SYSTEMATIC REVIEW

The Effect of E-cigarette on the Role of Genetics Changes and Epigenetics Alterations: A Systematic Review of Recent Studies

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ABSTRACT

Introduction: With the rapid increasing prevalence of electronic cigarette (e-cigarette) use, its impact on human health particularly genetic and epigenetic modifications remains a public health concern. This study aims to examines the evidence on genetic and epigenetic changes associated with e-cigarette use. **Materials and methods:** This systematic review followed the PRISMA guidelines and was registered with PROSPERO (CRD42024603820). Databases including ScienceDirect, Scopus, PubMed, Web of Science, and ProQuest were used for literature search by using keywords related to e-cigarettes, genetics, and epigenetics. Articles published since 2014 and in English, with human participants reporting e-cigarette use, were included. Studies that solely focused on traditional cigarettes, animal models, microbial, in vitro, or non-research articles were excluded. A total of 1,475 records were initially identified, 19 of which met the inclusion criteria after screening. **Results:** Nineteen studies, predominantly comparative observational studies, were included, encompassing over 22,779 participants from multiple countries, including the United Kingdom, the USA, and Germany. Studies involved a variety of e-cigarette exposure statuses (current, former, or dual use) and utilized markers like DNA methylation, gene expression, and epigenetic aging to assess biological impacts. Findings showed notable genetic and epigenetic modifications among e-cigarette users, including DNA methylation patterns, altered gene expression, and changes in epigenetic aging, potentially implicating these alterations in disease risk. **Conclusion:** E-cigarette use is associated with measurable genetic and epigenetic changes that may contribute to adverse health outcomes. This review highlights the importance of further research to understand the long-term health implications of these molecular alterations in e-cigarette users, potentially informing public health guidelines.
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Keywords: E-cigarette, Vaping, Genetic changes, Gene expression, Biomarkers

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INTRODUCTION

Electronic cigarettes (e-cigarettes), sometimes referred to as 'vapes', 'e-hookahs', 'vape pens', have become increasingly popularity among new generations as an alternative to traditional cigarette smoking (1). E-cigarettes battery powered devices that heat and vaporize a solution typically containing glycerol, propylene glycol, water, flavors, and varying concentrations of nicotine (2). Initially marketed as a safer alternative to traditional cigarettes, e-cigarettes have become socially well-accepted and widely used, particularly among young individuals. Despite their perceived safety, emerging evidence suggests that e-cigarettes may have significant health effects including genetic and epigenetic impacts.

In the recent years, e-cigarettes have surpassed traditional combustible cigarettes as the most popular tobacco product in many countries (3). According to a prediction study, tobacco-related deaths are predicted to treble globally by 2030, particularly in low- and middle-income nations (4). It is commonly known that smoking traditional cigarettes increases the chance of developing cancer, heart disease, chronic respiratory conditions, and problems with the reproductive system. These adverse health effects are largely attributed to the noxious substances released during the combustion of tobacco, which cause genome damage and alter the transcriptome. In contrast, e-cigarettes do not involve combustion, leading to the assumption that they are less harmful. Due to this perception, the prevalence of e-cigarette user is increasing rapidly. Since 2014, e-cigarette has been most popular used tobacco products among youth, middle and high school students, and also other adult groups (3,5). E-cigarette usage continues to rise despite ongoing debates about its benefits and harms. Sales are projected to grow significantly, from

$7.4 billion in 2021 to $40 billion by 2028 only in USA (6). E-cigarette use has risen notably among young adults and high school students, raising concerns about its growing prevalence in vulnerable age groups, though they may potentially reduce harm and aid in cigarette cessation (7). However, recent studies showed that the e-cigarettes contain various toxic substances such as nicotine, ultrafine particulate matter, flavoring agents, volatile organic compounds, and heavy metals (8). These harmful substances can cause similar cellular damage and other health toxicity.

It has been demonstrated that e-cigarettes cause inflammation and oxidative stress, which alters gene expression. For instance, pulmonary and oral epithelial cells' DNA has been linked to exposure to e-cigarette aerosol (9). In general, genes are responsible for producing important proteins that run everything in animal body including immunity, metabolism, signal transduction, apoptosis, transportation, coagulation, and proliferation. These proteins have been shown to be up- and down-regulated following exposure to carcinogens from e-cigarettes (10,11). Additionally, e-cigarettes can alter the expression of genes involved in the immune response and circadian clock regulation. These genetic changes may contribute to the development of various diseases, including cancer (11).

Epigenetic is the study of heritable changes in gene expression without altering DNA sequences, primarily through DNA methylation, histone modifications, and noncoding RNA expression (12). Different forms of epigenetic alterations, such as DNA methylation and histone modifications, have also been observed in e-cigarette users. For example, a significant decrease in DNA methylation levels in long interspersed nucleotide element 1 (LINE-1) regions has been reported in e-cigarette users, suggesting a potential link to genomic instability and cancer risk (13). Furthermore, e-cigarette exposure has been shown to deregulate the expression of numerous microRNAs (miRNAs), which play crucial roles in gene regulation.

Given the increasing prevalence of e-cigarette use and the potential health risks associated with genetic and epigenetic alterations, it is crucial to systematically review the recent studies on this topic. This systematic review aims to provide a comprehensive overview of the current evidence on the genetic and epigenetic impacts of e-cigarettes, highlighting the mechanisms underlying these changes and their potential health implications. This study provides a comprehensive understanding of the genetic and epigenetic impacts of e-cigarette usage, filling a significant knowledge gap in the rapidly developing field of vaping research. By synthesizing findings from several studies, it provides valuable insights into potential health risks and biomarkers of harm, which can be used to inform public health policies and campaigns. Furthermore, the review highlights research priorities and encourages the development of targeted strategies to reduce the negative effects of e-cigarette use.

MATERIALS AND METHODS

Study Protocol and Registration

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A study protocol was developed prior to conducting the review and can be requested from the corresponding authors. The protocol was registered with PROSPERO, the International Prospective Register of Systematic Reviews at the University of York, in October 2024 (registration number CRD42024603820). This study aimed to inform researchers and e-cigarette users by addressing the research question: "What is the impact of electronic cigarette use (vaping) on genetic and epigenetic changes?"

Search Strategy

This study depends on peer-reviewed original research articles published in international journals to find the answer of research question. To obtain the target articles, we performed literature search in several databases such as ScienceDirect, Scopus, PubMed, Web of Science, and ProQuest. The relevant article was search by using relevant keywords or MeSH terms such as "Electronic cigarettes", "e-cigarette", "vape", "e-hookah", "electronic nicotine", "nicotine end", "Electronic Nicotine Delivery Systems"[Majr], "Vaping"[Mesh], "Genetic", "genomic", "Epigenomics"[Mesh], "Epigenesis, Genetic"[Mesh], "Gene Expression"[Mesh], etc. Search strategy also employed combinations of all the prospective keywords by using Boolen operators to search in different databases (Table I). A manual search also conducted through citation and references to check potential articles. The last search was conducted on October 10, 2024.

Table I: Search strategy used in this systematic review

Database	Search strategy	Filter	Records
ScienceDirect	#1 ("Electronic cigarettes" OR "e-cigarette" OR Vaping) AND (Genetic OR Epigenetic OR mutation OR genomic OR "DNA methylation" OR "gene expression") #2 ("electronic nicotine delivery system" OR ENDS OR vape) AND (Genetic OR Epigenetic OR mutation OR genomic OR "DNA methylation" OR "gene expression") #3 ("personal vaporizer" OR "e-hookah" OR "tobacco products") AND (Genetic OR Epigenetic OR mutation OR genomic OR "DNA methylation" OR "gene expression") #4 nicotine AND (Genetic OR Epigenetic OR mutation OR genomic OR "DNA methylation" OR "gene expression")	Search in Title, 2014-2025 Research article	124

CONTINUE

Table I: Search strategy used in this systematic review (CONT.)

Database	Search strategy	Filter	Records
PubMed	#1 ((((((“Electronic cigarettes” OR “e-cigarette”) OR vape) OR “e-hookah”) OR “electronic nicotine”) OR “nicotine end”) OR “Electronic Nicotine Delivery Systems”[Majr]) OR “Vaping”[Mesh] #2 (((Genetic OR genomic) OR “Epigenomics”[Mesh]) OR “Epigenesis, Genetic”[Mesh]) OR “Gene Expression”[Mesh] #1 AND #2	2014-2024 Full Text English	421
Web of Science	(“Electronic cigarettes” OR “e-cigarette” OR Vaping OR “electronic nicotine delivery system” OR ENDS OR vape OR “personal vaporizer” OR “e-hookah” OR “tobacco products” OR “electronic nicotine” OR “nicotine end”) AND (Genetic OR Epigenetic OR mutation OR genomic OR “DNA methylation” OR “gene expression”)	Search in Title 2014-2025 Article English	360
SCOPUS	(“Electronic cigarettes” OR “e-cigarette” OR Vaping OR “electronic nicotine delivery system” OR ENDS OR vape OR “personal vaporizer” OR “e-hookah” OR “tobacco products” OR “electronic nicotine” OR “nicotine end”) AND (Genetic OR Epigenetic OR mutation OR genomic OR “DNA methylation” OR “gene expression”) TITLE ((“Electronic cigarettes” OR “e-cigarette” OR vaping OR “electronic nicotine delivery system” OR ends OR vape OR “personal vaporizer” OR “e-hookah” OR “tobacco products” OR “electronic nicotine” OR “nicotine end”) AND (genetic OR epigenetic OR mutation OR genomic OR “DNA methylation” OR “gene expression”)) AND PUBYEAR > 2013 AND PUBYEAR < 2026 AND (LIMIT-TO (DOCTYPE , “ar”)) AND (LIMIT-TO (LANGUAGE , “English”))	Search in Article Title 2014-2025 Article English	373
ProQuest	(“Electronic cigarettes” OR “e-cigarette” OR Vaping OR vape OR “electronic nicotine”) AND (Genetic OR Epigenetic OR genomic OR “gene expression”)	2014-2025 Article English	197

Inclusion and Exclusion Criteria

The records included in this study were based on several inclusion criteria as shown below in Table II. Records were considered ineligible based on exclusion criteria. Generally, we searched for studies involving human participants of any age or gender exposed to electronic cigarette and it contributed to any genetic or epigenetic changes in human body.

Table II: The study selection criterion for this systematic review

Inclusion criteria	Exclusion criteria
Original research article	Review, editorial, perspective and any other article except original research
Published since 2014	Published before 2014
Reported E-cigarette or vaping use status: (current use, ever use, former e-cigarette status)	Reported traditional cigarette smoking only or any other tobacco product without reporting the e-cigarette, or nicotine product only
Reported any of outcome of genetic and epigenetic changes	No report of any of the genetic/genomic outcomes
Human studies	Animal studies, microbial studies, in vitro studies
Studies reported in English language	Studies reported in a language other than the English Language
Availability of full paper	Unavailability of full paper

Identification of Relevant Study

Two reviewers were carried out the screening process independently to evaluate the eligibility of records. In the first phase, title and abstract of all records have been screened to select potential records for full paper screening. After that the full paper in PDF format were retrieved. The PDF of full paper used for screening at second phase. At this stage, records that did not meet the inclusion and exclusion criteria were removed. The entire process of record identification, screening, and eligibility evaluation was independently conducted by two reviewers using a blinded and standardized approach. Any disagreements or uncertainties regarding the inclusion of a study were resolved through discussion, and, when necessary, a third reviewer was consulted to make the final decision. Additionally, the final selection was rechecked by other team members to ensure accuracy and consistency.

Data Extraction

The data extraction and collection started after the screening processes. Data were extracted from finally included studies by using a structured data extraction form in Excel sheet containing several information including authors, publication year, article title, study design, population, sample size, study location, age, gender, exposure or e-cigarette type, study topic or research objectives, tissue or body parts used for analysis, gene used in investigation, epigenetic alteration, any biomarkers effect, and study findings.

Summary Measure

This study provides a synthesis of the research findings from the included studies: structured about the individual study characteristics and main findings regarding the genetic or epigenetic changes due to e-cigarette.

RESULTS

Reporting to the Study Selection

The primary literature search from five different databased retrieved 1475 records, 1047 of which remined for screening process after removing the duplicates (428 records). During the first phase of screening, titles and abstract screening, 986 records were excluded due to not matching with the study interest or research question. Then the remaining 61 records were retrieved for full paper (PDF) download. In addition, 2 records were

retrieved through manual search. During the second phase of screening, total 63 records were allowed for detailed review to check the eligibility criteria. During the eligibility check phase, a total of 44 records were removed due to the inability to fulfil the inclusion criteria. Among the excluded records, 10 records were unmatched exposure, 13 records were in vitro or in silico study, 17 records were animal study, 2 records were microbial study, and study type was unmatched for 2 records. Following the database literature search and screening process based on PRISMA guidelines, a total of 19 studies were ultimately included in this review study (Figure I).

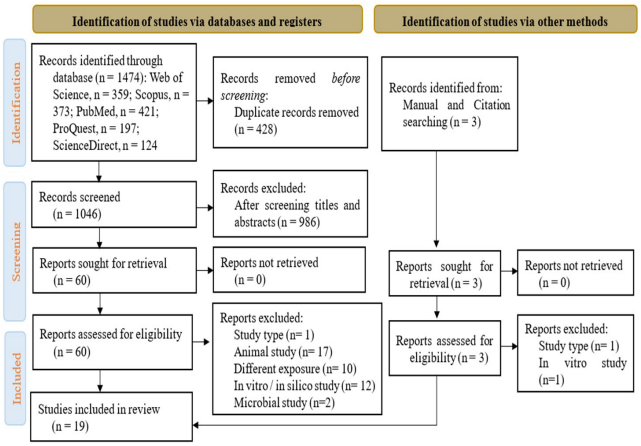

Figure 1: Flow diagram of the PRISMA guideline for the study selection

Overview of the Included Studies

The general characteristics of the included studies have been reported in Table III. Most of the studies were comparative observational study or COS (14 studies) and other study design included pilot comparative observational study, cohort study, longitudinal cohort study, cross-sectional study, and prospective observational cross-sectional study. The selected studies were from several countries including Colombia, Czech Republic, Germany, Italy, Norway, Poland, UK, and SA. The target study population was e-cigarette users and other tobacco cigarette users or non-smokers were as for comparison. From the available data, there were more than 22,779 samples were included in those studies. Among the participants, there were diverse age group mainly adults and from both male and females.

Genetic changes and epigenetic alterations associated with electronic cigarette use

The research findings from the relevant studies included in this review are summarized in Table IV. Recent studies reveal that using electronic cigarette (e-cigarette) is linked with distinct patterns of genetic and epigenetic modifications, suggesting potential long-term health impacts and mechanistic insights into vaping-related cellular changes. The primary mechanisms explored include DNA methylation, gene expression variations, and polymorphisms in genes related to addiction and inflammatory responses.

Table III: Characteristics of literatures included in this review study

Author, year	Study design	Population	Sample size	Study area	Age and gender	Study topic
Richmond et al. 2021 (14)	COS	Vapers, smokers, non-smokers	350 participants (117 smokers, 117 non-smokers, 116 vapers)	United Kingdom	Age: 16-35 years Gender: Not specified	Investigate the DNA methylation profile of e-cigarette use
Herzog et al. 2024 (15)	COS	E-cigarette users, smokers, non-smokers	Over 3,500 samples	Norway, United Kingdom, Czech Republic, Italy, Germany	Age: 18-86 years Gender: Not specified	Investigate the cell- and tissue-specific epigenetic effects of e-cigarette use on DNA methylation
Andersen et al. 2022 (16)	COS	E-cigarette users, smokers, smokeless tobacco users, and controls	435 participants (112 smokers, 35 e-cigarette users, 19 smokeless tobacco users, 269 controls)	Not specified	Age and gender: Not specified	Determine whether a combination of methylomic and metabolite profiling can accurately classify the use status of various nicotine-containing products
Corbett et al. 2019 (17)	COS	Current tobacco cigarette smokers, current e-cigarette users (former tobacco cigarette smokers), and former tobacco cigarette smokers	45 participants (9 current tobacco cigarette smokers, 15 current e-cigarette users who are former tobacco cigarette smokers, 21 former tobacco cigarette smokers)	USA	Age: 18-55 years Gender: Not specified	Compare bronchial airway gene expression in former tobacco smokers now using e-cigarettes with that of former and current tobacco smokers
Davis et al. 2022 (18)	COS	E-cigarette users, never-smokers, smokers	41 participants (17 nonsmokers, 13 smokers, 11 vapers)	USA	Age and gender: Not specified	Impact of vaping on gene expression and alveolar macrophage phenotype

CONTINUE

Table III: Characteristics of literatures included in this review study (CONT.)

Author, year	Study design	Population	Sample size	Study area	Age and gender	Study topic
Grzywacz et al. 2020 (19)	COS	E-cigarette users and controls	394 volunteers (144 e-cigarette users and 250 controls)	Poland	Age: E-cig users 26.82 ± 9.26 years; Controls 21.84 ± 3.98 years Gender: Not specified	Impact of genetic and personality factors on e-cigarette usage
Khouja et al. 2021 (20)	Cohort study	Young adults of European ancestry	7,859 young adults	United Kingdom	Mean age of 24 years Gender: Not specified	Examine if polygenic risk scores (PRS) for smoking initiation are linked to e-cigarette use
Song et al. 2023 (21)	COS	Young adults aged 21-30 years, including electronic cigarette vapers, smokers, and non-smokers	69 participants (14 vapers, 16 smokers, 39 non-smokers)	USA	Age: 21-30 years Gender: Not specified	Effects of smoking and vaping on lung epigenetic aging, inflammation, and gene expression
Camila et al. 2023 (13)	COS	Vapers, smokers, and non-smokers	90 subjects (32 vapers, 18 smokers, 32 non-smokers)	Colombia	Age: Vapers 23 (18-59 years), Smokers 24 (19-65 years), Controls 22 (18-59 years) Gender: Not specified	Assess genotoxicity levels and DNA methylation changes linked to vaping
Suchanecka et al. 2022 (22)	COS	E-cigarette users and controls	135 e-cigarette users and 106 controls	Poland	Age: E-cigarette users 26 ± 9.44 years, Controls 23.79 ± 8.72 years Gender: Not specified	Examine the impact of HTR3A gene polymorphisms and personality traits on nicotine dependence in e-cigarette users
Cooke et al. 2022 (23)	Data from longitudinal cohort study	College-aged young adults	9,541 young adults	USA	Age: College-aged (specific age range not provided) Gender: Not specified	Evaluate if genetic risk for combustible cigarette frequency relates to e-cigarette initiation or usage
Tommasi et al. 2021 (24)	COS	Healthy adult vapers, exclusive cigarette smokers, and controls (non-users of any tobacco products)	37 vapers, 22 smokers, and 23 controls	USA	Age: Adults Gender: Not specified	Analyze global gene expression and functional pathways in vapers' peripheral blood leukocytes
Mori et al. 2022 (25)	Cross-sectional study	Smokers, electronic cigarette users, and never-smokers.	84 participants (26 smokers, 15 electronic cigarette users, 43 never-smokers)	USA	Age: 21-30 years Gender: Not specified	Investigate lung mitochondrial DNA copy number and related mutations, immune responses, DNA methylation, and gene expression across e-cig users, smokers, and non-smokers
Singh et al. 2022 (26)	COS	E-cigarette users cigarette smokers, waterpipe smokers, dual smokers (cigarette & waterpipe), and non-smokers	Not specified	USA	Age and gender: Not specified	Compare plasma exosomal microRNAs among e-cig users, waterpipe and dual smokers, and cigarette smokers versus non-smokers
Martin et al. 2016(27)	Prospective, observational cross-sectional study	Nonsmokers, cigarette smokers, and e-cigarette users	39 individuals (13 nonsmokers, 14 cigarette smokers, 12 e-cigarette users).	USA	Age: 18-50 years Gender: Not specified	Examine e-cigarette effects on respiratory immune responses via nasal epithelial cell gene expression
Hamad et al. 2021 (11)	Pilot COS	E-cigarette users	3 individuals, each analyzed three times before and after exposure.	USA	Age and gender: Not specified	Identify genes involved in DNA damage and cancer as potential biomarkers of e-cigarette aerosol exposure
Kaur et al. 2020 (28)	COS	Non-smokers, cigarette smokers, E-cigarette users, waterpipe smokers, and dual smokers	6-8 subjects per group	USA	Age: 18-65 years Gender: Not specified	Explore plasma exosomal lncRNA content in tobacco users to find biomarkers relevant to lung health

CONTINUE

Table III: Characteristics of literatures included in this review study (CONT.)

Author, year	Study design	Population	Sample size	Study area	Age and gender	Study topic
Tommasi et al. 2019 (29)	COS	Exclusive e-cigarette users, cigarette smokers, and non-smokers	42 e-cig users, 24 cigarette smokers, and 27 non-smokers.	USA	Age: 22-55 years Gender: Not specified	Investigate deregulated genes and pathways in the oral epithelium of e-cigarette users
Caliri et al. 2020 (30)	COS	Exclusive e-cigarette users, cigarette smokers, and non-smokers	45 subjects (15 per group)	USA	Age: Vapers 22-43 years, Smokers 23-46 years, Controls 22-47 years Gender: Not specified	Analyze epigenetic changes associated with vaping through LINE-1 DNA methylation and global DNA hydroxymethylation

Note: COS = Comparative observational study

Table IV: Literature on genetic changes, epigenetic alterations, and any biomarker effect related to electronic cigarette use

Tissue	Gene	Epigenetic	Biomarkers	Results/effects	Reference
Saliva	Various CpG sites, including those in RPP14, IGF1R, and GABRP	DNA methylation	Not specified	DNA methylation profiles differ significantly between e-cigarette users and cigarette smokers. While smokers showed an enrichment of smoking-related CpGs, vapers did not. Methylation scores linked to smoking and biological aging were comparable between vapers and non-smokers but higher in smokers	(14)
Buccal/saliva, cervical, and blood samples	Various genes, including NOTCH1 and RUNX3	DNA methylation	DNA methylation loci (CpGs)	Both smoking and vaping impact cell-specific epigenetic markers predictive of carcinogenesis. Smokers and vapers exhibited hypermethylation in buccal epithelial cells tied to cancer pathways	(15)
Blood and urine samples	AHRR gene (cg05575921)	DNA methylation	Serum cotinine, urinary CEMA, anabasine, and propylene glycol	Smoking was linked to dose-dependent demethylation of cg05575921 and elevated CEMA and anabasine levels, while e-cigarettes did not affect cg05575921. Methylomic and metabolite profiling may distinguish nicotine product use	(16)
Bronchial epithelial cells.	3,165 genes whose expression varied between the three study groups, including 468 genes altered in e-cigarette users relative to former smokers	Not specified	Not specified	E-cigarettes cause distinct and overlapping gene expression changes in the bronchial airway epithelium, with evidence suggesting these changes may result directly from e-cigarette exposure	(17)
Alveolar macrophages from bronchoalveolar lavage fluid and epithelial cells from bronchial brushings.	Various genes, including those involved in immune response and inflammation	Not specified	Inducible nitric oxide synthase (iNOS), CD301a	Vapers' alveolar macrophages show increased iNOS and reduced CD301a expression compared to nonsmokers or smokers. They also exhibit unique gene expression changes, with 124 genes downregulated specifically in vapers	(18)
Venous blood	DRD2 gene polymorphisms (rs1076560, rs1799732, rs1079597)	Not specified	Not specified	E-cigarette users scored higher on neuroticism, openness, and STAI scales, and DRD2 polymorphisms indicated that genetic and psychological traits influence vaping	(19)
Not applicable (genetic study)	Polygenic risk scores (PRS) for smoking initiation	Not specified	Not specified	A shared genetic risk between smoking and vaping was noted, with a 24% higher likelihood of e-cigarette use among those genetically predisposed to smoking	(20)
Lung tissue	Various genes, including those involved in immune-related pathways and cell morphology	DNA methylation age (mAge) and its acceleration (mAA)	Inflammatory cytokines (IL-1β, IL-6, IL-8)	Both smokers and vapers experienced accelerated lung epigenetic aging, with a correlation between vaping frequency and Horvath-mAA. Inflammatory cytokines IL-1β, IL-6, and IL-8 were associated with Grim-mAA, suggesting adverse pulmonary aging effects from vaping	(21)
Peripheral blood	LINE-1	DNA methylation	Not specified	Vaping is associated with higher genotoxicity levels and epigenetic changes, notably reduced methylation in LINE-1 elements	(13)

CONTINUE

Table IV: Literature on genetic changes, epigenetic alterations, and any biomarker effect related to electronic cigarette use (CONT.)

Tissue	Gene	Epigenetic	Biomarkers	Results/effects	Reference
Venous blood	HTR3A gene polymorphisms rs1985242 and rs1062613	Not specified	Not specified	E-cigarette users score higher in neuroticism and lower in extraversion and conscientiousness than controls. Homozygote variants of rs1985242 are more common, suggesting combined psychological and genetic factors in substance use disorders	(22)
Not applicable (genetic study)	Polygenic scores (PGS) for regular combustible cigarette use (PGS-RCU) and cigarettes per day (PGS-CPD)	Not specified	Not specified	PGS-RCU was linked to lifetime e-cigarette use in European ancestry samples, but not in other groups	(23)
Peripheral blood leukocytes	Various genes, including mitochondrial genes and immune response genes	Not specified	Not specified	Vaping, unlike past smoking, is linked to gene dysregulation, particularly in mitochondrial and immune-related genes. Dysregulation is present in both vapers and smokers but more pronounced in smokers	(24)
Lung epithelial cells.	mtND1, mtND2, mtCO1, mtCO2.	DNA methylation (71,487 CpGs)	Inflammatory biomarkers (IL-2, IL-4, neutrophils)	Smokers have higher mtDNA copy numbers than non-smokers, with e-cigarette users in between. Only e-cigarette users show positive associations of mtDNA with IL-2 and IL-4, linking mtDNA changes to lung toxicity risks	(25)
Blood plasma	Various microRNAs, including hsa-let-7a-5p, hsa-miR-21-5p, hsa-miR-29b-3p, hsa-let-7f-5p, hsa-miR-143-3p, hsa-miR-30a-5p, and hsa-let-7i-5p	Not specified	Exosomal microRNAs	Plasma exosomes from cigarette, waterpipe, e-cig users, and dual smokers had distinct microRNA profiles, with hsa-let-7a-5p effectively distinguishing non-smokers from users	(26)
Nasal epithelial cells	Various immune-related genes, including EGR1, DPP4, CXCL2, CX3CR1, and CD82	Not specified	Not specified	Both smoking and vaping reduce immune-related gene expression in nasal cells, with e-cigarette users showing a greater suppression, indicating possible immune suppression in nasal mucosa	(27)
Blood and buccal samples.	Genes involved in DNA repair, cell cycle, and cancer.	Not specified	Potential biomarkers of exposure to e-cigarette aerosols	E-cigarette exposure leads to differential expression in genes related to DNA repair, cell cycle, and cancer	(11)
Blood plasma	Various long non-coding RNAs (lncRNAs)	Not specified	Exosomal lncRNAs.	Exposure to e-cig vapor, cigarette smoke, waterpipe smoke, or dual smoke alters distinct sets of lncRNAs, with overlaps in pathways related to steroid metabolism, cell differentiation, and proliferation	(28)
oral epithelial cells	Various genes involved in critical biological processes	Not specified	Not specified	Key genes and molecular pathways are deregulated in the oral epithelium of vapers, with similarities and differences compared to smokers and nonsmokers	(29)
Peripheral blood leukocytes	DNA methyltransferases (DNMT1, DNMT3A, DNMT3B) and ten-eleven translocation (TET1, TET2, TET3) enzymes	DNA methylation and hydroxymethylation.	Not specified	Both vapers and smokers showed significant LINE-1 methylation loss and reduced global 5-hmC levels, with minor changes in DNA methyltransferase and TET enzyme transcription compared to controls	(30)

Multiple studies have identified changes in DNA methylation among e-cigarette users, often contrasting with traditional smokers. Richmond et al. (2021) found that e-cigarette use resulted in a distinct DNA methylation profile in saliva samples, particularly at CpG sites in genes such as RPP14 and IGF1R, which differed notably from those seen in cigarette smokers (14). Herzog et al. (2024) further noted cell- and tissue-specific DNA methylation alterations in buccal, cervical, and blood samples, with hypermethylation patterns linked to carcinogenesis in buccal epithelial cells of both smokers and vapers (15).

Andersen et al. (2022) found that while cigarette smoking demethylated the AHRR gene at cg05575921 in blood and urine samples, e-cigarette use did not induce this demethylation, indicating potentially distinct biochemical effects on this specific marker (16). The relationship between e-cigarette use and distinct DNA methylation profiles was further supported by Camila et al. (2023), who showed a decrease of methylation in LINE-1 regions in the blood of e-cigarette users (13).

Changes in gene expression, particularly in respiratory tissues, are another hallmark of e-cigarette use. Corbett et al. (2019) observed that former cigarette smokers who transitioned to e-cigarettes showed altered bronchial airway gene-expression profiles, with distinct expression patterns compared to both former and current cigarette smokers (17). In alveolar macrophages and bronchial epithelial cells, Davis et al. (2022) identified specific genes linked to immune response, such as elevated iNOS expression and reduced CD301a in e-cigarette users, suggesting an immune-modulatory effect of vaping (18).

Additionally, studies like Tommasi et al. (2021) noted significant dysregulation in gene networks associated with mitochondrial function and immune response in vapers' blood samples, reflecting both unique and overlapping patterns with cigarette smokers (24). This dysregulation might contribute to oxidative stress and immune suppression associated with e-cigarette exposure.

Several studies focused on genetic predispositions to nicotine use via e-cigarettes. Khouja et al. (2021) found that polygenic risk scores (PRS) for smoking start were significantly associated with increased likelihood of e-cigarette use, suggesting a genetic overlap between e-cigarette use and susceptibility to smoking (20). Similarly, Grzywacz et al. (2020) identified polymorphisms in the DRD2 gene in e-cigarette users, implicating both genetic and psychological factors in the use of e-cigarettes (19).

Emerging evidence suggests a link between e-cigarette use and accelerated biological aging and inflammation. Song et al. (2023) observed that both smokers and vapers exhibited accelerated lung epigenetic aging, with e-cigarette users demonstrating correlations between vaping frequency and DNA methylation age acceleration (21). Similarly, inflammatory biomarkers, such as IL-1β, IL-6, and IL-8, were elevated in e-cigarette users, indicating increased inflammatory responses.

DISCUSSION

This systematic review synthesized evidence on the genetic and epigenetic impacts of electronic cigarette (e-cigarette) use, revealing multiple biological alterations associated with vaping. E-cigarette users exhibited DNA methylation changes, differential gene expression, and alterations in epigenetic markers, with certain findings paralleling those observed in traditional cigarette smokers. Most studies showed that e-cigarette use might trigger changes in specific genes linked to inflammatory responses, cellular repair mechanisms, and metabolic pathways, and impairs fetal brain development by AT2R (angiotensin II receptor type 2) gene repression (31). The similarities in some biomarkers between smokers and vapers may imply overlapping risks, albeit with differences in intensity and affected biological pathways.

There are several studies on animal and in vitro studies also indicates the effect of e-cigarettes on genetic and epigenetic changes. Study of Hung et al. (2020) showed that certain flavor compounds and ingredients in tobacco products exhibited genetic toxicity in both in vitro and in silico assays (32). According to another study, e-cigarette smoke solution causes major transcriptome alterations in primary human airway epithelial cells, including those pertaining to translation and ribosomal proteins, impacts rRNA transcription, and reduces the synthesis of new proteins (33). Both traditional smoke and e-cigarette smoke may enhance chromosomal abnormalities at important locations and decrease DNA methylation, which in turn may upregulate oncogenic eRNAs and downregulate tumor-suppressing eRNAs. By changing their interactions with immune cells, these eRNAs may increase the pathophysiology of LUSCs and decrease patient survival (34).

These findings contribute to an expanding evidence of literature suggesting that, while e-cigarettes are often promoted as a safer alternative to traditional cigarettes, they still pose genetic and epigenetic risks. Prior studies on traditional cigarettes have consistently shown significant associations with genetic mutations and epigenetic modifications that contribute to the pathogenesis of cancer, cardiovascular, and respiratory diseases (35). This review indicates that while the profile of changes may differ slightly, vaping similarly impacts DNA methylation and gene expression—changes that could elevate health risks. Such effects raise questions about the underlying mechanisms by which nicotine and other e-cigarette components impact genetic stability and health.

The genetic and epigenetic modifications identified in this review suggest potential health consequences. Changes in DNA methylation, particularly in genes regulating immune responses and cellular repair, could predispose e-cigarette users to increased inflammation and compromised immune defenses. Alterations in gene expression related to lung and cardiovascular function may increase susceptibility to conditions such as chronic obstructive pulmonary disease (COPD) and heart disease (36). Notably, the accelerated epigenetic aging observed in some studies might serve as an early indicator of premature disease onset, highlighting a possible need for genetic monitoring among e-cigarette users.

Several studies included in this review highlight the role of biomarkers in understanding the impact of e-cigarette use on genetic and epigenetic changes. For example, plasma-derived exosomal microRNAs were identified as potential biomarkers for assessing pulmonary pathologies in e-cigarette users (26). Similarly, changes in DNA methylation levels and epigenetic markers, such as LINE-1 methylation, were observed as early indicators of exposure-related effects. These biomarkers

offer promising tools for monitoring the long-term health impacts of vaping, providing opportunities for early detection and intervention (37). Future research should focus on validating these biomarkers across larger populations and diverse demographic groups to enhance their clinical applicability.

It is essential to recognize limitations in the studies reviewed. Many were observational, limiting causal inferences regarding the relationship between e-cigarette use and genetic changes. The majority of studies lacked longitudinal follow-up, restricting our understanding of the long-term consequences of vaping. Additionally, considerable heterogeneity existed in the types of e-cigarettes and exposure metrics used across studies, which may have influenced the outcomes. Sample populations were often restricted to specific age groups and regions, reducing the generalizability of results to diverse populations.

Further research is needed to clarify the long-term genetic risks of e-cigarette use and investigate specific pathways through which these effects are mediated. Future studies should focus on diverse populations and consider both frequency and duration of vaping exposure. Furthermore, these findings suggest a need for policy evaluation regarding the regulation of e-cigarette products. Increased public awareness about the potential genetic risks associated with vaping, especially among young users, could play a critical role in shaping responsible usage practices and regulatory standards.

CONCLUSION

This systematic review highlights the potential health risks of e-cigarette use is related with genetic and epigenetic changes, including altered DNA methylation, gene expression, and other biomarkers. While e-cigarettes are often marketed and considered as a safer alternative of traditional smoking, the research findings of biological changes indicate possible links to long-term health consequences, especially concerning genetic effect related to respiratory, cardiovascular, and immune system functions. These findings highlight the need for future research to investigate the chronic effects of vaping on genetic pathways in human health, individual susceptibility, and mode of actions, which are essential for public awareness, social perceptions, and policy development.

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