Cancer Prevention Research

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

Long-term Nicotine Replacement Therapy: Cancer Risk in Context

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Abstract

Nicotine replacement therapy (NRT) for up to 12 weeks is well established, safe and efficacious for fostering smoking cessation. Some smokers at a high risk of relapse may benefit from long-term use, and so long-term NRT safety and efficacy have become a paramount question for the FDA and others. Laboratory studies have indicated a carcinogenic potential of nicotine. Animal model studies reported in this issue of the journal by Maier and colleagues (beginning on page 1743) and Murphy and colleagues (beginning on page 1752), however, provide additional reassurance that NRT does not promote lung cancer. Very long-term studies of NRT effects do not yet exist and would be needed to definitively answer the question about NRT efficacy and cancer risk and some decision making will need to be made based on limited human data and experimental studies. The overall NRT safety question is complex and requires consideration of three contexts and comparator groups (long-term NRT/abstinence vs. smoking, long-term intermittent NRT/reduced smoking vs. smoking, and long-term NRT/abstinence vs. abstinence without long-term NRT). Although the data on these issues are insufficient, the first comparison seems intuitive and may be compelling enough to allow the FDA to approve a long-term indication for NRT. An important public health goal is to help smokers and their health care providers understand the implications of potential long-term NRT risks in the context of its potential benefits and the far greater risks of continued smoking. *Cancer Prev Res; 4(11); 1719–23. ©2011 AACR.*

The efficacy and safety of short-term nicotine replacement therapy (NRT) for fostering long-term smoking cessation is well established, and up to 12 weeks of therapy is approved by the U.S. Food and Drug Administration (FDA; refs. 1–4). A meta-analysis indicates that there are measurable benefits in studies of 12 to 18 months of continued NRT use for relapse prevention (5), and other studies also indicate that this use is cost effective (6). An important question of considerable interest that remains today, however, is whether NRT can be recommended for long-term use, even years, to continue to promote smoking abstinence. The answer to this question requires both an efficacy and safety assessment. In this context, NRT conceptually has substantial benefits compared with long-term smoking but also, as explained later and addressed in this issue of the journal, laboratory studies suggest a potential for nicotine to foster the development of cancer.

The premise of long-term NRT use is that it would prevent smoking relapse, and the risks would be limited to maintaining nicotine addiction, but without the adverse consequences of continued smoking, such as increased lung cancer risk. Like the consideration of other long-term medications, on face value it is a simple risk–benefits equation. In actuality, however, this question is not simple to answer because the risk can be considered in 3 different contexts and comparator groups namely: (i) what is the risk of smoking abstinence with long-term NRT use compared with continued smoking? (ii) what is the risk of a lifetime pattern of repeatedly quitting with NRT and relapsing but reduced overall smoking, compared with continued smoking? (iii) what is the risk of long-term NRT use without relapse compared with long-term abstinence without NRT or relapse? The answer to the first comparator seems intuitive—smokers inhale numerous carcinogens plus nicotine, whereas the exposure for NRT eliminates exposure to virtually all tobacco toxicants, and so there is likely a substantial risk reduction from exposure reduction. And so, based on this alone, long-term users of NRT could be counseled to continue long-term use even if they relapse or are at a high risk of relapse (7). The answer to the second question also seems relatively intuitive because "less ought to be better," but consideration of this comparator group needs to examine: whether the reduction in lifetime consumption is enough to reduce smoking risks; whether smoking intensity (cigarettes per day) or duration (years smoking) has a greater contribution to risk; and whether NRT contributes to the continued smoking (e.g., by maintaining the nicotine addiction) and precludes the use of an alternate successful quitting strategy. The third comparator

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is even more difficult to consider because most relevant data come from experimental studies, and sufficient human data is not yet available.

Notwithstanding a typically imperfect world with limited data, the FDA is considering the indication of NRT for long-term use (http://www.fda.gov/Drugs/NewsEvents/ucm221185.htm) because of the substantial toll that smoking continues to take on smokers and society. For approving a long-term use indication, the FDA will consider laboratory data and human data, where the latter is both required and would be given great weight in the decision process for both efficacy and safety. It is worth noting that in 2010, the U.K. Medicines and Healthcare Products Regulatory Agency extended the indication for NRT to long-term use, considering mostly the risks compared with continued smoking and cited mostly supportive evidence on risks and benefits derived from short-term use and studies that considered reduced smoking (but not abstinence) and concurrent NRT use. But in their final guidance, the U.K. Agency did not discuss the potential long-term adverse effects of NRT such as cancer.

The best human data for considering the long-term use of NRT for both efficacy and safety would be long-term clinical trials or observational studies. The only such study to date that is somewhat helpful, however, is the Lung Health study which was a 5-year randomized trial to assess the effect of smoking cessation and reduction on chronic lung disease and pulmonary lung function. Among 5,887 subjects initially enrolled, they conducted surveillance for 7 additional years in 3,220 subjects (8). All subjects, without consideration of randomization or study design, were offered NRT. Although subjects were encouraged to use NRT for only 6 months, many continued to use it long term. A total of 75 lung cancers were diagnosed among smokers and quitters of the extended surveillance group, and so, although there was no difference for risk of lung (or other) cancers, the study was small. A major limitation was the short follow-up of the 7 additional years. Also, the study could not adequately address the efficacy of NRT use as no randomized control group was included in its design, and it used lower than currently approved doses of nicotine. Notwithstanding the limitations, this study at least does not indicate a strong role for nicotine in promoting cancer in humans, and clearly a risk, if any, is less than continued smoking.

Another approach to considering the long-term effects of NRT would be to consider it in the context of long-term smokeless tobacco (ST) use. ST clearly is a tobacco product with a reduced exposure to tobacco smoke carcinogens, compared with smoking, because the ST does not undergo combustion. However, it is not a reduced nicotine delivery product, and so, if ST is not associated with cancer risk, this could indicate that long-term exposure to NRT might not increase cancer risk. Indeed, although ST studies indicate that ST increases the risk of oral cavity and pancreatic cancer, at least for some forms of ST (9–11), both are substantially less than the risk of these cancers from smoking (11, 12). The former risk seems to be a consequence of exposure to tobacco-specific nitrosamines (TSNA) because in Sweden, where ST products are produced in a way to substantially reduce TSNAs, the risk of oral cavity cancer does not seem to be increased (11). The risk of pancreatic cancer, however, is slightly elevated among Swedish ST users, but whether this increase is due to nicotine or to the concurrent exposure to numerous chemical carcinogens in the ST other than TSNAs is unknown. Still, it should be noted that the risk of pancreatic cancer from low-TSNA tobacco is substantially lower than from smoking, and so this comparison adds reassurance for the long-term safety of NRT. Notably, an important finding is that lung cancer risk is not increased for exclusive ST users (10, 11). Thus, the ST studies provide some insight into the question of an increased lung cancer promotion and risk for complete smoking abstainers on long-term NRT versus those without NRT, given the lack of direct human data on this question.

Consideration of laboratory data, namely *in vitro* cell culture and *in vivo* experimental animal studies, placed into proper context is essential to a safety assessment of long-term NRT. Not surprisingly given its potency for addiction, nicotine is a highly active biomolecule, affecting a large number of cell functions and pathways important in carcinogenesis. Nicotine stimulates the nicotinic acetylene receptors that are present in numerous tissues and tumors (13–16). The stimulation of these receptors triggers a wide range of downstream cellular pathways intimately related to the cancer process; depending on the subunit configuration of the receptor, nicotine can both stimulate progression and decrease the effect of inhibitory pathways (17, 18). Numerous cell culture and experimental animal studies show the potent effect of nicotine in enhancing proliferation in lung, bladder, and other tumors (13, 15, 16, 18–20), decreasing apoptosis including preventing apoptosis by chemotherapeutic agents for lung and oropharyngeal cancers (18, 21–24) and enhancing angiogenesis (19, 25, 26). There also is evidence that nicotine may promote metastasis because of stimulation of cell motility and migration (13, 18). Although nicotine may be able to form DNA adducts, it generally is not genotoxic (27–33). Taken together, these studies support the hypothesis that nicotine could enhance carcinogenesis and raise a concern that nicotine could promote carcinogenesis in former smokers, who have a background of initiated cells with genetic damage left over from the earlier smoking days.

Another concern about the long-term use of NRT is evidence that the carcinogenic TSNAs, 4-(methylnitrosamino)-1-(-3-pyridyl)-1-butanone (NNK) and *N*-nitrosonornicotine (NNN), can be formed endogenously from nicotine. A smoking cessation study by Stepanov and colleagues, however, showed that NNK metabolites were not detectable in persons using NRT (34, 35). However, they did find intermittently high levels of NNN similar to baseline smoking levels among some oral NRT users and in 1 of 9 persons using the NRT patch (36). Although these data indicate a potential cancer risk to NRT users, especially oral users, it is important to realize that NNN is only one of the TSNAs in cigarette smoke, let alone of the many other tobacco smoke carcinogens, and so in this

context the risk, if any, seems small compared with continued smoking.

Two reports in this issue of the journal directly address the safety of NRT in experimental animal studies (37, 38). Maier and colleagues conducted a series of studies to determine whether nicotine would promote carcinogenesis induced by NNK (37). One model was a crossed A/J and C57BL/6 mouse. They also studied an animal model prone to develop lung tumors against the background of having mutant *K-Ras*, which is commonly found in human lung cancer. Finally, they determined whether nicotine enhanced lung tumor growth and metastases in a syngeneic lung cancer graft model with NNK-transformed lung cancer cells. The dosing of nicotine, albeit by drinking water, was specifically intended to be similar to levels human smokers receive by using NRT. In all the experiments, there was no tumorigenic effect by nicotine. An advantage of this study was the level of nicotine dosing and the corroborative experimental animal models they used.

The other study appearing in this issue of the journal is reported by Murphy and colleagues, who also focused on NNK-induced lung tumors in the A/J mouse (38). In an effort to assess whether nicotine could inhibit lung carcinogenesis by blocking NNK metabolism and to assess whether nicotine could enhance NNK-induced tumorigenesis or act as a complete carcinogen, they administered nicotine in different exposure scenarios comprising 2 weeks before, 2 weeks before and 46 weeks after, and 46 weeks after exposure to NNK. Saline controls also were used. The level of nicotine administered in drinking water greatly exceeded the nicotine dose equivalent to NRT in smokers as measured by cotinine, but nicotine blood levels in the mouse were substantially lower because of the increased metabolic capacity. In all the dosing scenarios, nicotine did not promote or cause lung tumors.

Other nicotine exposure studies in experimental animals also do not indicate that nicotine alone is tumorigenic (39–41). As a tumor promoter, however, nicotine has been reported to increase the frequency of tumors induced by agents other than NNK such as 7,12-dimethylbenz(*a*)anthracene (42), *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (43), and *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (44). There also are studies that show no effect for other *N*-nitrosamines (45) and an antitumor effect in some cases (46). Studies using cancer xenograft models also have shown that nicotine promotes tumor growth and metastases (25, 47–49). So, it is possible that nicotine could promote tumors induced by carcinogens other than NNK, but studies of a scope and quality similar to those of the studies reported in this issue of the journal need to examine this question.

Although the use of experimental studies for implicating human cancer risk is well accepted, it also is well accepted that the direct extrapolation from animals to humans is problematic. The many issues to consider when assessing animal models include species differences in metabolism and cell function, how the nicotine is delivered to the animal and the resulting nicotine and cotinine levels, high-dose exposures, the cancer susceptibility of the particular strain, and whether the animal model incorporates procarcinogenic host backgrounds such as immune incompetence and inflammation.

The studies of Maier and Murphy and respective colleagues provide some reassurance, but they do not entirely refute these data, as no experimental model can sufficiently predict safety and cannot fully address the various ways that nicotine could promote cancer. Nonetheless, weighing the balance between long-term nicotine use and continued smoking (with its attendant higher levels of nicotine), it is reasonable to assume that the recommendation for long-term NRT to prevent smoking relapse is a good one. A recent study by Apelberg and colleagues used a Monte Carlo analysis that indicated that NRT use in the general U.S. population could decrease overall premature mortality by 40,000 deaths (50). An interesting further analysis, with the assumption that NRT could cause cancer or cardiovascular disease, still found that the overall number of premature deaths would decrease by 32,000. Clearly, human studies, not just models, are needed to definitively ascertain the effects of long-term NRT use on smoking behavior (e.g., does it promote relapse because smokers remain in a state of nicotine dependence). Also, cohort studies need to include questions about sole NRT use so that we can assess its cancer risks, albeit in retrospect. These types of data, therefore, also are important for the FDA's consideration of a long-term NRT indication.

Along with an indication for long-term NRT use, an important issue that needs to be addressed is how best to deliver the following message to smokers and health care providers: Complete smoking cessation following short-term use of NRT is conceptually safer than is long-term NRT use to maintain abstinence, but if the smoker is at a high risk of relapse, then long-term NRT is better than resuming cigarette smoking. The challenge is to sufficiently inform smokers that there might be a small cancer risk, if any, with long-term NRT use compared with abstinence without NRT, but not to dissuade smokers from using NRT either in the short or long term because they perceive that nicotine is carcinogenic without regard for the context of smoking. Many medications approved for treating infections, seizures, cancer, and others have the potential to increase risk based on laboratory and even sometimes human studies, and the favorable risk–benefit equation leads to the use of these medications (although risk–benefit considerations of cancer prevention drugs have proven to be a very complex issue; refs. 51, 52). The same should be true for long-term NRT use given the large difference in carcinogen exposure between smoking and NRT.

It is critical that a conceptual increased cancer risk that lacks corroborative human data of long-term NRT (versus complete abstinence) does not cause any confusion among smokers and health care providers about short-term NRT: the efficacy and safety of short-term NRT are well established and certain. About long-term NRT, the animal model studies reported in this issue of the journal provide additional reassurance about the safety of long-term use of NRT.

Disclosure of Potential Conflicts of Interest

The author provides expert testimony and litigation support on behalf of plaintiffs in tobacco-related law suits.

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