Perspective
Perspective on Murphy et al., p. 1752, and Maier et al., p. 1743

Cancer Prevention Research

How Do We Safely Get People to Stop Smoking?

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Abstract

Nicotine replacement therapy (NRT) is a valuable, proven, and U.S. Food and Drug Administration–approved tool for smoking cessation. However, the discoveries of functional nicotinic acetylcholine receptors (nAChR) on lung epithelial and cancer cells and of nAChR polymorphisms associated with lung cancer risk, in addition to a large number of preclinical studies indicating that nicotine may promote or facilitate cancer development and growth, have prompted concern that NRT, although important for smoking cessation, may actually augment lung carcinogenesis. Therefore, it is of great public health interest that two independent studies reported in this issue of the journal (Murphy and colleagues, beginning on page 1752, and Maier and colleagues, beginning on page 1743) showed that nicotine given in drinking water at a dose to achieve blood concentrations in mice similar to those achieved in people receiving NRT did not enhance lung carcinogenesis or tumor growth in several mouse models of lung cancer. Effective non-nicotine alternatives to NRT, such as varenicline and bupropion, are also available and perhaps better than NRT for smoking cessation therapy. In the near future, nicotine vaccines will likely be added to the smoking cessation armamentarium. However, the normal and pathophysiologic role of nicotine, nAChRs, and the signaling pathways they activate in lung epithelial cells and lung cancer still requires elucidation. *Cancer Prev Res; 4(11); 1724–7. ©2011 AACR.*

Tobacco smoking is a major cause of lung cancer and cardiovascular and respiratory diseases and we need to do everything we can to prevent the initiation of smoking, to help current smokers quit, and to keep former smokers from relapsing (1, 2). Public education on the hazard of tobacco smoking and appropriate public health policy, such as cigarette taxation, have produced a steady fall in the prevalence of smoking in the United States and Europe (3). However, the prevalence of smoking in the United States still stands at 19% and the overall prevalence of smoking in other parts of the world, although reduced, has reached a plateau. In addition, there may be a global trend of smoking initiation at younger ages (2, 4). The World Health Organization (WHO) projects that cutting adult consumption in half would produce a greater reduction in tobacco-related deaths by 2050 than would cutting in half the proportion of young adults taking up tobacco smoking (2). Further benefits of smoking cessation include its recently reported association with sensitivity (of former smokers) to targeted lung cancer prevention agents (5, 6) and with improved adherence to established cancer chemoprevention (7), in addition to forestalling the adverse effects of smoking on cancer therapy (8). Therefore, strategies to assist in smoking cessation will provide an important public health benefit (3).

Tobacco smoking is an addictive behavioral disorder where smokers have a constant craving for nicotine (9, 10). Through chronic tobacco smoking, smokers not only take in nicotine but also other harmful and carcinogenic chemical compounds, which are inhaled into airways or absorbed through the oral or upper aerodigestive tract mucosa (9, 11). Nicotine can also be metabolized to potent carcinogens such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK; ref. 11). Human lung epithelial cells and lung cancers express nicotinic acetylcholine receptors (nAChR) and nicotine (and NNK) acting through these receptors can activate different signaling pathways including the phosphoinositide-3-kinase (PI3K), mitogen-activated protein kinase (MAPK), AKT, SRC, and NF-κB pathways. These upregulated nAChR activities promote lung epithelial cell and lung cancer cell survival and growth, inhibition of apoptosis, and, in other cancer systems, epithelial–mesenchymal transition and resistance to chemotherapy (12–20). These preclinical studies in both human and mouse model systems have raised concern that nicotine replacement therapy (NRT; commonly administered in nicotine patches or gum), which is a valuable, proven, and U.S. Food and Drug Administration (FDA)-approved tool for smoking cessation, has possible harmful effects on lung carcinogenesis, particularly in facilitating tumor progression of already initiated precancerous lesions (16, 18). Indeed, it has been suggested that nicotine is the "estrogen" of lung cancer, with an analogous role in the lung to that of estrogen in

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doi: 10.1158/1940-6207.CAPR-11-0449

promoting breast carcinogenesis (21). Thus and in contrast to the foregoing preclinical evidence, it is good to know that an evaluation of people treated with nicotine showed that their smoking was associated with increased lung cancer risk but NRT was not (22).

These preclinical studies are now seen in the context of recent genome-wide associations studies that have linked the risk of developing lung cancer to polymorphisms in the *nAChR* gene complex encoding nAChR α3 and α5 (23–25). Although, one of these genome-wide associations studies (a study by Thorgeirsson and colleagues) reported associations between single-nucleotide polymorphisms (SNP) in nAChR α3 and α5 and the amount of smoking in ever-smokers (24), similar studies by Hung and colleagues (23) and Amos and colleagues (25) came to a different conclusion, finding a stronger association of these SNPs with the risk of cancer rather than with the amount of smoking. Whether these SNPs are mediating lung carcinogenesis via the effects of nicotine was not established. To further complicate matters, one of the studies found an association of the polymorphisms with lung cancer risk in nonsmokers (23) and the other did not (25).

Therefore, it is of great interest that two reports in this issue of the journal indicate that nicotine given in a manner to model the concentrations achieved in human NRT did not facilitate lung carcinogenesis or tumor growth in several mouse models of lung cancer (26, 27). Murphy and colleagues found that nicotine did not increase tumor multiplicity or size or adenoma-to-carcinoma progression in female mice of the classic NNK-induced A/J mouse model of lung carcinogenesis (26). Maier and colleagues had similar results in a related mouse model that also introduced nicotine preference (C57BL/6) and propensity for NNK-induced tumor formation (A/J) in the F1 strain background (27). Because NNK lung cancers usually have *KRAS* mutations, the investigators also used a transgenic mouse model of mutant *KRAS*–driven lung cancer (on a C57Bl/6 background) and studied gender effects (nicotine levels in female mice are lower than in males in association with metabolism differences). Nicotine given at doses equivalent to human NRT did not increase tumor numbers or size or progression from adenoma to carcinoma and did not affect overall survival in either model, thus paralleling the findings of Murphy and colleagues. Maier and colleagues also found that oral nicotine did not enhance tumor growth and metastasis in a syngeneic mouse lung cancer xenograft model developed from tumors derived from NNK treatment. To explain the discrepancies with prior reports, both groups noted that prior studies had used doses of nicotine higher than the doses in NRT and often given intraperitoneally (but also by nicotine patch); they hypothesized that there may be a threshold effect for nicotine tumor promotion similar to that seen for its metabolite NNK (28).

Many controlled trials have shown the value of NRT in aiding smoking cessation (Table 1; refs. 2, 10, 29, 30). Current FDA approval of NRT is for 6 to 12 week duration. However, very addicted smokers will relapse, when NRT is stopped. Therefore, the FDA is considering long-term NRT for approval. Besides potential effects on lung carcinogenesis, chronic intake of nicotine could have harmful effects on the cardiovascular and respiratory system (31), causing hypertension, coronary artery disease, and chronic obstructive pulmonary disease (32). NRT is not the only therapeutic option for smoking cessation (10). Other pharmacotherapy includes bupropion and the new agent varenicline, which are as or more effective than is NRT (Table 1). Varenicline is a partial agonist for α4β2 (an nAChR), not only blocking nicotine at the receptor level but also allowing the release of moderate to low levels of dopamine to reduce nicotine craving and withdrawal symptoms (2, 9, 29, 30, 32–35). Targeting nAChR for smoking cessation stemmed from

Table 1. Results of smoking cessation studies from reviews of randomized controlled trials

	Abstinence rates[a,b]	
	Therapy I	**Therapy II**
NRT	13%–19%	7.5%–14% (placebo)
NRT	10%–14%	17%–19% (bupropion)
NRT + bupropion	22%	6% (placebo)
NRT + bupropion	22%–17%	10%–12% (NRT)
Bupropion	19%	11% (placebo)
Varenicline	26%	11%–15% (placebo)
Varenicline	22%	14% (bupropion)
Varenicline	26%	20% (NRT)
Comparison	**Risk ratio[c]**	**95% CI**
NRT/control[d]	1.58	1.50–1.66
Varenicline/control[e]	2.31	2.01–2.66
Varenicline/NRT[f]	1.13	0.94–1.35

[a]Data from reference 2.
[b]Abstinence at 24 weeks or more or 6 months or more.
[c]Risk ratios reflect success in quitting smoking, usually measured at 6 months.
[d]Data from 111 trials involving more than 40,000 persons and comparing treatment with NRT with placebo or non-NRT as a control (10). Different forms of commercially available NRT included chewing gum, transdermal patches, nasal spray, inhalers, and tablets/lozenges. Although, there may be differences in abstinence rates between different forms of NRT, the effects were largely independent of the duration of therapy, the intensity of additional support provided, or the setting in which the NRT was offered. Thus, NRT increases the rate of quitting by 50% to 70%, regardless of setting.
[e]Data from 11 trials involving more than 10,300 persons and comparing varenicline with placebo or control treatment (34).
[f]Data from 2 trials with 778 persons and comparing varenicline with NRT (34). Although, there may be a modest benefit of varenicline, the CIs do not rule out equivalence.

the understanding that specific types of nAChR are present in the brain; a high level of nAChR α4β2 expression in neurons in the ventral tegmental area is thought to be responsible for the psychologic addiction to nicotine (2, 29, 36). On the other hand, varenicline has an antagonist effect that blocks the reinforcing effects of nicotine and thus reduces the risk of relapse of smoking behavior and addiction (2, 29, 37). A major concern for both bupropion and varenicline was whether they would increase depression and suicidal ideation (2, 29). However, a recent compilation of clinical trials data has shown varenicline to be no different than other methods of smoking cessation with regard to depression or suicidal feelings (35).

An even newer approach for targeting nicotine addiction is nicotine vaccines, which currently are under clinical evaluation (38). Nicotine vaccines induce nicotine-specific antibodies that bind nicotine as it enters the blood stream, thus preventing it from entering the brain (39). Phase II/III clinical trials of different nicotine vaccines are in progress, and preliminary results seem to be promising in that the vaccine is virtually free of adverse effects and may be suitable for combinatorial use with other pharmacologic agents for smoking cessation (38).

Given the present studies of Murphy and colleagues and Maier and colleagues combined with the other relevant evidence, it would seem prudent to continue smoking cessation efforts with NRT. It is important to note that the majority of people on NRT receive it for a defined period (6–12 weeks), and the risk of long-term NRT still needs to be studied. This research is important given FDA consideration of expanding the NRT indication to allow more chronic use. More epidemiologic studies of the effect of NRT on lung cancer risk in large populations are in order, and it will be important to compare the human lung cancer risk of NRT alone with that of other smoking cessation therapies such as bupropion and varenicline. Last, although nicotine did not increase lung cancer progression in the *in vivo* preclinical models of Murphy and colleagues and Maier and colleagues, we still need to understand whether nicotine has a role in lung carcinogenesis and, if so, what it is in relation to nAChRs in normal lung epithelial and lung cancer cells.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This work was supported in part by NCI SPORE in Lung Cancer (P50CA70907).

Received September 20, 2011; revised September 22, 2011; accepted September 28, 2011; published online November 3, 2011.

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