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The Pivotal Role of *CDKN2A* in Esophageal Carcinogenesis: Molecular Mechanisms, Genetic Alterations, and Clinical Implications

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ABSTRACT

Recent attention has been paid to the study of complex interactions of genetic and environmental factors in the pathogenesis of esophageal carcinomas since the development of esophageal carcinoma is complicated by numerous loci. Research on this precise type of neoplasm is still in progress, as it has involved multiple loci. The tumor suppressor gene p16 is one of the major genes, which include absolute genetic alterations, like mutations, deletions, and dysregulation occurring within this region at very early stages of esophageal carcinogenesis. The p16 alterations are morbid homozygous events specific for histotype, this favoring p16 as a candidate marker for diagnosis prognostics even therapeutics. Though extensive studies are necessary with a view to leading to further tests on p16 in large population-based studies, i.e., to develop feasible and valid sample collection approaches. The esophageal carcinogenesis is multifactorial, driven first and foremost by lifestyle risk factors including tobacco smoking, alcohol abuse, and chronic inflammation, but also significant genetic factors. At present, the best-known genetic factor in the development of esophageal carcinoma is the mutation of the p53 gene. But other genes, like p16, are even more critical for defining the onset and progression of esophageal squamous cell carcinoma. This review attempts to shed light on the function of CDKN2A, which is tied to p16, and its important role in ruling out an esophageal cancer diagnosis, development, and management.

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1. Introduction

A malignant tumor that greatly affects public health and is common in esophageal cancer. Esophageal cancer is the fifth in incidence in men and ninth in women, while its fatality rate is ranked fourth in men

and seventh in women [1]. Generally, East Asian countries are high-incidence areas of esophageal cancer. Long-term heavy drinking and irritation from hot food residues are considered to be some of the reasons in high-incidence areas. The main types of esophageal cancer are esophageal adenocarcinoma and esophageal squamous cell carcinoma, with squamous cell carcinoma accounting for about 95% of cases [2,3].

Esophageal cancer is an invasive tumor that has accumulated gene mutations during continuous genetic evolution from normal esophageal epithelium or precursor lesions. It is the result of "many genes and many steps" in the long-standing pathogenic process of the disease [4,5]. Esophageal cancer is a complex disease affected by multiple genetic factors and lifestyle. Lifestyle includes multiple dangerous factors such as metal poisoning, extreme hot beverages and foods, alcoholism, obesity, and smoking. Among them, smoking and alcohol consumption are considered to be causes of esophageal cancer. People who often drink alcohol or smoke usually have a five to tenfold higher risk of esophageal cancer [6,7]. Nowadays, there are primarily six types of cancer genome molecular changes: activation of oncogenes, inactivation of proto-oncogenes, inactivation of tumor suppressor genes, multi-clone carrying, epigenetic changes, and gene mutations. Some risk factors, such as low intake of vegetables and fruits and low socio-economic status, enhance cancer risk by influencing tumor promoter and suppressor genes [8,9]. Until now, researchers have found that most changes are caused by the simultaneous occurrence of two or more of the six types of molecular changes. Single molecular changes are relatively rare in esophageal cancer. Management of esophageal cancer has changed completely in the past decade, and the molecular changes in esophageal cancer also require complete research in the genomic era [10]. In this current review, an attempt is made to throw some meaningful lights on the function of *CDKN2A* closely connected to p16 and its crucial participation in obtaining diagnosis, its development and therapeutic approaches.

2. Definition and Epidemiology

Esophageal cancer, arising from the lining of the esophagus, is either due to cancer of the squamous cells or esophageal adenocarcinomas of Barrett's mucosa. Esophageal cancer, like every other type, is far too common and since the figure below shows the number of deaths about it, it has a high case fatality rate in recent years making it the eighth most common cancer and the sixth cause of cancer deaths [11]. High-risk regions like China and the Eastern Cape of South Africa report notably higher rates. The disease is more prevalent in certain populations, particularly among males and the elderly (60 and older). Considering the prevalence worldwide and the dearth of effective therapies, identifying risk factors is essential [12,13]. Esophageal SCC is more common in the UK than EAC, which is more widespread in the Americas, Australia, and some parts of Europe. Since 1980, when it peaked historically, the death rate has decreased [14]. Currently, the median diagnosis age is 68, and the median death age is 71. Esophageal cancer is 3.2

times more prevalent in men and varies by race and ethnicity. It is most prevalent in South Africa's Eastern Cape and certain Asian regions, exceeding 100 cases per 100,000 [15].

3. Types of Esophageal Cancer

Lower-third esophageal adenocarcinoma is becoming the most common type of cancer in Western nations, while there is squamous cell carcinoma in developing low-income countries. In most cases, both are seen as ill-defined lesions. Smoking, drinking alcohol, previous cancer of the head and neck, and neck radiation are related mostly to squamous cell carcinoma, and adenocarcinoma risks relate mainly to obesity, Barrett's oesophagus, and gastroesophageal reflux disease [16]. Significant biological differences exist in the mechanisms of esophageal carcinogenesis between the two main types of esophageal cancer, each having unique genetic profiles. Notably, unique genetic mutation profiles are suggested based on populations in countries with high rates of squamous cell cancer and adenocarcinoma (Table 1).

Studies have demonstrated several molecular genetic differences between the types and it is expanding to investigate disparities in esophageal mucosa versus cancer and associated dysplasia, all preoperative chemoradiotherapy, surgery, definitive chemoradiotherapy, and palliative chemotherapy options are available for both types [17,18]. For squamous cell carcinoma, the five-year survival rate is approximately 30%, and for adenocarcinoma, it is 15%. Treatment resistance is a result of allelic losses in these cancers. Conducting targeted therapeutic studies and creating organized clinical trials for esophageal cancer requires an understanding of these malignancies [19,20].

Table 1: Epidemiological and etiological comparison of esophageal cancer subtypes

Feature	Esophageal Squamous Cell Carcinoma (ESCC)	Esophageal Adenocarcinoma (EAC)	References
Global Prevalence	~95% of cases globally; high incidence in East Asian countries.	Increasing in Western nations (Americas, Europe, Australia).	[2,3]
Risk Factors	Tobacco smoking, alcohol abuse, and irritation from hot food.	Obesity, Barrett's esophagus, and GERD.	[16]
5-Year Survival	Approximately 30%.	Approximately 15%.	[18]

4. Function and Mechanisms of *CDKN2A*

The proteins p16 and p14, which help to regulate the cell cycle, are both expressed by the *CDKN2A* gene. p16, also known as INK4A/ARF and p16 appears to be responsible for causing cellular quiescence through inhibition of cyclin-dependent kinases targeting mainly the retinoblastoma pathway. On the other hand, by attaching to MDM2 and preventing TP53 degradation, p14 increases the tumor suppressor protein TP53. The way that TP53, p14, and p16 interact shows a positive feedback loop. Through stimulating

mechanisms, carcinogenic pathways may be promoted and *CDKN2A* inactivated [21,22]. Among other factors, this universally acknowledged tumor suppressor, *CDKN2A*, was also reported in cancer of the brain, lungs, colon, breast, pancreas, and skin. It is found that the gene, p16INK4a, is the one responsible for the control of nuclear division and maintenance of the cellular balance. It has three ARL/INK4 isoforms with one exon and is located on the 9p21 chromosome. To regulate the appropriate attachment of retinoblastoma (pRb) protein to cyclin D-CDK4/6, the G1 phase progression of products p16INK4a and p14ARF is requisitioned. While p14arf acts as a positive regulator of p53 under DNA-damage circumstances, p16INK4a, a cell cycle inhibitor, acts on cyclin-dependent kinases 4 and 6, hence arresting cellular division. Cancer is the excessive activity caused by the substitution of the *CDKN2A* in the enhancement of p21cip1-waf1 and p53 synthesis. Despite changes made to p16INK4a, occasional risks of colonization increases of colorectal cancer colonization are inevitable [23-25]

Two pathways are affected by *CDKN2A*, one is the retinoblastoma pathway, inhibiting G1 arrest, and the other p53 pathway, controlling G1 arrest due to genotoxicity. Understanding the *CDKN2A* gene is very important when considering the progression of cancer, especially when it is esophageal cancer. However, there is very little data provided, and the few that exist show a conflict of interest; that is, while *CDKN2A* is recessive in this situation, its main responsibility is to act as a positive cancer suppressor. Future studies might look at *CDKN2A* both in terms of biomarkers of disease presence and in the context of pharmacological discovery [26-28].

CDKN2A is an indispensable tumor suppressor gene, and upon loss of function, it is further implicated in numerous cancer pathways, including *CDKN2A* inhibition being a generally poor prognostic factor. The targets in cyclin d-cc-kinase 4-6-pg16-pRb, an important growth control pathway, are also a threat to cellular integrity. Abnormalities with proteins with a similar function to oncogenes or tumor suppressors may modify growth [29,30]. The mutation and deletion of *CDKN2A* have been noted as changing forms in the clinical aspects of the disease. *CDKN2A* deletion gives rise to chimeric proteins that inhibit the cyclin-CDK4/6- pRb pathway. Loss of p53 is often associated with p16 loss or low levels, which involves interactions with p14ARF. Early assessment of *CDKN2A* and p53 is useful at the onset of the disease since the two markers help in the early detection of abnormal growth regulation and potentially poor prognosis, such as missing p16 or p53. Therapy aimed at restoring p53 activity has been a major focus of recent clinical trials (Table 2) [31,32].

Table 2: Interaction of *CDKN2A* with key signaling pathways in esophageal carcinogenesis

Signaling Pathway	Interaction with <i>CDKN2A</i>	Effect on Tumorigenesis	References
Rb/E2F Pathway	p16 inhibits CDK4/6, preventing Rb phosphorylation.	Loss of p16 indications to uncontrolled S-phase entry.	[2]
p53 Pathway	p14ARF inhibits MDM2, stabilizing p53 protein.	<i>CDKN2A</i> deletion results in rapid p53 degradation.	[51]
Wnt/β-catenin	Synergistic action in promoting EMT transitions.	Enhances cell migration and invasive potential.	[40]

5. Esophageal Cancer Pathogenesis

Cancer of the esophagus is a heterogeneous cancer of the alimentary canal of genetic origin. Initiation is also influenced by major environmental factors, which include high NO₂ and low SO₂. Smoking and alcohol cause greater than 90% of all possible cases. Other risk factors include poor food choices characterized by low intakes of fresh fruits and vegetables [17]. Esophageal cancer is a multifactorial metabolic neoplasm originating from genetic and behavioral characteristics. Sources associated with the development of this condition include many genetic and epigenetic modifications. Specifically, the deletions at chromosome 9p21 also make patients lose genes that are so vital in the body, for instance, *CDKN2A* and FHIT [33,34]. Other methods included methods applied for investigating functions and signaling pathways associated with esophageal cancer and tumorigenesis. Results showed downregulation of *CDKN2A* gene mutations and protein in patients with grade 2 squamous cell carcinoma, which may be associated with tumor advancement. The patterns of developing esophageal and other cancers are a result of complex molecular pathways from many factors [35].

6. Risk Factors and Etiology

Earlier, disease frequency had been region-specific, but, in the recent past, the low-risk groups have exhibited rather sharp trends peaking towards esophageal adenocarcinoma, while others are experiencing rising trends towards esophageal squamous cell carcinoma. This is partly attributed to risk factors associated with the development of esophageal cancer [36]. Based on the preceding review of esophageal cancer risk factors, they can be broadly classified into environmental or lifestyle risk factors and genetic risk factors. Other known risk factors are smoking, alcohol, obesity, particularly central obesity, low consumption of fruit and vegetables, and intake of nitrosamine-containing foods. Family history is well established; about half of patients with first-degree relatives who have been diagnosed with esophageal cancer end up also developing the disease [37].

Other works also correlate facial characteristics and work with esophageal cancer. Barrett's esophagus is known to be connected with esophageal adenocarcinoma and gastroesophageal reflux disease (GERD), though GERD is not thought to be a cause [38]. The progression of esophageal cancer is due to an accumulation of genetic and epigenetic alterations that occur due to damage. Most classical concepts of risk factors are known to be linked, expressing positive interaction, pointing straight to intertwined mechanisms of harm. Molecular epidemiology helps to identify mechanisms of malignant transformation and to improve the prevention and early diagnosis of esophageal cancer [39].

7. Molecular Pathways Involved

It is based on the role of the Wnt/ β -catenin signaling pathway in using mutations in the APC gene to deposit β -catenin in the nucleus and turn normal stem cells into tumor-initiating cells. While Notch signaling is crucial to development and homeostasis, the decline in Notch signaling has been observed to have tumor suppressor properties in esophageal carcinomas [40]. The PI3K/Akt pathway is frequently activated in cancers; mutant PI3K can enhance cyclin D1 nuclear localization via mTOR, affecting cell cycle control. However, categorizing cancer signaling pathways is overly simplistic, as they interconnect and influence each other, forming a complex signaling network. Such an interaction has given rise to multipronged drugs that do not focus on a single cell target in the cancer site [41,42].

Molecular changes in Wnt, Notch, and PI3K signaling pathways have been observed through Systems Biology using esophageal cancer cell lines. It remains unknown in what way *CDKN2A* participates in these pathways. Taken together, these observations emphasize the possibility that theory needs to shift its focus towards identifying core signaling pathways to prevent and treat tumorigenesis and future drug targets [10].

8. *CDKN2A* Alterations in Esophageal Cancer

These genetic changes occur in the tumor suppressor *CDKN2A* in esophageal cancer cases, which we detail the functional aspects of cancer genetics. Let alone the mechanism, the text systematically studies even the change in the frequency and correspondence to the clinical effects. Esophageal cancer is histologically categorized into two primary subtypes that are characterized by different risk factors and molecular changes [28]. The importance of *CDKN2A* alteration is apparent because research in EAC showed deletions with a range of 14-97% and mutations with 0-35%. The most frequent alteration in cases of squamous cell carcinoma was described as structural: *CDKN2A* was deleted or had a missense mutation in 17.24% of affected patients. Analysis revealed that patients with *CDKN2A* mutation lived shorter than patients with wild-type cases [43].

In particular, twenty-five patients with deletions suffered shorter survival compared to those without *CDKN2A* alterations, and these data support the role of tumor suppressor variation on cancer evolution and prognosis advisement. In conclusion, the overall types of alteration in the genes *CDKN2A* across the aggressive esophageal tumor differ, whereby EAC presented more alterations as compared to squamous cell carcinoma. However, it is not linked to variations in the incidence of cancer progression out there. We provided evidence that *CDKN2A* genetic changes are experimentally validated for early diagnosis of esophageal cancer, which needs a more careful investigation (Table 3) [44,45].

Table 3: Frequency and nature of *CDKN2A* alterations in EC

Alteration Type	Frequency/Rate	Clinical Impact	References
Homozygous Deletion	66% in untreated patients; range, 14-97% in EAC.	Related with higher stages, metastasis, and lower survival.	[51,52]
Point Mutations	8% in tumors, range 0-35% in EAC studies	Generally minimal impact on prognosis compared to deletions.	[50]
Hypermethylation	ranges from 8 to 57%	Correlates with tumor stage but not necessarily relapse.	[51]

9. Frequency of Alterations

The *CDKN2A* gene is a powerful cell cyclin regulatory gene; 60 percent of the cell lines have deletions, while 20 percent of them have a missense mutation in this gene. Such deletions are frequently accompanied by deletions affecting protein interactions, mainly owing to non-co-broken chromosomes. Most of the 12 deletions identified reside on chromosome segment 9p21, yet no major association peak is observed on chromosome 9, which includes three notable cell lines. Among these was a line maintaining a normal chromosome 9 alongside alterations in distinct chromosomal regions [46,47].

Additionally, altered gene expression levels without synaptic contacts were noted in 30% of the lines, hinting at the potential advantages provided by these genetic changes. The high occurrence of homozygous deletions and mutations at this locus in cancer cell lines aligns with findings showing that 12 patients exhibit one or more alterations. Of 69 patients studied, five had missense mutations confirmed by a restriction site assay, with two patients showing a mutation in one allele alongside lost heterozygosity and a mutation in the intact allele. While three other patients had identical alterations, one showed no association evidence, and subsequent size analysis of polymorphic markers in the other instances revealed uninformative polymorphisms [48].

10. Types of Alterations

Two *CDKN2A* changes, point mutations and deletions, along with promoter methylation, are seen in EC. 66% of individuals who have not received treatment had deletions, and 8% have mutations. 9% of pretreated patients had mutations, 20% had hypermethylation, and 62% had homozygous loss. The main mutation affects codon p16/INK4A 169, altering the ARF transcript. Re-expressing ARF can cause G1 arrest, which could stop the growth of tumors. The p14ARF transcript is found in normal organs such as the fetal liver and renal cortex, however, it lacks exon 2 [49,50].

Homozygous deletions and hypermethylation are the primary genetic aberrations of *CDKN2* that are identified with very few point mutations. Among 246 cancers analyzed, homozygous deletion was observed in 66% of cases and point mutation in 8% of tumors. Patients with homozygous deletions are generally considered to have poorer prognoses because they are associated with higher stages of the disease, nondifferentiation, more frequent metastasis to the lymph nodes, higher incidence of recurrence, and lower survival. These deletions could be targets for therapy in addition to chemotherapy or radiotherapy. On the other hand, point mutations in esophageal cancer patients did not affect their prognosis. Methylation in these patients ranged from 8% to 57%, correlating with tumor stage but not with metastasis or relapse. Treatment approaches are affected by the disparity between the early loss of homozygous deletions and the later methylation [51,52].

11. Clinical Implications of *CDKN2A* in Esophageal Cancer

Gene variants affecting *CDKN2A* are associated with worse outcomes in esophageal cancer and could serve as a prognostic indicator. Clinical studies and treatment plans can be influenced by variations in *CDKN2A* signaling pathways. Thirteen clinical trials are now investigating treatments that target aberrant *CDKN2A* pathway activity, with six trials concentrating on esophageal cancer and thirteen on other malignancies. Ongoing studies could reveal whether patients with *CDKN2A* alterations benefit from personalized therapies and if these alterations contribute to resistance against immuno-oncology treatments [43].

Biomarker analyses for early disease detection through non-invasive testing are gaining significant interest. *CDKN2A* alteration-positive plasma fragments likely represent true genomic alterations. Various plasma diagnostics for imaging *CDKN2A* show promise for early detection and response monitoring in clinical trials. Landmark trials will provide evidence on using *CDKN2A* alterations in exons 1-2 as blood-based biomarkers for treatment stratification. Currently, patients with suspicious Barrett's or early-grade dysplasia undergo endoscopy, with biopsies being sequenced using next-generation methods [53,54].

12. Prognostic Value

According to the given research, a bio-marker of a poor prognosis in esophageal cancer, *CDKN2A*, is over-expressed in gastrointestinal malignancies. Clinical research was designed to assess the effectiveness of *CDKN2A* as a prognosis biomarker. The tumor sample loss was determined by calculating the differences between the cohorts, it was found that the overall survival of patients with aberrant *CDKN2A* protein expression was lower than in patients without aberrant expression. Patients with normal *CDKN2A* transcripts had a 60% greater one-year survival rate than those with reduced expression. Studies demonstrate that downregulation of miR-335-5p enhances *CDKN2A* expression, indicating its usefulness as a prognostic indicator. Conversely, high *CDKN2A* levels predict poor disease-free survival, with a hazard ratio of 1.3 (Table 4). It is proven that overexpressed *CDKN2A* is closely correlated to poor prognosis of patients with esophageal cancer [55,56]. In general, disturbances of *CDKN2A* emphasize its role not only as a biomarker but also as a guideline in the identification of patients with high-intermediate and high-risk malignancies and further management of patients with relevant genetic alterations. High-risk patients can be distinguished, and probably this would allow the administration of prompt tumor management therapy. However, there are limitations to what *CDKN2A* can reveal about a tumor's behavior and fate; the density and variability of a tumor and co-expression of other proteins such as p53 and E-cadherin can limit the impact of *CDKN2A* [57,58].

Table 4: Prognostic and therapeutic implications of *CDKN2A* status

Clinical Parameter	Finding/Data Point	Scientific Significance	References
One-Year Survival	60% higher in normal vs. reduced expression.	Reliable biomarker for overall survival.	[56]
Disease-Free Survival	High expression Hazard Ratio (HR: 1.3).	Predictor of cancer recurrence risk.	[55]
Therapeutic Target	PDE10A neutralization/ORF restoration.	Roadmap for personalized medicine.	[61,62]
Resistance Factor	Link to PD-L1 and radiotherapy resistance.	Informs the need for immunotherapy.	[68]

13. Therapeutic Opportunities

It remains an important topic of concern to understand how to therapeutically address changes in the *CDKN2A* gene in oesophageal malignancy that resulted in great improvement in the patient's treatment plan. The fact that *CDKN2A* balances the expression of many genes, some of which can be damaged by downregulation, complicates this research. Combination therapies may be necessary to address such severe dysregulation, as single-agent treatments are unlikely to be effective in doing so. However, the viability of a multidrug strategy depends on our ability to comprehend how these changes affect the esophageal

carcinogenesis process. Historically, targeting a driver gene has been the primary focus for therapy design, yet evidence supporting *CDKN2A* alterations as a driver in esophageal cancer remains inadequate [59,60].

Further evidence from preclinical studies may bolster the development of this therapeutic class. This core has also raised speculations about using small molecules that can neutralize *CDKN2A* activation through the use of PDE10A. Although gene editing is the most feasible technique for clinical application, other forms of gene therapy may be designed to attempt to restore the open reading frame of the *CDKN2A* gene. Preclinical testing of *CDKN2A*-targeting techniques in vivo is essential to identify the best therapeutic vectors for restoring gene expression. In the end, therapeutic decision-making about the treatment of esophageal cancer patients may hinge on the stratification of patients according to their gene status [61,62].

14. Experimental Models for Studying *CDKN2A* in Esophageal Cancer

Several models are also available for dissecting the role of *CDKN2A* in ESCC development as an experimental model. Because of the foregoing, it is more effective to use in vitro cell lines, especially those with molecular changes in the *CDKN2A* gene. Additional in vivo studies are performed using genetically modified mice, like conditional knockout mice with *CDKN2A* deletion, and mice with silenced or mutated alleles. An in vivo ESCC model can be generated by oncogene activation, carcinogenic drugs, short interfering RNA, transplantation in immunodeficient mice, and changes in *CDKN2A*. While these models have advantages and limitations, they provide significant platforms to research *CDKN2A* roles in human cancer, even if they do not entirely mirror the actual ESCC microenvironment [63].

Functional forms of *CDKN2A* are thought to be carcinogenic, which presents difficulties for preclinical models in vivo or in cells used to assess potential treatments. The results show that to improve clinical relevance and gain a deeper understanding of *CDKN2A* activity, a variety of experimental techniques are required. Effective translation into translational research is made possible by the use of these models, especially when it comes to validating treatment targets in ESCC [64,65].

15. Cell Lines and Animal Models

Several dedifferentiated esophageal squamous cancer cell lines have been examined for phenotypic or molecular alterations. Some of these lines differ in the status of *CDKN2A* alterations and copy number variations, which are the first, second, and third most frequent alterations in esophageal cancer, as well as mutant TP53. Several generated orthotopic xenograft tumors in mice closely resembled the immunobiology, lipid metabolism, epithelial-to-mesenchymal transition, and local tumourigenesis seen in the patient population. These patient-derived lines also show clinical relevance in vitro when engraftment

capacity, locoregional invasion, architectural asymmetry, immune evasion, and other viable cancer cell elimination are tested with secondary 3D culture [66,67]. Animal models indicate that *CDKN2A* inactivation can lead to invasive esophageal tumors by enhancing TP53 function through lowered cellular stress responses or increased immune suppression. Elevated PD-L1 levels in *CDKN2A*-aberrant cancers in humans and mice contribute to resistance against radiotherapy. This emphasizes the necessity of developing novel models to investigate survival signals in chemoradiotherapy cases of esophageal malignancies lacking *CDKN2A*. Cancer cell lines from patients may be used to investigate immunotherapy resistance linked to *CDKN2A* inactivation [68].

16. Challenges and Future Directions

While the present years have brought predawn knowledge in molecular aetiology of esophageal cancer about *CDKN2A*, some issues are still unresolved. Previous studies mainly encompass partial elements of *CDKN2A* mechanistic processes, thus critically restricting the applicability of knowledge. We determine potential integration errors of animal studies, precisely discussing the relation of the reads to the *CDKN2A* biology. Most research has concentrated on genetic models, while co-deletion occurs infrequently in human esophageal cancer. Although *CDKN2A* backgrounds have expedited tumor onset in some deficient mice, studies indicate that *CDKN2A* deletion does not significantly affect outcomes in the absence of deficiencies [69,70]. *CDKN2A* is a gene with complex regulation, producing at least four distinct products through alternative splicing. Its variants and proteins remain inadequately studied in esophageal cancer. Key questions include identifying the cell of origin, studying splice variants and protein trafficking, exploring genetic events downstream of defective *CDKN2A*, and conducting preclinical biomarker-driven studies [71].

17. Limitations of Current Research

Investigation of the implication of *CDKN2A* in the development of esophageal carcinoma is well underway. However, the variation in the findings may be because of factors that make the comparison of the studies difficult. Esophageal cancer shows intertumor heterogeneity in etiologic and clinical characteristics, histopathology, and biomolecules. Therefore, a comprehensive evaluation is challenging to achieve in one study. But, the pathway is made more complex with the different experimental models and designs. Frequently, the absence of co-reference is not indicative of real differences between genetic and histological findings. A good experimental design will follow a marker through defined genetic tissue changes [72].

The use of multiple endpoints in the carcinogenic development pathway is crucial to assess the marker gene inactivation, ranging from reversible alterations to malignant conversion. Research needs to take into

account existing extensive case information. One of the major drawbacks is the lack of enough information on *CDKN2A* in esophageal cancer; hence, conclusions are limited. Instead, they have high variability between the studies, which complicates the recognition of *CDKN2A*'s characteristics and stability. On balance, it can be concluded that the current data do not clarify well enough the steps of progression of etiopathogenesis. Limitations include labor and time constraints, the shortfall in sample size, and selective bias. For example, recruiting aggressive tumors may distort the inactivation rates. Reporting investigations also requires the enhancement of methodologies to improve their reproducibility. It is therefore important to note research limitations to have accurate evaluations done [73].

18. Potential Areas for Further Investigation

This section gives some new information about *CDKN2A* in connection with esophageal cancer and explains why there is no information about its mutations. Future work may explore other signaling pathways that are regulated by *CDKN2A* to understand what pathophysiologic agents give rise to esophageal cancer and to solidify *CDKN2A* as a target for treatments related to the TGF- β pathway. Recent empirical studies present issues in categorizing diagnostics for *CDKN2A* [74]. The approach of work is to examine the pathway and utilize *CDKN2A* as a prognosis biomarker for specified therapies. Therefore, early detection of *CDKN2A*-related molecular patterns is crucial. Studying *CDKN2A* may help to understand targeted therapies as their ability is challenged. It is therefore conclusive that *CDKN2A* plays the role of a tumor suppressor in the development of esophageal cancer, mainly due to its role in cell cycle regulation. Codifying CNV, somatic changes in *CDKN2A* are central to the condition's genetics. However, the disease is still a leading cause of cancer morbidity and mortality due to the high difficulty level [75].

19. Conclusion

Even in this more molecular setting, a single molecule *CDKN2A* by itself is insufficient; no single gene underlies, or is causally primary to, the absolutely causal structure of any given esophageal carcinoma. Additional skillful mechanistic investigation will be needed to begin to define the precise chart of each available tumor type. This will be critical for such phenotypic variations as the profoundly more aggressive biology, and chemoradiotherapy resistance, conferred by structural variants, namely homozygous deletions, that far outweigh the prognostic factors conferred by the single nucleotide variants. Importantly, because the biology of EAC is distinguishable from ESCC, these charts will have to be drawn for each histological esophageal subtype. Finally, a shift of sufficient depth into the nuances of epigenetic alterations and immune-checkpoint frequency (i.e. PD-L1 expression) can elucidate precisely how the axis interact with and breach the DNA damage response, A lot contributing to the proffering of radio- and immunotherapy resistance, and to the ultimate toll on survival.

20. Conflict of Interest

Authors declare no conflict of interest.

21. Funding

None.

22. References

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