Journal of Pharmaceutical Advanced Research
(An International Multidisciplinary Peer Review Open Access monthly Journal)
Available online at: www.jparonline.com

REVIEW ARTICLE JPAR 2024

Relationship between Nicotin and Cancer – A Comprehensive Review

Priyanka Tanwar[1], Mamta Naagar[2], Manish Kumar Maity[2]*

[1]Department of Pharmacology, Bhagvan Mahavir Institute of Medical Sciences, Sonipat-131030, Haryana, India.
[2]Department of Pharmacy Practice, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be university), Mullana-133207, Ambala, Haryana, India.

Received: 06.09.2024 Revised: 16.09.2024 Accepted: 22.09.2024 Published: 30.09.2024

ABSTRACT: It is widely accepted that smoking is the single most significant preventable human cause of cancer. In this study, the data linking nicotine to the development of cancer is reviewed and discussed. Tobacco-related cancer is definitely influenced by the carcinogenic chemicals found in tobacco smoke and tobacco products intended for oral use, including tobacco-specific N-nitrosamines (TSNA) and polycyclic hydrocarbons. Recent research has demonstrated that nicotine can affect many critical stages in the cancer formation process and raises the possibility that it could exacerbate and recurrence the illness. Nicotine has the ability to generate TSNA in the body. It is possible that the primary addictive ingredient in tobacco products, nicotine, diverted our focus from the harmful effects of these substances on angiogenesis, cell proliferation and tumour malignancy. When assessing potential long-term impacts from nicotine sources, such e-cigarettes and products for nicotine replacement therapy, which both have a lifetime usage potential, effects on cancer illness are significant factors to consider.

Corresponding author:
Mr. Manish Kumar Maity
Research Scholar,
Department of Pharmacy Practice,
MM College of Pharmacy,
Maharishi Markandeshwar (Deemed to be university), Mullana-133207, Ambala, Haryana, India
Tel: +91-8945048395
E. Mail ID: manishkumarmaity@gmail.com

Keywords: Nicotine, Tobacco, Cancer, Carcinogen, N-nitrosamines, Tumor.

INTRODUCTION:

The main ingredient in tobacco products that causes addiction is nicotine. Nicotine is in the non-ionized form and easily absorbed by the skin, nasal mucosa, lung epithelium, and oral mucosa with high pH (alkaline). A daily smoker of 25 cigarettes will absorb around 0.43 mg of nicotine per kilogramme of body weight and achieve a blood concentration of nicotine between 4 to 72 ng/ml (0.025 - 0.444 μM) [1,2]. Nicotine's half-life in plasma is approximately 2 h [3]. In the liver, about 80 % of the absorbed nicotine is metabolised, mostly by CYP2A6, UDP-glucuronosyltransferase and a monooxygenase that contains flavin. One of the main metabolites is cotinine. Nornicotine is a minor tobacco alkaloid and a metabolite of nicotine that is created when nicotine is demethylated. Up to 85 to 90 % of nicotine is metabolised before being

excreted by the kidneys [1]. Smokers had a blood concentration of 200 to 400 ng/ml (1.1 to 2.2 μM) of cotinine [3]. Nicotine acts by stimulating the nicotinic acetylcholine receptors (nAChRs), which are part of the parasympathetic autonomic nervous system and are found in the central nervous system (CNS), at autonomic nervous system interganglionic junctions, and on target organs throughout the body. The five membrane-spanning subunits that make up nAChRs, which are ligand-gated ion channels, come together to create a functioning receptor [4]. Although other receptor subunits could possibly be involved, the homomeric α7-nAChR has been identified as the main receptor mediating nicotine-mediated cell proliferation.[5] Nicotine exhibits a greater affinity for nAChRs than does acetylcholine (Ach). Cotinine and N-nitrosamines (TSNA) unique to tobacco may also bind to nAChRs [5 –7].The rewarding effects of nicotine and the modifications that follow long-term exposure, which lead to dependence and withdrawal symptoms are both influenced by nicotine's binding to nAChR in the brain. Dopamine is released as a primary cause of the positive reinforcing effects of nicotine addiction.[1] Numerous lines of evidence suggest that nicotine may have a role in the onset of cancer. Experimental in vitro research on cell cultures, *in vivo* research on rodents, and research on humans, including epidemiological studies, provide evidence that nicotine, alone or in combination with other tobacco constituents, may stimulate several effects important for the development of cancer [5, 6].

Endogenous Formation of TSNA:

N-nitrosation of tobacco's alkaloids produces tobacco-specific N-nitrosamines. NNK (4-(metylnitrosamino)-1-(3-pyridyl)-1-butanon) and NNN (N′-nitrosonornicotine) are two of the most significant and powerful carcinogens found in tobacco and tobacco smoke. A common method to evaluate the potential involvement of TSNA in tumour formation is to measure the total amount of NNAL (NNAL and its glucuronides) in urine. NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) is a metabolite of NNK. Total NNAL has been reported to be significantly correlated with lung cancer risk in smokers' blood samples [8]. The International Agency for Cancer Research (IARC) has designated NNN and NNK as human carcinogens [9,10]. It is commonly known that NNN and NNK may be found in moist snuff as well as in mainstream and sidestream cigarette smoke [11]. Bartsch and Spiegelhalder noted in the 1996 review that people might naturally produce N-nitrosamines [12]. In rats given tobacco alkaloids and NaNO2, endogenous TSNA production has been shown [13,14]. Although NNK is not produced *in vivo*, as some early investigations stated [13,15], more recent results refute this notion. Consequently, total NNAL (a NNK metabolite) in the urine of Swedish snus users is still significant and only decreased to roughly half of that found in smokers and users of old-style snuff, despite the fact that the level of NNK in Swedish snus is significantly lower than in cigarette smoke and the old-style snuff [16]. When compared to non-smokers exposed to ETS,[18] users of nicotine replacement therapy (NRT) [17] also had higher levels of total NNAL. It is interesting to note that there does not seem to be a significant difference in the risk of pancreatic cancer across the various tobacco products [9]. Additionally, it has been noted that nornicotine in human saliva can generate NNN [19]. According to a recent study by Hecht, *et al*, there was very little endogenous TSNA production following nicotine inhalation in the urine of e-cigarette users [20]. According to the aforementioned findings, TSNA may develop endogenously following nicotine absorption through the skin and mucous membranes in the oral cavity, but it may not occur at all following lung absorption. Therefore, the mode of administration may affect the toxicokinetics of nicotine.

Table 1. Level of NNAL in urine from smokers, users of "old" snuff in USA (smokeless tobacco), users of "modern" Swedish snus and of NRT compared to people exposed to ETS [17,18,21].

Group	Total NNAL (pmol/mg creatinine)
Smokers	2.6 (0.3 to 3.9) (95% Confidence interval)
Snuff (Old type)	3.3 (1.5–5.1)
Swedish snus	1.4 (0.9–2.0)
NRT	0.3 (0.1–0.4)
Non-smokers exposed to ETS	0.042 ± 0.020 [±SD]

Genotoxicity of Nicotine:

Rats exposed to nicotine had their urine tested for Salmonella in most trials, but the results were negative. On the other hand, the Escherichia coli pol A+/pol− assay has demonstrated that nicotine causes damage to DNA [22]. In two investigations using the CHO cell line, chromosomal aberration (CA) and sister chromatid exchange (SCE) were shown to be present [23,24]. Later, in studies using human lymphocytes, Ginzkey, *et al*. [25] verified these findings. At the lowest measured

concentration of 1 µM nicotine, which is just 2 to 3 times greater than what is seen in smokers' blood, they discovered a substantial rise in both CA and SCE [2]. The most significant lesion causing the observed CA is thought to be DNA double-strand breaks (DSB) with incomplete repair. Studies utilising the "Comet" assay have documented the effects of nicotine on human tonsillar tissue,[28] parotid gland cells [29], spermatozoa [30], and nasal mucosa [26,27]. However, after 24 h of incubation, Ginzkey, *et al*, [25] could not find any evidence of nicotine's impact on human lymphocytes. The absence of effects could be caused by potential repair of DNA single-strand breaks during the 24-hour incubation period, according to the authors, since the Comet assay is known to detect DNA single-strand breaks (SSB), alkali-labile sites, and incomplete excision-repair sites in proliferating and non-proliferating cells. When Argentin and Cicchett used human gingival fibroblasts to study the creation of micronuclei (MN) by nicotine, they discovered that treating the cells with 1 µM nicotine greatly increased the frequency of MNs [31]. Antioxidant additions dramatically reduced the development of MN, hence mitigating the effects of nicotine. A work involving human cells, also reported induction of MN; nevertheless, a larger dosage of nicotine (100 µM) was required [25]. Chromosome breakage and disruption of the chromosome-segregation system are the mechanisms that contribute to the creation of MN; hence, MN formation constitutes an irreversible harm to DNA. Cheng et al. demonstrated the production of an adduct between nicotine and DNA [32]. Hecht, however, has conducted a more recent investigation that does not support this [33]. The processes that give rise to nicotine's genotoxic effects are yet unknown. However, it is crucial that the effects are felt at nicotine concentrations that are not all that different from what smokers' blood contains. The observation that the effects of nicotine diminish when antioxidants are present implies the involvement of oxidative radicals. Furthermore, co-incubation with a nAChR antagonist has been shown to reduce DNA damage, suggesting a receptor-dependent mechanism for oxidative stress generation [27].

In Vitro STUSIES ON CELL CULTURES:

Signaling pathways:

High nicotine doses are lethal, but low nicotine concentrations promote cell growth [34]. The amounts of nicotine in the bloodstreams of smokers and oral tobacco users match the amounts that promote cell division in cells. In this regard, it is significant that nAChR antagonists block the promotion of cell proliferation by nicotine and that nAChRs are also expressed on non-neuronal epithelial and endothelial cells [35]**.** It has been suggested that nicotine increases cyclin D1 to encourage cell division [36]. When nicotine and other nicotine metabolites bind to nAChRs, signalling pathways and reactions are triggered, which promotes cell survival and proliferation. Epidermal growth factor receptor (EGFR) transactivation and the activation of mitogenic and antiapoptotic pathways are the outcomes of nicotine-mediated release of EGF via nAChRs [37, 38]. β-adrenergic receptors (β-ARs) are physiologic ligands for adrenaline and noradrenaline, which are released by nicotine. This process causes β-AR to bind to and become activated. Numerous oncogenic and mitogenic signalling cascades are triggered as a result, activating proliferative pathways and causing the production of arachidonic acid, VEGF, and EGF [39–41]. Furthermore, it has been discovered that nicotine binds to β-ARs themselves [39]. One of the essential processes for the development of a malignant phenotype is the epithelial–mesenchymal transition (EMT), which is induced by nicotine. The cell can become migratory as a result of this transformation, which could help cancer metastasis [42]. Damage to DNA activates the tumour suppressor Chk2, which is reduced by nicotine. The reduction in Chk2 seen in nicotine-exposed cells implies that nicotine has the ability to bypass DNA damage checkpoint activation, interfere with genetic monitoring, and raise the risk of oncogenesis [43].

Angiogenic growth:

In vitro, nicotine mimics the actions of other angiogenic growth factors by promoting endothelial cell migration, proliferation, survival, tube formation, and nitric oxide (NO) generation [44,45]. At tissue and plasma concentrations comparable to those brought on by mild to moderate smoking, nicotine was discovered to be a powerful angiogenic agent in 2001 [46]. Numerous tumour cells, including breast, colon, and lung cells, have shown effects of nicotine on angiogenesis [47,48]. Comparable outcomes have also been shown among in vivo lung cancer mice models, where nicotine markedly increased lung tumour size and quantity as well as improved metastasis [49].

Interference with cancer therapy:

Nicotine at concentrations as low as 1 µM was reported to reduce the anti-proliferative and pro-apoptotic effects of chemotherapy on a variety of malignant cell lines in many in vitro investigations [50–52]. Exposure to α-bungarotoxin (α-BTX), an inhibitor of α7-nAChR, partially reversed these effects [51]. Nicotine treatment improved the survival of H460 and A549 lung cancer cells under radiotherapy (RT). Adding α-BTX before adding nicotine and radiation also reduced this impact [53]. It is anticipated that the use of nicotine products during cancer therapy may lessen the effects caused by reactions that arise from the interaction between nicotine and α7-nAChR. In 1998, it was discovered [54] that in lung cancer cells, nicotine stimulates the mitogen-activated protein (MAP) kinase signalling pathway. As a result, apoptosis is inhibited and the bcl-2 protein is expressed more often. These side effects could potentially lessen the impact of chemotherapy in smokers [44].

Cotinine:

At a dosage of 0.1 µM, it was discovered that cotinine greatly increased the growth of human lung adenocarcinoma A549 cells. The phosphoinositide 3-kinase inhibitor LY294002 eliminated the effect [55]. Furthermore, a 0.01 µM dose of cotinine was discovered to decrease caspase-mediated apoptosis, hence inhibiting doxorubicin-induced apoptosis. For programmed cell death, cysteine-aspartic proteases, also known as caspases, are required. These findings revealed that cotinine, like nicotine, inhibited apoptosis via the PI3K/Akt pathway.

***IN VIVO* STUDIES ON RODENTS:**

Carcinogenicity studies with nicotine:

Sixty-eight female Sprague-Dawley rats were inhaled with nicotine for twenty hours, five days a week [56]. There were thirty-four animals in the control group. The amount of nicotine in the air was 500 µg/m^3, and in the plasma of exposed rats, the quantity of nicotine was slightly more than 100 ng/ml. At one year, forty-four (65 %) exposed rats and seventeen (50 %) controls were alive; at 1.5 years, thirty (44 %) exposed rats and nine (26 %) controls remained alive. After 24 months of research, the surviving rats - 22 (32 %) of which had been exposed to nicotine, and 7 (21 %) of which had not - were slaughtered and their tumours checked. In the exposed group, the percentage of pituitary gland tumours was greater (5/59 versus 0/25). However, because the exact moment of tumour discovery is unknown, evaluating the data is challenging. Furthermore, the dosages utilised in animal trials to assess possible carcinogenic effects are often many times larger than those that humans may be exposed to, owing to the low sensitivity of these investigations. In an animal trial, the greatest dose should typically cause toxicity and a 10 % weight loss. In the current study, the exposed animals' plasma nicotine level was only marginally higher than that of smokers, and their weight loss after 24 months was only 3 % less than that of the controls. Therefore, it is impossible to draw definite conclusions from the experiment because of the exposure dosages employed and the missing information in the publication. During a 24-month period, female A/J mice were given subcutaneous (s.c.) injections of nicotine hydrogen tartrate (3 mg/kg bw/day, 5 days/week), whereas a control group was given saline injections [57]. According to the study, neoplasms originating from the uterine or skeletal muscle occurred in 73 % of the nicotine-treated mice but not in any of the control animals. Rhabdomyosarcoma was the diagnosis for the tumours in the quadriceps, and leiomyosarcoma for those in the uterus. Metastases were not seen. While leiomyosarcoma in A/J mice can develop spontaneously, rhabdomyosarcoma cannot [58], suggesting that the development of leiomyosarcoma was unique to the experimental nicotine therapy. Thus, the results of the experiment could indicate that nicotine is a whole carcinogen. For the duration of their lives (up to 64 weeks), male Syrian golden hamsters kept in 60 % hyperoxia and given subcutaneous nicotine injections developed a small but noteworthy number of tumours (2/16 adenocarcinomas of the nasal cavity; one of these hamsters also had an adenocarcinoma of the adrenal gland, and 2/16 carcinomas and 2/16 adenomas of the lung) [59]. Metastases were not seen. No organ tumours appeared in hamsters that were given saline injections and kept in 60 % hyperoxia or that were given nicotine and kept in room temperature. The addition of nicotine hydrogen tartrate to the drinking water of female C57Bl/6 mice and female Wistar Han rats for four weeks caused the epithelium of their bladders to enlarge [60]. There is no way to conclude anything from this 4-week trial, even if these data would be compatible with induction of an early-stage carcinogenicity. There are no documented long-term animal trials of the kind often used to assess carcinogenicity for nicotine, with the exception of the inhalation experiment by Waldum, *et al*

[56]. This study's flaws prevent any conclusions from being made. In general, results from injection-based trials are regarded as less significant for assessing carcinogenicity, unless the tumours cause metastasis. Therefore, it is now unable to make any conclusions on the potentially carcinogenic impact of long-term nicotine therapy.

Cocarcinogenicity and promoter activity:

In a rat stomach model, nicotine demonstrated promoter activity with MNNG (N-methyl-N′-nitro-N-nitrosoguanidine) as initiator and cocarcinogenic impact with DMBA (7,12-dimethylbenz[a]anthracene) [61]. Nicotine treatment alone had no impact in the aforementioned tests. In a rat mammary tumour model, nicotine had no effects when NMU (N-nitrosomethylurea) was used as an initiator. On the other hand, tumours occurred in all mice treated with NMU alone [63]. In a rat experiment [64] nicotine was shown to have an anticancer impact on hormone-dependent autochthonous mammary carcinomas produced by water-soluble nitrosourea HECNU. After initiation with FANFT (N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide), both trans-nicotine-N′-oxide and a combination of cis- and trans-nicotine-N′-oxides increased induction of forestomach tumours in the rat, but not urinary bladder tumours. Additionally, cotinine was investigated as a promoter, but it had no impact [65].

Initiation by NNK:

Five studies using NNK (100 mg/kg bw, weekly in 1 to 4 weeks) as an initiator and nicotine as a promoter have been found in mice. In two investigations [49,66], nicotine was given intraperitoneally (1 mg/kg bw) three times a week for a duration of 10 to 28 weeks, and in three other experiments [55,67,68], it was injected into the drinking water (0.07 to 0.1 mg/ml) for a duration of 12 to 44 weeks. In the two trials, nicotine following an intraperitoneal injection demonstrated promoter activity; however, following nicotine in the drinking water, there was either no promoter activity or very little non-significant activity. As the dosage per injection was the same in all trials, it is doubtful that variations in the effects of nicotine are the result of the initiator NNK's delivery. Furthermore, Iskandar, *et al*.'s experiment [66] had just one NNK injection among the i.p. injection of nicotine studies. The mice in the drinking water trials were injected with 1-3 NNK. Furthermore, it is improbable that the variation may be explained by the length of the promotion period, which varied between 10 and 28 weeks for intraperitoneal injection studies and between 12 and 44 weeks for drinking water studies. Because the parietal section of the peritoneum drains directly into the systemic circulation, the variation in findings is most likely a function of the method used to administer the nicotine. There are very few studies that have tested the amounts of nicotine and cotinine in blood and urine. The finding that Murphy, *et al*,[67,68] found modest levels of cotinine and nicotine in blood following the addition of nicotine to drinking water is the most intriguing. They discovered 29 ng/ml of cotinine and 0.26 ng/ml of nicotine. Hence, the cotinine to nicotine ratio is almost 100. The serum levels from the other investigations are not accessible. Nevertheless, Zhou, *et al*,[69] assessed the levels of nicotine and cotinine in the blood following an intraperitoneal dose of 1 mg/kg bw in CYP2A5 WT mice. They found a nicotine level of 45 ng/ml, which decreased to 0 after 60 min and a cotinine level 300 ng/ml, which decreased to 0 after 240 min. Hence, the cotinine and nicotine ratio is around 5, and the amount of nicotine was almost 100 times greater than that [68]. When tested concurrently in blood or other tissues, the cotinine concentration following tobacco product use in humans is typically 10 times or less greater than the nicotine concentration [1,70]. The drinking water trials may have had less control over the mice's total nicotine intake due to a significant first-pass metabolism of nicotine in the liver before it enters the systemic circulation, which might account for the significant variation in nicotine consumption. Only around 30 % of oral nicotine administration is estimated to reach the circulation, according to a study conducted by Matta and colleagues [71]. The other 70 % is metabolised predominantly to cotinine before to entering the bloodstream. The measures taken right after intraperitoneal (i.p.) nicotine injections yielded findings comparable to those of smokers who consume around 25 cigarettes per day. It is possible that low blood nicotine levels are the cause of the absence of effects of nicotine in the drinking water tests. Because the A/J strain of mice is more sensitive to lung carcinogens than the C3H and C57BL/6 strains, most studies including promotion following commencement with NNK have used this strain. There might be more than one contributing element to the unknown mechanisms of varying susceptibility. NNK has been shown to significantly upregulate the expression of COX-2 and α7-nAChRs in the A/J lung, which may explain why this lung type is more vulnerable to NNK-induced lung cancer [72].

Effects on tumor progression:

There are six studies that address how nicotine affects the growth of tumours. In these tests, mice were given injections of cancerous cells, and then they were given nicotine treatments. In two studies, the addition of nicotine to drinking water did not result in any noticeable effects. In the first investigation, conducted by Jarzynka, *et al*. [73] nicotine (0.2 mg/ml drinking water) was given to ovariectomised nude mice for five weeks following the implantation of human A549 bronchioloalveolar cancer cells. The tumour sizes dramatically increased in the mice if oestradiol was additionally administered. The other experiment conducted by Maier, *et al*. [67] involved injecting CL13, IO33, or CL25 cells (all cell lines originating from a lung adenocarcinoma) with nicotine 0.1 mg/ml in drinking water or 0.8 mg/kg bw by intraperitoneal injection three times a week for two to five weeks. Nicotine drinking water and intraperitoneal (i.p.) injections did not promote tumour development or metastasis formation. According to the researchers, there is a dosage at which nicotine has no discernible effects. Conversely, after implanting Line1 murine adenocarcinoma cells subcutaneously into syngenic BALB/c mice, Davis, *et al.* [49] found that nicotine treatment by intraperitoneal injections or transdermal patches subsequently increased tumour development, metastasis formation, and tumour recurrence. The mice given nicotine intraperitoneally (i.p.) had an average cotinine content of 3 µg/ml in their urine, but the mice given nicotine transdermally (t/d) had an average cotinine concentration of 5 µg/ml, according to the authors. Cotinine levels in urine have been observed to range from 1.5 to 8.0 µg/ml in human smokers. Male athymic nude mice were injected subcutaneously (s.c.) with Panc-1 cells, a cell line derived from a human pancreatic cancer, by Al-Wadei, *et al*. [74] who discovered that 0.2 mg/ml of nicotine in drinking water markedly enhanced the xenograft volumes. Both nicotine (0.1 mg/ml) and cotinine (0.1 mg/ml) in drinking water significantly boosted tumour growth when Lewis lung carcinoma cells were implemented in mice, according to a research conducted by Nakada, *et al*. [55] using an *in vivo* lung cancer model. Furthermore, vascular endothelial cells' capillary development was increased by both nicotine and cotinine. In the Lewis lung cancer model, Heeschen, *et al*. [46] investigated whether nicotine may promote tumour angiogenesis. After the cancer cells were implanted and the mice were given nicotine (0.1 mg/ml) for 16 days, the tumour development in the nicotine group significantly outpaced that of the vehicle-treated group, necessitating the mice's death. The enhanced vascularization of the tumour tissue correlated with the acceleration of tumour development seen in the nicotine group. In a follow-up study, it was discovered that nAChR antagonists eliminated nicotine's proangiogenic impact. In four out of the six trials, nicotine accelerated the growth of the tumour. Improvements were observed following nicotine exposure by intraperitoneal injection, oral medication, and skin application. Additionally, cotinine did promote the formation of tumours.

Reduced protection from cancer immunosurveillance:

Vaccines have a lower effect on smokers [75,76]. It is unknown yet how this impact on host immunity works. Reduced interleukin-2 (IL-2) production in mitogen-stimulated human peripheral blood mononuclear cells demonstrated a general immunosuppressive impact of nicotine [77]. It was shown by Nouri-Shirazi and Guinet[78] that mice given a protein-based vaccination containing Th1 adjuvants would not generate a sufficient number of effector/memory T cells in response to nicotine exposure. Furthermore, the animals were not protected against an otherwise preventive and therapeutic vaccine by the prime-boost immunisation, which remembered insufficient memory response. Furthermore, it has been noted that nicotine exposure has a negative impact on dendritic cells, a kind of cell involved in immunosurveillance against cancer [79].

Chemotherapy and radiotherapy:

In 1988, Berger and Zeller [80] observed that giving nicotine to transplanted rats with L5222 leukaemia lessened the anticancer efficacy of cyclophosphamide (CPA). However, it was shown that administering nicotine, as opposed to the anticancer medication HECNU alone, led in higher tumour suppression using a mammary carcinoma model. The authors made the point that more research is necessary in conjunction with other groups of cytotoxic medications. *In vivo* responses to radio therapy (RT) and chemoradiotherapy (CRT) were examined by Warren, *et al*. [53] Athymic male nude H460 human lung cancer cells were injected into Foxn1nu mice to create single xenografts in the right rear flank. When compared to RT or CRT alone, the addition of nicotine throughout the 5-day fractionated RT or CRT therapy boosted xenograft regrowth. Further evidence that nicotine exposure, particularly during treatment, is a crucial factor in determining therapeutic outcome comes

from the observation that short-term nicotine (every other day for six days) produced tumour regrowth curves that were similar to those of long-term nicotine (every other day during treatment, maximum 28 days). Subsequent investigation reveals that nicotine seems to boost the expression of HIF-1α (hypoxia-inducible factor 1, alpha subunit) in vivo while leaving a clinical indicator of tumour hypoxia (immunohistochemical CAIX expression) unchanged. The in vivo effects of nicotine on therapeutic response, according to the scientists, validate its role as a systemically accessible tobacco component that lowers the effectiveness of cancer therapies. Male athymic nude mice were subcutaneously injected with BXPC-3 cells, which are known to cause pancreatic ductal adenocarcinoma, in the flank area by Banerjee, *et al*. [52]The mice received treatment with either 50 mg/kg bw gemcitabine administered intraperitoneally twice a week, 1 μM nicotine added to the drinking water, or both of these treatments. The mice were followed for 30 days after the tumour cells were injected subcutaneously, and all treatments commenced one day after. In weeks 2 to 4, mice treated with gemcitabine alone had a 20 % reduction in xenograft volumes. In weeks 2 to 4, the therapeutic benefit of gemcitabine was considerably ($p<0.001$) diminished by nicotine therapy. BXPC-3 xenografts of the mice treated with gemcitabine alone demonstrated elevated protein levels of cleaved caspase-3, which is consistent with the drug's known capacity to cause apoptosis. On the other hand, nicotine totally eliminated the induction of cleaved caspase in response to gemcitabine ($p<0.001$). Concerns about the use of NRT in cancer treatment have been raised due to the effects of nicotine during in vivo chemotherapy and radiation therapy [52,53]. NRT has the benefit of not contributing to the high concentration of carcinogens seen in cigarette smoke [53].

Effects on Humans:

As far as we are aware, no pertinent human studies have been conducted on the carcinogenic potential of pure nicotine, including its use in NRT and e-cigarettes. Because exposures to some tobacco-specific elements may be identical, observational research on smokers and oral tobacco users may still offer valuable insights into possible consequences. Nicotine is a tobacco component where blood concentrations are similar during smoking and use of oral tobacco [81]. Thus, a quick summary of the effects of tobacco usage on people will be provided.

***Use of tobacco prior to cancer diagnoses*:**

It has been shown in the literature for a number of different forms of cancer that current tobacco users, both those who smoke and those who use smokeless tobacco, have a greater risk of dying from cancer than do never users [82–93]. This section will only cover a small number of studies. In a study conducted by Nordenvall, *et al*, [90] 336,381 Swedish construction workers' tobacco usage and cancer patients' risk of mortality were examined. There were 40,230 confirmed cases of cancer. The analysis included hazard ratios and 95 % confidence intervals (CIs) for death from cancer, death from other causes, and death from any cause. References were never smokers of any kind. Both never-smoking snus users (HR = 1.15, 95 % CI: 1.05 to 1.26) and exclusive smokers (HR = 1.15, 95 % CI: 1.10 to 1.21) had higher odds of dying from cancer. It should be mentioned that the oral mucosa absorbs the majority of the nicotine in the case of snus consumers. To explain these results, the authors suggested that nicotine may be the common cause for all this. The fact that the consequences extend beyond individuals with malignancies attributable to tobacco use is intriguing. Men who smoke cigarettes before to diagnosis seem to have a poorer prognosis, even though smoking is not believed to be a risk factor for prostate cancer [87,89,93,94]. A recent abstract by Wilson, *et al*, [93] detailed a research on 9582 Swedish construction workers who had prostate cancer. Exclusive smokers were more likely to die from prostate cancer (HR = 1.15, 95% CI: 1.05 to 1.27) and from all causes (HR = 1.17, 95% CI: 1.09 to 1.26) than those who never used tobacco. Additionally, users of exclusive snus were more likely to die from prostate cancer (HR = 1.24, 95 % CI: 1.03 to 1.49) and from all causes (HR = 1.19, 95 % CI: 1.04 to 1.37). The findings, according to the scientists, point to the possibility that nicotine, rather than the combustion products of tobacco smoke, may accelerate the development of cancer.

***Use of tobacco after diagnosis and during cancer treatment*:**

Individuals who have smoked both before and after receiving a cancer diagnosis and treatment have also previously used tobacco. When evaluating survival or recurrence, it can be challenging to distinguish between the effects of tobacco use before diagnosis and throughout cancer therapy. Furthermore, the majority of the research focuses on smokers and just a small portion on alternative drugs that contain nicotine, such as oral

tobacco. The next section discusses certain trials where it is made clear that the participants smoked while receiving therapy. It is well known that smoking has a negative impact on surgery. This has been shown in the context of cancer surgery as well. A research by Sorensen, *et al*. [95] on 425 patients who had breast cancer surgery at a Danish hospital that included basic mastectomy, modified radical mastectomy, or breast conserving surgery serves as an example. The scientists came to the conclusion that smoking is a predictor of epidermolysis, skin flap necrosis, and post-mastectomy wound infection, regardless of other risk variables. In every instance, heavy smoking had greater impacts than low smoking. Patients with prostate cancer who smoked after a radical prostatectomy experienced a greater rate of recurrence (34.3 versus 14.8 %) in a study [96]. About 2358 patients with clinically localised prostate cancer who had external beam radiation treatment (EBRT) between 1988 and 2005 were monitored by Steinberger, *et al* [97]. The odds of distant metastases [HR 2.30 (1.57 to 3.36), prostate cancer-specific mortality [HR 2.25 (1.30 to 3.88)], and prostate-specific antigen recurrence [HR 1.37 (1.04 to 1.84)] were all substantially elevated by current smoking. Furthermore, after EBRT, smokers both present and past were more likely to experience long-term genitourinary toxicity, irrespective of the length or intensity of their exposure. It is well acknowledged that quitting smoking during cancer therapy improves responsiveness and increases survival [98]. This finding is supported by epidemiological research as well as *in vitro* and *in vivo* trials. Nicotine might be a factor in these outcomes.

CONCLUSION:

Carcinogenic chemicals, including polycyclic hydrocarbons (PAH) and tobacco smoke aerosol (TSNA) are present in varying concentrations in all tobacco products. These compounds are known to be significant in the development of cancer. Experimental in vitro research on cell cultures, in vivo studies on rodents, and human investigations, including epidemiological studies, have shown evidence that nicotine may have a role in the development of cancer by activating many critical pathways. Nicotine binds to nicotine acetylcholine receptors (nAChRs) more strongly than acetylcholine, and nicotine functions largely by activating these receptors. Moreover, following oral administration, nicotine may be converted to the TSNA compounds NNN (N′-nitrosonornicotine) and NNK (4-(metylnitrosamino)-1-(3-pyridyl)-1-butanon). The examination of possible hazardous effects from non-tobacco related sources of nicotine, such as e-cigarettes and NRT, is crucial due to the role that nicotine plays in carcinogenesis. In vitro studies have demonstrated that nicotine causes MN, CA, SCE, and single-strand DNA strand breaks. Since the effects are lessened when antioxidants are present, oxidative stress is most likely involved. The results show that co-incubation with a nAChR antagonist reduces the effects, suggesting a receptor-dependent mechanism for oxidative stress generation. Nicotine's interaction with nAChRs triggers signalling pathways that lead to a variety of outcomes, including enhanced cell survival and proliferation. While nAChRs are the main receptors, nicotine binding to EGFRs and β-ARs may potentially be significant. EMT, which is triggered by nicotine, contributes to the development of a malignant phenotype. Furthermore, nicotine causes modifications that resemble angiogenic growth factor actions. It is currently impossible to determine if nicotine by itself has the potential to cause cancer. Nicotine functions as a promoter following injection or skin absorption in mice experiments using NNK as an initiator, but not following oral treatment. Before nicotine enters the systemic circulation, there is significant first-pass metabolism of nicotine in drinking water trials. Hence, compared to intraperitoneal treatment, the serum level is much lower after consumption. Nicotine accelerated the formation and spread of tumours in mice injected with cancerous cells. Improvements were observed following the intraperitoneal, oral, and cutaneous delivery of nicotine. Additionally, cotinine did promote the formation of tumours. The antitumor immune response may be inhibited by nicotine. Additionally, it has been shown that nicotine exposure has a negative impact on dendritic cells, a kind of cell involved in immune surveillance against cancer. Furthermore, nicotine has been shown to lessen the effects of RT and CRT in tests on mouse xenografts. Even for malignancies believed to be unrelated to tobacco use, users of smokeless tobacco, such as snus, and current smokers have been found to have worse overall survival and specific disease survival following cancer diagnoses when compared to never smokers. Patients should be encouraged not to use nicotine products during cancer treatment unless it is temporarily necessary to quit tobacco use, even if additional research on the health consequences of

nicotine in people is necessary based on *in vitro* and *in vivo* effects of nicotine.

ABBREVIATIONS:

α-BTX: α-bungarotoxin; β-AR: β-adrenergic receptor; Ach: acetylcholine; CA: chromosomal aberration; CI: confidence interval; CPA: cyclophosphamide; CRT: chemoradiotherapy; DMBA: 7,12-dimethylbenz[a]anthracene; DSB: double-strand breaks; EBRT: external beam radiotherapy; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; EMT: epithelial–mesenchymal transition; FANFT: N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide; HR: hazard ratio; IARC: International Agency for Cancer Research; MAP: mitogen-activated protein; MNNG: N-methyl-N′-nitro-N-nitrosoguanidine; nAChRs: nicotinic acetylcholine receptors; MN: micronuclei; NMU: N-nitrosomethylurea; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK: 4-(metylnitrosamino)-1-(3-pyridyl)-1-butanon; NNN: N′-nitrosonornicotine; NRT: nicotine replacement therapy; PAH: polycyclic hydrocarbons; RT: radiotherapy; SCE: sister chromatide exchange; SSB: single-strand breaks; TSNA: tobacco-specific *N*-nitrosamines.

ACKNOWLEDGEMENT:

Authors wish to thank the authority of MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be university), Mullana-133207, Ambala, Haryana, India, for providing all the facilities to complete this study.

REFERENCES:

1. Benowitz NL, Hukkanen J, Jacob P, III. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol, 2009; 92: 29-60.
2. Russell MAH, Jarvis M, Iyer R, Feyerabend C. Relation of nicotine yield of cigarettes to blood nicotine concentrations in smokers. Br Med J, 1980; 280: 972-976.
3. Hukkanen J, Jacob P, III, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev, 2005; 57: 79-115.
4. Lindstrom J, Anand R, Gerzanich V, Peng X, Wang F, Wells G. Structure and function of neuronal nicotinic acetylcholine receptors. Prog Brain Res, 1996; 109: 125-137.
5. Schaal C, Chellappan SP. Nicotine-mediated cell proliferation and tumor progression in smoking-related cancers. Mol Cancer Res, 2014; 12: 14-23.
6. Sergei A, Grando SA. Connections of nicotine to cancer. Nat Rev Cancer, 2014; 14: 419-129.
7. O'Leary K, Parameswaran N, McIntosh JM, Quik M. Cotinine selectively activates a subpopulation of $\alpha 3/\alpha 6\beta 2$* nicotinic receptors in monkey striatum. J Pharmacol Exp Ther, 2008; 325: 646-654.
8. Church TR, Anderson KE, Caporaso NE, Geisser MS, Le CT, Zhang Y, et al. A prospectively measured serum biomarker for a tobacco-specific carcinogen and lung cancer in smokers. Cancer Epidemiol Biomarkers Prev, 2009; 18: 260-266.
9. International Agency for Research on Cancer. A Review of Human Carcinogens. Part E: Personal Habits and Indoor Combustions. IARC Monograph. Vol. 100E. Lyon: International Agency for Research on Cancer, 2012; 14: 602.
10. International Agency for Research on Cancer. Smokeless Tobacco and Some Tobacco-Specific N-Nitrosamines. IARC Monograph. Vol. 89. Lyon: International Agency for Research on Cancer, 2007; 56: 641.
11. Hecht SS, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis, 1988; 9: 875-884.
12. Bartsch H, Spiegelhalder B. Environmental exposure to N-nitroso compounds (NNOC) and precursors: an overview. Eur J Cancer Prev, 1996; 5: 11-18.
13. Carmella SG, Borukhova A, Desai D, Hecht SS. Evidence for endogenous formation of tobacco-specific nitrosamines in rats treated with tobacco alkaloids and sodium nitrite. Carcinogenesis, 1997; 18: 587-892.
14. Porubin D, Hecht SS, Li ZZ, Gonta M, Stepanov I. Endogenous formation of *N*‘-nitrosonornicotine in F344 Rats in the presence of some antioxidants and grape seed extract. J Agric Food Chem, 2007; 55: 7199-7204.
15. Hecht SS, Carmella SG, Chen M, Dor Koch JF, Miller AT, Murphy SE, et al. Quantification of urinary metabolites of a tobacco-specific lung carcinogen after smoking cessation. Cancer Res, 1999; 59: 590-596.
16. Stepanov I, Jensen J, Hatsukami D, Hecht SS. Tobacco-specific nitrosamines in new tobacco products. Nicotine Tob Res, 2006; 8: 309-813.
17. Hatsukami DK, Lemmonds C, Zhang Y, Murphy SE, Le C, Carmella SG, *et al*. Evaluation of carcinogen exposure in people who used “reduced exposure” tobacco products. J Natl Cancer Inst, 2004; 96: 844-852.

18. Carmella SG, Han S, Fristad A, Yang Y, Hecht SS. Analysis of total 4(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human urine. Cancer Epidemiol Biomarkers Prev, 2003; 12: 1257-1261.
19. Knezevich A, Muzic J, Hatsukami DK, Hecht SS, Stepanov I. Nornicotine nitrosation in saliva and its relation to endogenous synthesis of N'-nitrosonornicotine in humans. Nicotine Tob Res, 2013; 15: 591-595.
20. Hecht SS, Carmella SG, Kotandeniya D, Pillsbury ME, Chen M, Ransom BWS, *et al*. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. Nicotine Tob Res, 2015; 17: 704-709.
21. Hecht SS, Carmella SG, Murphy SE, Riley WT, Le C, Luo X, *et al*. Similar exposure to a tobacco-specific carcinogen in smokeless tobacco users and cigarette smokers. Cancer Epidemiol Biomarkers Prev, 2007; 16: 1567-1572.
22. Riebe M, Westphal K, Fortnagel P. Mutagenicity testing, in bacterial test systems, of some constituents of tobacco. Mutat Res, 1982; 101: 39-43.
23. Riebe M, Westphal K. Studies on the induction of sister-chromatid exchanges in Chinese hamster ovary cells by various tobacco alkaloids. Mutat Res, 1983; 124: 281-286.
24. Trivedi AH, Dave BJ, Adhvaryu SG. Assessment of genotoxicity of nicotine employing in vitro mammalian test system. Cancer Lett, 1990; 54: 89-94.
25. Ginzkey C, Friehs G, Koehler C, Hackenberg S, Hagen R, Kleinsasser NH. Assessment of nicotine-induced DNA damage in a genotoxicological test battery. Mutat Res, 2013; 751: 34-39.
26. Sassen AW, Richter E, Semmler MP, Harreus UA, Gamarra F, Kleinsasser NH. Genotoxicity of nicotine in mini-organ cultures of human upper aerodigestive tract epithelia. Toxicol Sci, 2005; 88: 134-141.
27. Ginzkey C, Stueber T, Friehs G, Koehler C, Hackenberg S, Richter E, et al. Analysis of nicotine-induced DNA damage in cells of the human respiratory tract. Toxicol Lett, 2012; 208: 23-29.
28. Kleinsasser NH, Sassen AW, Semmler MP, Harréus UA, Licht AK, Richter E. The tobacco alkaloid nicotine demonstrates genotoxicity in human tonsillar tissue and lymphocytes. Toxicol Sci, 2005; 86: 309-317.
29. Ginzkey C, Kampfinger K, Friehs G, Kohler C, Hagen R, Richter E, *et al*. Nicotine induces DNA damage in human salivary glands. Toxicol Lett, 2009; 184: 1-4.
30. Arabi M. Nicotinic infertility: assessing DNA and plasma membrane integrity of human spermatozoa. Andrologia, 2004; 36: 305-310.
31. Argentin G, Cicchetti R. Genotoxic and antiapoptotic effect of nicotine on human gingival fibroblasts. Toxicol Sci, 2004; 79: 75-81.
32. Cheng Y, Li HL, Wang HF, Sun HF, Liu YF, Peng SX, *et al*. Inhibition of nicotine-DNA adduct formation in mice by six dietary constituents. Food Chem Toxicol, 2003; 41: 1045-1050.
33. Hecht SS. Lung carcinogenesis by tobacco smoke. Int J Cancer, 2012; 131: 2724-2732.
34. Villablanca AC. Nicotine stimulates DNA synthesis and proliferation in vascular endothelial cells *in vitro*. J Appl Physiol, 1998; 84: 2089-2098.
35. Cattaneo MG, Codignola A, Vicentini LM, Clementi F, Sher E. Nicotine stimulates a serotonergic autocrine loop in human small-cell lung carcinoma. Cancer Res, 1993; 53: 5566-5568.
36. Chu M, Guo J, Chen CY. Long-term exposure to nicotine, via Ras pathway, induces Cyclin D1 to stimulate G1 cell cycle transition. J Biol Chem, 2005; 280: 6369-6379.
37. Schuller HM. Nitrosamines as nicotinic receptor ligands. *Life Sci*, 2007; 80: 2274-2280.
38. Singh S, Pillai S, Chellappan S. Nicotinic acetylcholine receptor signaling in tumor growth and metastasis. J Oncol, 2011; 2011: 456-743.
39. Wong HPS, Yu L, Lam EKY, Tai EKK, Wu WKK, Cho CH. Nicotine promotes colon tumor growth and angiogenesis through β-adrenergic activation. Toxicol Sci, 2007; 97: 279-287.
40. Schuller HM. Is cancer triggered by altered signalling of nicotinic acetylcholine receptors? Nat Rev Cancer, 2009; 9: 195-205.
41. Lee CH, Wu CH, Ho YS. From smoking to cancers: novel targets to neuronal nicotinic acetylcholine receptors. J Oncol, 2011; 6: 693-724.
42. Dasgupta P, Rizwani W, Pillai S, Kinkade R, Kovacs M, Rastogi S, *et al*. Nicotine induces cell proliferation, invasion and epithelial-mesenchymal transition in a variety of human cancer cell lines. Int J Cancer, 2009; 124: 36-45.
43. Bartek J, Lukas J. Chk1 and Chk2 kinases in checkpoint control and cancer. Cancer Cell, 2003; 3: 421-429.
44. Cardinale A, Nastrucci C, Cesario A, Russo P. Nicotine: specific role in angiogenesis, proliferation and apoptosis. Crit Rev Toxicol, 2012; 42: 68-89.

45. Lee J, Cooke JP. Nicotine and pathological angiogenesis. Life Sci, 2012; 91: 1058-1064.
46. Heeschen C, Jang JJ, Weis M, Pathak A, Kaji S, Hu RS, *et al*. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. Nat Med, 2001; 7: 833-839.
47. Heeschen C, Weis M, Aicher A, Dimmeler S, Cooke JP. A novel angiogenic pathway mediated by non-neuronal nicotinic acetylcholine receptors. J Clin Invest, 2002; 110: 527-536.
48. Mousa S, Mousa SA. Cellular and molecular mechanisms of nicotine's pro-angiogenesis activity and its potential impact on cancer. J Cell Biochem, 2006; 97: 1370-1378.
49. Davis R, Rizwani W, Banerjee S, Kovacs M, Haura E, Coppola D, et al. Nicotine promotes tumor growth and metastasis in mouse models of lung cancer. PLoS One, 2009; 4(10): e7524.
50. Shen T, Le W, Yee A, Kamdar O, Hwang PH, Upadhyay D. Nicotine induces resistance to chemotherapy in nasal epithelial cancer. Am J Rhinol Allergy, 2010; 24: e73-e77.
51. Dinicola S, Morini V, Coluccia P, Proietti S, D'Anselmi F, Pasqualato A, *et al*. Nicotine increases survival in human colon cancer cells treated with chemotherapeutic drugs. Toxicol In Vitro, 2013; 27: 2256-2263.
52. Banerjee J, Al-Wadei HA, Schuller HM. Chronic nicotine inhibits the therapeutic effects of gemcitabine on pancreatic cancer *in vitro* and in mouse xenografts. Eur J Cancer, 2013; 49: 1152-1158.
53. Warren GW, Romano MA, Kudrimoti MR, Randall ME, McGarry RC, Singh AK, *et al*. Nicotinic modulation of therapeutic response *in vitro* and *in vivo*. Int J Cancer, 2012; 131: 2519-2527.
54. Heusch WL, Maneckjee R. Signalling pathways involved in nicotine regulation of apoptosis of human lung cancer cells. Carcinogenesis, 1998; 19: 551-556.
55. Nakada T, Kiyotani K, Iwano S, Uno T, Yokohira M, Yamakawa K, *et al*. Lung tumorigenesis promoted by anti-apoptotic effects of cotinine, a nicotine metabolite through activation of PI3K/Akt pathway. J Toxicol Sci, 2012; 37: 555-563.
56. Waldum HL, Nilsen OG, Nilsen T, Rervik H, Syversen U, Sandvik AK, *et al*. Long-term effects of inhaled nicotine. Life Sci, 1996; 58: 1339-1346.
57. Galitovskiy V, Chernyavsky AI, Edwards RA, Grando SA. Muscle sarcomas and alopecia in A/J mice chronically treated with nicotine. Life Sci, 2012; 91: 1109-1112.
58. Sher RB, Cox GA, Mills KD, Sundberg JP. Rhabdomyosarcomas in ageing A/J mice. PLoS One, 2011; 6: e23498.
59. Schuller HM, McGavin MD, Orloff M, Riechert A, Porter B. Simultaneous exposure to nicotine and hyperoxia causes tumors in hamsters. Lab Invest, 1995; 73: 448-456.
60. Dodmane PR, Arnold LL, Pennington KL, Cohen SM. Orally administered nicotine induces urothelial hyperplasia in rats and mice. Toxicology, 2014; 315: 49-54.
61. Chen YP, Squier CA. Effect of nicotine on 7,12-dimethylbenz[a]anthracene carcinogenesis in hamster cheek pouch. J Natl Cancer Inst, 1990; 82: 861-864.
62. Gurkalo VK, Volfson NI. Nicotine influence upon the development of experimental stomach tumors. Arch Geschwulstforsch, 1982; 52: 259-265.
63. Habs M, Schmähl D. Influence of nicotine on N-nitrosomethylurea-induced mammary tumors in rats. Klin Wochenschr, 1984; 62(Suppl 2): 105-108.
64. Zeller WJ, Berger MR. Nicotine and estrogen metabolism – possible implications of smoking for growth and outcome of treatment of hormone-dependent cancer? Discussion of experimental results. J Cancer Res Clin Oncol, 1989; 115: 601-603.
65. LaVoie EJ, Shigematsu A, Rivenson A, Mu B, Hoffmann D. Evaluation of the effects of cotinine and nicotine-N′-oxides on the development of tumors in rats initiated with N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide. J Natl Cancer Inst, 1985; 75: 1075-1081.
66. Iskandar AR, Liu C, Smith DE, Hu KQ, Choi SW, Ausman LM, *et al*. β-Cryptoxanthin restores nicotine-reduced lung SIRT1 to normal levels and inhibits nicotine-promoted lung tumorigenesis and emphysema in A/J mice. Cancer Prev Res, 2013; 6: 309-320.
67. Maier CR, Hollander MC, Hobbs EA, Dogan I, Linnoila RI, Dennis PA. Nicotine does not enhance tumorigenesis in mutant K-Ras-driven mouse models of lung cancer. Cancer Prev Res, 2011; 4: 1743-1751.
68. Murphy SE, von Weymarn LB, Schutten MM, Kassie F, Modiano JF. Chronic nicotine consumption does not influence 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. Cancer Prev Res, 2011; 4: 1752-1760.
69. Zhou X, Zhuo X, Xie F, Kluetzman K, Shu YZ, Humphreys WG, et al. Role of CYP2A5 in the clearance

of nicotine and cotinine: insights from studies on a *Cyp2a5*-null mouse model. J Pharmacol Exp Ther, 2010; 332: 578-587.
70. SCENIHR. Scientific Opinion on the Health Effects of Smokeless Tobacco Products. (2008). Available from: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_013.pdf
71. Matta SG, Balfour DJ, Benowitz NL, Boyd RT, Buccafusco JJ, Caggiula AR, *et al*. Guidelines on nicotine dose selection for *in vivo* research. Psychopharmacology, 2007; 190: 269-319.
72. Razani-Boroujerdi S, Sopori ML. Early manifestations of NNK-induced lung cancer role of lung immunity in tumor susceptibility. Am J Respir Cell Mol Biol, 2007; 36: 13-19.
73. Jarzynka MJ, Guo P, Bar-Joseph I, Hu B, Cheng SY. Estradiol and nicotine exposure enhances A549 bronchioloalveolar carcinoma xenograft growth in mice through the stimulation of angiogenesis. Int J Oncol, 2006; 28: 337-344.
74. Al-Wadei HAN, Plummer HK, III, Schuller HM. Nicotine stimulates pancreatic cancer xenografts by systemic increase in stress neurotransmitters and suppression of the inhibitory neurotransmitter γ-aminobutyric acid. Carcinogenesis, 2009; 30: 506-511.
75. Shaw FE, Jr, Guess HA, Roets JM, Mohr FE, Coleman PJ, Mandel EJ, *et al*. Effect of anatomic injection site, age and smoking on the immune response to hepatitis B vaccination. Vaccine, 1989; 7: 425-430.
76. Roseman C, Truedsson L, Kapetanovic MC. The effect of smoking and alcohol consumption on markers of systemic inflammation, immunoglobulin levels and immune response following pneumococcal vaccination in patients with arthritis. Arthritis Res Ther, 2012; 14: R170.
77. van Dijk AP, Meijssen MA, Brouwer AJ, Hop WC, van Bergeijk JD, Feyerabend C, *et al*. Transdermal nicotine inhibits interleukin 2 synthesis by mononuclear cells derived from healthy volunteers. Eur J Clin Invest, 1998; 28: 664-671.
78. Nouri-Shirazi M, Guinet E. Exposure to nicotine adversely affects the response to vaccination dendritic cell system and compromises host. J Immunol, 2012; 188: 2359-2370.
79. Töpfer K, Kempe S, Müller N, Schmitz M, Bachmann M, Cartellieri M, et al. Tumor evasion from T cell surveillance. J Biomed Biotechnol, 2011; 2011: 918471.
80. Berger MR, Zeller WJ. Interaction of nicotine with anticancer treatment. Klin Wochenschr, 1988; 66(Suppl XI): 127-133.
81. Bolinder G, Alfredsson L, Englund A, de Faire U. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. Am J Public Health, 1994; 84: 399-404.
82. Johnston-Early A, Cohen MH, Minna JD, Paxton LM, Fossieck BE, Jr, Ihde DC, *et al*. Smoking abstinence and small cell lung cancer survival. An association. JAMA, 1980; 244: 2175-2179.
83. Hinds MW, Yang HY, Stemmermann G, Lee J, Kolonel LN. Smoking history and lung cancer survival in women. J Natl Cancer Inst, 1982; 68:395–9.
84. Stevens MH, Gardner JW, Parkin JL, Johnson LP. Head and neck cancer survival and life-style change. Arch Otolaryngol, 1983; 109: 746-749.
85. Accortt NA, Waterbor JW, Beall C, Howard G. Chronic disease mortality in a cohort of smokeless tobacco users. Am J Epidemiol, 2002; 156: 730-737.
86. Fox JL, Rosenzweig KE, Ostroff JS. The effect of smoking status on survival following radiation therapy for non-small cell lung cancer. Lung Cancer, 2004; 44: 287-293.
87. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. JAMA, 2011; 305: 2548-2555.
88. Braithwaite D, Izano M, Moore DH, Kwan ML, Tammemagi MC, Hiatt RA, *et al*. Smoking and survival after breast cancer diagnosis: a prospective observational study and systematic review. Breast Cancer Res Treat, 2012; 136: 521-533.
89. Islami F, Moreira DM, Boffetta P, Freedland SJ. A systematic review and meta-analysis of tobacco use and prostate cancer mortality and incidence in prospective cohort studies. Eur Urol, 2014; 66: 1054-1064.
90. Nordenvall C, Nilsson PJ, Ye W, Andersson TML, Nyrén O. Tobacco use and cancer survival: a cohort study of 40,230 Swedish male construction workers with incident cancer. Int J Cancer, 2013; 132: 155-161.
91. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. Int J Cancer, 2013; 132: 401-410.
92. Sharp L, McDevitt J, Carsin AE, Brown C, Comber H. Smoking at diagnosis is an independent prognostic factor for cancer-specific survival in head and neck cancer: findings from a large, population-based, study. Cancer Epidemiol Biomarkers Prev, 2014; 23: 2579-2590.

93. Wilson KM, Fang F, Nordenvall C, Ye W, Adami HO, Nyrén O, *et al*. Snus use, smoking and prostate cancer survival. Prostate Cancer Foundation, Abstract no. 146, 21st Annua PCF Scientific Retreat October 23–25, 2014; Available from: http://www.pcf.org/atf/cf/%7B7c77d6a2 -5859-4d60-af47-132fd0f85892%7D/2014
94. Zu K, Giovannucci E. Smoking and aggressive prostate cancer: a review of the epidemiologic evidence. *Cancer Causes Control*, 2009; 20: 1799-1810.
95. Sørensen LT, Hørby J, Friis E, Pilsgaard B, Jørgensen T. Smoking as a risk factor for wound healing and infection in breast cancer surgery. Eur J Surg Oncol, 2002; 28: 815-820.
96. Joshu CE, Mondul AM, Meinhold CL, Humphreys EB, Han M, Walsh PC, *et al*. Cigarette smoking and prostate cancer recurrence after prostatectomy. J Natl Cancer Inst, 2011; 103: 835-838.
97. Steinberger E, Kollmeier M, McBride S, Novak C, Pei X, Zelefsky MJ. Cigarette smoking during external beam radiation therapy for prostate cancer is associated with an increased risk of prostate cancer-specific mortality and treatment-related toxicity. BJU Int, 2015; 116(4): 596-603.
98. Bristow BJ. Smoking cessation basics: an essential component of radiation therapy clinical practice. J Med Imag Radiat Sci, 2013; 44: 106-116.

Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Tanwar P, Naagar M, Maity MK*. Relationship between Nicotin and Cancer – A Comprehensive Review. J Pharm Adv Res, 2024; 7(9): 2378-2390.