THE IMPACT OF TABACCO SMOKING ON THE EFFECTIVENESS OF ANTICANCER THERAPY: CLINICAL IMPLICATION AND MOLECULAR MECHANISMS

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Abstract. Tobacco smoking is one of the most widespread modifiable risk factors for the development of malignant neoplasms. Beyond its role in initiating carcinogenesis, smoking negatively affects the effectiveness of anticancer therapy by reducing tumor sensitivity to treatment and worsening overall patient survival. This monograph aims to provide a comprehensive analysis of the clinical and molecular aspects of the relationship between smoking and treatment response in oncology. *Materials and Methods.* A systematic review of current scientific literature was conducted, focusing on the impact of smoking on the outcomes of immunotherapy, chemotherapy, and radiotherapy, as well as on the molecular mechanisms of therapy resistance. The study includes data from clinical trials, experimental models, and meta-analyses. Special attention was given to the role of nicotine, its metabolites, and nicotinic acetylcholine receptors in modulating cancer cell signaling pathways. *Results.* It was found that smoking activates signaling cascades that promote cancer cell survival, inhibit apoptosis, stimulate epithelial–mesenchymal transition and angiogenesis, and maintain cancer stem-like properties. Smoking alters the metabolism of chemotherapeutic agents via induction of cytochrome P450 enzymes, thereby reducing treatment efficacy. Despite some paradoxical findings suggesting that certain smokers may respond better to immunotherapy due to higher tumor mutational burden, the overall impact of smoking remains detrimental. Electronic cigarettes and nicotine replacement products may partially reproduce these effects. Pharmacological agents (varenicline, bupropion, cytisine) and non-pharmacological approaches for smoking cessation

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have shown high efficacy without impairing cancer treatment outcomes. *Conclusions.* Smoking is associated with poorer treatment results, increased toxicity, and reduced survival in cancer patients. Smoking cessation – even after diagnosis – improves clinical prognosis. These findings emphasize the need to integrate smoking cessation programs into standard oncologic care, as this can significantly enhance treatment effectiveness and improve patients' quality of life.

1. Introduction

Cancer represents a substantial global burden and remains one of the primary causes of death worldwide. Its development is influenced by a range of behavioral and environmental determinants, and it is widely acknowledged that improved public health awareness, alongside the introduction of innovative therapeutic approaches, can contribute to lowering cancer-related mortality [1]. Recent evidence indicates a significant decline in cancer mortality rates, which has been linked to behavioral modifications, increased public awareness, and advances in treatment strategies. Among these factors, the most impactful contributor to reduced mortality has been the decline in tobacco consumption, particularly the smoking of cigarettes and other combustible products [2].

The harmful consequences of tobacco use were comprehensively addressed in the 1964 U.S. Surgeon General's report, which highlighted the strong connection between smoking and cancer development. Later studies confirmed that tobacco smoking is significantly linked to cancers of the stomach, pancreas, kidney, oral cavity and pharynx, ureter, bladder, and lungs, along with acute myeloid leukemia. The 2014 update to the Surgeon General's report expanded this list to include colorectal and liver cancers [3]. Moreover, subsequent Surgeon General publications reported a rising prevalence of smokeless tobacco use among children and young adults, a pattern that may predispose these populations to future smoking behavior [4]. A large-scale meta-analysis demonstrated a clear relationship between smoking and the development of sixteen distinct cancer types, in addition to an elevated risk of several other diseases. Collectively, these findings underscore the critical importance of smoking cessation as a key strategy for reducing cancer risk and preventing other serious smoking-related conditions [5].

It is now well established that tobacco use not only contributes to cancer initiation but also exerts a profound influence on multiple aspects of tumor biology. Components of tobacco smoke are capable of triggering carcinogenic processes, facilitating tumor progression and metastatic spread, and significantly diminishing the effectiveness of anticancer treatments [6]. Higher levels of smoking have been associated with inferior responses to the main therapeutic approaches used in oncology. Importantly, accumulating evidence indicates that smoking cessation confers substantial clinical benefits. These benefits are attributed both to improved treatment results and to reduction in therapy-related toxicity [7].

This publication seeks to provide an overview of current evidence on how smoking influences the success of cancer treatments, to explore the biological pathways through which these effects manifest, and to highlight the critical role of smoking cessation throughout cancer care. To support this objective, a targeted literature review was conducted using the PubMed database to retrieve relevant studies on the relationship between tobacco use and treatment efficacy. The search was guided by specific combinations of keywords, including: smoking, immune checkpoint inhibitors, immunotherapy response, chemotherapy, smoking-associated inflammation, radiotherapy, effectiveness of anticancer treatment, resistance to treatment, smoking cessation, anticancer therapy response, nicotine, drug resistance, apoptosis, metabolism, cancer survival, e-cigarette and replacement therapy. Emphasis was placed on clinical trials analyzing therapeutic outcomes based on smoking status, alongside studies that clarify the underlying molecular and cellular processes.

2. Immune checkpoint inhibitors and smoking

Immunotherapeutic approaches based on immune checkpoint inhibition have demonstrated high efficacy in the treatment of lung malignancies [8]. In addition, several other smoking-associated cancers, such as head and neck, urothelial carcinoma and bladder tumors, have also shown meaningful responses to immunotherapy [9–11]. Consequently, immune checkpoint inhibitors, including pembrolizumab, nivolumab, ipilimumab, durvalumab, cemiplimab, and atezolizumab, are now commonly used as first-line treatment options for lung cancer [12; 13].

Checkpoint blockade is particularly effective in tumors characterized by a high tumor mutational burden, a feature frequently observed in lung cancer and cutaneous malignancies such as melanoma [14; 15]. Given this background, the relationship between smoking status and immunotherapy outcomes in lung cancer patients warrants careful consideration [16]. Tobacco smoke is a well-established source of DNA damage ultimately leading to an increased mutational burden [17]. This association has been consistently demonstrated across various cancer types [18, 19]. Smoking-induced somatic mutations generate a broader repertoire of cancer-specific neoantigens, potentially expanding neoantigen-reactive T-cell populations and thereby enhancing responsiveness to immune checkpoint blockade [20].

However, while smoking-related increases in mutational burden may theoretically improve immunotherapy response, the chronic inflammation and tumor-promoting effects associated with tobacco exposure may counteract the benefits of anticancer treatments. In contrast, never-smokers typically exhibit a lower mutational burden but are also not subject to the pro-tumorigenic influences of tobacco smoke, which may likewise shape their response to immunotherapy. This apparent paradox has been the focus of multiple investigations conducted over recent years, aiming to clarify the net impact of smoking status on immunotherapy efficacy [21].

A recent matched case–control study evaluated the comparative effectiveness of first-line chemotherapy versus immunotherapy in smokers and never-smokers with NSCLC. The analysis included 962 patients treated with immunotherapy and 462 persons treated with platinum-based chemotherapy. The results showed that never-smokers experienced a significantly higher risk of disease progression when treated with pembrolizumab, whereas no such increased risk was observed among never-smokers receiving chemotherapy. To further minimize confounding, the investigators performed random case–control matching in a subset of 424 patients drawn from both treatment cohorts. In this matched analysis, non-smokers in the immunotherapy group exhibited poorer survival, while never-smokers treated with chemotherapy demonstrated significantly prolonged progression-free survival. Drawing from these results, the researchers concluded that patients with NSCLC who had a history of

smoking experienced improved progression-free survival when treated with immunotherapy, especially in the early stages of the disease. In contrast, individuals who had never smoked appeared to benefit more significantly from chemotherapy [22].

Comparable observations have been reported by other research groups across different clinical settings, consistently suggesting that never-smokers may respond more favorably to chemotherapy and targeted therapies. These conclusions were further reinforced by a meta-analysis of published studies. In parallel, the KEYNOTE-024 trial highlighted the beneficial impact of smoking cessation among patients receiving immunotherapy. Although these results may seem paradoxical, they raise the possibility that, at least in early-stage lung cancer, smokers may exhibit a more pronounced response to immunotherapy compared with never-smokers [23; 24].

The biological mechanisms that may account for the enhanced responsiveness to immunotherapy observed in smokers have been investigated by several research groups, revealing contributions beyond tumor mutational burden alone. It is well recognized that patients with programmed death-ligand 1 (PD-L1) expression more than 50% of tumor cells derive greater benefit from first-line immune checkpoint inhibitors. Experimental and clinical studies have demonstrated that nicotine exposure and tobacco smoking can upregulate expression of PD-L1receptors in lung cancer cells [25; 26]. In particular, analyses comparing patients with KRAS mutation-associated NSCLC have shown significantly higher PD-L1 expression in smokers, with a clear association to cumulative tobacco exposure measured in pack-years, whereas no similar relationship was identified for PD-L2 expression. Although elevated PD-L1 levels suppress T-cell–mediated antitumor activity, they simultaneously increase tumor susceptibility to blockade of immune checkpoints, thereby enhancing the effectiveness of immunotherapy [27].

Nevertheless, it should be emphasized that tobacco smoke exposure also promotes chronic inflammation and induces the expression of immunosuppressive and tumor-promoting factors, including proteins such as YAP1. Despite these unfavorable effects on tumor biology and immune regulation, evidence from clinical trials supports the conclusion that immunotherapy remains an effective treatment strategy for smokers with NSCLC [28; 29].

The impact of smoking on immune cell populations within the oncological context has been extensively characterized. Tobacco exposure influences both innate and adaptive immune compartments, affecting most immune cell subsets. Studies have reported increased levels of T helper cells, particularly the Th17 population, accompanied by elevated concentrations of pro-inflammatory interleukins. Smoking has also been associated with higher numbers and enhanced functional activity of $CD8^+$ cytotoxic T cells. In contrast, overall $CD4^+$ T-cell populations, and especially regulatory T cells (Tregs), appear to be reduced in smokers, a shift that may further exacerbate inflammatory responses [30]. Collectively, these immune alterations contribute to systemic inflammation and to smoking-related comorbidities such as chronic obstructive pulmonary disease (COPD), ultimately impairing quality of life [31]. Importantly, although smokers may experience greater benefit from immunotherapy, particularly at earlier disease stages, cessation of smoking after cancer diagnosis does not diminish immunotherapy efficacy and is instead associated with improved overall well-being and quality of life [32].

3. Smoking and Radiotherapy

A growing body of evidence indicates a consistent association between smoking status and treatment response to radiotherapy or combined chemoradiotherapy across multiple cancer types [33]. Although the precise molecular mechanisms responsible for this effect have not yet been fully clarified, the reproducibility of poorer radiotherapy outcomes among smokers suggests that this relationship is clinically meaningful rather than incidental. Head and neck cancers provide a well-studied example, as radiotherapy or chemoradiotherapy constitutes a cornerstone of treatment for these tumors, many of which are strongly linked to tobacco exposure [34].

Pala et al. [35] demonstrated that patients with head and neck cancer who continued smoking during radiotherapy exhibited significantly reduced treatment response rates and inferior overall survival compared with patients who abstained from smoking. The authors conducted a retrospective study of 73 patients with nasopharyngeal carcinoma treated with curative radiotherapy or chemoradiotherapy. They found that smoking within 5 years before treatment was an independent negative prognostic

factor for overall survival. In other words, patients who smoked close to the time of radiotherapy had significantly worse long-term survival outcomes, with about a four-fold higher risk of death compared to non-smokers. Smoking was one of the strongest predictors of poor outcome alongside age and initial treatment response, suggesting that recent smoking reduces the effectiveness of curative (chemo)radiotherapy.

Additional investigations in head and neck cancer cohorts have further shown that patients who actively smoked during radiotherapy experienced significantly worse overall survival and disease-free survival compared with individuals who had ceased smoking before the start of radiation treatment [36].

Similar patterns have been observed in lung cancer. In an analysis of 237 patients with NSCLC receiving chemoradiation, two-year overall survival was assessed from the start of treatment. Early-stage non-smokers showed significantly better overall survival (56% survival rate; median survival 27.9 months) compared with smokers (41% survival rate; median survival 27.9 months). In contrast, no significant survival difference was identified among patients with stage III disease. Based on these findings, the authors concluded that smoking adversely affected the response to chemoradiation predominantly in patients with earlier-stage disease [37].

Nguyen et al. [38] reports about the influence of smoking status on treatment outcomes after post-operative radiotherapy for NSCLC. The study retrospectively analyzed 152 NSCLC patients who underwent surgery followed by post-operative radiotherapy. Patients were classified as smokers or non-smokers at the time of initial consultation. The authors found that smokers had significantly poorer local and locoregional tumor control after radiotherapy compared to non-smokers, with lower rates of disease control at 5 years. Although the difference in overall survival between smokers and non-smokers was not statistically significant, smoking remained an independent negative factor for locoregional control on multivariate analysis. The results suggest that smoking at the time of treatment is associated with worse treatment outcomes after post-operative radiation therapy in NSCLC, and that quitting smoking before therapy may improve the effectiveness of radiotherapy.

The involvement of nicotinic acetylcholine receptors (nAChRs) in the development of resistance to radiotherapy has been investigated through

detailed molecular studies. In particular, Shen et al. [39] demonstrated that the α5 subunit of the nAChR plays a critical role in mediating radioresistance in laryngeal squamous cell carcinoma. Lin et al. [40] reports about the biological roles and prognostic significance of nAChR subunits α3, α5, and α7 in oral squamous cell carcinoma (OSCC). The authors investigated how different nAChR subunits, such as α3, α5, and α7 (encoded by CHRNA3, CHRNA5, CHRNA7), are expressed in OSCC and relate to tumor biology and patient outcomes. They combined experiments in cancer cell models, immunohistochemistry of tumor samples, and analyses of public genomic datasets to explore these receptors' roles. The study found that all three subunits are associated with epithelial-mesenchymal transition (EMT) marker expression and invasive tumor patterns, but each has distinct effects: α3 expression promotes EMT traits, α5 is linked to more aggressive, disseminated tumor behavior and predicts poorer prognosis, and α7 is associated with a hybrid EMT state. These findings suggest that specific nAChR subunits influence tumor invasiveness and could serve as biological markers for prognosis in OSCC.

Overall, these data indicate that exposure to tobacco smoke or its constituents, particularly nicotine, can contribute to enhanced resistance to radiotherapy, whereas smoking cessation may restore or improve tumor sensitivity to radiation treatment [41].

4. Chemotherapy and smoking

One of the earliest landmark studies about the impact chemotherapy on the anticancer treatment efficacy was published in 1980 by Minna et al. [42]. Reseachers evaluated 112 patients with small-cell lung cancer who were categorized into three groups according to smoking behavior: individuals who had stopped smoking before diagnosis, those who quit at the time of diagnosis, and those who continued smoking during treatment. Survival outcomes were most favorable among patients who had ceased smoking prior to diagnosis, followed by those who stopped at diagnosis, whereas patients who continued to smoke experienced the poorest survival. These findings underscored that smoking cessation, even when initiated at the time of cancer diagnosis, confers a meaningful survival advantage. Notably, survivors of tobacco-associated malignancies have been reported to maintain higher smoking prevalence compared

with survivors of non–tobacco-related cancers or individuals without a cancer history [43].

Further evidence supporting the negative impact of smoking on chemotherapy outcomes was provided by Tsao et al. [44]. This analysis demonstrated significantly improved overall survival among never-smokers receiving chemotherapy compared with patients with a history of smoking. Moreover, Huang et al. [45] investigated how nicotine influences the growth and spreads of NSCLC at the molecular level. The authors found that nicotine upregulates the epigenetic regulator EZH2, which is highly expressed in lung tumors, especially in smokers. Nicotine does this by increasing the expression of OTUB1, a deubiquitinating enzyme, which stabilizes the c-Myc oncoprotein. Stabilized c-Myc then drives increased EZH2 expression. This OTUB1–c-Myc–EZH2 signaling axis enhances NSCLC cell proliferation and metastatic ability in cell culture and animal models. Inhibiting EZH2 or c-Myc reduced the nicotine-induced tumor growth and metastasis, suggesting that this pathway is a key mechanism through which nicotine promotes lung cancer progression.

Earlier investigations have also highlighted a dose–response relationship between cumulative tobacco exposure and chemotherapy efficacy. In a retrospective study involving NSCLC patients treated with chemotherapy, responders had a substantially lower lifetime smoking exposure (38.7 ± 27.1 pack-years) compared with non-responders, whose exposure averaged 67.8 ± 35.1 pack-years [46]. Based on these observations, the authors concluded that a smoking history exceeding 40 pack-years was associated with a markedly diminished response to chemotherapy, relative to patients with lower cumulative tobacco exposure.

High rates of continued smoking have also been documented among cancer survivors, underscoring the need for more effective educational interventions addressing the harmful impact of tobacco use on quality of life. Participants in this study were asked whether they were aware of the consequences of continued smoking during cancer therapy. Interestingly, many participants did not realize that smoking during cancer treatment could negatively affect therapy outcomes, heighten the likelihood of complications after surgery, and diminish their overall well-being [47]. This lack of awareness was particularly pronounced among current smokers. Importantly, the study also demonstrated that improved understanding of

the links between continued smoking, suboptimal therapeutic outcomes, and heightened treatment-related toxicity was associated with increased rates of smoking cessation [48].

Comparable findings have been reported in cohorts of patients with NSCLC, where individuals who stopped smoking after diagnosis exhibited better performance status than those who continued smoking. This benefit was observed consistently at both 6- and 12-month follow-up and was independent of baseline patient characteristics. In addition, another study reported significantly impaired quality of life among lung cancer survivors who remained smokers compared with never-smokers, as assessed using a lung cancer–specific symptom scale [49].

Beyond overall survivorship outcomes, the influence of smoking on treatment-related symptom burden has also been investigated. A study published in 2011 evaluated 947 patients scheduled to receive chemotherapy or radiotherapy to determine how smoking status affected the severity of treatment-related side effects. Smoking status was analyzed in relation to commonly reported toxicities during active treatment and over a 6-month follow-up period. The results indicated that smokers experienced substantially higher symptom burden during therapy compared with non-smokers, with this difference persisting at follow-up. Notably, patients who had ceased smoking before initiating treatment reported symptom levels comparable to those of never-smokers [50]. Collectively, these findings further emphasize the critical importance of smoking cessation during cancer therapy.

More recent evidence further supports the negative impact of continued smoking on treatment results. Head and neck cancer patients who had stopped smoking after diagnosis but before initiation of therapy, substantial benefits of smoking cessation were observed [51]. In an analysis of 134 individuals, patients who stopped smoking after receiving a cancer diagnosis showed a markedly higher likelihood of responding to first-line therapy – approximately 3.7-fold – compared with those who continued to smoke, and they also achieved improved disease-free survival outcomes. Moreover, individuals who remained abstinent from smoking during treatment had a significantly lower risk of all-cause mortality than persistent smokers. These findings reinforce the clinical importance of smoking cessation both prior to and throughout the course of cancer therapy.

Similar associations have been reported in non–muscle-invasive bladder cancer. Patients who quit smoking after diagnosis and before starting treatment showed a reduced risk of tumor recurrence [52]. These results are consistent with observations across other smoking-related malignancies, in which continued tobacco use has been strongly linked to higher rates of recurrence. Comparable outcomes were also reported in studies evaluating the influence of smoking on response to neoadjuvant chemotherapy in patients with bladder cancer [53].

A study involving 120 patients revealed that both current and former smokers had significantly worse ECOG performance scores and a reduced response to neoadjuvant therapy. Notably, individuals who continued smoking were far more likely to show no pathological response. The researchers emphasized that the degree of pathological response to neoadjuvant chemotherapy strongly influenced survival outcomes and proposed that, as in lung cancer, immunotherapy might be more beneficial for smokers. Similar conclusions have been supported by other investigations focused on muscle-invasive bladder cancer [54]. Additionally, a retrospective study of 1,382 cases identified a clear link between smoking and inadequate or absent response to neoadjuvant therapy, with persistent smoking also associated with a heightened risk of cancer recurrence [55].

Pancreatic cancer remains one of the most lethal malignancies, characterized by limited overall survival and poor responsiveness to currently available treatment modalities. Tobacco use is strongly associated with the development of pancreatic cancer, and clinical evidence indicates that patients who smoke experience significantly worse survival outcomes compared with never-smokers or individuals who stop smoking after diagnosis. Moreover, this survival disadvantage has been shown to increase in parallel with cumulative tobacco exposure, as reflected by higher pack-year histories [56]. Multiple studies have consistently reported an association between smoking and reduced overall survival in pancreatic cancer. One proposed explanation for this effect is the heightened inflammatory state observed in smokers, which has been linked to both pancreatic inflammation and pancreatitis, conditions that adversely influence disease course and prognosis [57]. These observations suggest that while smoking-related cancers may share certain pathogenic pathways, distinct tumor- and tissue-

specific mechanisms also contribute to impaired treatment response and reduced survival.

More broadly, smoking has been associated with elevated systemic inflammation among cancer patients and survivors. In this context, an investigation conducted in breast cancer survivors explored stress-induced inflammatory responses as a potential contributing factor. In that study, which included patients who had completed cancer therapy at least three months earlier, inflammatory markers were compared between former smokers and never-smokers [58]. When exposed to controlled laboratory stressors – like public speaking or solving mental arithmetic problems – former smokers exhibited notably elevated levels of interleukin-6 compared to those who had never smoked. According to the authors, this heightened inflammatory reaction to stress might account for the continued presence of systemic inflammation in both current and former smokers, even after they have quit smoking or completed cancer therapy [59].

5. Biological Pathways Through Which Smoking Influences Treatment Outcomes

Cigarette smoke consists of a chemically diverse blend of substances, many of which are known carcinogens. Among these are tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons like benzo[a]pyrene, along with compounds such as aldehydes, benzene, and various aromatic amines. These substances act as potent mutagens that form DNA adducts and induce alterations in key oncogenes or tumor suppressor genes, thereby promoting malignant transformation. In addition to their direct genotoxic effects, other constituents of tobacco smoke influence intracellular signaling pathways, leading to enhanced cellular proliferation, inhibition of apoptosis, and increased survival of exposed cells. Several tobacco-derived compounds have also been shown to induce aberrant DNA methylation patterns and other epigenetic modifications, which further contribute to oncogenic processes [60].

Pharmacokinetic differences between smokers and non-smokers represent another important mechanism affecting therapy response. Smokers have been shown to metabolize certain chemotherapeutic agents more rapidly than non-smokers [61]. When chemotherapy-induced neutropenia is used as an indirect marker of drug exposure and toxicity, non-smokers treated

with gemcitabine for various malignancies have been reported to experience more pronounced neutropenia compared with smokers. Although lower neutrophil counts are generally undesirable, greater neutropenia in this context reflects higher circulating levels of gemcitabine and, consequently, greater therapeutic efficacy. Conversely, reduced neutropenia observed in smokers suggests lower systemic drug levels and diminished treatment effectiveness, a pattern documented across multiple tumor types [62].

Nicotine, the primary addictive component of tobacco, exemplifies how individual smoke constituents can facilitate tumor progression and metastasis independently of direct genetic alterations [63]. At concentrations typically detected in the bloodstream of heavy smokers, nicotine itself is not considered a classical carcinogen; however, carcinogenic effects have been reported at higher doses, albeit through mechanisms that remain incompletely understood. Nicotine plays a critical role in the formation of potent carcinogens known as tobacco-specific nitrosamines –most notably, nicotine-derived nitrosamine ketone and N-nitrosonornicotine – which are generated during the processes of tobacco curing and burning. Experimental studies suggest that high concentrations of nicotine can lead to the formation of small amounts of these nitrosamines, potentially contributing to cancer development. Activation of many such nitrosamines depends on cytochrome P450 enzymes, whose production is upregulated by exposure to tobacco smoke. Notably, these same enzymes are responsible for metabolizing and eliminating various anticancer drugs, which can reduce their effective concentration and weaken therapeutic outcomes [64].

Nicotine exerts its cellular effects primarily through nAChRs, which are classically expressed in neuronal tissue and at neuromuscular junctions [65]. However, these pentameric ligand-gated ion channels are also present on a wide range of non-neuronal cells, including epithelial and endothelial cells. Accumulating evidence indicates that signaling mediated by specific nAChR subunits enables nicotine-driven stimulation of cell proliferation and inhibition of apoptotic pathways. Notably, earlier genome-wide association studies identified variants in genes encoding several nAChR subunits – such as α3, α4, α5, β2, and β4 – as contributors to both nicotine dependence and lung cancer susceptibility, highlighting a genetic link between smoking behavior and carcinogenesis [66]. In parallel, experimental studies have shown that the α7 subunit, along with certain other receptor subtypes,

directly promotes cellular proliferation, whereas α3β2-containing receptors are implicated in the suppression of apoptosis [67]. Beyond these effects, nicotine has been shown to enhance epithelial–mesenchymal transition, angiogenesis, cancer stem–like properties, and metastatic potential in multiple tumor types through nAChR-dependent mechanisms. Collectively, these findings underscore the central role of nAChRs in mediating many of the harmful oncological effects of tobacco exposure [68].

Given their involvement in tumor growth, angiogenesis, metastatic dissemination, and resistance to anticancer drugs, nAChRs have been proposed as potential therapeutic targets [69]. A number of antagonists targeting specific nAChR subunits, including neuronal and muscle-type receptors, are currently known. However, the clinical applicability of most of these compounds is severely limited by their toxicity. For example, α7-selective antagonists such as bungarotoxin and cobratoxin, derived from snake venom, are highly toxic to humans. Other agents, including hexamethonium bromide and α-conotoxins, likewise exert harmful systemic effects, precluding their use as anticancer therapies. At present varenicline and bupropion are commonly prescribed for smoking cessation. To date, neither agent has demonstrated substantial anticancer or antiproliferative activity, likely because the receptor subunits they inhibit are not the predominant functional forms expressed in non-neuronal tissues [70].

Multiple molecular pathways have been proposed to explain how smoking induces resistance to anticancer therapies. Early experimental work identified several mechanisms mediated by activation of nAChRs, with specific receptor subunits playing a central role. Although various nAChR subtypes have been implicated in therapy resistance, including α2/β3, α7, and α5, a common feature is the activation of prosurvival signaling that counteracts the cytotoxic effects of chemotherapy. For instance, in in vitro models of non-small-cell lung cancer, pretreatment with nicotine at concentrations of 1 μM was shown to markedly inhibit apoptosis induced by commonly used first-line chemotherapeutic agents such as cisplatin, gemcitabine, and taxanes. The observed protective effect was linked to the stabilization of the anti-apoptotic protein XIAP (X-linked inhibitor of apoptosis) and increased transcription of survivin. Nicotine-driven upregulation of survivin has also been identified in oral carcinomas and diminished the apoptotic response to cisplatin treatment. Supporting

these in vitro results, experiments using mouse xenograft models showed that nicotine exposure accelerated the progression and metastatic behavior of pancreatic tumors while concurrently decreasing sensitivity to gemcitabine therapy [71].

Nicotine has also been found to trigger critical prosurvival signaling pathways, notably those involving extracellular signal–regulated kinases (ERK) and protein kinase B (Akt), which contribute to enhanced viability of colorectal cancer cells [88,89]. Additionally, NNK – a tobacco-specific nitrosamine – has been shown to activate both Akt and NF-κB signaling, supporting the persistence of small-cell lung cancer cells [72]. Other suggested mechanisms involve increased expression of sirtuins, pointing to an epigenetic dimension of nAChR-mediated therapy resistance. Moreover, stimulation of β-adrenergic receptors and their downstream molecular pathways have been linked to nicotine's role in fostering tumor growth and resistance to treatment [73,74].

Nicotine contributes to tumor development in part by functionally disrupting key tumor suppressor pathways, particularly those regulated by the retinoblastoma protein (Rb) and p53. Simultaneously, various constituents of tobacco smoke have been shown to enhance the expression or activation of oncogenes such as c-Myc and KRAS [75]. Nicotine also promotes cell cycle progression by elevating the levels of cyclins D and E, along with their associated kinase activities, leading to Rb hyperphosphorylation and its subsequent inactivation. This cascade enables unchecked proliferation of lung cancer cells. These processes are mechanistically driven by the activation of Src kinase via β-arrestin-1–mediated signaling. Notably, β-arrestin-1 can translocate to the nucleus, where it binds to the E2F1 transcription factor, thereby increasing the expression of genes involved in epithelial–mesenchymal transition and metastatic behavior [76]. Supporting this, nicotine has also been shown to upregulate various matrix metalloproteinases through E2F-dependent transcription, further promoting invasion and metastasis. Collectively, these pathways enable cancer cells to survive despite cytotoxic treatments, while also accelerating tumor expansion and spread [77].

In addition to these effects on differentiated tumor cells, nicotine has been implicated in the regulation of cancer stem cells, also known as tumor-initiating cells, which have emerged over the past decade as key

contributors to therapeutic resistance [78]. Cancer stem cells are known for their high levels of survival-promoting proteins, transcription factors typical of embryonic stem cells, such as Oct4, Sox2, and Nanog, and the presence of drug resistance transporters like ABCG2. Research by various teams, including our own, has shown that nicotine exposure boosts the self-renewing ability of stem-like cells originating from NSCLC lines. This enhancement was linked to upregulated expression of transcription factors associated with cellular "stemness," particularly Sox2, along with the oncogenic co-activator YAP1. Interestingly, similar effects, marked by increased stem-like features and self-renewal, have also been documented after treating cancer cells with aerosols from electronic cigarettes [79]. Boo et al. [80] investigated how NNK – a potent carcinogen found in tobacco smoke – promotes lung cancer formation at the molecular level. They showed that NNK binds to nAChRs on lung cells, which activates Src kinase and then STAT3 signaling. This leads to increased expression of angiotensinogen (AGT) and activation of the renin-angiotensin (RA) system, particularly the Ang II/AGTR1 pathway. Simultaneously, NNK boosts production and secretion of insulin-like growth factor 2 (IGF2), which activates the IGF-1R/insulin receptor signaling. The combined activation of RA and IGF-1R pathways enhances tumorigenic activity in lung epithelial and stromal cells. Lung tumor development driven by NNK or Src activation was reduced when the RA system was genetically or pharmacologically inhibited, indicating these pathways are key mediators of NNK-induced lung carcinogenesis seen in smokers. Collectively, these data suggest that promotion of cancer stemness represents a key mechanism by which nicotine contributes to chemotherapy resistance.

In addition to its direct effects on tumor cell signaling, smoking influences the systemic availability of chemotherapeutic agents by modifying their metabolic processing. As discussed in a comprehensive review published several years ago, tobacco exposure alters the metabolism of a wide range of chemotherapy and targeted agents through induction of drug-metabolizing enzymes. Wang et al. [81] studied how tobacco smoking rewires cellular metabolism in NSCLC. They discovered that smoking increases a specific post-translational modification called succinylation at lysine 251 (K251-Su) of GAPDH, a key glycolytic enzyme. This modification was found at higher levels in tumors from smokers compared to nonsmokers. Exposure

of lung cancer cells to cigarette smoke extract increased glutamine uptake, providing more succinyl-CoA donors for GAPDH succinylation, which was catalyzed by the enzyme p300. Succinylation at K251 stabilized GAPDH by reducing its ubiquitination and enhanced both glycolysis and glutamine metabolism. These metabolic changes help cancer cells survive and grow in hypoxic and nutrient-deficient environments, thereby promoting tumor growth and metastasis. The study highlights that smoking-induced metabolic reprogramming via GAPDH succinylation is a mechanism driving lung cancer progression and suggests that quitting smoking could be a strategy to target cancer metabolism.

Tobacco smoke components have been shown to induce the expression of cytochrome P450 enzymes, particularly CYP1A1 and CYP1A2, which play key roles in metabolizing drugs like erlotinib. As a result, the active levels of such medications in the bloodstream may be significantly reduced. Additionally, the heightened activity of CYP1 enzymes, along with glucuronyl transferases, can markedly alter both the pharmacokinetics and pharmacodynamics of various anticancer therapies, leading to reduced treatment effectiveness. In addition, CYP2A6, an enzyme involved in nicotine metabolism, has been implicated in susceptibility to chronic obstructive pulmonary disease, further illustrating the systemic impact of tobacco-induced metabolic alterations. Taken together, these enzyme-mediated metabolic effects, in combination with nAChR-driven prosurvival signaling pathways, provide cancer cells with a significant survival advantage and substantially reduce the effectiveness of systemic chemotherapy [82].

Electronic cigarettes, also referred to as electronic nicotine delivery systems, have been promoted as safer alternatives to conventional tobacco products. This perception is largely based on the absence of many classical tobacco carcinogens, as e-cigarettes typically deliver nicotine along with various stabilizing and flavoring agents [83]. As a result, they have been advocated as tools to aid smoking cessation and may indeed offer benefits in that context. Nevertheless, because e-cigarettes still deliver nicotine and contain additives with incompletely characterized biological effects, prolonged use may exert tumor-promoting influences similar to those of nicotine itself and potentially interfere with cancer therapy. At present, data regarding the impact of e-cigarette use on the efficacy of chemotherapy, immunotherapy, or radiotherapy remain limited. However, it is likely that

further evidence addressing these issues will emerge in the coming years. In addition to e-cigarettes, other nicotine delivery modalities, such as water pipes and hookahs, may produce comparable biological effects and warrant similar consideration [84].

Several pharmacological agents that modulate different nAChR subunits have received FDA approval for smoking cessation. These include cytisine, bupropion, and varenicline. They have been shown to exert negative effects on the efficacy of anticancer therapies. Although these drugs differ in their mechanisms of action, they are generally considered safe and well tolerated by most individuals attempting to quit smoking [85,86]. In parallel, non-pharmacological approaches such as behavioral interventions have also demonstrated effectiveness in supporting smoking cessation. Crucially, these approaches completely eliminate the use of nicotine and nicotine-based replacement therapies. Given the documented adverse biological effects of nicotine and certain components of nicotine replacement therapies, the use of approved pharmacological agents or behavioral approaches is often preferable.

6. Conclusions

A substantial body of evidence indicates that smoking adversely affects the efficacy of cancer therapies. Various harmful compounds found in tobacco smoke, such as nicotine and tobacco-specific carcinogens, trigger signaling cascades that support cancer cell survival and alter the tumor microenvironment. These substances also impair drug metabolism and elimination, leading to reduced concentrations of anticancer agents and weaker therapeutic responses. Additionally, the inflammatory nature of tobacco smoke and nicotine compromise's immune function and intensifies treatment-related side effects. Collectively, these effects, along with systemic physiological disturbances, contribute to poorer survival rates among patients who smoke. Persistent smoking after a cancer diagnosis has been consistently associated with worse clinical outcomes, whereas smoking cessation following diagnosis improves treatment response and prognosis. These observations strongly argue for intensified educational and clinical efforts aimed at encouraging smoking cessation among cancer patients. Although e-cigarettes and other nicotine-containing alternatives are sometimes used to facilitate quitting, their long-term use may carry

tumor-promoting risks. Therefore, if such products are employed, their use should ideally be restricted to the shortest possible duration. Enhanced awareness of the benefits of smoking cessation, combined with improved access to cessation resources, has the potential to further decrease cancer incidence and contribute to ongoing reductions in cancer-related mortality.

References:

1. Filho, A. M., Laversanne, M., Ferlay, J., Colombet, M., Piñeros, M., Znaor, A., Parkin, D. M., Soerjomataram, I., & Bray, F. (2025). The GLOBOCAN 2022 cancer estimates: Data sources, methods, and a snapshot of the cancer burden worldwide. *International Journal of Cancer, 156*(7), 1336–1346. https://doi.org/10.1002/ijc.35278

2. Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2022). Cancer statistics, 2022. *CA: A Cancer Journal for Clinicians, 72*(1), 7–33. https://doi.org/10.3322/caac.21708

3. Glantz, S. A., & Johnson, K. C. (2014). The Surgeon General report on smoking and health 50 years later: Breast cancer and the cost of increasing caution. *Cancer Epidemiology, Biomarkers & Prevention, 23*(1), 37–46. https://doi.org/10.1158/1055-9965.EPI-13-1081

4. Lau, L., Conti, A. A., Hemmati, Z., & Baldacchino, A. (2023). The prospective association between the use of e-cigarettes and other psychoactive substances in young people: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews, 153*, 105392. https://doi.org/10.1016/j.neubiorev.2023.105392

5. Dai, X., Gil, G. F., Reitsma, M. B., Ahmad, N. S., Anderson, J. A., Bisignano, C., Carr, S., Feldman, R., Hay, S. I., He, J., Iannucci, V., Lawlor, H. R., Malloy, M. J., Marczak, L. B., McLaughlin, S. A., Morikawa, L., Mullany, E. C., Nicholson, S. I., O'Connell, E. M., … Gakidou, E. (2022). Health effects associated with smoking: A Burden of Proof study. *Nature Medicine, 28*(10), 2045–2055. https://doi.org/10.1038/s41591-022-01978-x

6. Bele, T., Turk, T., & Križaj, I. (2024). Nicotinic acetylcholine receptors in cancer: Limitations and prospects. *Biochimica et Biophysica Acta – Molecular Basis of Disease, 1870*(1), 166875. https://doi.org/10.1016/j.bbadis.2023.166875

7. Xu, Y., Wang, J., He, Z., Rao, Z., Zhang, Z., Zhou, J., Zhou, T., & Wang, H. (2024). A review on the effect of COX-2-mediated mechanisms on development and progression of gastric cancer induced by nicotine. *Biochemical Pharmacology, 220*, 115980. https://doi.org/10.1016/j.bcp.2023.115980

8. Altaf, R., Jadoon, S. S., Muhammad, S. A., Ilyas, U., & Duan, Y. (2022). Recent advances in immune checkpoint inhibitors for non-small lung cancer treatment. *Frontiers in Oncology, 12*, 1014156. https://doi.org/10.3389/fonc.2022.1014156

9. Vallianou, N. G., Evangelopoulos, A., Kounatidis, D., Panagopoulos, F., Geladari, E., Karampela, I., Stratigou, T., & Dalamaga, M. (2023). Immunotherapy

in head and neck cancer: Where do we stand? *Current Oncology Reports, 25*(8), 897–912. https://doi.org/10.1007/s11912-023-01425-1

10. Song, Y., Jiang, S., Peng, Y., Qin, C., Du, Y., & Xu, T. (2024). Effect of FGFR alteration on prognosis in 1963 urothelial carcinoma patients with immune checkpoint inhibitors: Implying combination of FGFR inhibitor and immunotherapy for FGFR-altered urothelial carcinoma. *Pharmacological Research, 205*, 107230. https://doi.org/10.1016/j.phrs.2024.107230

11. Alqarni, K. A. (2025). Recent advances in immunotherapy for bladder cancer treatment. *Cureus, 17*(2), e79002. https://doi.org/10.7759/cureus.79002

12. Roussot, N., Kaderbhai, C., & Ghiringhelli, F. (2025). Targeting immune checkpoint inhibitors for non-small-cell lung cancer: Beyond PD-1/PD-L1 monoclonal antibodies. *Cancers, 17*(5), 906. https://doi.org/10.3390/cancers17050906

13. Aden, D., Zaheer, S., Sureka, N., Trisal, M., Chaurasia, J. K., & Zaheer, S. (2025). Exploring immune checkpoint inhibitors: Focus on PD-1/PD-L1 axis and beyond. *Pathology Research and Practice, 269*, 155864. https://doi.org/10.1016/j.prp.2025.155864

14. Cheng, W., Kang, K., Zhao, A., & Wu, Y. (2024). Dual blockade immunotherapy targeting PD-1/PD-L1 and CTLA-4 in lung cancer. *Journal of Hematology & Oncology, 17*(1), 54. https://doi.org/10.1186/s13045-024-01581-2

15. Liang, L., Kuang, X., He, Y., Zhu, L., Lau, P., Li, X., Luo, D., Gong, L., Zhou, W., Zhang, F., Liang, X., Li, Z., Hu, B., Liu, D., Ding, T., Li, H., Zhao, S., Su, J., … Chen, X. (2025). Alterations in PD-L1 succinylation shape anti-tumor immune responses in melanoma. *Nature Genetics, 57*(3), 680–693. https://doi.org/10.1038/s41588-025-02077-6

16. Minervini, F., Lampridis, S., Kestenholz, P., Pardo, E., Crommelinck, J., Putora, P. M., Schnider, M., Petroncini, M., Mayer, N., & Bertoglio, P. (2025). The impact of smoking on lung cancer patients. *European Respiratory Review, 34*(176), 240175. https://doi.org/10.1183/16000617.0175-2024

17. Chen, Y. B., Yang, X., Lv, D., Tang, L. Y., & Liu, Y. W. (2025). A prognostic model constructed by ferroptosis-associated genes (FAGs) in papillary renal cell carcinoma (PRCC) and its association with tumor mutation burden (TMB) and immune infiltration. *Clinical and Translational Oncology, 27*(3), 1232–1247. https://doi.org/10.1007/s12094-024-03617-y

18. Wang, X., Ricciuti, B., Elkrief, A., Alessi, J. V., Di Federico, A., Pecci, F., Nishino, M., Gulhan, D., Ananda, G., Rodig, S. J., Sholl, L., Johnson, B., Lin, X., Schoenfeld, A., Awad, M. M., Christiani, D. (2025). Multi-omics analysis reveals differential benefits of immunotherapy ± chemotherapy based on detailed smoking history in advanced non-small cell lung cancer. *Journal for ImmunoTherapy of Cancer, 13*(12), e012205. https://doi.org/10.1136/jitc-2025-012205

19. Mimura, K., & Yoshida, K. (2025). The genetic footprint of tobacco smoking: Unraveling the mutational signatures in head and neck cancer. *Cancer Research, 85*(15), 2781–2783. https://doi.org/10.1158/0008-5472.CAN-25-1990

20. Griffith, B. D., Kadiyala, P., McGue, J., Sun, L., Kumar, A., Espinoza, C. E., Donahue, K. L., Iyer, M. K., Speyer, C., Nelson, S., Spiteri, A., Elhossiny, A. M.,

Brown, K., Attebury, H., Bednar, F., Carpenter, E. S., Kryczek, I., Zhang, Y., Zou, W., … Frankel, T. L. (2025). Aryl hydrocarbon receptor ligands drive pancreatic cancer initiation and progression through pro-tumorigenic T cell polarization. *Cancer Discovery.* https://doi.org/10.1158/2159-8290.CD-25-0377

21. Yang, L., Wang, H., Tian, P., & Li, W. (2025). Prognostic stratification through smoking status and cumulative smoking dose in advanced non-small cell lung cancer immunotherapy: A dose-dependent real-world analysis. *Frontiers in Oncology, 15*, 1590825. https://doi.org/10.3389/fonc.2025.1590825

22. Cortellini, A., De Giglio, A., Cannita, K., Cortinovis, D. L., Cornelissen, R., Baldessari, C., Giusti, R., D'Argento, E., Grossi, F., Santoni, M., Catino, A., Berardi, R., Sforza, V., Rossi, G., Antonuzzo, L., Di Noia, V., Signorelli, D., Gelibter, A., Occhipinti, M. A., Follador, A., … Ficorella, C. (2021). Smoking status during first-line immunotherapy and chemotherapy in NSCLC patients: A case-control matched analysis from a large multicenter study. *Thoracic Cancer, 12*(6), 880–889. https://doi.org/10.1111/1759-7714.13852

23. Zhao, W., Jiang, W., Wang, H., He, J., Su, C., & Yu, Q. (2021). Impact of smoking history on response to immunotherapy in non-small-cell lung cancer: A systematic review and meta-analysis. *Frontiers in Oncology, 11*, 703143. https://doi.org/10.3389/fonc.2021.703143

24. Lackovic, L. N., Tomic, M. S., Novakovic, M., Turic, M., Kajkut, A., Macinkovic, T., Stanetic, M., & Glamocak, R. (2025). Pembrolizumab in the treatment of non-small cell lung cancer – experiences from clinical practice. *Frontiers in Medicine (Lausanne), 12*, 1635626. https://doi.org/10.3389/fmed.2025.1635626

25. Ullah, A., Pulliam, S., Karki, N. R., Khan, J., Jogezai, S., Sultan, S., Muhammad, L., Khan, M., Jamil, N., Waheed, A., Belakhlef, S., Ghleilib, I., Vail, E., Heneidi, S., & Karim, N. A. (2022). PD-L1 over-expression varies in different subtypes of lung cancer: Will this affect future therapies? *Clinical Practice, 12*(5), 653–671. https://doi.org/10.3390/clinpract12050068

26. Zhu, P., Jin, Z., Kang, G., Jia, Y., Liu, D., Zhang, Q., Guo, F., Jia, Y., Jiao, Y., Li, J., Sun, H., & Ma, X. (2022). Alpha5 nicotinic acetylcholine receptor mediated immune escape of lung adenocarcinoma via STAT3/Jab1-PD-L1 signalling. *Cell Communication and Signaling, 20*(1), 121. https://doi.org/10.1186/s12964-022-00934-z

27. Peng, L., Guo, J., Kong, L., Huang, Y., Tang, N., Zhang, J., Wang, M., He, X., Li, Z., Peng, Y., Wang, Z., & Han, X. (2023). Efficacy of immunotherapy in KRAS-mutant advanced NSCLC: A real-world study in a Chinese population. *Frontiers in Oncology, 12*, 1070761. https://doi.org/10.3389/fonc.2022.1070761

28. Gao, Y., Gong, Y., Lu, J., Hao, H., & Shi, X. (2024). Targeting YAP1 to improve the efficacy of immune checkpoint inhibitors in liver cancer: Mechanism and strategy. *Frontiers in Immunology, 15*, 1377722. https://doi.org/10.3389/fimmu.2024.1377722

29. Yang, K. (2025). Impact of smoking on the effectiveness of different non-small-cell lung cancer therapies. *Translational Cancer Research, 14*(7), 4461–4473. https://doi.org/10.21037/tcr-2025-145

30. Johnson, M. M., Kaushik, A., Kline, O. A., Smith, E. M., Zhou, X., Pat, Y., Buergi, L., Aguilera, J., Alkotob, S., Simonin, E. M., Favaro, A., Couto, M., Bennett, O., Chinthrajah, R. S., Parsons, E., Shamji, M., Burke, M., Bondy, M., Akdis, M., … Nadeau, K. C. (2025). Immune impacts of fire smoke exposure. *Nature Medicine, 31*(9), 3110–3120. https://doi.org/10.1038/s41591-025-03777-6

31. de Oca, M. M., Perez-Padilla, R., Celli, B., Aaron, S. D., Wehrmeister, F. C., Amaral, A. F. S., Mannino, D., Zheng, J., Salvi, S., Obaseki, D., Buist, A. S., & Menezes, A. (2025). The global burden of COPD: Epidemiology and effect of prevention strategies. *The Lancet Respiratory Medicine, 13*(8), 709–724. https://doi.org/10.1016/S2213-2600(24)00339-4

32. Huang, Y., Liang, B., Chen, X., Li, Z., Deng, Y., Du, J., Zhong, Y., Lin, X., Fu, J., Xie, J., Zhang, X., & Huang, Z. (2025). Enhanced immunotherapy response in lung adenocarcinoma patients with COPD: Insights into tumor cells and immune microenvironment characteristics. *Cell Communication and Signaling, 23*(1), 324. https://doi.org/10.1186/s12964-025-02332-7

33. Schaefers, C., Seidel, C., Bokemeyer, F., & Bokemeyer, C. (2022). The prognostic impact of the smoking status of cancer patients receiving systemic treatment, radiation therapy, and surgery: A systematic review and meta-analysis. *European Journal of Cancer, 172*, 130–137. https://doi.org/10.1016/j.ejca.2022.05.027

34. Jun, S., Park, H., Kim, U. J., Lee, H. A., Park, B., Lee, S. Y., Jee, S. H., & Park, H. (2024). The combined effects of alcohol consumption and smoking on cancer risk by exposure level: A systematic review and meta-analysis. *Journal of Korean Medical Science, 39*(22), e185. https://doi.org/10.3346/jkms.2024.39.e185

35. Pala, M., Novakova, P., Drbohlavova, T., Vrana, A., Pechacova, Z., Votavova, K., Subrt, A., Krejci, D., Holeckova, P., & Tesarova, P. (2023). Negative prognostic impact of smoking on long-term survival in patients with nasopharyngeal carcinoma treated with curative (chemo)radiotherapy. *In Vivo, 37*(4), 1775–1785. https://doi.org/10.21873/invivo.13266

36. Caini, S., Del Riccio, M., Vettori, V., D'Ecclesiis, O., Bonomo, P., Locatello, L. G., Salvestrini, V., Gallo, O., Tagliabue, M., Raimondi, S., Saieva, C., Cozzolino, F., Bendinelli, B., & Gandini, S. (2022). Post-diagnosis smoking cessation and survival of patients with head and neck cancer: A systematic review and meta-analysis. *British Journal of Cancer, 127*(11), 1907–1915. https://doi.org/10.1038/s41416-022-01945-w

37. Fox, J. L., Rosenzweig, K. E., & Ostroff, J. S. (2004). The effect of smoking status on survival following radiation therapy for non-small cell lung cancer. *Lung Cancer, 44*(3), 287–293. https://doi.org/10.1016/j.lungcan.2003.11.012

38. Nguyen, S. K., Masson-Côté, L., Fortin, A., & Dagnault, A. (2010). Influence of smoking status on treatment outcomes after post-operative radiation therapy for non-small-cell lung cancer. *Radiotherapy and Oncology, 96*(1), 89–93. https://doi.org/10.1016/j.radonc.2010.05.008

39. Shen, Y., Huang, Q., Yuan, X., Gong, H., Xu, C., Du, H., Hsueh, C. Y., & Zhou, L. (2024). Nicotine-induced activation of cholinergic receptor nicotinic alpha 5 subunit mediates the malignant behaviours of laryngeal squamous

epithelial cells by interacting with RABL6. *Cell Death Discovery, 10*(1), 286. https://doi.org/10.1038/s41420-024-02051-x

40. Lin, C. H., Lee, H. H., Kuei, C. H., Lin, H. Y., Lu, L. S., Lee, F. P., Chang, J., Wang, J. Y., Hsu, K. C., & Lin, Y. F. (2019). Nicotinic acetylcholine receptor subunit alpha-5 promotes radioresistance via recruiting E2F activity in oral squamous cell carcinoma. *Journal of Clinical Medicine, 8*(9), 1454. https://doi.org/10.3390/jcm8091454

41. Chellappan, S. (2022). Smoking cessation after cancer diagnosis and enhanced therapy response: Mechanisms and significance. *Current Oncology, 29*(12), 9956–9969. https://doi.org/10.3390/curroncol29120782

42. Johnston-Early, A., Cohen, M. H., Minna, J. D., Paxton, L. M., Fossieck, B. E. Jr., Ihde, D. C., Bunn, P. A. Jr., Matthews, M. J., & Makuch, R. (1980). Smoking abstinence and small cell lung cancer survival: An association. *JAMA, 244*(19), 2175–2179.

43. Gummerson, S. P., Lowe, J. T., Taylor, K. L., Lobo, T., & Jensen, R. E. (2022). The characteristics of patients who quit smoking in the year following a cancer diagnosis. *Journal of Cancer Survivorship, 16*(1), 111–118. https://doi.org/10.1007/s11764-021-01009-7

44. Tsao, A. S., Liu, D., Lee, J. J., Spitz, M., & Hong, W. K. (2006). Smoking affects treatment outcome in patients with advanced non-small cell lung cancer. *Cancer, 106*(11), 2428–2436. https://doi.org/10.1002/cncr.21884

45. Huang, H., Ding, C., Zhao, W. H., Zhang, H. B., Zhao, Z. X., Li, X. G., Wang, Y. J., Chen, P. J., Li, B. S., Li, X. B., Li, Y. W., Liu, H. Y., & Chen, J. (2025). Nicotine promotes the progression and metastasis of non-small cell lung cancer by modulating the OTUB1–c-Myc–EZH2 axis. *Acta Pharmacologica Sinica, 46*(9), 2509–2521. https://doi.org/10.1038/s41401-025-01527-5

46. Duarte, R. L., Luiz, R. R., & Paschoal, M. E. (2008). The cigarette burden (measured by the number of pack-years smoked) negatively impacts the response rate to platinum-based chemotherapy in lung cancer patients. *Lung Cancer, 61*(2), 244–254. https://doi.org/10.1016/j.lungcan.2007.12.008

47. Eng, L., Alton, D., Song, Y., Su, J., Zhang, Q., Che, J., Farzanfar, D., Mohan, R., Krys, O., Mattina, K., Harper, C., Liu, S., Yoannidis, T., Milne, R., Abdelmutti, N., Brown, M. C., Vennettilli, A., Hope, A. J., Howell, D., ... Liu, G. (2020). Awareness of the harms of continued smoking among cancer survivors. *Supportive Care in Cancer, 28*(7), 3409–3419. https://doi.org/10.1007/s00520-019-05175-4

48. Halms, T., Strasser, M., Hasan, A., Rüther, T., Rabenstein, A., Trepel, M., Raab, S., & Gertzen, M. (2025). Determinants of quality of life among lung cancer patients: Insights from a cross-sectional study. *European Archives of Psychiatry and Clinical Neuroscience*. Advance online publication. https://doi.org/10.1007/s00406-025-02086-w

49. Halms, T., Strasser, M., Hasan, A., Rüther, T., Trepel, M., Raab, S., & Gertzen, M. (2024). Smoking and quality of life in lung cancer patients: Systematic review. *BMJ Supportive & Palliative Care, 13*(e3), e686–e694. https://doi.org/10.1136/spcare-2023-004256

50. Peppone, L. J., Mustian, K. M., Morrow, G. R., Dozier, A. M., Ossip, D. J., Janelsins, M. C., Sprod, L. K., & McIntosh, S. (2011). The effect of cigarette smoking on cancer treatment-related side effects. *The Oncologist, 16*(12), 1784–1792. https://doi.org/10.1634/theoncologist.2011-0169

51. Krutz, M., Acharya, P., Chissoe, G., Raj, V., Driskill, L., Krempl, G., Zhao, D., Mhawej, R., & Queimado, L. (2022). Tobacco cessation after head and neck cancer diagnosis is an independent predictor of treatment response and long-term survival. *Oral Oncology, 134*, 106072. https://doi.org/10.1016/j.oraloncology.2022.106072

52. Xiang, L., Xie, Q. Q., Xu, S. S., Ruan, W. J., Xu, D. H., Gan, Y. Y., Zuo, J., Xu, W. J., & Li, Z. P. (2024). Association between tobacco exposure and bladder cancer recurrence: A systematic review and meta-analysis. *World Journal of Methodology, 14*(2), 91889. https://doi.org/10.5662/wjm.v14.i2.91889

53. Marcq, G., Kassouf, W., Roumiguié, M., Pradere, B., Mertens, L. S., Albisinni, S., Cimadamore, A., Teoh, J. Y.-C., Moschini, M., Laukhtina, E., Mari, A., Soria, F., Gallioli, A., Del Giudice, F., d'Andrea, D., Krajewski, W., Beauval, J. B., Xylinas, E., Pouessel, D., ... Ploussard, G. (2025). Oncological outcomes of patients with node positive disease following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive bladder cancer: A multicenter observational study of the EAU Young Academic Urologists (YAU) urothelial carcinoma working group. *Actas Urológicas Españolas (English Edition), 49*(2), 501701. https://doi.org/10.1016/j.acuroe.2025.501701

54. Ślusarczyk, A., Zapała, P., Zapała, Ł., & Radziszewski, P. (2023). The impact of smoking on recurrence and progression of non-muscle invasive bladder cancer: A systematic review and meta-analysis. *Journal of Cancer Research and Clinical Oncology, 149*(6), 2673–2691. https://doi.org/10.1007/s00432-022-04464-6

55. He, T., Hu, J., Qiu, D., Deng, H., Hu, J., Chen, J., & Zu, X. (2021). Smoking status and pathological response to neoadjuvant chemotherapy among patients with bladder cancer: A pooled analysis. *Translational Andrology and Urology, 10*(1), 374–383. https://doi.org/10.21037/tau-20-1086

56. Lauri, G., Apadula, L., Archibugi, L., Lazzano, P., Ponz de Leon Pisani, R., Cobreros, M., Tacelli, M., Marchegiani, G., Crippa, S., Falconi, M., Arcidiacono, P. G., & Capurso, G. (2025). Association of smoking with progression from low-risk to high-risk intraductal papillary mucinous neoplasms and pancreatic cancer. *Digestive and Liver Disease, 57*(1), 38–43. https://doi.org/10.1016/j.dld.2024.05.017

57. Du, R., Wang, Y., Pan, M., Zhu, J., Zhao, Y., Zhang, C., Liu, C., & Gao, Y. (2025). Global, regional, and national burdens of pancreatic cancer attributable to smoking from 1990 to 2021 and the projections to 2035: A systematic analysis from the Global Burden of Disease Study 2021. *Frontiers in Oncology, 15*, 1547029. https://doi.org/10.3389/fonc.2025.1547029

58. Caliri, A. W., Tommasi, S., & Besaratinia, A. (2021). Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. *Mutation Research/Reviews in Mutation Research, 787*, 108365. https://doi.org/10.1016/j.mrrev.2021.108365

59. Ji, T., Huang, G., Cao, Y., Gao, Y., & Gao, X. (2025). Advances in interleukin-6 family cytokines and the role in respiratory diseases. *Journal of Inflammation Research, 18*, 3125–3141. https://doi.org/10.2147/JIR.S508031

60. Li, Y., & Hecht, S. S. (2022). Carcinogenic components of tobacco and tobacco smoke: A 2022 update. *Food and Chemical Toxicology, 165*, 113179. https://doi.org/10.1016/j.fct.2022.113179

61. Perlík, F. (2020). Impact of smoking on metabolic changes and effectiveness of drugs used for lung cancer. *Central European Journal of Public Health, 28*(1), 53–58. https://doi.org/10.21101/cejph.a5620

62. O'Malley, M., Healy, P., Daignault, S., & Ramnath, N. (2013). Cigarette smoking and gemcitabine-induced neutropenia in advanced solid tumors. *Oncology, 85*(4), 216–222. https://doi.org/10.1159/000355107

63. Vivarelli, F., Morosini, C., Rullo, L., Losapio, L. M., Lacorte, A., Sangiorgi, S., Ghini, S., Fagiolino, I., Franchi, P., Lucarini, M., Candeletti, S., Canistro, D., Romualdi, P., & Paolini, M. (2024). Effects of unburned tobacco smoke on inflammatory and oxidative mediators in the rat prefrontal cortex. *Frontiers in Pharmacology, 15*, 1328917. https://doi.org/10.3389/fphar.2024.1328917

64. Peterson, L. A., Stanfill, S. B., & Hecht, S. S. (2024). An update on the formation in tobacco, toxicity and carcinogenicity of N'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. *Carcinogenesis, 45*(5), 275–287. https://doi.org/10.1093/carcin/bgae018

65. Wang, M. L., Hsu, Y. F., Liu, C. H., Kuo, Y. L., Chen, Y. C., Yeh, Y. C., Ho, H. L., Wu, Y. C., Chou, T. Y., & Wu, C. W. (2020). Low-dose nicotine activates EGFR signaling via α5-nAChR and promotes lung adenocarcinoma progression. *International Journal of Molecular Sciences, 21*(18), 6829. https://doi.org/10.3390/ijms21186829

66. Yamamoto, S., Koyanagi, Y. N., Iwashita, Y., Shinozaki, T., Fujiwara, Y., Sakakura, N., Hara, M., Nishida, Y., Otonari, J., Ikezaki, H., Tanoue, S., Koriyama, C., Kasugai, Y., Oze, I., Koyama, T., Tomida, S., Michihata, N., Nakamura, Y., Suzuki, S., ... Matsuo, K. (2025). Smoking behavior-related genetic variants and lung cancer risk in Japanese: An assessment by mediation analysis. *Carcinogenesis, 46*(2), bgaf011. https://doi.org/10.1093/carcin/bgaf011

67. Jackson, D. C., Hall, M. K., & Sudweeks, S. N. (2025). The human alpha3 beta2 neuronal nicotinic acetylcholine receptor can form two distinguishable subtypes. *International Journal of Molecular Sciences, 26*(19), 9506. https://doi.org/10.3390/ijms26199506

68. Wang, J., Cai, J., Wang, Z., Yang, S., Wang, J., Jia, Y., Sun, H., & Ma, X. (2025). α5-nAChR/NETO2 contributed to chronic stress-promoted lung adenocarcinoma progression. *Cancer Cell International, 25*(1), 67. https://doi.org/10.1186/s12935-025-03701-5

69. Zhao, J., Yu, L., Xue, X., Xu, Y., Huang, T., Xu, D., Wang, Z., Luo, L., & Wang, H. (2023). Diminished α7 nicotinic acetylcholine receptor (α7nAChR) rescues amyloid-β induced atrial remodeling by oxi-CaMKII/MAPK/AP-1 axis-mediated mitochondrial oxidative stress. *Redox Biology, 59*, 102594. https://doi.org/10.1016/j.redox.2022.102594

70. Tsetlin, V. I., Kasheverov, I. E., & Utkin, Y. N. (2021). Three-finger proteins from snakes and humans acting on nicotinic receptors: Old and new. *Journal of Neurochemistry, 158*(6), 1223–1235. https://doi.org/10.1111/jnc.15123

71. Dasgupta, P., Kinkade, R., Joshi, B., Decook, C., Haura, E., & Chellappan, S. (2006). Nicotine inhibits apoptosis induced by chemotherapeutic drugs by up-regulating XIAP and survivin. *Proceedings of the National Academy of Sciences of the United States of America, 103*(16), 6332–6337. https://doi.org/10.1073/pnas.0509313103

72. Tsurutani, J., Castillo, S. S., Brognard, J., Granville, C. A., Zhang, C., Gills, J. J., Sayyah, J., & Dennis, P. A. (2005). Tobacco components stimulate Akt-dependent proliferation and NFκB-dependent survival in lung cancer cells. *Carcinogenesis, 26*(7), 1182–1195. https://doi.org/10.1093/carcin/bgi072

73. Cheng, W. L., Chen, K. Y., Lee, K. Y., Feng, P. H., & Wu, S. M. (2020). Nicotinic-nAChR signaling mediates drug resistance in lung cancer. *Journal of Cancer, 11*(5), 1125–1140. https://doi.org/10.7150/jca.36359

74. Tang, J., Li, Z., Lu, L., & Cho, C. H. (2013). β-Adrenergic system, a backstage manipulator regulating tumour progression and drug target in cancer therapy. *Seminars in Cancer Biology, 23*(6 Pt B), 533–542. https://doi.org/10.1016/j.semcancer.2013.08.009

75. Yang, Y., Cheng, C., He, B., Du, X., Liu, J., Xia, H., Wang, P., Wu, M., Wu, H., & Liu, Q. (2023). Cigarette smoking, by accelerating the cell cycle, promotes the progression of non-small cell lung cancer through an HIF-1α-METTL3-m6A/CDK2AP2 axis. *Journal of Hazardous Materials, 455*, 131556. https://doi.org/10.1016/j.jhazmat.2023.131556

76. Pakharukova, N., Thomas, B. N., Bansia, H., Li, L., Bassford, D. K., Abzalimov, R. R., Kim, J., Kahsai, A. W., Pani, B., Xiao, K., Ochakovski, R., Liu, S., Zhang, X., Ahn, S., des Georges, A., & Lefkowitz, R. J. (2025, September 27). Mechanism of beta-arrestin 1 mediated Src activation via Src SH3 domain revealed by cryo-electron microscopy. *bioRxiv*. https://doi.org/10.1101/2024.07.31.605623

77. Pillai, S., Trevino, J., Rawal, B., Singh, S., Kovacs, M., Li, X., Schell, M., Haura, E., Bepler, G., & Chellappan, S. (2015). β-arrestin-1 mediates nicotine-induced metastasis through E2F1 target genes that modulate epithelial-mesenchymal transition. *Cancer Research, 75*(6), 1009–1020. https://doi.org/10.1158/0008-5472.CAN-14-0681

78. Cortes-Dericks, L., & Galetta, D. (2022). Impact of cancer stem cells and cancer stem cell-driven drug resiliency in lung tumor: Options in sight. *Cancers, 14*(2), 267. https://doi.org/10.3390/cancers14020267

79. Perumal, D., Pillai, S., Nguyen, J., Schaal, C., Coppola, D., & Chellappan, S. P. (2014). Nicotinic acetylcholine receptors induce c-Kit ligand/Stem Cell Factor and promote stemness in an ARRB1/β-arrestin-1 dependent manner in NSCLC. *Oncotarget, 5*(21), 10486–10502. https://doi.org/10.18632/oncotarget.2395

80. Boo, H. J., Min, H. Y., Hwang, S. J., Lee, H. J., Lee, J. W., Oh, S. R., Park, C. S., Park, J. S., Lee, Y. M., & Lee, H. Y. (2023). The tobacco-specific carcinogen NNK induces pulmonary tumorigenesis via nAChR/Src/STAT3-

mediated activation of the renin-angiotensin system and IGF-1R signaling. *Experimental & Molecular Medicine, 55*(6), 1131–1144. https://doi.org/10.1038/s12276-023-00994-2

81. Wang, K., Li, J., Zhang, H., Ma, H., Cui, H. Y., Ju, H. Q., Zhang, J., Ma, Q. Z., Zhao, M., Zeng, Q. M., Zou, J., Sun, X. X., Nan, G., Qian, M., Jing, L., Li, Y., Xiong, C. F., Yang, Q. Z., Wang, H., ... Huang, W. (2025). Tobacco smoking rewires cell metabolism by inducing GAPDH succinylation to promote lung cancer progression. *Cancer Research, 85*(15), 2838–2857. https://doi.org/10.1158/0008-5472.CAN-24-3525

82. von Weymarn, L. B., Thomson, N. M., Le Marchand, L., & Murphy, S. E. (2025). CYP2A6 activity and deuterated 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) metabolism in cigarette smokers. *Chemical Research in Toxicology, 38*(10), 1771–1777. https://doi.org/10.1021/acs.chemrestox.5c00310

83. Lindson, N., Butler, A. R., McRobbie, H., Bullen, C., Hajek, P., Wu, A. D., Begh, R., Theodoulou, A., Notley, C., Rigotti, N. A., Turner, T., Livingstone-Banks, J., Morris, T., & Hartmann-Boyce, J. (2025). Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews, 1*(1), CD010216. https://doi.org/10.1002/14651858.CD010216.pub9

84. Lee, P. N., & Farsalinos, K. (2025). Comparing smoking-related disease rates from e-cigarette use with those from tobacco cigarette use: A reanalysis of a recently-published study. *Harm Reduction Journal, 22*(1), 78. https://doi.org/10.1186/s12954-025-01230-y

85. Meng, Y., Xiang, S., Qu, L., & Li, Y. (2024). The efficacy and acceptability of pharmacological monotherapies and e-cigarette on smoking cessation: A systemic review and network meta-analysis. *Frontiers in Public Health, 12*, 1361186. https://doi.org/10.3389/fpubh.2024.1361186

86. Mir, H., Heshmati, J., Mullen, K. A., Baldwin, A., Quirouette, E., Pipe, A., & Reid, R. (2025). Cytisine compared to combination nicotine replacement therapy to reduce cigarette consumption in relapsed smokers: Protocol for a pilot randomized controlled trial. *Pilot and Feasibility Studies, 11*(1), 10. https://doi.org/10.1186/s40814-024-01591-4