite-derived secretory products; and
- sustained proliferative signalling.

The histopathological progression may include biliary epithelial hyperplasia, metaplasia, biliary intraepithelial neoplasia, and invasive cholangiocarcinoma. Established tumours frequently show gland-forming adenocarcinoma within a dense desmoplastic stroma.

4.11 Human Immunodeficiency Virus

HIV increases cancer risk predominantly through immunosuppression, impaired immune surveillance, and inadequate control of other oncogenic infections rather than through consistent direct cellular transformation.

Important HIV-associated malignancies include:

- KSHV-associated Kaposi sarcoma;
- EBV-associated non-Hodgkin lymphoma;
- primary central nervous system lymphoma;
- HPV-associated cervical carcinoma;
- HPV-associated anal carcinoma; and
- selected Hodgkin lymphomas.

Effective antiretroviral therapy has reduced the incidence of several AIDS-defining malignancies. Nevertheless, risk remains influenced by the duration and severity of immunosuppression, persistent coinfection, behavioural factors, screening access, and ageing.

4.12 Emerging Bacterial and Microbiome Associations

Additional bacteria have been associated with cancer, including:

- *Fusobacterium nucleatum* in colorectal carcinoma;
- enterotoxigenic *Bacteroides fragilis* in colorectal neoplasia;
- colibactin-producing *Escherichia coli* in colorectal carcinogenesis; and
- chronic *Salmonella Typhi* carriage in gallbladder carcinoma.

Proposed mechanisms include:

- direct genotoxicity;
- production of DNA-damaging metabolites;
- biofilm formation;
- activation of β-catenin and inflammatory signalling;
- suppression of antitumour immunity;
- modification of the tumour microenvironment; and
- alteration of therapeutic response.

The strength of these associations does not yet equal that of established carcinogens such as high-risk HPV, HBV, HCV, EBV, or *H. pylori*. Detection of a microorganism in tumour tissue does not itself establish that the organism initiated malignant transformation. Certain organisms may preferentially colonise tissue after a tumour has altered oxygen tension, nutrient availability, vascular permeability, epithelial barriers, and local immunity.

5. Integrated Mechanisms of Microbial Carcinogenesis

5.1 Direct Oncogenic Protein Activity

Several oncogenic viruses encode proteins that directly disturb normal cellular growth and survival.

Examples include:

- HPV E6-mediated degradation of p53;
- HPV E7-mediated inactivation of retinoblastoma protein;
- EBV latent membrane protein-mediated activation of nuclear factor-κB;
- HTLV-1 Tax- and HBZ-mediated transcriptional dysregulation;
- KSHV-mediated activation of angiogenic and anti-apoptotic pathways; and
- Merkel cell polyomavirus T-antigen-mediated disruption of retinoblastoma-related control.

These proteins provide infected cells with a selective growth or survival advantage. Additional host alterations are generally required before invasive malignancy develops.

5.2 Integration of Microbial Genetic Material

Integration of viral DNA may:

- interrupt host genes;
- alter chromatin organisation;
- activate oncogenes;
- disrupt tumour-suppressor genes;
- create chromosomal rearrangements; and
- maintain viral oncogene expression.

HPV, HBV, and Merkel cell polyomavirus provide important examples. Clonal integration indicates that viral infection occurred before expansion of the malignant clone.

5.3 Chronic Inflammation and Oxidative Stress

Chronic inflammation is central to *H. pylori*-, HBV-, HCV-, schistosome-, and liver-fluke-associated carcinogenesis.

Activated inflammatory cells produce reactive oxygen and nitrogen species that damage DNA, proteins, and lipids. Pro-inflammatory cytokines promote:

- cellular proliferation;
- angiogenesis;
- stromal remodelling;
- epithelial-to-mesenchymal transition;
- recruitment of immunosuppressive cells; and
- survival of genetically altered clones.

Persistent tissue injury causes repeated cycles of cell death and regeneration, increasing the opportunity for mutation and clonal selection.

5.4 Immune Evasion and Immunosuppression

Oncogenic microorganisms evade immune clearance through:

- latent infection;
- reduced antigen expression;
- interference with interferon signalling;
- inhibition of apoptosis;
- production of viral cytokines;

- induction of regulatory immune cells;
- immune-checkpoint activation; and
- exhaustion of cytotoxic lymphocytes.

HIV-associated immunodeficiency demonstrates how loss of immune control permits secondary oncogenic microorganisms to drive malignant proliferation.

5.5 Genomic Instability and Impaired DNA Repair

Microbial oncogenes and chronic inflammation may interfere with DNA-damage recognition and repair. Inappropriate cell-cycle progression allows genetically damaged cells to divide rather than undergo arrest or apoptosis.

The resulting abnormalities include:

- chromosomal gains and losses;
- point mutations;
- DNA breaks;
- centrosomal abnormalities;
- aneuploidy;
- microsatellite instability; and
- structural rearrangements.

5.6 Epigenetic Reprogramming

Persistent infection can alter:

- DNA methylation;
- histone modifications;
- chromatin accessibility;
- microRNA expression; and
- long non-coding RNA regulation.

These alterations may silence tumour-suppressor genes, maintain viral latency, support stem-like phenotypes, and reduce immune recognition. EBV-associated gastric carcinoma and chronically inflamed *H. pylori*-exposed gastric mucosa are important examples of infection-associated epigenetic alteration.

5.7 Alteration of the Tissue Microenvironment

Oncogenic microorganisms influence tumour-associated fibroblasts, endothelial cells, macrophages, lymphocytes, and extracellular matrix components.

The resulting microenvironment may promote:

- angiogenesis;
- immune suppression;
- fibrosis;
- tissue remodelling;
- tumour-cell survival;
- invasion; and
- metastatic dissemination.

5.8 Microbiome Dysbiosis

The tissue and intestinal microbiome can affect epithelial barriers, metabolism, inflammation, and antitumour immunity. Dysbiosis may increase exposure to microbial genotoxins, alter bile-acid metabolism, reduce protective metabolites, and support a tumour-promoting immune environment. However, microbiome studies require careful interpretation. Sampling contamination, low microbial biomass, antibiotic use, diet, age, geography, sequencing platform, and bioinformatic methods may substantially affect the reported microbial composition.

6. Histopathological Progression of Microorganism-Associated Cancers

Despite important organism-specific differences, many infection-associated cancers follow a common multistep continuum: Microbial acquisition → persistence or latency → chronic inflammation and/or microbial oncogene expression → genomic and epigenetic injury → metaplasia, hyperplasia, or clonal expansion → dysplasia or premalignant proliferation → invasive malignancy → vascular or lymphatic invasion → metastasis.

Table 2. Principal histopathological sequences associated with oncogenic microorganisms

Microorganism	Initial pathological alteration	Precursor lesion	Invasive malignancy
High-risk HPV	Productive epithelial infection and koilocytosis	Low-grade and high-grade squamous intraepithelial lesions	Squamous cell carcinoma or selected adenocarcinomas

H. pylori	Chronic active gastritis	Atrophy, intestinal metaplasia, low-grade and high-grade dysplasia	Gastric adenocarcinoma
H. pylori	Acquired gastric lymphoid tissue	Clonal marginal-zone B-cell proliferation	Gastric MALT lymphoma
HBV/HCV	Chronic hepatitis	Fibrosis, cirrhosis, dysplastic nodules	Hepatocellular carcinoma
EBV	Latent epithelial infection or lymphoid-cell infection	Clonal epithelial or lymphoid expansion	Nasopharyngeal carcinoma, gastric carcinoma, or lymphoma
HTLV-1	Persistent infected T-cell population	Oligoclonal or clonal T-cell expansion	Adult T-cell leukaemia/lymphoma
KSHV	Reactive and inflammatory vascular proliferation	Patch- and plaque-stage Kaposi sarcoma	Nodular Kaposi sarcoma
Merkel cell polyomavirus	Clonal viral integration in susceptible cells	No consistently recognised morphological precursor	Merkel cell carcinoma
S. haematobium	Chronic granulomatous cystitis	Squamous metaplasia and dysplasia	Urinary bladder squamous cell carcinoma
Liver flukes	Chronic cholangitis and periductal fibrosis	Biliary epithelial hyperplasia and biliary intraepithelial neoplasia	Cholangiocarcinoma

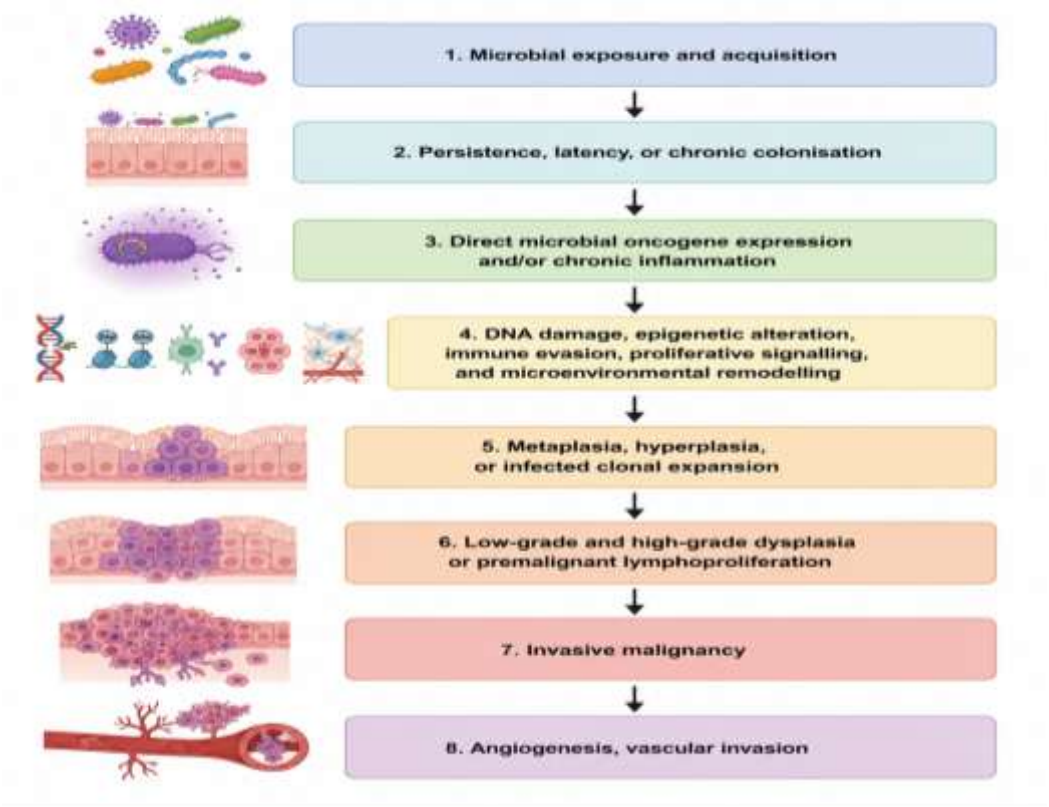

Figure 2. Integrated pathway of microorganism-associated carcinogenesis

7. Diagnostic and Clinical Implications

7.1 Demonstration of Microorganisms in Tumour Tissue

Microbial detection should ideally demonstrate that the microorganism is present within the relevant neoplastic cells rather than exclusively in adjacent inflammatory cells, surface material, blood, or contaminating tissue.
Available methods include:

- polymerase chain reaction;
- quantitative polymerase chain reaction;
- reverse-transcription polymerase chain reaction;
- DNA or RNA in-situ hybridisation;
- immunohistochemistry;
- serology;
- microbial culture;
- sequencing;
- special histochemical stains; and
- direct histological identification of microorganisms or parasite eggs.

In-situ methods provide spatial localisation but may have lower analytical sensitivity. Amplification-based assays are highly sensitive but may not establish whether microbial material is located within viable tumour cells or represents contamination or incidental colonisation.

7.2 Immunohistochemical and Molecular Surrogate Markers

Diffuse block-type p16 immunoreactivity is a useful surrogate for transforming HPV infection in appropriate settings, particularly oropharyngeal squamous cell carcinoma. However, p16 expression is not universally specific for HPV and must be interpreted according to anatomical site and validated testing algorithms.
EBV-encoded RNA in-situ hybridisation is widely used to demonstrate latent EBV within tumour cells.
KSHV latency-associated nuclear antigen immunohistochemistry supports the diagnosis of Kaposi sarcoma, primary effusion lymphoma, and other KSHV-associated proliferations.
Merkel cell polyomavirus large T-antigen immunohistochemistry can assist in distinguishing virus-associated Merkel cell carcinoma, although molecular and morphological correlation remains necessary.

7.3 Prevention

Microorganism-associated cancers are particularly suitable for preventive intervention.
Major strategies include:

- HPV vaccination;
- hepatitis B vaccination;
- screening for cervical precancerous lesions;
- prevention of blood-borne and sexually transmitted infections;
- diagnosis and treatment of HBV and HCV;
- testing and eradication of *H. pylori*;
- early and sustained antiretroviral therapy;
- sanitation and parasite-control programmes;
- safe food and water practices;
- surveillance of individuals with cirrhosis or advanced gastric precancerous lesions; and
- education of high-risk populations.

7.4 Therapeutic Relevance

Eradication of *H. pylori* may result in regression of early gastric MALT lymphoma. Antiviral therapy for hepatitis B or hepatitis C reduces chronic hepatic injury and future hepatocellular carcinoma risk, although individuals with advanced fibrosis or cirrhosis may continue to require surveillance.
Microorganism-associated cancers may also present therapeutic opportunities through:

- immune-checkpoint inhibition;
- therapeutic vaccination;
- adoptive virus-specific T-cell therapy;
- antiviral therapy;
- targeted disruption of microbial oncogenic pathways; and
- modulation of the tumour-associated microbiome.

8. DISCUSSION

This systematic review demonstrates that oncogenic microorganisms comprise a biologically diverse group of viruses, bacteria, and parasites that promote human cancer through interacting direct and indirect mechanisms. Although the molecular pathways vary among organisms, several common themes emerge: microbial persistence, failure of immune clearance, sustained cellular proliferation, genomic or epigenetic injury, chronic inflammatory remodelling, altered tissue architecture, and clonal selection.
The strongest causal relationships were supported by multiple complementary forms of evidence. These included consistent epidemiological associations, demonstration of microbial material in tumour cells, expression of organism-

specific oncogenic proteins, evidence that infection preceded clonal tumour expansion, identification of biologically plausible mechanisms, and reduction in cancer or precursor-lesion risk following vaccination or treatment.

HPV-associated carcinogenesis provides one of the clearest examples of direct microbial interference with tumour-suppressor pathways. Persistent expression of E6 and E7 disables p53- and retinoblastoma-mediated control, resulting in abnormal proliferation and genomic instability. These molecular events correspond to a well-characterised histopathological progression from productive infection and low-grade intraepithelial abnormalities to high-grade dysplasia and invasive carcinoma.

The relationship between *H. pylori* and gastric cancer provides a prominent example of chronic inflammation-mediated carcinogenesis. Long-standing gastritis, glandular atrophy, intestinal metaplasia, dysplasia, and adenocarcinoma represent a morphological continuum through which inflammatory injury, microbial virulence, host susceptibility, and environmental exposures interact. The association with gastric MALT lymphoma further demonstrates that persistent microbial antigenic stimulation can promote lymphoid neoplasia and that elimination of the causative microorganism may reverse early disease.

HBV and HCV both contribute to hepatocellular carcinoma, but their mechanisms are not identical. HBV can integrate into the host genome and exert direct oncogenic effects through viral proteins, while HCV acts predominantly through persistent necroinflammation, metabolic disturbance, and cirrhosis. The ability of HBV-associated hepatocellular carcinoma to develop without established cirrhosis supports an additional direct viral contribution.

EBV is notable for its association with both lymphoid and epithelial malignancies. The effect of EBV depends on viral latency, infected cell type, host immune status, and cooperating genetic abnormalities. Clonal viral genomes and localisation of EBV to malignant cells support its role in tumour development rather than incidental infection.

Parasite-associated cancers illustrate the consequences of prolonged mechanical injury and granulomatous or biliary inflammation. Chronic *S. haematobium* infection produces a sequence of cystitis, fibrosis, squamous metaplasia, dysplasia, and bladder squamous cell carcinoma. Liver-fluke infection produces chronic cholangitis, periductal fibrosis, epithelial hyperplasia, biliary dysplasia, and cholangiocarcinoma.

Recognition of histopathological sequences has important clinical value. Precancerous lesions offer opportunities for screening, surveillance, antimicrobial treatment, and prevention before invasive malignancy develops. The cervical, gastric, hepatic, urinary bladder, and biliary pathways demonstrate how microbial aetiology can be integrated with tissue morphology for risk stratification.

Microbial status may also define tumour subgroups with distinct clinical behaviour. HPV-associated oropharyngeal carcinoma differs from conventional tobacco-associated carcinoma in its molecular profile and prognosis. EBV-associated gastric carcinoma shows distinctive epigenetic and immune-related features. Virus-positive and ultraviolet-associated virus-negative Merkel cell carcinomas represent different molecular pathways.

The emerging cancer-microbiome literature requires particular caution. Highly sensitive sequencing has demonstrated bacterial and fungal material in many tumours, but the presence of an organism does not establish causality. Tumours alter oxygen tension, nutrient availability, epithelial barriers, vascular permeability, and local immunity, potentially creating conditions that favour secondary microbial colonisation. Longitudinal studies, spatial localisation, absolute microbial quantification, strain-level analysis, and functional validation are needed to distinguish carcinogenic drivers from tumour-associated passengers.

8.1 Implications for Pathology Practice

Pathologists have an important role in recognising infection-associated tumour patterns and selecting appropriate ancillary investigations. A reliable diagnostic conclusion should integrate:

Compatible morphology + validated demonstration of the microorganism or an accepted surrogate marker + localisation to the relevant cells + appropriate clinical context.

Detection of microbial nucleic acid through polymerase chain reaction or sequencing alone should not automatically be interpreted as causal. Assay contamination, latent infection, non-viable organisms, and microorganisms located outside tumour cells should be considered.

8.2 Public-Health Implications

Infection-associated cancers represent some of the most preventable human malignancies. HPV and hepatitis B vaccines can prevent the initiating infection. Screening can detect HPV-associated precursor lesions before invasion. *H. pylori* eradication can reduce gastric cancer risk and treat selected gastric MALT lymphomas. Antiviral treatment can reduce chronic liver injury and cancer risk associated with HBV and HCV.

The burden remains disproportionately high in regions with limited vaccination, sanitation, screening, molecular diagnostics, pathology infrastructure, and access to treatment. Cancer-control programmes should therefore combine infection prevention with accessible screening, diagnostic pathology, antimicrobial therapy, surveillance, and oncological care.

8.3 Research Priorities

Future studies should:

1. standardise definitions of microbial positivity;
2. distinguish active infection from latent or incidental microbial presence;
3. establish temporality through prospective longitudinal cohorts;
4. localise microorganisms within tumour and precursor-lesion cells;

5. integrate microbiological findings with histopathology, genomics, epigenomics, transcriptomics, proteomics, and immune profiling;
6. improve contamination control in low-biomass tissue studies;
7. investigate strain-level differences in microbial virulence;
8. assess interactions between coinfections and environmental carcinogens;
9. determine whether microbial markers predict prognosis or treatment response; and
10. evaluate whether microbial eradication or modulation prevents progression of established precursor lesions.

9. LIMITATIONS

This systematic review has several limitations.

First, this review was not prospectively registered in PROSPERO, and no formal protocol was publicly deposited before the review was conducted. Although the review question, eligibility criteria, and principal analytical methods were defined before completion of screening, the absence of prospective registration may have increased the possibility of protocol deviations or selective reporting.

Second, the included microorganisms, malignancies, molecular mechanisms, and histopathological outcomes were highly heterogeneous. The studies used different designs, sample types, microbial assays, positivity thresholds, histological classifications, and outcome measures. Consequently, a statistically meaningful meta-analysis could not be performed.

Third, much of the evidence was derived from retrospective, cross-sectional, and tissue-based studies. These designs may be affected by selection bias, incomplete control of confounding factors, variation in specimen preservation, and an inability to establish whether infection preceded tumour development.

Fourth, highly sensitive molecular techniques may detect microbial DNA or RNA from latent infection, incidental colonisation, non-viable microorganisms, adjacent non-neoplastic cells, blood, laboratory reagents, or environmental contamination. Detection of microbial nucleic acid does not necessarily demonstrate transcriptional activity, intracellular localisation, or causal involvement.

Fifth, despite the structured multi-database search, relevant studies may have been missed because of variation in terminology, indexing, language, and database coverage. Terms such as “oncogenic microorganism,” “tumour microbiota,” “microbial carcinogenesis,” “dysbiosis,” and “cancer-associated microbiome” have evolved over time and may not have been consistently used in earlier publications.

Sixth, only studies with extractable microbiological, molecular, histopathological, or clinicopathological findings were included. Studies with incomplete outcome reporting were excluded, which may have introduced selection bias.

Seventh, unpublished data and individual participant data were not obtained from study authors. The synthesis was therefore limited by the completeness and quality of published reports.

Finally, publication bias and selective outcome reporting may have favoured positive associations between microorganisms and cancer. This concern is particularly important for emerging microbiome associations, for which negative findings may be less likely to be published.

10. CONCLUSIONS

Specific viruses, bacteria, and parasites are established causes or major promoters of human cancer. They induce malignant transformation through direct microbial oncogene activity, integration of microbial genetic material, chronic inflammation, oxidative stress, genomic instability, epigenetic reprogramming, immune evasion, altered signalling, and modification of the tissue microenvironment.

These mechanisms produce recognisable histopathological sequences. Important examples include HPV-associated squamous intraepithelial lesions, *H. pylori*-associated gastric atrophy and intestinal metaplasia, chronic viral hepatitis-associated cirrhosis and dysplastic nodules, schistosomal cystitis-associated squamous metaplasia, and liver-fluke-associated biliary dysplasia.

The diagnosis of microorganism-associated malignancy should integrate histomorphology with validated microbiological, immunohistochemical, and molecular techniques. Detection of a microorganism without appropriate cellular localisation, biological activity, temporality, and clinicopathological correlation should not be considered sufficient evidence of causality.

Several infection-associated cancers can be prevented through vaccination, sanitation, infection-control measures, screening, microbial eradication, antiviral therapy, and surveillance of high-risk populations. Integration of microbiology, pathology, oncology, immunology, and public health is therefore essential for reducing the global burden of microorganism-associated cancers.

Declarations

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

Availability of Data and Materials- The information evaluated in this review was obtained from published literature. The complete database-search strategies, screening records, data-extraction forms, and quality-assessment sheets may be made available by the corresponding author upon reasonable request.

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data extraction, preparation of tables, and drafting of the manuscript. Dr. Mohd Sanan Khan contributed to data collection, histopathological interpretation, reference management, and review and editing of the manuscript. All authors read and approved the final manuscript.

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