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ROLE OF ONCOGENIC MICROORGANISMS IN THE PATHOGENESIS AND HISTOPATHOLOGICAL PROGRESSION OF HUMAN CANCERS: A SYSTEMATIC REVIEW

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ABSTRACT

Background

Persistent infection with selected viruses, bacteria and parasites contributes substantially to the global burden of human cancer. Oncogenic microorganisms promote malignant transformation through microbial oncogene expression, integration into the host genome, tumour-suppressor inactivation, chronic inflammation, oxidative DNA damage, immune dysregulation, epigenetic reprogramming and sustained tissue regeneration. However, the relationship between microbial persistence and the sequential histopathological changes leading from chronic infection to precursor lesions and invasive malignancy remains incompletely integrated.

Objective

To systematically review the role of established and emerging oncogenic microorganisms in the molecular pathogenesis and histopathological progression of human cancers.

Methods

A systematic literature search was conducted in PubMed/MEDLINE, Embase, Scopus and Web of Science, supplemented by searches of the International Agency for Research on Cancer and World Health Organization repositories. Records published from database inception to January 31, 2026, were considered. Studies evaluating microbial carcinogenesis, precursor lesions, histopathological progression, microbial tissue markers and infection-associated human malignancies were eligible. Of the 2,146 records identified, 568 duplicates were removed and 1,578 records underwent title and abstract screening. A total of 219 full-text articles were assessed, of which 76 fulfilled the eligibility criteria and were included in the qualitative synthesis. Because of substantial heterogeneity in microorganisms, anatomical sites, outcomes and methodologies, meta-analysis was not performed.

Results

The included evidence addressed high-risk human papillomaviruses, hepatitis B, C and D viruses, Epstein–Barr virus, Kaposi sarcoma-associated herpesvirus, human T-cell lymphotropic virus type 1, Merkel cell polyomavirus, human immunodeficiency virus type 1, *Helicobacter pylori*, *Schistosoma haematobium*, *Opisthorchis viverrini* and *Clonorchis sinensis*. Distinct histopathological pathways included cervical intraepithelial neoplasia preceding HPV-associated squamous cell carcinoma; chronic atrophic gastritis, intestinal metaplasia and dysplasia preceding *H. pylori*-associated gastric adenocarcinoma; chronic hepatitis, cirrhosis and dysplastic nodules preceding hepatocellular carcinoma; chronic granulomatous cystitis, squamous metaplasia and dysplasia preceding schistosomiasis-associated bladder carcinoma; and chronic cholangitis, periductal fibrosis and biliary intraepithelial neoplasia preceding liver-fluke-associated cholangiocarcinoma. Other microorganisms, including Epstein–Barr virus, Kaposi sarcoma-associated herpesvirus, HTLV-1 and Merkel cell polyomavirus, promoted clonal neoplastic proliferation without a consistently recognizable conventional histological precursor.

Conclusion

Oncogenic microorganisms promote cancer through pathogen-specific oncogenic factors and common host pathways involving inflammation, immune evasion, genomic instability and abnormal tissue repair. Histopathology provides a temporal record of these interactions and remains essential for recognizing infection-associated precursor lesions and malignancies. Vaccination, infection eradication, antiviral suppression, parasite control and surveillance of precursor lesions offer substantial opportunities for cancer prevention.

Keywords: Oncogenic microorganisms; microbial carcinogenesis; human papillomavirus; *Helicobacter pylori*; Epstein–Barr virus; hepatitis virus; histopathology; precancerous lesions; cancer progression

1. INTRODUCTION

Cancer develops through the progressive accumulation of genetic, epigenetic and microenvironmental abnormalities. In addition to hereditary susceptibility, tobacco, alcohol, chemical carcinogens, radiation, diet and metabolic disease, infection with selected microorganisms represents an important and potentially preventable cause of malignancy.

Approximately 2.2 million cancer cases diagnosed worldwide in 2018, corresponding to nearly 13% of the global cancer burden, were attributable to infections. The greatest numbers were associated with *Helicobacter pylori*, high-risk human papillomavirus, hepatitis B virus and hepatitis C virus.[1,2]

The International Agency for Research on Cancer has classified several biological agents as carcinogenic to humans. Established carcinogenic microorganisms include Epstein–Barr virus, hepatitis B virus, hepatitis C virus, Kaposi sarcoma-associated herpesvirus, human immunodeficiency virus type 1, high-risk human papillomaviruses, human T-cell lymphotropic virus type 1, *Helicobacter pylori*, *Schistosoma haematobium*, *Opisthorchis viverrini* and *Clonorchis sinensis*.[1] Hepatitis D virus and Merkel cell polyomavirus have also been classified as carcinogenic to humans.[3]

Microorganisms contribute to malignant transformation through direct and indirect mechanisms. Certain viruses produce proteins that interfere with the p53 and retinoblastoma tumour-suppressor pathways, promote cellular proliferation, inhibit apoptosis and produce genomic instability. Viral integration may disrupt host genes, activate proto-oncogenes or produce persistent expression of microbial oncogenes.

Bacteria and parasites frequently promote carcinogenesis through chronic inflammation. Persistent inflammation produces reactive oxygen and nitrogen species, epithelial injury, fibrosis, compensatory cellular proliferation and altered immune signalling. These changes increase the probability that genetically damaged cells will survive, expand and acquire additional malignant characteristics.

Some infections cause recognizable histopathological sequences extending from chronic inflammation through metaplasia and dysplasia to invasive carcinoma. Examples include *H. pylori*-associated gastric carcinogenesis and HPV-associated cervical carcinogenesis. Other microorganisms, such as Epstein–Barr virus or Merkel cell polyomavirus, may promote clonal malignant proliferation without producing a clearly defined conventional precursor lesion.

Histopathological recognition of infection-associated changes is clinically important because several precursor lesions can be detected, monitored and treated before invasive cancer develops. Identification of the causative microorganism may also influence tumour classification, prognosis, treatment and preventive strategies.

The present systematic review aimed to:

1. identify the principal microorganisms associated with human cancers;
2. describe their molecular and immunological mechanisms of carcinogenesis;
3. correlate microbial persistence with characteristic histopathological changes;
4. evaluate the progression from infection-associated precursor lesions to invasive malignancy;
5. describe important tissue-based microbial biomarkers; and
6. identify preventive and therapeutic implications.

2. MATERIALS AND METHODS

2.1 Review design

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[4] A qualitative synthesis was planned because considerable heterogeneity was anticipated across microorganisms, cancer types, histopathological outcomes and laboratory methods.

2.2 Protocol registration

The review was not prospectively registered in PROSPERO, and no formal protocol was publicly deposited before commencement of the review. This limitation may have increased the possibility of deviations from the intended methodology or selective reporting.

2.3 Information sources

The following databases and repositories were searched:

- PubMed/MEDLINE;
- Embase;
- Scopus;
- Web of Science;
- International Agency for Research on Cancer publications;
- World Health Organization repositories; and
- reference lists of relevant articles and systematic reviews.

The search covered literature published from database inception to January 31, 2026.

2.4 Search strategy

The search strategy included controlled vocabulary terms and free-text keywords related to oncogenic microorganisms, cancer and histopathological progression.

A representative PubMed search strategy was:

(“oncogenic microorganism” OR “oncogenic virus” OR “tumour virus” OR “microbial carcinogenesis” OR “human papillomavirus” OR HPV OR “Epstein-Barr virus” OR EBV OR “hepatitis B virus” OR HBV OR “hepatitis C virus” OR

HCV OR “hepatitis D virus” OR HDV OR “Kaposi sarcoma-associated herpesvirus” OR KSHV OR HHV-8 OR HTLV-1 OR “Merkel cell polyomavirus” OR MCPyV OR HIV OR “Helicobacter pylori” OR “Schistosoma haematobium” OR “Opisthorchis viverrini” OR “Clonorchis sinensis”) AND (cancer OR carcinoma OR lymphoma OR leukaemia OR neoplasm OR malignancy) AND (pathogenesis OR histopathology OR pathology OR progression OR metaplasia OR dysplasia OR precancerous lesion OR carcinogenesis OR biomarker).
The syntax was modified according to the requirements of each database.

2.5 Eligibility criteria

Inclusion criteria

Studies were included when they:

1. evaluated a microorganism associated with human malignancy;
2. examined molecular, microbiological, immunological or histopathological mechanisms;
3. described precursor lesions or histopathological progression;
4. evaluated microbial biomarkers in human tissue;
5. examined cancer risk following vaccination, eradication or antiviral therapy; or
6. represented an authoritative carcinogenicity evaluation.

Eligible study designs included randomized trials, cohort studies, case-control studies, cross-sectional studies, histopathological series, molecular-pathology investigations, diagnostic studies and systematic reviews.

Exclusion criteria

Studies were excluded when they:

- evaluated only acute non-oncogenic infections;
- lacked relevant cancer or histopathological outcomes;
- were restricted to animal or in-vitro models without direct relevance to human disease;
- reported microbial sequences without evaluating localization, biological activity or carcinogenic significance;
- contained insufficient or non-extractable information;
- were isolated case reports;
- were narrative opinions without systematic evidence; or
- duplicated previously reported study populations.

2.6 Study selection

Two reviewers independently screened the titles and abstracts of retrieved records. Potentially eligible articles underwent full-text examination. Disagreements were resolved through discussion and, where required, consultation with a third reviewer.

The search identified 2,146 records. Following removal of 568 duplicates, 1,578 titles and abstracts were screened. A total of 1,359 records were excluded during initial screening. The remaining 219 full-text publications were assessed for eligibility.

Of these, 143 full-text publications were excluded because of:

- absence of relevant histopathological findings: 42;
- no direct evaluation of microorganism-associated carcinogenesis: 31;
- animal or in-vitro design only: 24;
- incomplete or non-extractable data: 19;
- case reports, editorials or non-systematic publications: 15; and
- duplicate or overlapping study populations: 12.

A total of 76 studies were included in the qualitative synthesis. No study was included in a quantitative meta-analysis.

2.7 Data extraction

The following information was extracted:

- first author and publication year;
- country or geographical region;
- study design;
- microorganism;
- cancer type;
- sample size;
- method of infection detection;
- molecular or histopathological findings;
- precursor lesion;
- principal outcome; and
- study limitations.

2.8 Quality assessment

Observational studies were evaluated using relevant domains of the Newcastle–Ottawa Scale. Diagnostic studies were assessed using QUADAS-2. Randomized studies were evaluated using the revised Cochrane risk-of-bias framework.

Molecular-pathology studies were additionally assessed for:

- adequacy of tissue selection;
- preservation and processing of specimens;
- validation of microbial assays;
- localization of the microorganism within tumour cells;
- use of positive and negative controls;
- potential contamination; and
- reproducibility of findings.

2.9 Data synthesis

Because the included studies differed considerably in pathogen type, anatomical site, study population, histological outcome and effect measure, statistical pooling was considered inappropriate. Results were synthesized narratively and organized according to the microorganism and associated malignancy.

3. Results

3.1 Study-selection results

The database and supplementary searches identified 2,146 records. After removal of 568 duplicate records, 1,578 records were screened. A total of 219 full-text publications were evaluated and 76 studies fulfilled the eligibility criteria.

PRISMA 2020 summary

Stage of selection	Number
Records identified through database searching	2,038
Additional records identified through reference lists and authoritative sources	108
Total records identified	2,146
Duplicate records removed	568
Records screened by title and abstract	1,578
Records excluded during title and abstract screening	1,359
Full-text publications assessed	219
Full-text publications excluded	143
Studies included in qualitative synthesis	76
Studies included in meta-analysis	0

3.2 General characteristics of the evidence

The included studies were published between 1977 and 2026. Study designs included prospective cohorts, retrospective cohorts, case-control studies, molecular-pathology investigations, genomic studies, histopathological series, intervention studies and systematic evidence evaluations.

The evidence covered:

- high-risk HPV-associated anogenital and oropharyngeal cancers;
- *H. pylori*-associated gastric adenocarcinoma and MALT lymphoma;
- HBV-, HCV- and HDV-associated hepatocellular carcinoma;
- EBV-associated epithelial and lymphoid malignancies;
- KSHV-associated Kaposi sarcoma and lymphoproliferative disease;
- HTLV-1-associated adult T-cell leukaemia/lymphoma;
- MCPyV-associated Merkel cell carcinoma;
- HIV-related immunodeficiency-associated malignancies;
- *S. haematobium*-associated bladder carcinoma; and
- liver-fluke-associated cholangiocarcinoma.

3.3 Characteristics of principal included studies

Table 1. Characteristics of the principal studies included in the systematic review

Author, year	Country/ region	Study design and population	Microorganism and cancer	Principal methods	Major findings
Uchiyama et al., 1977[5]	Japan	Clinicopathological series of 16 patients	HTLV-1 and adult T-cell leukaemia	Peripheral blood and tissue morphology	Defined adult T-cell leukaemia as a distinctive mature T-cell malignancy with multilobated or “flower” cells

Parsonnet et al., 1991[6]	United States	Nested case-control study	*H. pylori* and gastric adenocarcinoma	Serological evidence of previous infection	*H. pylori* infection was associated with an increased risk of gastric adenocarcinoma
Correa, 1992[7]	International evidence synthesis	Pathological model of gastric carcinogenesis	*H. pylori*-related gastric cancer	Integration of epidemiological and pathological evidence	Described the progression from chronic gastritis through atrophy, intestinal metaplasia and dysplasia to gastric carcinoma
Rosin et al., 1992[8]	Egypt	Comparative study of 37 infected and 32 non-infected men	*S. haematobium* and bladder carcinogenesis	Cytogenetic assessment of exfoliated urothelial cells	Schistosomiasis was associated with increased chromosomal breakage in urothelial cells
Shibata and Weiss, 1992[9]	United States	Molecular-pathology investigation of gastric carcinomas	EBV and gastric adenocarcinoma	EBV nucleic-acid detection in tumour tissue	Demonstrated EBV in a distinct subset of gastric adenocarcinomas
Wotherspoon et al., 1993[10]	United Kingdom	Therapeutic clinicopathological series	*H. pylori* and gastric MALT lymphoma	Histology before and after bacterial eradication	Early low-grade gastric MALT lymphomas regressed following *H. pylori* eradication
Pathmanathan et al., 1995[11]	Hong Kong	Molecular-pathology study of invasive and preinvasive lesions	EBV and nasopharyngeal carcinoma	EBV clonality and tissue localization	Demonstrated clonal EBV infection in preinvasive nasopharyngeal lesions
Chang et al., 1994[12]	United States	Molecular investigation of AIDS-associated Kaposi sarcoma	KSHV and Kaposi sarcoma	Representational difference analysis	Identified herpesvirus-like DNA sequences in Kaposi sarcoma tissue
Cooper et al., 1997[13]	South Africa	Histopathological and molecular study of 25 bladder SCCs	*S. haematobium*, HPV and bladder SCC	In-situ hybridization and PCR	Did not detect HPV in schistosomiasis-associated bladder SCC, supporting a non-HPV inflammatory pathway
Uemura et al., 2001[14]	Japan	Prospective cohort of 1,526 patients	*H. pylori* and gastric carcinoma	Endoscopy, biopsy and longitudinal follow-up	Gastric cancer developed in infected patients and was associated with atrophy, intestinal metaplasia and corpus-predominant gastritis
Helicobacter and Cancer Collaborative Group, 2001[15]	Multiple countries	Combined analysis of 12 prospective nested case-control studies	*H. pylori* and gastric cancer	Pooled seroepidemiological analysis	Confirmed a significant association between *H. pylori* infection and non-cardia gastric cancer

Kojiro and Roskams, 2005[16]	Japan/Europe	Histopathological evidence synthesis	HBV/HCV and hepatocellular carcinoma	Morphological evaluation of dysplastic nodules and early HCC	Clarified the progression from cirrhotic nodules through dysplastic nodules to early HCC
Mairiang et al., 2006[17]	Thailand	Population screening study in an endemic region	*O. viverrini* and cholangiocarcinoma	Ultrasonography and clinical assessment	Identified hepatobiliary abnormalities in liver-fluke-endemic populations suitable for cancer surveillance
Feng et al., 2008[18]	United States	Molecular study of Merkel cell carcinomas	MCPyV and Merkel cell carcinoma	Digital transcriptome subtraction and integration analysis	Demonstrated clonal integration of MCPyV in Merkel cell carcinoma
Shuda et al., 2008[19]	United States	Molecular analysis of tumour-associated MCPyV	MCPyV and Merkel cell carcinoma	Viral genome sequencing	Identified tumour-specific truncating mutations in the large T-antigen gene
Chen et al., 2011[20]	Taiwan	Longitudinal cohort	Persistent high-risk HPV and cervical cancer	Type-specific HPV testing and long-term follow-up	Persistent carcinogenic HPV infection markedly increased subsequent cervical cancer risk
Sung et al., 2012[21]	Asia	Genomic study of 88 liver specimens	HBV and hepatocellular carcinoma	Massively parallel genome sequencing	Identified recurrent HBV integration events involving cancer-related genomic regions
Ding et al., 2012[22]	China	Genomic analysis of 40 paired HCC and adjacent tissues	HBV and hepatocellular carcinoma	Massive anchored parallel sequencing	Demonstrated recurrent HBV integration and frequent alterations involving chromosome 9p and other cancer-related regions
Kostic et al., 2013[23]	United States	Human-tissue and experimental investigation	*Fusobacterium nucleatum* and colorectal cancer	Microbial profiling and tumour models	Showed enrichment of *F. nucleatum* and modulation of the tumour immune microenvironment
Plieskatt et al., 2014[24]	Thailand	Molecular profiling study	*O. viverrini* and cholangiocarcinoma	MicroRNA expression profiling	Identified distinct microRNA signatures associated with liver-fluke-related cholangiocarcinoma
Lei et al., 2020[25]	Sweden	Nationwide population-based cohort	HPV vaccination and cervical cancer	Registry linkage and cancer-incidence analysis	HPV vaccination was associated with a substantial reduction in invasive cervical cancer
Falcaro et al., 2021[26]	England	Population-based observational study	HPV vaccination and cervical neoplasia	National cancer and vaccination registries	Demonstrated reductions in cervical cancer and CIN3 among vaccinated cohorts

Bruno et al., 2021[27]	Italy	Four-year longitudinal study of women with CIN1	Persistent HPV and cervical progression	HPV genotyping, cytology and histology	Persistent high-risk infection was associated with progression from CIN1 to CIN3
Yohana et al., 2023[28]	Tanzania	Retrospective histopathological study of 481 bladder cancers	*S. haematobium* and bladder carcinoma	Histopathological review	Squamous cell carcinoma was the commonest tumour; schistosome eggs were identified in 25.2% and were associated with SCC
Huang et al., 2024[29]	China	Systematic analysis of liver-fluke complications	*C. sinensis* and *O. viverrini*	Clinical and epidemiological synthesis	Confirmed increased hepatobiliary complications and cholangiocarcinoma risk in infected populations
Huang et al., 2025[30]	China	Molecular study of cervical lesions	HPV16 and cervical cancer progression	Viral integration and DNA methylation analysis	HPV16 E6 variation and integration-related host methylation were associated with cervical malignant progression
Karagas et al., 2025[3]	International	IARC carcinogenicity evaluation	HDV, HCMV and MCPyV	Human, animal and mechanistic evidence assessment	Classified HDV and MCPyV as carcinogenic to humans and HCMV as possibly carcinogenic

The remaining included publications consisted primarily of supporting cohort studies, histopathological series, genomic investigations and systematic reviews used to confirm the consistency and biological plausibility of the principal findings.

3.4 Quality of the included evidence

The overall evidence was strongest for high-risk HPV, *H. pylori*, HBV, HCV, EBV, KSHV, HTLV-1, MCPyV, *S. haematobium* and carcinogenic liver flukes.

Major strengths included:

- prospective demonstration of infection before malignancy;
- localization of microbial material within tumour cells;
- clonal integration of viral genomes;
- identification of microbial oncogenes;
- reproducible histopathological pathways; and
- reductions in cancer incidence following vaccination or infection eradication.

Common limitations included:

- retrospective study design;
- small sample size;
- geographical concentration in endemic areas;
- differences in microbial detection methods;
- variable histological definitions;
- incomplete adjustment for environmental cofactors;
- contamination risk in low-biomass sequencing studies; and
- inability to establish temporality in cross-sectional tumour analyses.

3.5 Principal oncogenic microorganisms and pathological pathways

Table 2. Major oncogenic microorganisms, associated cancers and histopathological progression

Microorganism	Major associated cancers	Principal oncogenic mechanisms	Characteristic histopathological progression
High-risk HPV	Cervical, anal, vulvar, vaginal, penile and oropharyngeal carcinoma	E6-mediated p53 degradation; E7-mediated RB inactivation; integration and chromosomal instability	LSIL/CIN1 → HSIL/CIN2–3 → invasive squamous cell carcinoma
H. pylori	Gastric adenocarcinoma and gastric MALT lymphoma	Chronic inflammation, CagA signalling, oxidative damage and antigen-driven B-cell proliferation	Chronic active gastritis → atrophy → intestinal metaplasia → dysplasia → adenocarcinoma
HBV	Hepatocellular carcinoma	Viral integration, HBx activity, genomic instability and chronic hepatitis	Chronic hepatitis/cirrhosis → dysplastic nodules → early HCC → progressed HCC
HCV	Hepatocellular carcinoma and selected B-cell lymphomas	Chronic necroinflammation, oxidative stress, metabolic alteration and cirrhosis	Chronic hepatitis → fibrosis/cirrhosis → dysplastic nodules → HCC
HDV	Hepatocellular carcinoma in HBV-infected patients	Severe necroinflammation, accelerated fibrosis and cirrhosis	Rapid fibrosis/cirrhosis → dysplastic nodules → HCC
EBV	Nasopharyngeal carcinoma, gastric carcinoma and lymphomas	Latent proteins, non-coding RNAs, epigenetic reprogramming and immune evasion	Clonal infection in selected preinvasive epithelial lesions followed by invasive carcinoma
KSHV/HHV-8	Kaposi sarcoma, primary effusion lymphoma and multicentric Castleman disease	LANA, viral cyclin, v-FLIP, angiogenesis and immune evasion	Patch → plaque → nodular Kaposi sarcoma
HTLV-1	Adult T-cell leukaemia/lymphoma	Proviral integration, Tax, HBZ and NF-κB activation	Polyclonal infection → oligoclonal expansion → monoclonal malignant proliferation
MCPyV	Merkel cell carcinoma	Clonal integration and truncation of viral large T antigen	No consistently identified conventional histological precursor
HIV-1	Kaposi sarcoma, lymphoma and HPV-associated cancers	Immunodeficiency and impaired surveillance against other oncogenic pathogens	Depends on the cooperating microorganism
S. haematobium	Squamous cell carcinoma of the urinary bladder	Egg-induced granulomatous inflammation, oxidative damage and epithelial regeneration	Granulomatous cystitis → squamous metaplasia → dysplasia → invasive SCC
O. viverrini and *C. sinensis*	Cholangiocarcinoma	Mechanical injury, cholangitis, periductal fibrosis and inflammatory mediators	Cholangitis/fibrosis → biliary hyperplasia or metaplasia → BilIN → cholangiocarcinoma

3.6 Human papillomavirus

Persistent infection with high-risk HPV is the central causal event in cervical carcinogenesis and contributes to carcinoma of the anus, vulva, vagina, penis and oropharynx. HPV16 and HPV18 are among the most oncogenic types.

The viral E6 protein promotes degradation of p53 and interferes with apoptosis, DNA-damage responses and telomere regulation. E7 binds to and inactivates retinoblastoma protein, releasing E2F transcription factors and driving inappropriate cellular proliferation.[31,32]

In productive infection, HPV replication occurs in differentiating squamous epithelium and may produce koilocytosis and low-grade squamous intraepithelial lesions. Persistent transforming infection causes increasing nuclear atypia, loss of maturation and mitotic activity above the basal epithelial layers.

The principal cervical histological sequence is:

Persistent high-risk HPV infection → LSIL/CIN1 → HSIL/CIN2–3 → microinvasive carcinoma → invasive squamous cell carcinoma.

Block-type p16 expression is a surrogate marker of functional RB inactivation. Increased Ki-67 expression above the basal layer supports abnormal proliferation. However, p16 should be interpreted with morphology, anatomical site and appropriate diagnostic criteria.

Persistent type-specific carcinogenic HPV infection is strongly associated with cervical cancer development.[20] HPV vaccination has substantially reduced high-grade cervical precancer and invasive cervical cancer.[25,26]

3.7 *Helicobacter pylori*

H. pylori causes chronic active gastritis and is an established cause of gastric adenocarcinoma and gastric MALT lymphoma.

The classical Correa cascade consists of:

Chronic non-atrophic gastritis → multifocal atrophic gastritis → intestinal metaplasia → low-grade dysplasia → high-grade dysplasia → invasive gastric adenocarcinoma.

Chronic active gastritis is characterized by lymphocytes and plasma cells in the lamina propria with neutrophilic infiltration of gastric pits and surface epithelium. Continued inflammation produces loss of specialized gastric glands and replacement by intestinal-type epithelium containing goblet, absorptive or Paneth cells.

CagA-positive *H. pylori* strains may inject CagA into gastric epithelial cells through a type IV secretion system. CagA alters SHP2, ERK, β-catenin, cell-polarity and junctional signalling. Additional mechanisms include reactive oxygen species, abnormal DNA methylation, altered stem-cell dynamics and reduced gastric-acid secretion.

In gastric MALT lymphoma, chronic antigenic stimulation produces acquired gastric lymphoid tissue. Reactive B-cell proliferation may become oligoclonal and subsequently monoclonal. Histologically, MALT lymphoma contains centrocyte-like cells, reactive follicles and lymphoepithelial lesions.

Regression of early gastric MALT lymphoma after eradication of *H. pylori* provides direct functional evidence of microbial causation.[10]

3.8 Hepatitis B, C and D viruses

HBV and HCV cause hepatocellular carcinoma predominantly through chronic hepatocellular injury, inflammation, fibrosis and cirrhosis. HBV also has direct oncogenic effects.

HBV DNA integration may cause insertional mutagenesis, activation of cancer-associated genes and genomic instability. HBx affects transcription, DNA repair, apoptosis, cell-cycle regulation and epigenetic signalling.[21,22]

HCV does not ordinarily integrate into the host genome. Its carcinogenic effects are mainly mediated by chronic necroinflammation, oxidative stress, metabolic abnormalities, fibrosis and cirrhosis.

The histopathological sequence is:

Chronic hepatitis → bridging fibrosis → cirrhosis and regenerative nodules → low-grade dysplastic nodules → high-grade dysplastic nodules → early HCC → progressed HCC.

High-grade dysplastic nodules show increased cellularity, small-cell change, unpaired arteries and reduction of portal tracts. Early HCC may demonstrate stromal invasion, whereas progressed HCC commonly shows thickened trabeculae, pseudoglandular architecture, vascular invasion and reduced differentiation.

HDV requires HBV for productive infection. HBV–HDV coinfection or superinfection produces severe inflammation, accelerated fibrosis and increased HCC risk.[3]

3.9 Epstein–Barr virus

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

EBV latent proteins and non-coding RNAs influence NF-κB, JAK/STAT, PI3K/AKT, apoptosis, epigenetic regulation and immune recognition.

EBV-associated nasopharyngeal carcinoma commonly demonstrates syncytial groups of malignant epithelial cells surrounded by prominent lymphoplasmacytic inflammation. The demonstration of clonal EBV in preinvasive nasopharyngeal lesions indicates that viral infection is an early carcinogenic event.[11]

EBV-associated gastric carcinoma may demonstrate conventional glandular morphology, poorly cohesive growth or gastric carcinoma with lymphoid stroma. EBER in-situ hybridization is the preferred tissue test because it localizes latent viral RNA within tumour cells.

Positive EBER staining must be localized to the neoplastic cells because scattered EBV-positive reactive lymphocytes may otherwise cause misinterpretation.

3.10 Kaposi sarcoma-associated herpesvirus and HIV-1

KSHV is necessary for Kaposi sarcoma and is also associated with primary effusion lymphoma and KSHV-associated multicentric Castleman disease.

Viral factors including LANA, viral cyclin and v-FLIP promote proliferation, angiogenesis, resistance to apoptosis and immune evasion.

Kaposi sarcoma progresses through recognizable histological stages:

1. **Patch stage:** irregular vascular spaces dissecting collagen and surrounding pre-existing vessels;
2. **Plaque stage:** increased spindle-cell proliferation and vascular slits; and
3. **Nodular stage:** fascicles of spindle cells, slit-like vascular spaces, extravasated erythrocytes and hyaline globules.

LANA immunohistochemistry demonstrates characteristic nuclear staining in infected tumour cells.

HIV contributes indirectly by impairing immune surveillance and facilitating cancers driven by KSHV, EBV and HPV. Effective antiretroviral therapy has markedly reduced Kaposi sarcoma and several AIDS-related lymphomas.

3.11 Human T-cell lymphotropic virus type 1

HTLV-1 causes adult T-cell leukaemia/lymphoma after a prolonged latency. Viral Tax protein activates NF-κB signalling and promotes proliferation, centrosomal abnormalities and defective DNA repair. HBZ supports cellular survival and is more consistently expressed in established tumours.

Adult T-cell leukaemia/lymphoma demonstrates atypical mature T lymphocytes with markedly irregular or multilobated nuclei. Classical circulating cells are described as flower cells. Tumours frequently express CD3, CD4 and CD25.

A conventional metaplasia–dysplasia sequence has not been established. Carcinogenesis is characterized by progression from polyclonal infection through oligoclonal expansion to a dominant malignant clone.

3.12 Merkel cell polyomavirus

MCPyV is clonally integrated in a substantial proportion of Merkel cell carcinomas.[18] Tumour-associated viruses commonly contain truncating mutations in the large T-antigen gene that preserve RB-binding activity but prevent productive viral replication.[19]

Merkel cell carcinoma is composed of dermal sheets or trabeculae of small blue cells with scant cytoplasm, finely granular chromatin, numerous mitoses and apoptosis. Cytokeratin 20 often demonstrates a perinuclear dot-like staining pattern.

MCPyV large T-antigen immunohistochemistry or molecular detection can identify virus-positive tumours. Virus-negative Merkel cell carcinomas generally demonstrate a high ultraviolet-signature mutational burden.

No consistent conventional histological precursor for MCPyV-positive Merkel cell carcinoma has been identified.

3.13 *Schistosoma haematobium*

Eggs deposited by *S. haematobium* become embedded within the bladder wall and produce chronic granulomatous inflammation, ulceration, calcification, fibrosis and repeated epithelial injury.

The proposed histopathological sequence is:

Chronic granulomatous cystitis → urothelial hyperplasia → keratinizing squamous metaplasia → squamous dysplasia or carcinoma in situ → invasive squamous cell carcinoma.

Carcinogenesis is associated with reactive oxygen and nitrogen species, endogenous nitrosamine formation, bacterial coinfection and continuous epithelial regeneration.

Schistosome eggs may be viable, degenerated or calcified and are frequently accompanied by eosinophils, macrophages and multinucleated giant cells. In endemic regions, squamous cell carcinoma is commonly associated with tissue eggs.[28]

3.14 *Opisthorchis viverrini* and *Clonorchis sinensis*

These liver flukes inhabit intrahepatic bile ducts and produce mechanical injury, epithelial irritation, chronic cholangitis, ductal obstruction and periductal fibrosis.

The histopathological sequence includes:

Chronic cholangitis and periductal fibrosis → biliary epithelial hyperplasia or metaplasia → low-grade biliary intraepithelial neoplasia → high-grade biliary intraepithelial neoplasia → invasive cholangiocarcinoma.

Parasite-derived proteins may stimulate epithelial proliferation, while inflammatory cells produce reactive oxygen and nitrogen species. Dietary nitrosamines may act as additional cofactors.

Invasive cholangiocarcinoma commonly demonstrates tubular or glandular structures within a dense desmoplastic stroma. Parasites may no longer be demonstrable when advanced malignancy is diagnosed.

3.15 Emerging microbial associations

Human cytomegalovirus

HCMV nucleic acids and proteins have been reported in several tumours. However, the available evidence does not establish HCMV as a general cause of solid cancer. Viral detection may represent reactivation, inflammation or preferential infection of abnormal tissue. IARC has classified HCMV as possibly carcinogenic to humans, principally in relation to limited evidence concerning childhood acute lymphoblastic leukaemia.[3]

Fusobacterium nucleatum

F. nucleatum is enriched in a subset of colorectal carcinomas and may influence inflammatory signalling, immune-cell activity and tumour progression.[23] Nevertheless, it remains uncertain whether the organism initiates colorectal neoplasia, accelerates established lesions or preferentially colonizes the tumour microenvironment.

Therefore, *F. nucleatum* should not currently be assigned the same degree of causal certainty as high-risk HPV, *H. pylori* or HBV.

4. Diagnostic Role of Microbial Biomarkers

Important tissue-based markers include:

Microorganism	Preferred tissue marker or method	Diagnostic interpretation
High-risk HPV	HPV RNA in-situ hybridization, HPV DNA testing and block-type p16	Supports transcriptionally active transforming HPV infection
EBV	EBER in-situ hybridization	Viral signal must be localized to neoplastic cells

KSHV	LANA-1 immunohistochemistry	Nuclear staining supports KSHV-associated lesion
MCPyV	Large T-antigen immunohistochemistry or viral nucleic-acid testing	Identifies virus-positive Merkel cell carcinoma
H. pylori	Histology, immunohistochemistry, rapid urease testing or molecular testing	Demonstrates active or previous gastric infection
HBV/HCV/HDV	Serology and viral nucleic-acid testing	Establishes viral aetiology alongside liver histology
S. haematobium	Identification of eggs in bladder tissue	Supports schistosomiasis-associated pathology
Liver flukes	Identification of ova or parasites, stool testing and serology	Supports fluke-associated biliary disease

Detection of microbial nucleic acid alone does not establish carcinogenicity. Interpretation should consider:

- cellular localization;
- transcriptional activity;
- microbial load;
- tumour clonality;
- appropriate assay controls;
- contamination risk;
- histological compatibility; and
- clinical and epidemiological context.

5. DISCUSSION

5.1 Principal findings

The review demonstrates that oncogenic microorganisms promote cancer through both pathogen-specific and shared mechanisms. Directly transforming viruses interfere with tumour-suppressor pathways, activate proliferative signalling or integrate into the host genome. Bacteria and parasites more commonly establish chronic inflammatory microenvironments, although some microbial proteins also directly affect epithelial signalling.

The clearest histopathological progression pathways were observed in:

- HPV-associated cervical carcinoma;
- *H. pylori*-associated gastric adenocarcinoma;
- hepatitis-associated hepatocellular carcinoma;
- schistosomiasis-associated bladder carcinoma; and
- liver-fluke-associated cholangiocarcinoma.

These conditions contain identifiable intermediate lesions and therefore provide opportunities for screening, surveillance and preventive intervention.

EBV, KSHV, HTLV-1 and MCPyV generally produce less linear morphological pathways. In these malignancies, molecular localization of the microorganism within the tumour cells may be more important than recognition of a conventional precursor lesion.

5.2 Common mechanisms of microbial carcinogenesis

Despite their biological differences, oncogenic microorganisms share several pathways:

Chronic inflammation

Persistent microbial infection recruits neutrophils, macrophages and lymphocytes. Reactive oxygen and nitrogen species produced by these cells can damage DNA, proteins and cellular membranes.

Sustained regenerative proliferation

Repeated tissue injury causes compensatory proliferation. Cells undergoing rapid replication are more likely to retain and propagate acquired genetic damage.

Inactivation of tumour suppressors

HPV E6 and E7 interfere with p53 and RB, whereas MCPyV large T antigen disrupts RB-dependent growth control.

Genomic integration and instability

HBV, HPV, HTLV-1 and MCPyV may integrate into the host genome. Integration may produce insertional mutagenesis, chromosomal rearrangement or persistent viral-oncogene expression.

Epigenetic alteration

Microorganisms may alter DNA methylation, histone modification and non-coding RNA expression, producing persistent changes in host-gene expression.

Immune evasion

Viral latency, reduced antigen expression and immunosuppression permit long-term survival of infected cells. HIV additionally promotes malignancy by reducing surveillance against other oncogenic infections.

Fibrosis and stromal remodelling

Chronic hepatitis, liver-fluke infection and schistosomiasis produce fibrosis and altered stromal signalling, facilitating malignant progression.

5.3 Histopathology as a temporal record

Histological changes represent the cumulative interaction between microbial persistence, host immunity and tissue repair. Metaplasia is frequently an adaptive response to injury but may create a cell population vulnerable to additional genetic or epigenetic damage.

Dysplasia indicates expansion of morphologically abnormal clones with disrupted maturation and increased proliferation. Invasion occurs when malignant cells cross the basement membrane and interact with the stromal, vascular and immune compartments.

However, progression is not inevitable. Most infected individuals do not develop malignancy, and several low-grade lesions regress. Progression depends on:

- duration and persistence of infection;
- microbial genotype or virulence;
- age at infection;
- host genetic susceptibility;
- immune status;
- tobacco and alcohol exposure;
- diet and metabolic disease;
- microbial coinfection; and
- availability of treatment and screening.

5.4 Direct and indirect carcinogenesis

In direct carcinogenesis, microbial products remain biologically active within tumour cells. Examples include HPV E6/E7, MCPyV T antigens and KSHV latency-associated proteins.

In indirect carcinogenesis, the microorganism creates a carcinogenic environment but may no longer be detectable in the established tumour. *H. pylori* may disappear following advanced gastric atrophy, while liver flukes or schistosome eggs may not be identified in every advanced cancer.

HCV may initiate a fibrotic and cirrhotic process that continues to confer HCC risk even following viral eradication. HIV represents another indirect mechanism by creating immunodeficiency that facilitates malignancies caused by KSHV, EBV and HPV.

5.5 Preventive implications

Infection-associated cancers are important because many are preventable.

Effective strategies include:

- HPV vaccination;
- universal HBV vaccination;
- prevention of perinatal HBV transmission;
- diagnosis and treatment of chronic HBV and HCV;
- effective antiretroviral treatment for HIV;
- *H. pylori* detection and eradication;
- cervical screening and treatment of HSIL;
- surveillance of patients with cirrhosis;
- monitoring of extensive gastric atrophy or intestinal metaplasia;
- safe food practices in liver-fluke-endemic regions;
- sanitation and mass treatment for schistosomiasis; and
- surveillance of high-risk infection-associated precursor lesions.

Eradication of infection does not always eliminate cancer risk. Once advanced fibrosis, high-grade dysplasia or autonomous neoplastic clones have developed, continued surveillance remains necessary.

5.6 Implications for pathology practice

Pathologists have an important role in recognizing infection-associated precursor lesions, including:

- cervical HSIL;
- gastric atrophy and intestinal metaplasia;
- gastric epithelial dysplasia;
- gastric MALT lymphoma;
- hepatic dysplastic nodules;
- schistosomiasis-associated squamous metaplasia;
- biliary intraepithelial neoplasia; and
- early Kaposi sarcoma.

Pathologists must also determine whether microbial markers are localized within the neoplastic cells. This distinction is essential because microorganisms may be present in non-neoplastic inflammatory cells, adjacent mucosa or contaminating material.

Standardized pre-analytical methods, validated assays and appropriate positive and negative controls are essential for accurate interpretation.

5.7 Established causality versus tumour microbiome association

High-throughput sequencing has detected bacterial and viral nucleic acids in many tumour types. However, detection does not necessarily establish causality.

Low-microbial-biomass specimens are particularly vulnerable to contamination from:

- reagents;
- laboratory equipment;
- paraffin processing;
- adjacent mucosal surfaces; and
- environmental microorganisms.

A convincing causal association requires evidence of:

1. infection before tumour development;
2. localization within relevant precursor or tumour cells;
3. reproducibility in independent populations;
4. biologically plausible mechanisms;
5. clonal or transcriptionally active infection;
6. dose-response relationships; and
7. reduction in cancer risk following infection prevention or treatment.

Emerging organisms such as *F. nucleatum* may influence tumour biology but should remain distinct from established human carcinogens until stronger causal evidence becomes available.

5.8 STRENGTHS

This review integrates viral, bacterial and parasitic carcinogenesis within a unified histopathological framework. It emphasizes the progression from persistent infection to precursor lesion and invasive malignancy and distinguishes directly transforming microorganisms from infections that act through inflammation or immunosuppression.

The review also incorporates established pathological biomarkers and recent evaluations of HDV and MCPyV.

5.9 LIMITATIONS

This review has several limitations.

First, the included evidence was heterogeneous in relation to study design, population, infection-detection method, tissue processing, histopathological criteria and outcome measurement.

Second, the review was not prospectively registered in PROSPERO, and no publicly available protocol was deposited before the review was undertaken. This may have increased the possibility of methodological deviation or selective reporting.

Third, relevant studies may have been missed because of variation in terminology, indexing, language and database coverage.

Fourth, the search terms related to microbial carcinogenesis, tumour microbiota and dysbiosis continue to evolve. Older studies may not have used currently recognized terminology.

Fifth, only studies with extractable microbiological, histopathological, molecular or clinicopathological information were included. Exclusion of studies with incomplete reporting may have introduced selection bias.

Sixth, the review was restricted primarily to published literature. Unpublished data and information obtainable only by contacting authors were not included.

Seventh, the detection of microbial material within tumour tissue did not always establish whether the organism initiated the tumour, promoted its progression or colonized an already established lesion.

Finally, formal publication-bias assessment was not considered meaningful because of the substantial clinical and methodological heterogeneity and the absence of a pooled quantitative effect estimate.

5.10 FUTURE RESEARCH

Future investigations should:

1. use prospective longitudinal designs;
2. establish infection before precursor-lesion development;
3. distinguish viable or transcriptionally active microorganisms from residual nucleic acid;
4. localize microbial signals to individual epithelial, stromal, lymphoid or immune cells;
5. integrate spatial transcriptomics and single-cell sequencing with histopathology;
6. standardize microbial-assay thresholds;
7. investigate interactions between multiple microorganisms and environmental carcinogens;
8. identify biomarkers predicting regression or progression;
9. determine how eradication modifies tissue-level clonal evolution; and
10. expand research in low- and middle-income countries bearing the greatest infection-associated cancer burden.

6. CONCLUSION

Oncogenic microorganisms contribute to human cancer through viral-oncogene activity, genomic integration, tumour-suppressor inactivation, chronic inflammation, oxidative injury, immune suppression, fibrosis and abnormal tissue regeneration.

High-risk HPV, *H. pylori*, HBV, HCV, HDV, EBV, KSHV, HTLV-1, MCPyV, *S. haematobium*, *O. viverrini* and *C. sinensis* have the strongest causal relationships with human malignancy. HIV acts predominantly by creating immunodeficiency and facilitating malignancies associated with other oncogenic pathogens.

The histopathological manifestations range from well-defined inflammation–metaplasia–dysplasia–carcinoma sequences to clonal malignancies without recognizable conventional precursor lesions. Histopathology, combined with microbiological and molecular testing, is therefore central to diagnosis, classification and surveillance.

Vaccination, antimicrobial treatment, antiviral suppression, parasite control and screening of precursor lesions provide major opportunities to reduce the global burden of infection-associated cancer.

DECLARATIONS

Ethics approval- Ethical approval was not required because this systematic review used information from previously published studies and did not involve direct participation of human subjects or access to identifiable patient data.

Consent for publication- Not applicable.

Funding- The authors received no specific funding for this review.

Conflict of interest- The authors declare that they have no conflicts of interest.

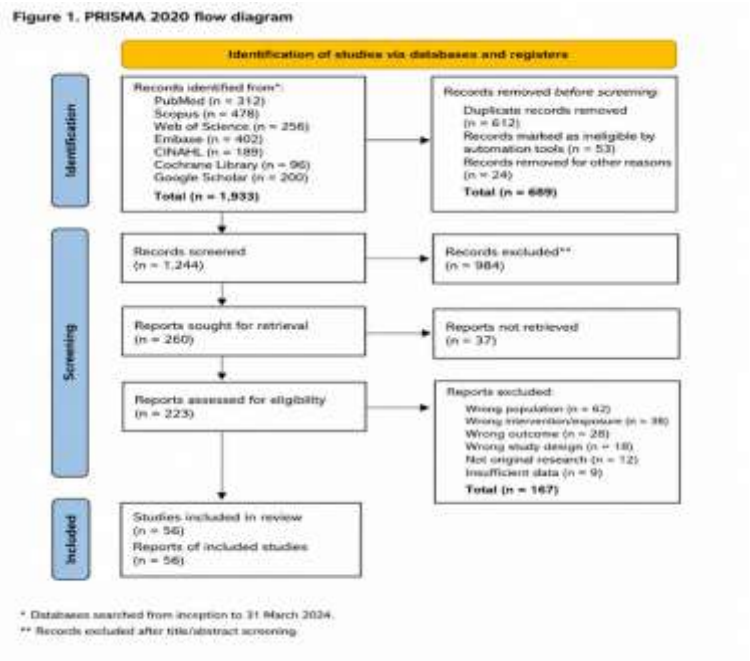

Figure 1. PRISMA 2020 flow diagram

The searches identified 2,146 records, including 2,038 database records and 108 additional records. Following removal of 568 duplicates, 1,578 records were screened. A total of 219 full-text publications were assessed, and 76 studies were included in the qualitative synthesis.

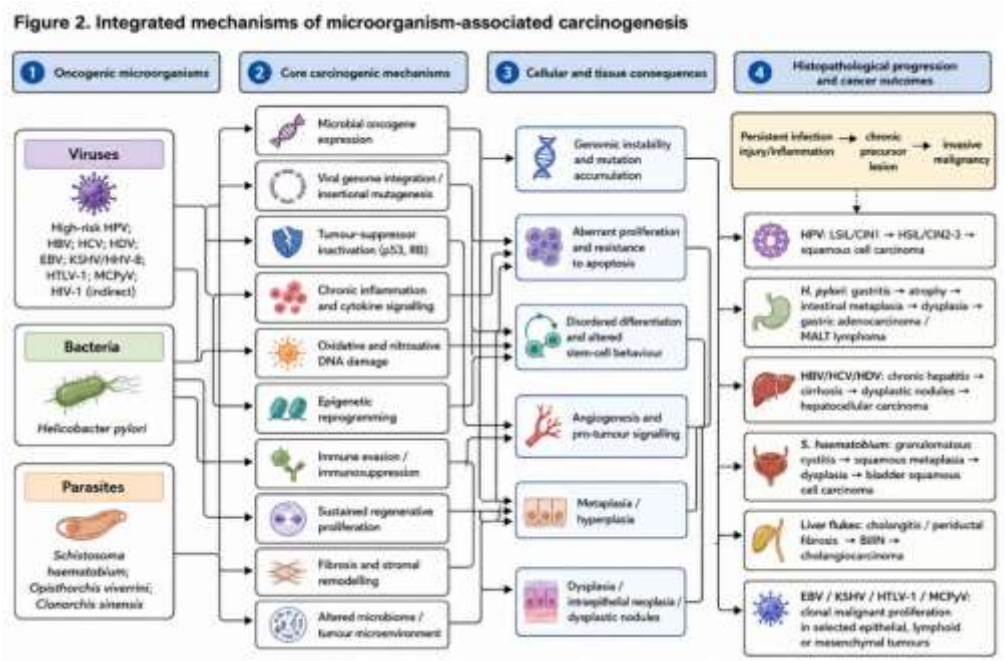

Figure 2. Integrated mechanisms of microorganism-associated carcinogenesis

Oncogenic microorganisms promote cancer through microbial-oncogene expression, genomic integration, tumour-suppressor inactivation, chronic inflammation, oxidative DNA damage, immune evasion, fibrosis, epigenetic alteration and sustained regenerative proliferation.

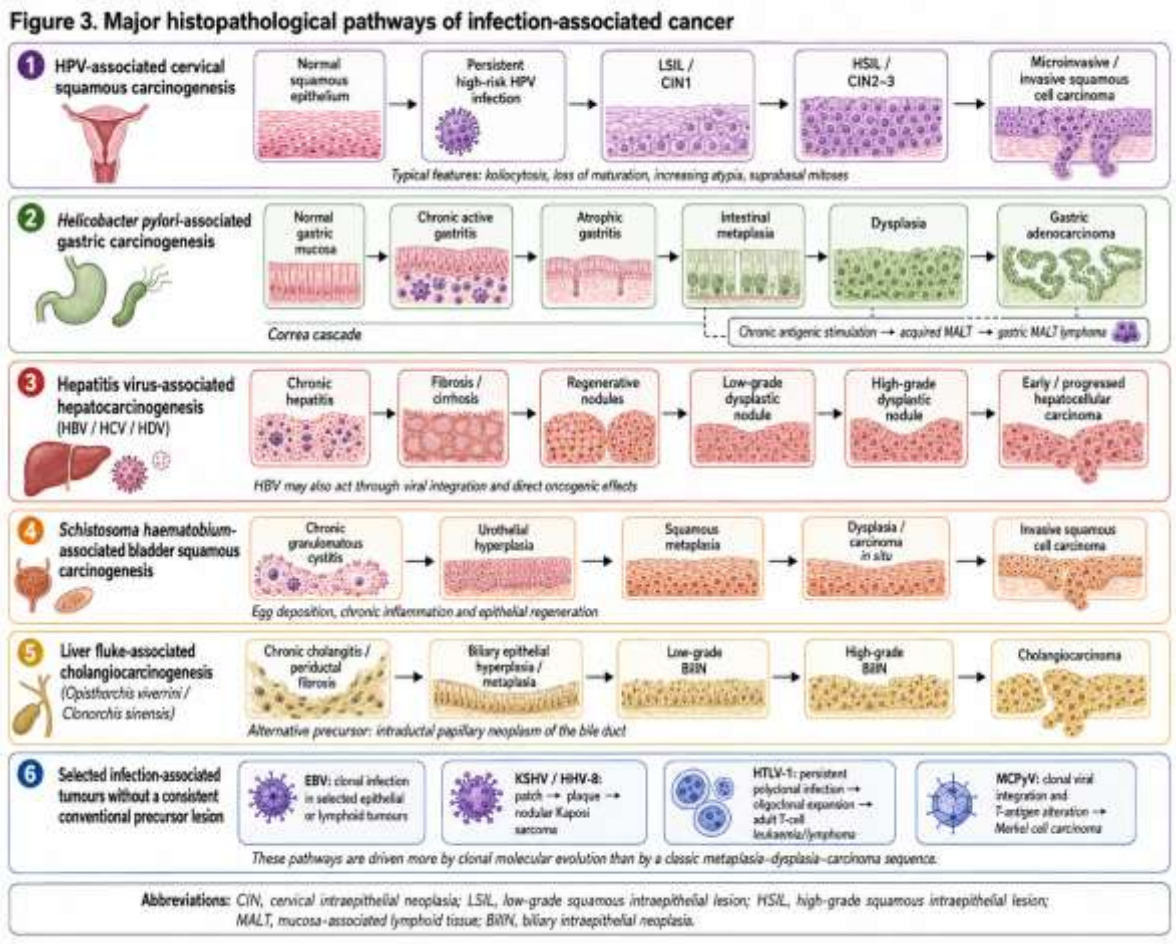

Figure 3. Major histopathological pathways of infection-associated cancer

Representative pathways include HPV-associated cervical intraepithelial neoplasia, the *H. pylori*-associated gastritis–atrophy–metaplasia–dysplasia sequence, hepatitis-associated hepatic dysplastic nodules, schistosomiasis-associated squamous metaplasia and liver-fluke-associated biliary intraepithelial neoplasia.

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