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Distinct Heritable Architectures in Esophageal Cancer Revealed by Two Decades of Genome-Wide Association Studies

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Abstract

Objective: To integrate the latest evidence regarding inherited genetic risk factors for esophageal cancer while emphasizing contrasting susceptibility profiles between esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC)/Barrett's esophagus as this integration also allows assessment of how genome-wide association studies (GWAS) together with new trans-ancestry genomic methods have advanced the discovery of risk loci and their potential clinical application.

Methods: An extensive narrative review was carried out using repeated searches across PubMed/MEDLINE Embase Web of Science and Google Scholar from 2005 to 2025 through carefully refined keyword sets that focused on germline variants familial clustering polygenic risk and histology-specific genetic signals.

Results: More than 30 reliable risk loci are now recognized for ESCC mostly identified in East Asian populations with major signals located in PLCE1 alcohol/aldehyde metabolism genes ADH/ALDH2 (showing strong interaction with alcohol consumption) CHEK2 and HLA-region immune pathways whereas recent trans-ancestry studies have validated shared loci such as PLCE1 while uncovering novel African-enriched variants that highlight population-specific genetic architecture. By comparison EAC and Barrett's esophagus present a separate genetic profile shaped largely by European-ancestry consortia featuring risk loci near BARX1 FOXP1 CRTC1 (involved in mucosal development) as well as CFTR MSRA BLK (linked to barrier function and oxidative stress) and although fewer loci have been found overall EAC exhibits considerable shared heritability with Barrett's esophagus which supports the value of genetically guided surveillance.

Conclusion: ESCC and EAC display strikingly different inherited risk patterns that closely reflect their distinct environmental risk factors as this difference now permits the construction of polygenic risk scores that incorporate subtype-specific GWAS findings together with emerging rare-variant and functional genomic information thereby enabling personalized risk assessment and more targeted screening in high-risk families and populations.

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Introduction

Esophageal cancer continues to pose a major global health challenge characterized by pronounced geographic variation and persistently high mortality rates. Its worldwide burden remains among the most severe as rapid tumor progression and poor survival persist despite improvements in diagnosis and treatment [1–4]. Disease patterns are steadily changing so that squamous cell carcinoma still predominates in many resource-limited regions whereas

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adenocarcinoma has increased sharply in highly developed countries driven in part by gastroesophageal reflux obesity and Barrett's metaplasia [1 2 4]. In contrast squamous tumors are often associated with longstanding socioeconomic disadvantage chronic exposure to toxins specific dietary practices and thermal injury from very hot beverages [1–3]. Early detection programs though implemented unevenly have demonstrated benefit in high-incidence areas and broader surveillance of precursor lesions could significantly improve outcomes if widely adopted [1–4].

Inherited genetic factors appear to play a significant yet variable role across the two main histologic subtypes as numerous studies suggest that germline susceptibility is intertwined with complex biologic and clinical phenotypes. Earlier investigations indicated that germline DNA changes might modestly influence vulnerability and prognosis although initial findings were inconsistent and limited by methodological shortcomings [5]. Other research proposed that the metaplastic progression toward Barrett-related adenocarcinoma may partially arise from inherited predispositions that interact with reflux-induced cellular changes thus implying shared genetic risk with environmental cofactors such as obesity or tobacco use [6]. Although rare familial aggregation of esophageal adenocarcinoma highlights a genuine hereditary component that can present with earlier onset and occasionally follows dominant inheritance patterns specific causative genes have remained unidentified [7]. Studies of squamous cell carcinoma further reinforce this idea by showing that individuals with affected first-degree relatives frequently develop tumors at younger ages and sometimes present with multiple primary lesions which points to germline effects beyond shared environment [8]. Population studies in East Asian groups similarly reveal that particular variants for example in ZNF208 can elevate risk through unique inherited patterns [9]. Additional familial and population evidence in Barrett's esophagus supports the notion that a notable fraction of cases stem from genetic predisposition which may eventually refine screening and prevention approaches [10]. Finally when a first-degree relative has esophageal adenocarcinoma patients with Barrett's esophagus face substantially higher odds of progression to malignancy as this observation underscores the practical importance of heritable risk in planning surveillance [11].

Genome-wide association studies (GWAS) examine millions of common genetic variants to identify small effect signals that together contribute to cancer susceptibility via polygenic inheritance [12]. Although hundreds of risk loci have been detected a large portion of heritability remains unexplained until newer methods target coding and regulatory regions thereby uncovering thousands of critical genes linked to core oncogenic pathways and even overlapping with somatic alterations [13]. Combining these discoveries with functional genomics now facilitates accurate risk prediction and early intervention strategies [13 12]. The present review therefore seeks to summarize progress and trends of GWAS in esophageal cancer.

Methods

This narrative review synthesizes evidence on inherited genetic risk factors for esophageal cancer, focusing on differences between esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) and the role of genome-wide association studies (GWAS) and other genomic methods in identifying heritable variants. Literature was collected through targeted searches in PubMed/MEDLINE, Embase, Web of Science, and Google Scholar using keywords and MeSH terms, supplemented by hand-searching reference lists, follow-up searches on emerging genes/regions, and selective inclusion of gray literature and conference abstracts. Articles were screened in two stages by a reviewer to confirm focus on germline variants, use of reliable methods, and statistical robustness. The synthesis was organized thematically, often chronologically within each subtype, with major findings from large consortia serving as the framework and smaller candidate-gene, regional, and trans-ancestry studies placed around them.

Results

Genome-wide association studies (GWAS) have uncovered numerous susceptibility loci for esophageal squamous cell carcinoma (ESCC) mainly in Chinese Han populations. The pioneering study by Wang et al. (2010) identified the first firmly established ESCC risk loci at 10q23 (PLCE1) and 20p13 (C20orf54) [18]. Larger subsequent GWAS quickly confirmed PLCE1 and revealed further loci including powerful alcohol- and aldehyde-metabolism signals at the ADH cluster and ALDH2 (especially rs671) with clear gene-environment interaction among East Asian alcohol consumers [19 21 35]. Later meta-analyses and combined analyses of Chinese datasets greatly expanded the catalog of credible risk loci highlighting immune pathways (HLA at 6p21 TMEM173) and additional genes such as CHEK2 and FAM120A [20 25 33]. A very recent trans-ancestry GWAS that included African cohorts validated PLCE1 as a shared risk locus while detecting African-specific variants as this finding emphasizes both universal and population-specific genetic contributions to ESCC [33].

By comparison GWAS advances in esophageal adenocarcinoma (EAC) and Barrett's esophagus have been driven by European-ancestry consortia. Levine et

al. (2013) reported the first EAC-specific loci near developmental transcription factors CRTC1 BARX1 and FOXP1 [22]. The large 2016 BEACON meta-analysis led by Gharahkhani et al. markedly boosted discovery by identifying eight new loci (e.g. CFTR MSRA BLK SATB2 HTR3C) implicated in mucosal barrier function oxidative stress and immune modulation [27]. Although fewer loci exist compared to high-risk ESCC populations these studies show that EAC shares genetic predisposition with its precursor Barrett's esophagus and reveal distinct etiologic pathways from ESCC despite overlapping environmental risks such as reflux and obesity (table 1).

Table 1. Key Genome-Wide Association Studies (GWAS) and Related Genomic Investigations in Esophageal Cancer (2005–2025)

Study ID	Year	Cancer Type	Method	Key Finding(s)	Top Genes / Loci	Population	Citation
Hu et al.	2005	ESCC	GWAS (Affymetrix 10K)	37–53 SNPs, new candidate regions	GASC1, EPHB1, PIK3C3	Chinese	[14]
Statnikov et al.	2007	Esophageal cancer	Re-analysis of early GWAS	No true genetic signal, highlights pitfalls	None	Not specified	[15]
Bass & Meyerson	2009	ESCC	Commentary	No primary data	–	–	[16]
Zheng et al.	2009	ESCC	SNP array + telomere Q-FISH	Telomere attrition → chromosomal instability	4q, 13q, 15q	Not specified	[17]
Wang et al.	2010	ESCC	GWAS + replication	2 new loci	PLCE1, C20orf54	Chinese Han	[18]
Wu et al.	2011	ESCC	GWAS + replication	7 loci, gene-lifestyle interactions	PLCE1, 12q24, 6p21	Chinese	[19]
Abnet et al.	2012	ESCC	GWAS meta-analysis	Locus at 2q33	CASP8/ALS2CR12 region	Chinese	[20]
Wu et al.	2012	ESCC	GWAS + gene-environment	9 new loci, strong alcohol/ALDH2 interaction	ADH cluster, ALDH2	Chinese	[21]
Levine et al.	2013	EAC + Barrett's	GWAS	3 new loci	CRTC1, BARX1, FOXP1	European	[22]
Wang et al.	2014	EC (mainly ESCC)	Review in GWAS era	Environmental + genetic risk factors reviewed	Multiple GWAS hits	Chinese	[23]
Cao et al.	2014	ESCC	lncRNA microarray	154 dysregulated lncRNAs	ESCCAL_1, HOTAIR	Chinese	[24]
Wu et al.	2014	ESCC	Joint analysis of 3 GWAS	2 new loci + HLA locus	TMEM173, ATP1B2, HLA	Chinese	[25]
Hoshimoto et al.	2015	ESCC	DNA methylation profiling	Hypermethylation prognostic	RASSF1, APC, RARB	Not specified	[26]
Gharahkhani et al.	2016	EAC + Barrett's	GWAS meta-analysis	8 new risk loci (+1 after reweighting)	CFTR, MSRA, BLK, SATB2, HTR3C etc.	European	[27]
Tian et al.	2019	EC/ESCC	Meta-analysis + GWAS	5 variants with strong evidence	PLCE1, CYP1A1, HOTAIR, EGF, MMP2	Mostly Asian	[28]
Wanchai et al.	2019	Barrett's/EAC	Topological domains + exome	Repetitive elements in domain boundaries	NOTCH, WNT pathways	Not specified	[29]
Yu et al.	2020	ESCC	RRBS on cancer stem cells	13 differentially methylated genes	OTX1, ST8SIA2, GRM1, CADM3 etc.	Chinese	[30]
Xu et al.	2021	Esophageal cancer	lncRNA expression	Key regulatory lncRNAs in metastasis	Not listed	Not specified	[31]
Gehlen et al.	2022	Esophageal atresia	GWAS	3 risk loci identified	CTNNA3, FOXF1 cluster, HNF1B	European	[32]
Chen et al.	2023	ESCC	GWAS (African + trans-ancestry)	African-specific + shared loci	FAM120A, PLCE1, CHEK2, MYO1B	African + Chinese	[33]
van den Ende et al.	2023	EAC (resectable)	ctDNA + shallow WGS	Multi-signal ctDNA predicts progression	Tumor fraction + specific mutations	European	[34]
Koyanagi et al.	2024	Alcohol-related ESCC	Genotype-stratified GWAS	ALDH2 rs671 interaction loci	GCKR, KLB, ADH1B, ALDH2	Japanese	[35]
Sun et al.	2025	EC	RNA-binding protein signature	7-RBP prognostic signature	TRMT2A, PDHA1, MPRIP etc.	TCGA (mixed)	[36]

EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, EAC = esophageal adenocarcinoma, GWAS = genome-wide association study, ctDNA = circulating tumor DNA, CSCs = cancer stem cells, RRBS = reduced representation bisulfite sequencing.

Esophageal cancer genetics show two distinct patterns (as shown in figure 1): in squamous cell carcinoma, large-scale genomic studies consistently reveal multiple risk loci concentrated in East Asian populations, with strong contributions from genes involved in alcohol and aldehyde metabolism, immune regulation, and environmental interactions, alongside both shared and population-specific variants identified through broader trans-ancestry analyses. In contrast, adenocarcinoma research led in European cohorts

highlights susceptibility regions linked to developmental transcription factors, mucosal integrity, oxidative stress response, and immune pathways, with substantial overlap between adenocarcinoma and Barrett's esophagus. Together, these findings indicate that while both cancer types share some environmental risks, their inherited predisposition reflects fundamentally different biological mechanisms.

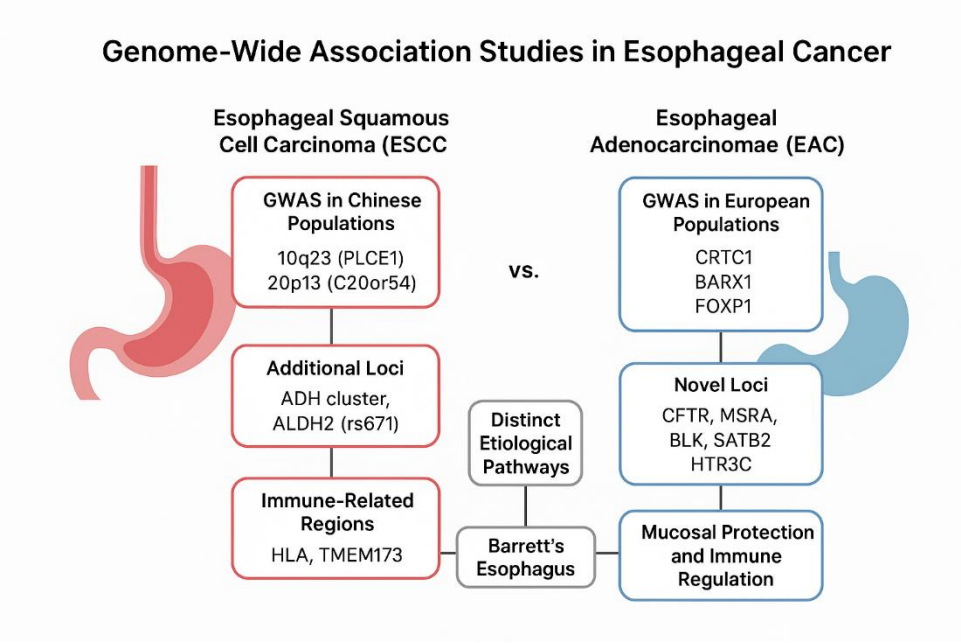

Figure 1. summary of evidence gathered in our review

Discussion

Our study provides a comprehensive synthesis of two decades of GWAS data, revealing that esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC)/Barrett's esophagus exhibit fundamentally distinct heritable architectures, a finding that aligns with the disparate environmental and lifestyle triggers driving these diseases. While acknowledging the urgent need for genetic biomarkers in Barrett's esophagus (BE) and EAC susceptibility and progression, as highlighted by Findlay et al. who identified 17 germline markers (level of evidence II-III) and five somatic markers of progression for BE through systematic review and meta-analysis [38], the genetic landscape of BE itself remains complex. Our work supports this by implicitly recognizing that genetic susceptibility contributes to BE, given its strong association with EAC and the identification of shared loci like PLCE1. Furthermore, the concept of polygenic risk scores (PRS) integrating subtype-specific GWAS hits, as championed by our review, offers a pathway towards personalized risk assessment; this approach is particularly relevant for BE/EAC, where Mendelian randomization studies, like those summarized by Huang et al., have begun to uncover potential causal genetic risk factors for EAC, including associations with body mass index, smoking, and type 2 diabetes mellitus [39]. However, despite the wealth of data now available, translating these genetic findings into robust clinical practice for EAC surveillance, potentially de-emphasizing intensive screening for high-risk individuals identified through genetic means as Callahan et al. suggest is needed, remains a significant challenge, largely due to the relative scarcity of established genetic loci for EAC compared to ESCC and the need for further validation [40]. This stark contrast in genetic underpinning between ESCC, with over 30 established risk loci heavily influenced by East Asian ancestry, and EAC/BE, which relies on a smaller number of loci often identified through European consortia, underscores the necessity for tailored genetic epidemiological studies and trans-ancestry analyses to fully capture the global burden of these distinct esophageal malignancies.

Conclusion

In conclusion, genome-wide analyses have substantially advanced our understanding of esophageal cancer genetics, revealing distinct susceptibility landscapes for squamous cell carcinoma and adenocarcinoma. ESCC is strongly influenced by population-specific loci, gene-environment interactions, and metabolic and immune pathways, particularly in East Asian populations, whereas EAC exhibits risk variants related to mucosal protection, developmental

regulation, and oxidative stress, mainly in European populations. These insights underscore the heterogeneity of esophageal cancer etiology and the importance of integrating genetic, environmental, and lifestyle factors for risk assessment and potential prevention strategies.

However, several limitations remain. Most studies are biased toward specific populations, limiting generalizability across ancestries. Sample sizes for some analyses, especially trans-ancestry and African cohorts, remain modest, reducing statistical power. Additionally, many identified loci have unclear functional consequences, and gene-environment interactions beyond alcohol, smoking, and reflux remain underexplored. Finally, integration with epigenetic, transcriptomic, and proteomic data is still limited, constraining the translation of genetic findings into mechanistic understanding and clinical applications.

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