Published in final edited form as:
Curr Cardiovasc Risk Rep. 2012 December 1; 6(6): 534–541. doi:10.1007/s12170-012-0266-9.

Very low nicotine content cigarettes and potential consequences on cardiovascular disease

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Abstract

Cigarette smoking remains highly prevalent in the U.S. and contributes significantly to cardiovascular disease (CVD). Tobacco control policies, including product regulation, can reduce smoking-related harm. One approach being considered in the U.S. is for the FDA to set a low nicotine standard for cigarettes. Such a standard could result in multiple beneficial outcomes including reduced cardiovascular toxicity related to nicotine, reduced smoking intensity in current smokers, increased cessation rates, decreased development of smoking dependence in youth, and decreased passive smoke exposure. Consequently, CVD risk in the U.S. could be dramatically improved by nicotine reduction in cigarettes. Possible pathways linking nicotine reduction in cigarettes to decreased CVD risk are discussed, while potential unintended consequences that could offset expected gains are also presented. Gaps in the literature, including limited data on CVD biomarkers and long-term CVD outcomes following the use of very low nicotine cigarettes, are discussed to highlight areas for new research.

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Disclosure: D.L. Joel: none; R.L. Denlinger: none; S. Dermody: none; D.K. Hatsukami: Funded by Nabi Biopharmaceuticals and NIDA to be a site for a nicotine immunotherapy trial, had travel/accommodations expenses covered or reimbursed by Selecta Biosciences; N.L. Benowitz: consultant to several pharmaceutical companies that have developed or market smoking cessation medications; E.C. Donny: none.

Keywords

smoking; cigarette; nicotine; cardiovascular disease; tobacco policy; nicotine reduction

Introduction

Cigarette smoking remains highly prevalent in the United States, with an estimated 19.3% of adult Americans still engaging in this deadly behavior [1]. Smoking contributes to major health problems, resulting in an estimated 443,000 deaths and over 193 billion dollars in lost productivity and health care expenditures per year [2]. Many of these deaths are related to cardiovascular disease. Smoking increases risk of stable angina, acute coronary syndromes, sudden death, stroke, and both aortic and peripheral atherosclerosis [3]. Compared to non-smokers, smokers' risk of coronary heart disease (CHD), the leading cause of death in the U.S., and stroke are increased by 2 to 4 times [4]. Multiple mechanisms have been suggested as underlying the link between smoking and cardiovascular disease including inflammation, endothelial dysfunction/injury, activation of thrombosis, modification of the lipid profile, and increased risk of diabetes [3, 5-7].

In recent years, tobacco control efforts aimed at reducing the harm associated with smoking in the U.S. have increased. In 2009, Congress passed the Family Smoking Prevention and Tobacco Control Act (FSPTCA), which for the first time allows the U.S. Food and Drug Administration (FDA) to regulate the manufacturing processes, enact product standards, and restrict the distribution and marketing of particular tobacco products to improve public health [8]. Some of its notable achievements to date include banning flavored cigarettes (excluding menthol), removing the descriptors "light", "low" and "mild" from cigarette packages, requiring face-to-face only sale of tobacco products, and requiring negative health warnings to cover 50% of the cigarette packaging.

However, the FDA has yet to exercise its power to set a standard for nicotine in cigarettes [8]. Nicotine is the critical constituent that sustains tobacco use [9]. Thus, reducing the nicotine content in cigarettes to a level that may be below a "threshold" for reinforcement and dependence may significantly decrease tobacco caused morbidity and mortality [10]. While the FDA does not have the legal authority to mandate a zero nicotine standard, the nicotine in cigarettes could feasibly be reduced to a non-addictive level, if such a level does indeed exist [8]. A maximum systemic delivery of nicotine of 0.2 mg per cigarette was proposed decades ago as the threshold yield for establishing and sustaining addiction, which is substantially lower than average nicotine intake of 1 to 1.5 mg from commercially available cigarettes [10, 11]. Research is underway which aims to more precisely evaluate the dose-response relationship between nicotine yield, behavior, and symptoms of dependence.

It is important to note that reductions in machine-estimated nicotine yield, such as are found in previously labeled commercial "light" cigarettes, are unlikely to reduce the harm from smoking. "Light" cigarettes were marketed as safer cigarettes that reduced smokers' exposure to tar and nicotine; however, due to compensatory changes in the smoker's behavior (e.g., blocking ventilation holes), they were in fact equally harmful in terms of carcinogen and toxin exposure [12]. Smokers also viewed these cigarettes as an alternative to quitting smoking because of their supposed health risk reductions, which increased public health harm [13, 14]. Thus, the preferred nicotine reduction strategy for the future would be to reduce the total nicotine content of tobacco in cigarettes (i.e., through genetically altered tobacco), instead of utilizing cigarette design changes (i.e., increased ventilation holes) like those used for "light" cigarettes, to truly reduce exposure in the user [15].

The introduction of the FSPTCA [8] raises the question of how risk for CVD in the U.S. might be influenced by tobacco regulation, and this paper will focus specifically on nicotine reduction in cigarettes as one action that may decrease risk. Two possible strategies might be employed in the implementation of a nicotine reduction policy, including abrupt reduction to a very low level versus gradual reduction over many years. Research is needed to determine the effects of both strategies. This paper will not address the reduction process per se but rather the end result of either strategy, which would be the exclusive availability of very low nicotine content (VLNC) cigarettes.

Theoretical Pathways Linking Nicotine Reduction in Cigarettes to CVD Risk

We hypothesize that cardiovascular disease risk may be decreased by nicotine reduction in cigarettes through five pathways. One pathway is decreased cardiovascular toxicity due to reduced exposure to nicotine. Additionally, four indirect pathways are based on expected decreases in smoking behavior, which include decreased smoking intensity (i.e., fewer cigarettes per day), complete smoking cessation, decreased progression to smoking dependence in youth experimenting with cigarettes, and decreased passive smoke exposure. These four indirect pathways would lead to decreased exposure to nicotine and other harmful toxicants of tobacco smoke such as particulates, oxidant chemicals, polycyclic aromatic hydrocarbons (PAHs) and carbon monoxide (CO) that contribute to CVD [6, 16]. Future research is needed to empirically test these pathways; however, existing data provides preliminary support for these mechanisms.

The Role of Nicotine in Cardiovascular Disease

Nicotine itself is not the major tobacco smoke constituent that is primarily responsible for smoking-related CVD. Indeed, it is important to keep in mind that nicotine replacement products (i.e., nicotine patch) are safely used for both short-term and long-term smoking cessation pharmacotherapy even in cardiac patients [17-20], suggesting that therapeutic nicotine does not significantly alter risk for initial or recurrent CVD. Thus, it is possible that nicotine reduction in cigarettes in the absence of any behavior change may have little impact on CVD risk. Nevertheless, due to a different route of administration and dose of nicotine compared to therapeutic nicotine products, the potential effect of altering nicotine content in cigarettes should be carefully considered.

Evidence suggests that nicotine may have some deleterious effects related to CVD disease. Nicotine is sympathomimetic, increasing the release of the catecholamines epinephrine and norepinephrine [16]. The catecholamine surge may contribute to arrhythmogenesis and the increased risk of sudden death in smokers [21]. Frequent smoking of normal nicotine cigarettes persistently activates the sympathetic nervous system [22]. Nicotine acutely increases blood pressure, heart rate, and coronary vasoconstriction after each cigarette and over time causes a persistent increase in heart rate throughout the day [16]. The hemodynamic effects result in increased cardiac work with associated increased demand for oxygen as well as decreased blood supply, creating a supply-demand imbalance that can produce myocardial ischemia. Moreover, nicotine has deleterious effects on the endothelium, and endothelial dysfunction can contribute to atherogenesis and may result in increased acute ischemic events [16, 23-26]. Finally, recent animal studies have found that nicotine itself contributes to the pathogenesis of abdominal aortic aneurysm by altering vascular smooth muscle cells [27, 28].

Though nicotine has some deleterious effects on the cardiovascular system, some data suggest that nicotine itself may counteract the increased risk of thrombosis due to tobacco smoke by mitigating increased platelet activation [29]. One study measured a marker of platelet activation state, platelet P-selectin (CD62P), in smokers who had smoked either 0.6

mg or 0.05 mg nicotine yield cigarettes [30]. The group that smoked 0.6 mg nicotine cigarettes demonstrated a 33% increase in platelet activation state following smoking, whereas the group that smoked 0.05 mg nicotine cigarettes demonstrated a 94% increase, suggesting that nicotine modulates platelet activation. However, the investigators did not measure smoking compensation (i.e., taking deeper or more frequent puffs), so it is unknown whether increased smoke exposure may have explained the findings. *In vitro* studies of platelets from nonsmokers exposed to smoke extracts from high nicotine, low nicotine, and very low nicotine cigarettes suggest the effect of VLNC cigarettes on platelet aggregation is not solely due to changes in smoking behavior [31]. The very low nicotine cigarette smoke rendered platelets most susceptible to activation. When nicotine was then added to the very low cigarette smoke extract, there was significant reduction in platelet activation rate, supporting the causal role of nicotine in modulating platelet activation state. Prospective studies following smokers using VLNC cigarettes that measure compensation and markers of platelet activation are needed to better understand these findings.

Nicotine Reduction through VLNC Cigarettes and Smoking Intensity

Reducing the nicotine in cigarettes might further affect CVD risk in current smokers by reducing how many cigarettes per day (CPD) they smoke. By decreasing CPD, smokers are exposed to fewer toxicants in cigarettes that play a role in the development of CVD. Smoking VLNC cigarettes (i.e., 0.05 mg of nicotine) has been associated with reduced CPD in smokers over time [32-35]. Significant smoking reductions have been found among non-treatment seeking smokers who smoked progressively reduced nicotine content cigarettes over 6 weeks, reducing weekly from 0.8 mg nicotine yield to 0.1 mg nicotine [32]. Participants were followed for an additional four weeks after returning to smoking their usual cigarettes. On average, participants reduced their smoking from approximately 18 CPD at baseline to approximately 10 CPD by the end of the 10-week period. A second study of non-treatment seeking smokers randomized participants to no smoking, 0.6 mg nicotine cigarettes only, or 0.05 mg nicotine cigarettes only conditions [33]. After 9 days in an inpatient research unit, smokers in the 0.6 mg nicotine group increased their CPD by 2.1 cigarettes compared to baseline smoking, while smokers in the 0.05 mg nicotine group decreased their CPD by 3.8 CPD compared to usual smoking. A third study found that 6 weeks of using 0.05 mg nicotine cigarettes in treatment-seeking smokers led to an average smoking reduction from 18 CPD to 12 CPD [34]. The most recent study followed participants who smoked five progressively reduced nicotine cigarettes over the course of 10 months [35]. The first four experimental cigarettes were used for one month each, and the final low nicotine cigarette (0.1 mg nicotine yield) was used for 6 months. Smoking rate remained stable until smokers were switched to the 0.1 mg nicotine yield cigarettes, after which CPD decreased by 4 cigarettes during the two-month follow-up. Only the analyses from the first 6 months of the study have been published, so the long-term outcomes are unknown.

These reported CPD reductions are average effects; some individual smokers may compensate for decreased nicotine by smoking more frequently or more intensely. Research suggests that VLNC may produce transient compensatory increases in smoking upon initial use, but over time smoke intake decreases. Likewise, changes in the way individuals smoke, such as an acute increase in total puff volume per cigarette, was found in smokers trying VLNC cigarettes, suggesting compensation [36]. However, with prolonged use of VLNC cigarettes, smoking rate, the volume of smoke inhaled and CO expiration decreases over time, indicating that compensation does not endure [34, 37].

Given the relatively short follow-up period of these studies, measurement of protracted disease outcomes is not often possible. However, biomarkers of effect provide valuable short-term information about the potential impact of smoking reduction on CVD risk.

Important CVD biomarkers include white and red blood cell counts, cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), blood pressure, heart rate, C-reactive protein (CRP), fibrinogen, and homocysteine. Three of the aforementioned VLNC cigarette studies measured many of these biomarkers [32, 34, 35], but detected no significant changes following the nicotine reduction period. Importantly, one of these studies measured P-selectin but found no significant changes, contrary to what would be predicted based on the platelet activation studies described in the previous section [32]. Interestingly, previous studies that have used nicotine replacement therapy (NRT) to aid participants in reducing the number of cigarettes they smoke have found significant improvements in CVD biomarkers. One study followed healthy smokers who used nicotine nasal spray *ad libitum* to aid them in reducing smoking for 8 weeks [38]. On average, participants reduced CPD from 21.5 at baseline to 10.8 after 8 weeks and there were significant improvements in fibrinogen, white blood cell counts, and the high-density/low-density lipoprotein ratio. Another study followed smokers who reduced their smoking for 12 weeks while using nicotine gum and nicotine patch and found significant improvements in hemoglobin, hematocrit, red and white blood cell counts, lipids, blood pressure and heart rate [39]. Thus, studies of VLNC cigarettes that have longer follow-up periods, with and without NRT, may be needed to replicate these changes in biomarkers.

Though smoking reduction might be a tenable harm reduction strategy, there is evidence that the relationship between the dose of tobacco smoke and CVD risk is not linear. Rather, a non-linear association has been described such that even low levels of smoking (i.e., 1 to 4 CPD) are associated with increased risk for CVD [40]. The risk for cardiovascular disease increases steeply at low levels of exposure to cigarette smoke but flattens out at higher exposures [41]. Thus, very heavy smokers who reduce their smoking to levels that remain moderate may experience little or no benefit with respect to CVD risk.

Nicotine Reduction through VLNC Cigarettes and Smoking Cessation

Reductions in cigarette dependence have been found in smokers using VLNC cigarettes, suggesting that they may help some smokers accomplish cessation. In one nicotine reduction study of non-treatment seekers described above, self-efficacy about quitting increased significantly, while cigarette dependence measured by the Fagerstrom Test for Nicotine Dependence (FTND) significantly declined [32]. Additionally, 5 out of 20 participants spontaneously quit smoking by the end of the tapering period even though subjects did not intend to quit upon entry into the study. During the VLNC cigarette treatment study described above, scores on the FTND dropped significantly and 35.9% of participants smoking 0.05 mg nicotine cigarettes quit smoking by the 6-week follow-up [34]. This is in contrast to a 13.5% quit rate in a second group smoking 0.3 mg nicotine cigarettes and a 20% quit rate in a third group using nicotine lozenges. The most recent treatment study found that participants who were given VLNC cigarettes to use *ad libitum* during smoking urges along with usual care (NRT plus behavioral support) for 8 weeks had higher cessation rates at the 6-month follow up and a longer time to relapse compared to the usual care group [42].

Though no data to date demonstrate a specific link between nicotine cessation achieved through the use of VLNC cigarettes and decreased cardiovascular risk, complete cessation from smoking via other methods has been shown to reduce the risk for and occurrence of CVD. Smokers who quit smoking using the nicotine patch had significant improvements in systolic blood pressure, heart rate, LDL and HDL [43]. A more recent study on the effects of 5 smoking cessation pharmacotherapies found significant improvements in endothelial function and lipids one year after the participants quit smoking [44, 45], though carotid intima-medial thickness (CIMT; a marker for development of atherosclerosis) progression was not reduced three years after the intervention as expected [46]. Some biomarkers may

take longer to demonstrate improvement following smoking cessation, as one study suggested CRP begins declining shortly after cessation but takes 5 years to fully return to baseline levels [47], a time course which parallels the observed reduction in clinical CVD risk after cessation. Despite uncertainty regarding the time course of specific biomarkers, smoking cessation significantly reduces CVD-related morbidity and mortality in the relatively short term (1-5 years). For example, one trial found that the relative risk (RR) of death due to CHD was significantly lower for quitters versus non-quitters (RR= 0.63) after one year of cessation, even when other risk factors were accounted for [48]. Additional years of maintained abstinence (i.e., at least three years) afforded quitters an even greater advantage (RR = 0.38) [48]. A more recent study that followed smokers for approximately 7.5 years found that having quit smoking for at least four years, compared to continued smoking, reduced the hazard ratio for any CVD events to 0.34 in Japanese men [49]. In addition, a review of 20 studies aimed at estimating the effect of cessation on CVD risk in patients with CHD reported a 36% reduction in crude RR of mortality and significant reduction in nonfatal MI risk for smokers who quit compared to smokers who did not [50]. It is clear that smoking cessation offers smokers the best improvement in cardiovascular health, and VLNC cigarettes may help smokers achieve this goal.

It is important to note that at least two unintended consequences related to smoking cessation could potentially occur following a nicotine reduction policy. One possibility is that current smokers may misconstrue VLNC cigarettes as carrying fewer health risks, thereby decreasing their motivation to quit smoking. This phenomenon occurred when previously-labeled so-called “light” cigarettes were marketed as a healthier alternative to regular cigarettes, driving smokers to switch to light cigarettes instead of quitting smoking [13]. Secondly, former smokers who have successfully maintained abstinence may begin smoking again if they believe that they will not become addicted to VLNC cigarettes or that the health risks are lower. Therefore, smoking cessation should remain the highest priority even with a nicotine reduction policy in place.

Nicotine Reduction and Smoking in Youth

At the population level, the risk of CVD may decline through reduced progression to smoking dependence in young people who try smoking if VLNC cigarettes have a lower abuse liability. This assumption has not been empirically tested in humans due to the ethical constraints of having nonsmokers try VLNC cigarettes. However, at least two methods could be used to estimate the effect of nicotine reduction on non-smokers. Animal models, such as rat nicotine self-administration, can be used to explore whether the dose of nicotine required to support operant behavior (i.e., voluntary lever presses or nose pokes that are reinforced by nicotine delivery) differs between nicotine-naïve animals and animals that have a history of self-administering a higher dose of nicotine. This approach would help us understand whether cigarettes with a nicotine dose below the addictive threshold in dependent smokers would be reinforcing to youth experimenting with cigarettes. The second approach would be to study the effect of VLNC cigarettes on young, non-daily smokers to determine if these cigarettes disrupt the progression to heavy, daily smoking that may occur with the use of regular nicotine cigarettes.

Moreover, rates of experimentation with smoking in youth may also be affected by the reduction of nicotine in cigarettes. If VLNC cigarettes are less desirable because of reduced pharmacological effects, young people may be less motivated to try them. However, young people may be susceptible to misconceptions about VLNC cigarettes carrying fewer health risks. Perceptions of lower health risks and decreased risk of becoming addicted may assuage fears about trying smoking. The expectation, however, is that experimentation would not lead to dependence. However, it is possible that people who experiment with VLNC cigarettes may smoke intermittently even if they do not develop dependence, so it

will be important for future research to determine the effects of intermittent VLNC cigarette use. By limiting the number of young people who become chronic smokers, a nicotine reduction policy would likely decrease the incidence of CVD.

Nicotine Reduction and Decreased Passive Smoke Exposure

If smoking rate and prevalence were reduced via a nicotine reduction policy, passive smoke exposure would also significantly decrease. Research suggests that passive smoke exposure results in increased CVD risk [51, 52]. In a study of never-smoking adults, individuals with secondhand smoke exposure quantified by low levels of cotinine (0.05-0.215 ng/ml) had increased levels of fibrinogen and homocysteine [53]. A prospective study of non-smoking males found that higher levels of serum cotinine were associated with an increased incidence of CHD. Men with heavy passive smoking exposure (0.8-14.0 ng/ml cotinine) developed CHD at rates similar to those of light active smokers (1-9 CPD) [54]. Reducing passive smoke exposure through policy interventions such as Clean Indoor Air Acts (CIAAs) has been shown to decrease the incidence of acute myocardial infarction (AMI) and CHD [55-58]). A nicotine reduction policy is expected to accomplish the similar goal of reducing exposure to harmful toxicants of cigarette smoke in non-smokers by decreasing smoking intensity and increasing cessation, which would minimize unintended increases in the risk of developing CVD in non-smokers.

VLNC Cigarettes in the Context of Other Nicotine Products

One must consider cigarette regulation in the context of other nicotine delivery devices on the market such as nicotine replacement therapies or smokeless tobacco (ST) products including snuff or snus. Smokers using VLNC cigarettes may choose to switch to these smokeless products. While some studies suggest there is an increased risk of AMI from using ST [59], the risks are far lower than those from smoking combustible products [60]. A strategic plan for tobacco harm reduction was developed to reduce tobacco related morbidity and mortality at the individual and population levels [15]. The long-term goal is to first eliminate the use of combustible tobacco products that produce the most harm. Tobacco experts have suggested that greater availability of nicotine replacement products such as the patch, gum or lozenge, which are even less harmful than ST products in terms of cardiovascular risk, would help smokers during this transition and produce the maximal reduction in harm, including risk of CVD.

Conclusion

Tobacco control policies are critical for reducing the harm caused by cigarette smoking. A nicotine reduction policy may lower the abuse liability of cigarettes so that current smokers may reduce or quit smoking and experimenters do not become addicted. Current data suggest that the extended use of VLNC cigarettes allows smokers to reduce the number of cigarettes they smoke each day and is associated with decreased cigarette dependence. By lowering their intake of cigarette smoke, smokers (as well as non-smokers affected by environmental tobacco smoke) accumulate less exposure to toxic constituents in tobacco smoke that contribute to the development of CVD. However, little data has been collected on the effect of VLNC cigarettes on known CVD biomarkers, and no studies to date have followed smokers using VLNC cigarettes long enough to determine whether the incidence of CVD decreases. The cardiovascular consequences of smoking reduction are not completely clear and likely depend on the magnitude of decline; however, complete cessation from smoking clearly reduces risk of CVD.

Though many of the expected outcomes associated with the reduction of nicotine in cigarettes would positively affect the risk of CVD in the U.S., potential inadvertent effects

must also be considered. VLNC cigarettes may be smoked more intensely temporarily or perceived as less risky and therefore tried more often; however, these negative effects are likely to be outweighed by the benefits of a less addictive cigarette, which would ultimately improve public health. Additionally, some data suggest that VLNC cigarettes would lose the protective effect of nicotine against platelet activation; however, studies of VLNC cigarettes with combined NRT are needed to clarify this issue. Still, the broader beneficial effects of reduced exposure to tobacco smoke on CVD risk are likely to outweigh the loss of this potential beneficial effect of nicotine.

Cigarettes are one of the many nicotine delivery devices on the market, and the regulation of nicotine content is one step in the direction towards limiting the harm caused by tobacco. Nevertheless, cigarettes are responsible for most CVD-related morbidity and mortality, and the prospect of smokers switching to noncombustible nicotine products is preferred to the maintenance of smoking. Perhaps the regulation of nicotine in all products will become another goal of the future, but the FDA has the ability now to first make cigarettes less addictive and therefore less harmful.

Acknowledgments

None

Funding This work was supported by grants from the National Institute on Drug Abuse, DA02277 and U54 DA031659.

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