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REVIEW

Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update

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Abstract

Gallbladder cancer is a malignancy of biliary tract which is infrequent in developed countries but common in some specific geographical regions of developing countries. Late diagnosis and deprived prognosis are major problems for treatment of gallbladder carcinoma. The dramatic associations of this orphan cancer with various genetic and environmental factors are responsible for its poorly defined pathogenesis. An understanding to the relationship between epidemiology, molecular genetics and pathogenesis of gallbladder cancer can add new insights to its undetermined pathophysiology. Present review article provides a recent update regarding epidemiology, pathogenesis, and molecular genetics of gallbladder cancer. We systematically reviewed published literature on gallbladder cancer from online search engine PubMed (http://www.ncbi.nlm.nih.gov/pubmed). Various keywords used for retrieval of articles were Gallbladder, cancer Epidemiology, molecular genetics and bullion operators like AND, OR, NOT. Cross references were manually searched from various online search engines (http://www.ncbi.nlm.nih.gov/pubmed,https://scholar.google.co.in/, http://www.medline.com/home.jsp). Most of the articles published from 1982 to 2015 in peer reviewed journals have been included in this review.

Key words: Gallbladder cancer; Epidemiology; Molecular genetics; Pathogenesis

Core tip: The Gallbladder cancer is a fatal malignancy which displays considerable differences in certain ethnicities and geographic regions. Indo-Gangetic plains of India, Mapuche Indians in Chile and South America are most affected regions with this cancer. Because of this cancer is largely unstudied as compare to other cancers Present review provides a comprehensive summery of the studies conducted regarding its Epidemiology, Pathogenesis and molecular genetics. This will be helpful for the researchers to understand the current scenario of research work and how much success we have gained till now. Based on which future research work can be planned in appropriate directions.

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INTRODUCTION

Gallbladder cancer (GBC) is a rare biliary tract malignancy in most western countries, but is much widespread in some other regions of the world. Moreover, this carcinoma is infrequent in developed countries but more common in some developing countries, characterized by its lack of symptoms at initial stage leading to difficulties in treatment.

The extensive variation in geography, ethnicity, and cultural differences in the incidence of gallbladder cancer suggests the role of key genetic and environmental factors associated with the development and progression of the disease[1,2]. The lack of a serosal layer of gallbladder adjacent to the liver thus enabling hepatic invasion and metastatic progression is one of the major cause of its miserable prognosis[3]. The present review provides a recent update of studies regarding epidemiology, pathogenesis and molecular genetics of gallbladder cancer as available in literature.

EPIDIMIOLOGY OF GALLLBLADDER CANCER

Gallbladder cancer shows an unusual geographic distribution worldwide with substantial geographic variation. Data from Mapuche Indians from Valdivia, Chile, South America shows the rate of gallbladder cancer as: 12.3/100000 for males and 27.3/100000 for females[3]. The native people is these countries exceed for gallbladder cancer mortality rates from cervical (8.0/100000), breast (8.7/100000), pancreatic (7.4/100000), and ovarian cancers (7.3/100000)[3]. American Indians in New Mexico, USA, have also very high average annual rate of GBC (8.9/100000)[4], [Surveillance, Epidemiology End-Results Program (SEER) The Four Most Common Cancers for Different Ethnic Populations 2013. Bethesda, MD: National Cancer Institute; 2013].

Although the worldwide occurrence of gallbladder cancer is less than 2/100000 individuals, but this has been recorded with extensive variance[5]. The residents of Indo-Gangetic belt particularly females of northern India (21.5/100000) and south Karachi Pakistan (13.8/100000) have been reported as one of the highest affected regions[4]. Gallbladder cancer is also found in high frequency in Eastern Europe include Poland (14/100000 in Poland), Czech Republic, and Slovakia and Asia whereas south Americans of Indian descent (3.7 to 9.1 per 100000), Israel (5/100000) and Japan (7/100000) have shown intermediate prevalence of gallbladder cancer[4,6]. The residents of Andean-area, North American Indians and Mexican-Americans are specially predisposed of GBC[6]. The majority of the world has decreasing mortality trends in gallbladder cancer but GBC frequency is constantly rising in Shanghai, China which is substantial cause of mortality[7]. Although Gallbladder cancer is more common in females still in some countries like Korea, Iceland and Costa Rica, higher mortality rate has been reported for males as compare to females[8]. The data from National Cancer Institute; SEER Program (http://seer.cancer.gov/) has revealed only little turn down in incidence over the past few decades.

ETIOLOGICAL FACTORS FOR GBC PATHOGENESIS

The development of gallbladder cancer has been linked to various genetic and environmental factors. Chronic infection of gallbladder or/and environmental exposure to specific chemicals, heavy metals, and even many dietary factors, have been found to be associated with GBC formation. The dramatic association of GBC with female gender and certain geographical regions (mostly developing countries) has been proposed to be influenced by various female hormones, cholesterol cycling and salmonella infections in existing literature[9,10]. Worldwide GBC affects females 2-3 times more commonly than males, but bias varies greatly in different parts of the world mostly in high prevalent regions of GBC[4,6]. To some extent, the female hormone estrogen causes increased cholesterol super saturation in bile and hence involved in gallstone mediated GBC pathogenesis[11]. Although the female gender GBC can be linked with the role of female hormones. However an article published previously has questioned the association of hormone receptor expression to tumor differentiation[12]. So the extent of female hormones contribution in Gallbladder cancer is still not certain and requires more investigation.

Other well-known GBC associated risk factors

Table 1 Etiological factors for gallbladder cancer pathogenesis

Major Independent Etiological factors	Dependent Etiological factors
Age[6]	Tobacco consumption[15]
Sex[6], BMI[16]	Mustard oil[17] Argemone oil (AO) and butter yellow (BY)[18]
Family history[7,19]	Early age at first pregnancy[20]
Cholelithiasis[6,22-24]	Use of Oral contraceptives[15,25,26]
Chronic cholecystitis, porcelain gallbladder[27,28]	Red Chili pepper[29,30]
Chronic infection by *Salmonella* species, *S. paratyphi* or *S. typhican*[6,10,31-34]	Occupational exposure, Benzene[17,35]
Helocobacter pylori[36,37]	Secondary bile acids[13,38-40]
High parity[20,21,24,26]	Xanthogranulomatous cholecystitis[41]
Anomalous pancreatobiliary duct junction[42,43]	Heavy metals[44,45]
Porcelain gallbladder[46]	Genetic factors[48]
Gallbladder polyp[47]	
Obesity[49]	Free radical oxidation products[50]

such as porcelain gallbladder, Mirizzi's syndrome and bile reflux has also been playing a major role as a predisposing factors of this disease[9]. Family history of gallstones, tobacco consumption, chemical exposure, residence in Gangetic belt and high concentrations of secondary bile acids, excessive intake of fried foods (reused oil), increases the risk for GBC[13]. Present data suggest that gallstones are a major risk factor for GBC but their role as a cause for gallbladder cancer is still not certain. A review article by Shrikhande *et al*[14] has also supported the fact that the populations reporting high incidence of gallbladder cancer with associated gallstones, prophylactic cholecystectomy should be done only after correlating with the epidemiological profile of the place. Convincing evidence also exists for the presence of gallstones as strongly associated factor for gallbladder cancer etiology[7]. Most of the etiological factors are summarized in Table 1[6,7,10,13,15-50].

Familial and linkage studies

Swedish family-cancer database and Utah cancer registry has reported the first ever data for familial clustering of GBC[51]. This study has provided the first data on familial clustering of gallbladder cancer based on medically confirmed records, in which it was estimated that 26% of gallbladder cancers are familial. The significant risk in 3rd degree relatives and the disease manifestation in several high risk pedigrees as reported in previous studies gives a strong indication for genetic susceptibility to GBC[51]. The high risk heritable factors are likely to contribute to a large extent to this cancer further modulated by environmental factors. The nationwide Swedish Family-Cancer Data base from the Swedish Cancer Registry (10.2 million individuals from the year 1961-1998), has reported maternal transmission favoring over paternal in familial gallbladder cancers[52]. Furthermore, the clustering of gallbladder cancer within families is suggestive of a critical role of genetics in its development[19]. Carcinoma gallbladder was detected in two siblings from Brazil as reported by Trajber *et al*[53]. Role of allele specific mutations in pathogenesis of carcinoma gallbladder has also been reported[54]. Another report by Pandey *et al*[55] has shown higher frequency of carcinoma gallbladder in patients with A+ and AB+ blood groups to which the reason is still unknown.

GENETIC AND MOLECULAR ALTERATION REPORTED IN GALLBLADDER CARCINOMA

The present existing information regarding genetic and molecular alterations in GBC is still very much limited. Like other neoplasms, GBC is a multifactorial disorder involving multiple genetic alterations[56-58]. Abnormality in tumor suppressor genes, oncogenes, and DNA repair genes, presence of microsatellite instability (MSI) and epigenetic alterations mainly caused by aberrant promoter methylation of gene areas are some of the various well known factors reported till now. The serious of genetic alteration leading to gallbladder cancer formation is still not established clearly. Some of the molecular alterations reported so far are enumerated in Tables 2-4.

GENETIC ALTERATIONS IN GBC

KRAS

KRAS act as initial key player in numerous signal transduction mechanisms and associated pathways. Many pathogenic mutations have been reported in *KRAS oncogene* in Gallbladder cancer tissue[58-63]. K*RAS* gene mutations identified in GBC mostly affects codons 12, 13 and 61. In north India *KRAS* codon 13 mutation is more common (about one third) than codon 12 and 61[64]. However many other studies have not detected any mutations in this gene[65,66]. Any activating point mutations in *KRAS* oncogene can give rise to abnormal growth signals which is one of the hallmarks of cancer. The previous reports have co-related a condition called anomalous arrangement of the pancreatico-biliary duct with presence of gallbladder cancer as patients harboring this condition have a higher frequency of *KRAS* gene mutation as compare

Table 2 Mutations detected in gallbladder cancer by low throughput methods

Studied gene	Type of study	Methods used	Studied population	Ref.
KRAS	Mutation at codon-12 (8%)	PCR-RFLP	India	[64]
	Mutation at codon-12 (29%-30%)	PCR-RFLP	Chile	[76,77]
	Mutation at codon-12 (0%-59%)	PCR-RFLP, Direct sequencing	Japan	[60,78,79]
	Mutation at codon-12 (50%-80%)	ELMA, SAB, PCR-SSCP, Direct sequencing	Japan	[63,80]
INK4A (p16)	Mutation, deletion	PCR-RFLP, direct sequencing, IHC	Japan, Chile	[54,79,81,82]
D310 mtDNA	Mutation (Displacement loop)	PCR-based assay, direct sequencing	Chile	[83]
TP53	Mutation, overexpression, LOH	PCR-RFLP, direct sequencing, IHC	Greece, Japan, Chile	[84-86]

Table 3 Mutations studies in gallbladder cancer by high throughput methods

Platform	Number of samples	Study population	Research planned	Key findings	Ref.
Sequenom Mass ARRAY technology	49 FFPE	India	390 mutations in 30 genes	*PIK3CA* (4%), *KRAS* (2%), *CTNNB1* (4%), *TP53* (18%)	[95]
Mass spectroscopy-based	57 FFPE	MD Anderson Centre	159 mutations in 33 genes	14 hotspot mutations in 9 cases including (*KRAS, NRAS, PIK3CA, IDH1, ALK, MET*) 26 mutations in 15cases	[94]
Next-generation sequencing (NGS)	15 FFPE		NGS of 182 cancer-related genes	(*P53, STK11, RICTOR,TSC2, FGF3-TACC* fusion, *FGF10* amplification) Preponderance of mutations involving the PI3 kinase pathway	[94]
Whole Exome and transcriptome Sequencing	29 Fresh Frozen	Japan	64 non silent mutations signatures	*EGFR, ERBB3, PTEN, ARID2, MLL2, MLL3, APOBEC, TERT* *APOBEC*-associated mutation signature were observed in GBC	[96]
Exome sequencing and targeted gene sequencing	57 Fresh Frozen	China	Whole exome sequencing	*TP53* (47.1%), *KRAS* (7.8%) and *ERBB3* (11.8%) ERBB pathway genes mostly mutated	[93]

FFPE: Fresh frozen paraffin embedded.

Table 4 Summary of global gene expression studies in gallbladder cancer

Biological sample used	Platform/studies key findings	Ref.
17 gallbladder tissue specimens (6 advanced GBC , 6 early GBC cancers and 5 normal control	Oligonucleotide Microarray platform Unregulated genes: 2270 Downregulated genes: 2412	[97]
5-Normal biliary epithelial scrapings, 11- surgically resected biliary carcinomas, 9-biliary cancer cell lines	Oligonucleotide Microarray platform Unregulated genes : 282 genes Downregulated genes: 513	[98]
37 biliary tract carcinomas (15 bile duct, 11 gallbladder, 11 of ampulla of Vater)	cDNA array platform 118 genes were identified with a prognostic value	[99]
12 advanced gallbladder carcinoma tissue 3 samples of normal control gallbladder epithelium	Oligonucleotide Array platform Upregulated: (TOPO II-alpha, cyclin B2, CDC28, ubiquitin-conjugating enzyme E2C), and one metabolism-related: (gamma-glutamyl hydrolase)	[100] [101]
34 biliary tract cancers including 13 intrahepatic (IHC), 12extrahepatic (EHC), 9 (GBC)	Oligonucleotide Array platform 1281 genes with deregulated expression pattern	

to normal condition[65,67,68]. However mutation of *KRAS* gene has never been detected in GBC having adenoma carcinoma sequence of development[69] (Table 2).

TP53

TP53 is a well-known tumor suppressor gene and has various mechanisms of anticancer function and plays significant role in maintenance of genome integrity, apoptosis, genomic stability, and inhibition of angiogenesis etc. Loss of *TP53* function allows deregulated survival of genetically impaired abnormal cells which can lead to neoplastic conversion of later on[70]. *TP53* mutations are relatively more common in later stages of the disease[63,66,71-73]. Most of the *TP53* mutations associated with GBC are missense mutations that produce a non-functional protein with an increased half-life. The existing literature has reported mutations of the *TP53* gene in between approximately 27% to 70% of gallbladder carcinomas[74]. Many codons of the *TP53* codons are affected by pathogenic

mutations of this gene. Functional molecular studies have discovered that mutations in exons 5 and 8 of *TP53* gene causes deregulation of this gene[75]. Details are shown in various existing literature is shown in Table 2[54,60,63,64,76-86].

C-ERB-B2

The oncogene *c-erb-B2* is a homologue for epidermal growth receptor, encoding a protein with tyrosine kinase activity. The immunohistochemical expression of c-erb-B2 has been found positive between 10%-46% of gallbladder cases. However its expression has been found to be absent in dysplasia or adenomas as shown by previous reports[87,88]. Animal model studies in transgenic mice have shown that *erbB2* overexpression in the basal layer of the biliary tract epithelium led to the development of GBC in all (100%) of mice. Moreover, the expression of HER2/neu was positively observed in 28% of GBCs which was directly correlated with advanced stage of cancer[89]. Therefore, it can be hypothesized that some oncogene is associated with in Gallbladder cancer progression. In a study from India, C-erbB2 was frequently expressed in well differentiated and stage Ⅱ to stage Ⅳ in about 9.4% of GBC cases[90]. A recent report showed HER2/neu overexpression occurred in 14% of the advanced gallbladder cancer cases, and this subgroup was expected to be benefited from HER2/neu pathway inhibitors[91]. Therapeutic targeting of *EGFR/HER2* pathways boosts the anti-proliferative effect of gemcitabine in biliary tract and gallbladder carcinomas as shown by a previous study[92]. Based on facts it can be concluded that *C-ERB-B2* expression can become a marker for a poor prognosis.

HIGH THROUGHPUT MUTATION STUDIES IN GBC

High throughput research has made large scale repetition of experiments feasible as it automates the experiments thus it has now become possible to study how all 21000 genes potentially contribute to cell function or disease. But in case of gallbladder cancer there are very limited high throughput studies. One of the pioneer studies published in nature genetics using high throughput approach by Chinese population has found recurrent mutations in ErbB pathway[93]. Javle *et al*[94] has found 26 missense mutations with more common *TP53* and *PIK3CA* mutations in GBC tumor using NGS technology. Mutation profiling of gallbladder cancer tissue in Indian population has found *PIK3CA* and *KRAS* mutations as most common among this ethnicity[95]. The variability in the results is an indicator of intra-tumoral heterogeneity of cancer, which describes the observation of different tumor cells showing distinct morphological and molecular profiles including variable gene expression but ultimately leading to a common phenotype. The high throughput mutation studies in GBC are presented in Table 3[93-96].

GENE EXPRESSION STUDIES IN GBC

In order to identify potential biomarkers for GBC progression, many studies have been performed to find out the differential gene expression profiles between normal and tumor cells. Existing data various greatly, despite of same grade and stage of the included study subjects. Table 4[97-101] and Table 5[54,66,75,84,86,90,102-180] are summarizing global and single gene expression studies reported in GBC respectively.

LOSS OF HETEROZYGOSITY AND MICROSATALLIE INSTABILITY

Loss of heterozygosity (LOH) is a common genetic alteration in cancer genome. The events like heterozygous deletion of one of the two alleles, or duplication of a maternal or paternal chromosome or chromosomal region and concurrent loss of the other allele gives rise to LOH. The studies focused to detect loss of heterozygosity (LOH) in GBCs have shown frequent heterozygous allelic loss which spans in 18 different chromosomal regions[57]. Cytogenetic locations involved in frequent loss of heterozygosity *i.e.,* 3p, 8p, 9p, and 22q regions have also been identified in GBC from different populations; which have also been reported in several other cancers like Retinoblastoma, melanoma, Squamous cell carcinoma of larynx[181-183]. In particular, gallbladder tumor shows numerous site of allelic loss in the short arm of chromosome 3, which harbors several known or putative tumor suppressor genes[109,181]. High degree of microsatellite instability (MSI) in 10% of GBC cases was observed as reported in research article published by Goldin *et al*[184]. A different pattern of allelic loss has also been detected in Japanese population. In this report the allelotype analysis of gallbladder carcinoma revealed an interesting associated with anomalous junction of pancreatico-biliary duct[68]. Table 6[54,57,66,68,109,112,185-193] enlists various studies conducted in GBC regarding LOH and MSI.

METHYLATION AND GALLBLADDER CANCER

Understanding of DNA methylation patterns of gallbladder tumors can prove to be important biomarkers to refine the diagnosis and prognostic information which ultimately helps in appropriate therapeutic selection. Hypermethylation in gene promoter regions is a common epigenetic mechanism for the inactivation of tumor suppressor genes. One of the important research article published previously has found an important link between methylation and survival. In this study methylation of genes *p73, MGMT,* and *DCL1* was significantly associated with

Table 5 Summary of single gene expression studied reported in gallbladder cancer

Studied single genes	Expression pattern	Studied population	Ref.
TP53	Expression (20%-70%)	India, Slovenia, Greece, Taiwan, Japan, Chile	[75,84-86,102-106]
p16	Overexpression	South Korea	[107]
FHIT	Expression loss (45%-75%)	Japan, Chile	[108,109]
ERBB2	Overexpression (25%-64%)	India, Japan, China, South Korea	[66,103,110,111]
	Expressed in 9.4%cases of well differentiated and stage Ⅱ to stage Ⅳ tumors	India	[90]
RB	20% cases allelic loss 4%-14%- loss of expression	Japan	[54,112]
CDKN1A	Reduced expression 49% cases	Japan	[113]
Cyclin D1, Cyclin E	Overexpression (41%-49%)	Japan	[114,115]
COX2	Over-expressed	Slovenia, Japan, Chile	[104,116,117]
BCL2	Over-expressed	Japan	[118]
CKIT	Expression 45%	Japan	[119]
SOX-4	Overexpression	China	[120]
Chemokine (C-X-C motif) ligand 12	Increased expression	South Korea	[121]
CXCR4, CXCR7	Increased expression	China	[122]
hedgehog pathway components (Shh, Ptch1 and Gli1)	*Shh*: 81.7% of cases expressed *Ptch1*: 75.3% of cases *Gli1*: 70.0% of cases	China	[123]
CD56, CD99	Altered expression	South Korea	[124]
CD97, CD55	*CD97*: 69.6% of cases expressed *CD55*: 65.2% of cases	China	[125]
HMGA2 and CD9	*HMGA2* positive expression *CD9* negative expression	China	[126]
cholecystokinin type-A	44.1% of cases expressed	India	[127]
vascular endothelial growth factor-A	53.6% of cases expressed	China	[128]
VEGF-C, VEGF-D	*VEGF-C*: 64.0% of cases *VEGF-D*: 62.0% of cases	China	[129]
Tumor endothelial marker 8 protein	Increased expression	India	[130]
L1 cell adhesion molecule	Increased expression	South Korea	[131]
Tissue factor pathway inhibitor-2	Down-regulated	China	[132]
HIF-1α	Increased expression	China	[133]
VHL	Reduces expression		
ERCC1(excision repair cross-complementing 1)	High expression in best differentiated tumors	Chile	[134]
NF-E2-related factor 2 (Nrf2)	Increased expression	China	[135]
CD34 , CA15-3	Highly expressed in stroma and in epithelium	Italy	[136]
ADAM-17	Overexpression	China	[137]
Cdx2	Aberrant expression	Japan	[138]
TLR4	Expressed in glandular and luminal epithelium	China	[139]
MiRNA	Loss of Dicer and Drosha expression	China	[140]
Inducible Nitric Oxide Synthase iNOS	Expressed	China	[141]
Prostate stem cell antigen (PSCA)	Down-regulated	Japan, China	[142]
OCT-4	Down-regulated	China	[143]
hTERT/Telomerase	Expressed in 56.66% cases	India	[144]
Aquaporins (AQPs)	Positive expression	Japan	[145]
Ornithine decarboxylase (ODC) and glutamate decarboxylase 65 (GAD65)	Overexpression	China	[146]
Alpha-methylacyl coenzyme A (racemase) AMACR	Overexpression	Taiwan	[147]
Sonic Hh (Shh)	Elevated expression	Japan	[148]
TGF-β induced miR-182	Overexpression	China	[149]
SLP-2	Overexpression	China	[150]
TMPRSS4	Higher expression	China	[151]
zinc finger X-chromosomal protein	Suppressed	China	[152]
multidrug resistance-associated protein 2 (MRP2)	Overexpression	South Korea	[153]
HuR	Overexpression	Taiwan	[154]
miR-155	Overexpression	Japan	[155]
LAPTM4B-35	Overexpressed(76%)	China	[156]
p27, P21	*p21* (75% cases) and *p27* (25% cases)	Jordan	[157]
Thymidylate synthase (TS)	Low expression	Japan	[158]
CD146	Elevated expression	China	[159]
AEG-1	Highly expressed (63.4%)	China	[160]
CCKAR	Expression increased (76.6%)	India	[127]
Nemo-like kinase (NLK)	Overexpression of *NLK*	China	[161]
C-erbB2	Overexpression (9.4%)	India	[90]

Phospho-mTOR expression	Positive expression (64.1%)	Chile	[162]
human telomerase reverse transcriptase (hTERT)	Expression increased	India	[163]
Phosphoglycerate kinase 1 (PGK1)	Decreased expression (54.7%)	China	[164]
Notch 1 and Notch 3	Positive expression	China	[165]
CCK-A	Decreased expression	India	[166]
3-phosphoinositide-dependent protein kinase 1 (PDK1)	Positively expressed	China	[167]
Zinc finger X-chromosomal protein (ZFX)	Overexpression	China	[151]
miR-138	Over expression	China	[168]
HSP gp96	Expression (90.7%)	China	[169]
Long non-coding RNA-LET	Overexpression	China	[170]
Survivin	higher expression (2.9- fold)	India	[171]
Long non-coding RNA CCAT1	Overexpressed	China	[172]
TEM8	Expression increased	India	[130]
Fhit,Mlh1, P53	Reduced expression of Fhit and Mlh1 protein and Overexpression of P53	Japan	[108]
NDRG2, CD24	NDRG2 down-regulation, CD24 up-regulation	China	[173]
IL-6	Overexpressed	China	[174]
SLP-2	Overexpression	China	[150]
BCL6, p19(ARF)	*BCL6* overexpression , p19 (ARF) Low Expression	Taiwan	[175]
VEGF-A	High expression of *VEGF-A*	Chile	[176]
MALAT1	Upregulation of MALAT1	China	[177]
miR-182	Upregulation of miR-182	China	[149]
miR-155	High expression level of miR-155	Japan	[155]
p53, S100A4, p27, p16, RB, Smad4, FHIT, E-cadherin and PML	*p53* and *S100A4* overexpressed, Loss of p27, p16, RB, Smad4, *FHIT*, E-cadherin and *PML* expression	South Korea	[178]
PEG10, TSG101	*PEG10* and *TSG101* overexpressed	China	[179]
CK7, CK20	*CK7* (69.05%), *CK20* (28.57%) expressed	Greece	[180]

Table 6 Loss of heterozygosity and microsatellite instability studies reported in gallbladder cancer

Studied reported in respective population	LOH/MSI	Ref.
Chilean	LOH reported in : 3p, 6q, 7q, 8p, 9p, 9q, 11q, 12q, 17p, 18q, 19p, 22q, and Xq	[57]
Japan	LOH reported in : 2p, 4p, 4q, 8q,9q, 10p,14p,14q,16p, 19p, 21p and Xp [Maximum deletion-2p24, 14q22 and 21q22]	[68]
Chilean, Japan	p53, 9p.8p, DCC, KRAS, p16, 16q24, 3p,9q, 22q and p161NK4	[54,66,109,112,185]
Greece	BAT-26	[186]
Chile, Japan	MSI reported (20%-33%)	[187,188]
India	E-cadherin (CDH1) 2p, 2q, 6q, 7q,17p	[189]
India	Fragile histidine triad (FHIT) MSI-H 17.5% LOH :27.5%	[190]
Japan	High incidences of LOH at 1p36 (19/36:53%), 9p21 (12/32:38%), 13q14 (20/36: 56%), 16q24 (31/54: 61%), and 17p13 (15/36: 42%)	[191]
Chile	FHIT gene locus (3p14.2)	[109]
India	LOH at 8 loci, that is 3p12, 3p14.2, 5q21, 9p21, 9q, 13q, 17p13, and 18q for tumor suppressor genes (DUTT1, FHIT, APC, p16, FCMD, RB1, p53, and DCC genes)	[192]
India	genomic instability at 2p, 2q, 6q, 7q, and 17p loci	[189]
Chile	DUTT1 (3p12), FHIT (3p14.2), BLU, RASSF1A, SEMA3B and hMLH1 (3p21.3)	[193]

LOH: Loss of heterozygosity; MSI: Microsatellite instability.

survival of gallbladder cancer patients[194,195]. The study was conducted in a series of 109 advanced gallbladder cancer cases. However genes like *CDH13* and *FHIT* did not show any significant tendency with respect to gallbladder cancer patient's survival[194,195]. Multivariate analysis found *MGMT* gene to be an independent prognostic factor for survival found, representing the important role of epigenetic process in gallbladder carcinogenesis[195]. The recent report showed that promoter methylation of specific genes like *CDH1, CDKN2A-p16*, *REPRIMO* (tumor suppressor gene family) and *UCHL1* (also known as PGP9.5) have important role in gallbladder carcinogenesis[196]. Other studies conducted on GBC have shown variable methylation pattern of a number of genes Table 7[81,82,193-208].

In addition, with the help of advanced technologies like high resolution allele stratification (allelotyping analysis) investigated very high frequencies of 3p (100%), 8p (100%), 9q (88%), 22q (92%) sites in gallbladder cancer that lead to positional identification of tumor suppressor genes associated with GBC malignancies and pathogenesis[57,58,109,209]. Moreover, some well-known tumor suppressor genes that

Table 7 Aberrant promoter methylation gene studies summary in gallbladder cancer

Gene	Full name	Function	Meth Freq	Population	Ref.
CDH1	Cadherin 1, type 1, E-cadherin (epithelial)	Tissue invasion (cell-cell adhesion)	11%-65%	Japan, Chile	[194-200]
FHIT	Fragile histidine triad gene	Regulation of DNA Replication, and apoptosis	30%-57%	Chile	[81,193-195,199]
APC	Adenomatous polyposis coli	Tumor suppressor gene (Cell migration, adhesion and apoptosis)	26%-35%	Chile, United States	[81,194,195,198,199]
hMLH1	Human homologs of MutL gene of bacteria	Mismatch repair	0%-14%	Chile, United States	[81,193-195,199]
p16	Cyclin-dependent kinase inhibitor 2A	Cell cycle regulation	15%-60%	Chile, United States, Germany	[81,82,195,197-199,201,202]
p15	Cyclin-dependent kinase inhibitor 2B	Cell cycle regulation	22%-44%	Chile	[81,198]
DAPK1	Death-associated protein kinase 1	Serine-threonine kinase	8%-61%	Japan, Chile	[81,197,198]
DLC1	Deleted in liver cancer 1	GTPase-activating protein	39%	Chile	[81]
RASSF1	RAS association domain family protein 1A	Signal transduction	0%-36%	Japan, Chile South Korea	[81,193,197,198,203]
MGMT	O-6-methylguanine-DNAmethyltransferase	Methyltransferase	13%-30%	Chile, United States	[81,195]
CDH13	CDH13 Cadherin 13, H-cadherin(heart)	Tissue invasion (cell-cell adhesion)	44%-70%	Chile	[81,198]
TIMP3	Metallopeptidase inhibitor 3	Degradation of extracellular matrix	0%-39%	Chile	[81,198]
GSTP1	Glutathione S-transferase pi 1	Conjugation of hydrophobic and electrophilic compounds	13%	Chile	[198]
RARβ2	Retinoic acid receptor, beta	Encodes retinoic acid receptor beta	4%-44%	Chile, United States	[81,198]
REPRIMO	TP53 dependent G2 arrest mediator candidate	Cell cycle regulation (p53 mediator)	62%	Chile	[204]
SHP1	Protein tyrosine phosphatase, non-receptor type 6	Regulate cell growth, differentiation, mitotic cycle	80%	Chile	[198]
3-OST-2	Heparan sulfate (glucosamine) 3-O-sulfotransferase 2	Osulfotransferase	72%	Chile	[198]
RUNX3	Runt-related transcription factor 3	TGF-beta signal pathway	22%-32%	Chile	[197,198]
RIZ1	PR domain containing 2, with ZNF domain	Histone/protein methyltransferase	26%	Chile	[198]
HPP1	Transmembrane protein with EGF-like and two follistatin-like domains 2	TGF-beta signal pathway	20%		[198]
P73	Tumor protein p73	Induction of apoptosis and cell cycle regulation	14%-28%	Chile, United States	[81,198]
SOCS-1	Suppressor of cytokine signaling 1	JAK-STAT pathway	12%	Chile	[198]
DCR2	Tumor necrosis factor receptor superfamily, member 10d	TNF-receptor superfamily	6%	Chile	[198]
SEMA3B	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted,(semaphorin) 3B	Induction of apoptosis	92%	Chile	[193]
DUTT1	Human homolog of Drosophila Roundabout (ROBO1)	Cell migration and metastasis	22%	Chile	[193]
BLU	Zinc finger, MYND-type containing 10	Cell cycle regulation	26%	Chile	[193]
p14	Ribonuclease P/MRP 14 kDa subunit	Cell cycle regulation	40%	Germany	[201]
MASPIN	Mammary serine protease inhibitor	Tumor suppressor gene	70%	India	[205]
THBS1	Thrombospondin 1	Platelet aggregation, angiogenesis, and tumorigenesis	52%		
HLTF	Helicase-like transcription factor	Regulate transcription	16%		
MYC	V-Myc Avian Myelocytomatosis Viral Oncogene Homolog transcription factor	Cell cycle progression, apoptosis and cellular transformation	80%	Brazil	[206]
APC	Adenomatous polyposis coli	Tumor suppressor gene	71%-95%	Chile	[207]
CDKN2A	Cyclin-dependent kinase inhibitor 2A	Cell cycle			
ESR1	Estrogen receptor 1	Transcription factor			
PGP9.5	Protein gene product 9.5	Neural and/or nerve sheath differentiation			
SSBP2	Single-stranded DNA-binding protein 2	Microsatellite instability			

PGP9.5	Protein gene product 9.5	Neural and/or nerve sheath differentiation	27.2%	South Korea	[208]
MLH1, CDKN2A	MutL homolog 1	Mismatch repair	5%	Chile	[194]
	Cyclin-dependent kinase inhibitor 2A	Cell cycle	35%		
FHIT	Fragile histidine triad protein	Purine metabolism	21%		
APC	Adenomatous polyposis coli	Tumor suppressor genes	25%		
CDH1	Cadherin-1	Cell cycle	66%		

are present in chromosomes like 3p, 5q, 8p,13q and 18q can also influence the gallbladder cancer formation[57,58,109,209].

Candidate genes for gallbladder cancer susceptibility

The merely successful mechanism for identifying low or moderate penetrance cancer genes, is the analysis of genes involved in candidate loci. Therefore, these genes are also termed as candidate genes. The candidate gene analysis is done via case-control study, in which allele frequencies in cancer patients and healthy controls are compared and obtained results are analyzed statistically. Candidate modifier genes are selected on the basis of biological plausibility. Most studies are based on genes that encode proteins, thought to be involved in carcinogenesis, such as those involved in apoptosis, cell-cycle control, DNA repair, xenobiotic metabolism, hormonal and inflammatory pathway or other risk factors. Moreover, known genes account for a small proportion of the heritability of gallbladder cancer, and it is likely that many genes with modest effects are yet to be found.

A study by Wang *et al*[210] from china suggested about CCK-induced impaired gallbladder emptying in patients having gallstones. Most of the candidate genes identified so far are related to the classical rate limiting enzymes and proteins of lipid metabolism, steroidogenesis, lipid transport, bile acid synthesis, bile canalicular transport, gallbladder contractility, cell cycle, DNA repair and Inflammatory pathway[211-233]. Till now there are very limited studies in GBC which are independently replicated which includes *OGG1*$_{rs1052133}$, *TP53*$_{rs1042522}$, *GSTM1* null polymorphism and *CYP1A1*$_{rs1048943}$ polymorphism[48]. No definitive conclusions can be drawn due to limited number of studies. Hence there is a great need to explore genes related to GBC susceptibility. Table 8[30,214-273] shows an overview of candidate gene studies reported in GBC.

The only one genome-wide association study conducted in gallbladder cancer identified a SNP (rs7504990) in *DCC* gene which was associated with six times gallbladder cancer risk in the Japanese population. It has also been reported that reduced expression of *DCC* gene (deleted in colorectal cancer, 18q21.3) was designated to be associated with the greater aggressiveness of the disease which include increased proliferation, poorly differentiated histology, and metastasis through loss of adhesiveness[234]. However genome wide association study (GWAS) identified SNPs was replicated in Indian population and the study found no individual association of *DCC*$_{rs7504990}$ but haplotype analysis of *DCC* gene found the cumulative effect of G$_{rs2229080}$-A$_{rs4078288}$-C$_{rs7504990}$ A$_{rs714}$ haplotypes in Gallbladder Cancer predisposition[235].

Molecular pathogenesis of GBC

Gallbladder carcinoma develops through a serious of events before converting in to invasive malignancy. Any exposure to carcinogens may convert normal gallbladder epithelium to condition called metaplasia which subsequently forms dysplasia to carcinoma *in situ* (CIS), and finally proceeding to invasive carcinoma in about 15 years[274,275]. The multistage pathogenesis of gallbladder carcinoma begins with gallstones giving rise to a condition called chronic cholecystitis, which increases to risk to gallbladder cancer formation. More than 90% of patients with gallbladder carcinoma show dysplasia and CIS[274,275]. There is an unusual asymmetric thickening of the gallbladder wall with infiltration to surrounding structures in gallbladder cancer. Maximum cases reported in carcinomas of gallbladder are adenocarcinomas (80%-95%). Adenocarconomas can further be of papillary, tubular, mucinous, or signet cell type. Some other types which are present in very low frequency include: squamous cell carcinoma (16%), undifferentiated or anaplastic carcinoma (2%-7%), and adeno-squamous carcinoma (1%-4%)[276]. Most of GBCs (60%) are found in the fundus, near about 30% in the body, and 10% in the neck region.

Tumor markers in GBC

Till date there is no reliable tumor marker developed which can be employed in diagnosis of gallbladder cancer. The only two markers *i.e.,* carcino-embryonic antigen (CEA) and carbohydrate antigen 19-9 are most often elevated in advanced stages with a low specificity. So most often they are not used in stand-alone diagnosis of GBC[277]. However, there are other tumor markers like CA125, CA199, CEA (carcino-embryonic antigen), cancer antigens (CA) and CA242, which are for diagnosis of different other types of cancer (*e.g.*, gastric, liver, pancreatic), have also been researched in diagnosis of gallbladder cancer but the obtained results are highly inconsistent[278-280]. In addition some previous reports have shown CA 242, RCAS1 (receptor binding cancer antigen expressed on SiSo cells) CA15-3, Mac-2BP (macrophage

Table 8 Candidate gene studies (low susceptibility genes) in gallbladder cancer

Pathway involved	Gene	Polymorphism	Population	Ref.
DNA repair pathway genes	*XPC*	(rs2228000) Ala499Val	China	[236]
		(rs2228001) Lys939Gln	China	
	ERCC2	(rs1799793) Asp312Asn	North Indian	[232]
		(rs13181) Lys751Gln	North Indian	
	MSH2	(rs2303426) IVS1+9G>C		
		(rs2303425) -118T>C		
	OGG1	(rs2072668) 748-15C>G		
	TP53	(rs1042522) Pro72Arg	Chilean, Hungary, Japanese	[237-239]
	XRCC1	(rs1799782) Arg194Trp	North Indian Shanghai, China	[222,231]
		(rs25487) Arg399Gln		
	APEX1	(rs3136820) Asp148Glu	Shanghai, China	[222]
	RAD23B	(rs1805335) IVS5-15A>G		[223]
		(rs1805329) EX7+65C>T		
	FEN1	FEN1-69G>A and haplotypes	China	[240]
Hormonal pathway genes	*CCKAR*	(rs1800857) IVS1-5T>C	North Indian	[227]
	CCK and CCKAR	(rs2071011G>C, rs915889C/T,	Shanghai, China,	[241]
		rs3822222C/T, rs1800855T/A		
	ESR1	(rs2234693) IVS1-397T>C	Shanghai, China, North India	[241-243]
		(rs3841686) IVS5-34->T		
		(rs2228480) Ex8+229G>A		
		(rs1801132) Ex4-122G>C		
		(rs9340799) IVS1-351A>G		
	ESR2	(rs1256049) Val328Val	Shanghai, China	
	PGR	Ins/Del	North India	
	AR	(CAG)n	Shanghai, China	[244]
		(rs4633) His62His	Shanghai, China	[224]
	COMT	(rs4818) Leu136Leu		
	CYP1A1	(rs2606345) IVS1+606G>T		
	CYP1B1	(rs10012)Arg48Gly		
		(rs1065778) IVS4-76A>G	Shanghai, China	[224]
	CYP19A1	(rs700518) Val80Val		
		(rs2304463) IVS7-106T>G		
		(rs700519) Arg264Cys		
		(rs1065779) IVS9-53G>T		
		(rs4646) Ex11+410G>T		
	HSD3B2	(rs1819698) Ex4-133C>T	Shanghai, China	[224]
		(rs1361530) Ex4-88C>G		
	HSD17B3	(rs2066479) Gly289Arg		
	HSD17B1	(rs2830) Ex1-486G>A		
	SHBG	(rs6259) Ex8+6G>A		
	SRD5A2	(rs523349) Ex1-17G>C		
	RXR-a	(rs1536475) IVS6+70A>G	Shanghai, China	[245]
		(rs1805343) IVS1-27A>G		
	RXR-b	(rs2744537) G392T		
		(rs2076310) C51T		
	INS	(rs689) A-6T	Shanghai, China	[245]
	PPARD	(rs2016520) Ex4+15C>T	Shanghai, China	
	PPARG	(rs3856806) His477His	Shanghai, China	
Inflammatory pathway genes	*CR1*	(rs2274567) His1208Arg	North Indian	[230]
		(rs12144461) Intron 27, HindIII		
	IL1RN	86-bp VNTR	North Indian	[220]
		(rs689466) -1195G>A		[233]
	PTGS2	(rs20417) -765G>C		
		(rs5275) +8473T>C	North Indian Shanghai, China	[233,246]
	IL1B	(rs16944) -1060T>C	Shanghai, China north Indian	[220,247]
	IL10	rs1800871)- 7334T>C	Shanghai	[247]
		(rs1800872) -6653A>C	Shanghai	
	IL-8	(rs10805066) IL8 -13985C>G	China	[248]
	EGF	(rs4444903) +61A>G	North Indian	[221]
	TGFb1	(rs1800469)-509C>T	Shanghai, north Indian	[219,221,247]
	TNF-α	(rs1800629) -308G>A		
	IL6	(rs1800795) 236C>G)		
	IL8	(rs10805066) -13985C>G	China	[248]

	MMP-2	(rs2285053) -735 C>T (rs9340799) -1306 C>T	North Indian	[249]
	MMP-7	(rs11568818) -181 A>G (rs2250889) P574R		
	MMP9	(rs 17576) R279Q (rs 17577) R668Q		
	TIMP2	(rs8179090) -418 G>C		
Metabolic pathway genes	*MTHFR*	(rs1801133) Ala222Val	Indian	[228]
	APOB	(rs17240441) 35_43del9	Indian	[217]
	NAT2	(rs1799929) NAT2*5A (rs1799930) NAT2*6B rs1799931, NAT2*7A	Indian	[216]
	GSTT1 *GSTP1*	Null polymorphism (rs1695) Ile105Val	Indian	[215]
	CYP17	(rs743572) Ex1+27T>C	Shanghai Indian (265)	[250,251]
	GSTM1	Null polymorphism	Indian, Chilean Hungary Japanese	[215,237,238]
	CYP1A1	(rs4646903) CYP1A1*2A (rs1048943) Ile462Val (*2C)	Indian, Chilean, Hungary Japanese China, Chilean, Hungary Japanese	[218,237,239] [224,237-239]
	Cyp1a1 cyp1b1	CYP1A1-MspI, CYP1A1-Ile462Val, and CYP1B1-Val432Leu	India	[252]
		(rs5930) EX10+55G>A	Shanghai	[253]
	LDLR	(rs6413504) IVS17_42A>G (rs14158) EX18+88G>A	Shanghai	
	LPL	(rs263) IVS5-540C>T		
	ALOX5	(rs2029253) IVS3+100G>A		
	ApoB	rs693) Thr2515Thr	Indian Chilean	[30,217]
	ABCG8	(rs11887534) Asp19His	North Indian Shanghai China	[229,254]
	CETP	(rs708272) TaqIB (rs1800775) -629C>A	Chilean Shanghai China Shanghai China	[30,254] [254]
	LRPAP1	(rs11267919)752_177_752_176 I 37	North Indian Shanghai China	[214,254]
	CYP7A1	(rs3808607) -204 A>C	North Indian	[255]
	CYP7A1	(rs3824260) -469 T>C	North Indian	
	CYP17	(rs743572)A/G	North Indian	[250,251]
	ApoB	(rs676210) Pro2739Leu (rs673548) IVS23-79T>C rs520354) IVS6+360C > T (rs1367117) Thr98Ile (rs440446) IVS1+69C>G	Shanghai	[253]
	CYP2C19	(rs4244285) CYP2C19*2, (rs4986893) CYP2C19*3	Japanese	[256]
	ADRB3	(rs4994)A/G	North Indian	[257]
Apoptosis pathway	*CASP8*	(rs3834129) -652 6N ins/del (rs1045485) Asp302His (rs3769818 A) IVS12-19 G>A	North Indian	[258]
Nuclear Receptors	*Lxr-alpha, Beta*	LXR-α (rs7120118) and LXR-β (rs35463555 and rs2695121)	North Indian	[259]
Cancer Stem cell gene	*CD44*	CD44 (rs13347) C>T, CD44 (rs353639)A>C, CD44 (rs187116) G>A, CD44 (rs187115) T>C	North Indian	[260]
	NANOG, ALCAM, EpCAM, SOX-2, OCT-4, NANOG	NANOG (rs11055786)T>C, ALCAM (rs1157)G>A EpCAM (rs1126497)T>C, SOX-2(rs11915160)A>C OCT-4 (rs3130932)T>G, NANOG (rs11055786)T>C	North Indian	[261]
Prostate stem cell antigen	*PSCA*	(rs2294008) T/C and rs2978974)	India, Japan	[262,263]
miRNA	*hsa-miR-146a*	(rs2910164) G>C	North Indian	[264]
	hsa-mir-196a2	(rs11614913) C>T		
	hsa-mir-499	(rs3746444)T>C		
	miR-27,miR-570,miR-181	miR-27a (rs895819)A>G, miR-570(rs4143815)G>C, miR-181a(rs12537)C>T	North Indian population	[265]
GWAS-associated genes	*DCC*	(rs7504990)C>T	Japan	[234]
		(rs2229080) C>G (rs4078288) A>G (rs7504990) C>T (rs714) A>G	North Indian	[235]

Wnt signaling pathway	*SFRP4, DKK2, DKK3, APC, AXIN-2, B-CATENIN, GLI-1*	SFRP4 (rs1802073) G>T, DKK2 (rs17037102) C>T DKK3 (rs3206824) C>T, APC (rs4595552)A/T APC (rs11954856) G>T, AXIN-2 (rs4791171)C>T β-CATENIN (rs4135385) A>G, GLI-1(rs222826) C>G	North Indian	[266]
Other genes	*KRAS*	codon 25 Gln25His	Eastern India	[267]
	ACE I/D	(rs4646994) 289 bp del	North Indian	[268]
	DNMT3B	(rs1569686) -579 G>T	North Indian	[269]
	TLR2	-196-174del	North Indian	[270]
	TLR4	(rs4986791) Thr399Ile	North Indian	
	Adrenergic receptors (ADRA)	ADRA2A C-1291G, ADRβ3 T190C or Trp64Arg, and ADRβ1 C1165G or Arg389Gly	North Indian	[271]
	Death Receptors and their ligands (DR4)	DR4 (rs20575, rs20576 and rs6557634), FAS (rs2234767) FASL (rs763110)	North Indian	
	PlCE1	(rs2274223) A>G and. (rs7922612) T>C	North Indian	[272]
	Vitamin D receptor (VDR)	FokI C>T	China	[273]

galactose-specific lectin-2 binding protein), Fragments of cytokeratin-19 (CYFRA 21-1) are frequently present in blood of cancer patients and shown to be associated with GBC with variable sensitivity and specificity[277,281,282].

CONCLUSION

Various lines of evidence suggest role for various environmental risk factors in Gallbladder carcinoma. Despite of many articles regarding genetic predisposition of gallbladder cancer there is no established genetic marker. Also, very limited Genome wide association studies (GWAS) have been conducted in gallbladder cancer till now.

The evidence-based model of gallbladder carcinogenesis and its dissemination by Barreto *et al*[283] serves as a basic platform for elucidation of molecular mechanisms involved in cancer development which based on recent data can be improved by discovery of other signature mutations using high throughput studies. Technological advancement can be helpful more understanding of pathogenic mechanisms underlying neoplastic conversion of gallbladder cancer muscosa. The tumor markers available for diagnosis GBC has also not of very high specificity and not discovered until advanced stage of the disease leading to complexity of the treatment. Exome sequencing of gallbladder cancer tissue has found ERBB pathway as most dysregulated pathway in this disease. Although the studies have been published in highly distinguished journals but they need to be validated before clinical implication. Moreover, limited studies with small sample size are not robust enough to conclude anything. Regardless of improvement in technologies in research field there is no accountable betterment in the prognosis of GBC patients. The future therefore should be engaged towards good quality research focused on early diagnosis and refinement of prognostic information to ultimately improve the management strategies of gallbladder cancer. Present review provides a comprehensive summery of the studies conducted regarding its Epidemiology, Pathogenesis and molecular genetics under a single umbrella. This will be helpful for the researchers to understand the current scenario of research work and how much success we have gained till now. Based on that future research work can be planned in appropriate directions.

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