Chapter 2

How Effective is Fear of Lung Cancer as a Smoking Cessation Motivator?

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Additional information is available at the end of the chapter

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Abstract

A risk score for lung cancer derived from genetic and clinical data has been shown to motivate smokers to quit. However, smokers with a relatively low (but not insignificant) risk score are more likely to carry on smoking. To understand this observation, the balance between smoking cessation motivators and de-motivators must be understood. A relatively low risk score can act as a de-motivator. Other de-motivators that have been recorded and were observed by researchers involved in this project were: nicotine addiction and fear of withdrawal symptoms, optimism bias, confirmation bias, attentional bias, post-traumatic stress disorder (PTSD), anxieties about smoking cessation and weight gain, side effects of smoking cessation therapy, fatalism, peer pressure and lack of family cohesion. This long list of de-motivators serves to emphasize the complexity of the psychological make-up of the individual smoker. This is illustrated by a set of case histories (anonymised for confidentiality). The future use of a risk score as a smoking cessation motivator is discussed and suggestions are made as to how a risk score could be made more effective including inclusion of scoring for cardiovascular risk.

Keywords: smoking cessation, genetic testing, lung neoplasms, primary health care

1. Introduction

The reasons why smokers either continue to smoke or stop smoking are diverse and every case is probably unique. However, there is a basic truth in that there is a constant seesaw between smoking cessation motivators and the rather less well understood de-motivators. The importance of de-motivators is illustrated by the simple fact that over 60% of smok-

ers say they would like to quit but most seem somehow unable to do so [1, 2]. The obvious explanation is that this is due to nicotine addiction but this may be only one of many de-motivators.

In 2014, my colleagues and I at the University of Surrey, United Kingdom (UK), carried out research into smoking cessation. We recruited 67 smokers who wanted to quit from a primary care database of 32,000 (**Table 1**) and randomized them to either a control group or a test group. The test group had an additional motivator to quit. This was the Respiragene risk score for lung cancer derived from a genetic test (19 single-nucleotide polymorphisms (SNPs) and one deletion mutation) and clinical criteria including history of chronic obstructive pulmonary disease, family history of lung cancer, and age. Both groups attended 8 weekly smoking cessation clinics which took place at the same primary care venue but with test group and control group attended on different weekdays. We published our protocol and outcome measures a priori [3]. Primary outcome was smoking cessation after 6 months.

Demographic/smoking feature	Test group (n=36)	Control group (n=31)	p-Values (test)
Gender: female	55.6%	53.3%	0.747 (Chi-square)
Mean age (at start of study)	49.7	49.0	0.812 (Unpaired t)
Mean age at completion of education	18.4	18.5	0.971 (Unpaired t)
Years in education (excluding interruptions)	22.8	26.2	0.517 (Unpaired t)
Pack years	32.0	28.9	0.396 (Unpaired t)
Cigarettes/day at start	18.1	18.1	0.993 (Unpaired t)

Table 1. Demographic and baseline smoking data for Respiragene trial.

During our research, we found that 36% of smokers had stopped smoking and were still not smoking after 6 months. Of the 64% who were still smoking at 6 months, all but two participants planned to stop smoking at some time in the future and 30% had cut down substantially (by 10 or more cigarettes/day) [4].So why don't they just quit?

Our hypothesis was that when participants were told their lung cancer risk, this would tend to outbalance any de-motivators such as issues around nicotine addiction (**Figure 1**) and give a high 6-month quit rate. However, we were probably underestimating the potency of known and unknown de-motivators. It certainly cannot be entirely due to nicotine addiction because varenicline blocks the physical addiction and prevents most withdrawal symptoms and yet 50–75% of subjects taking varenicline will still be smoking 6 months later [5, 6]. There must, therefore, be more to it than nicotine addiction.

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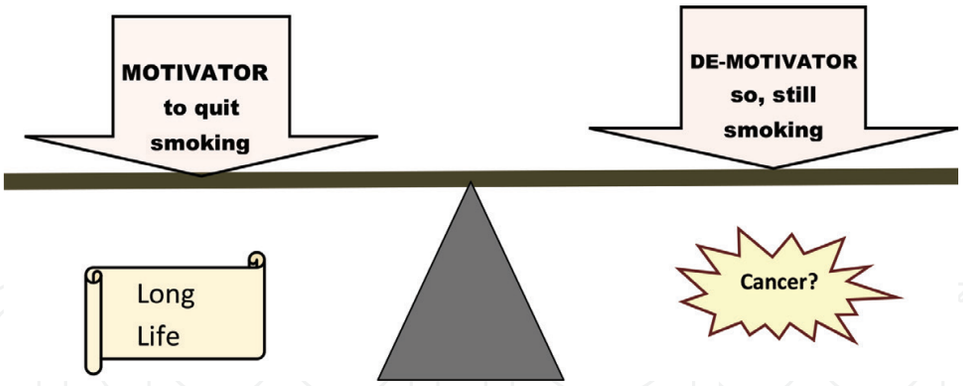

Figure 1. For smokers: the seesaw of destiny. The balance between motivators and de-motivators determines success or failure for smokers trying to quit.

2. The Respiragene project

As already reported [4], the 6-month quit rate in our Respiragene trial was more dependent on the risk score than we had expected. The laboratory reported the Respiragene risk score as three categories: average risk of lung cancer, high risk of lung cancer, and very high risk of lung cancer. Only non-smokers and ex-smokers can achieve the category "low risk". We were also able to estimate lifetime risk as a percentage (i.e., a 50% lifetime risk meant that the risk of lung cancer was like tossing a life/death coin). The 6-month quit rate results are summarized in **Figure 2**. However, assessing the balance of motivators and de-motivators was included in secondary outcomes. The relative importance of ten smoking cessation motivators was estimated using a feedback questionnaire at 8 weeks and again at 6 months. The results show the perceived importance of these motivators (**Figure 3**).

From taking notes on comments from patients during counselling and from responses to open-ended questions in feedback questionnaires that participants completed, we were able to clarify the roles of some of these de-motivating factors. Most smokers have two main de-motivators:

1. **Nicotine addiction and fear of withdrawal symptoms** [7–9]. Nicotine has been shown to be as addictive as illegal drugs such as morphine and cocaine.
2. **Optimism bias** [10–13].Tendency to underestimate the health risks of smoking and the feeling "It'll never happen to me".

We expected that our study would confirm the hypothesis that being told a risk score for lung cancer would cancel out both nicotine addiction and optimism bias in at least 50% of participants. An earlier study (n = 99) using the Respiragene risk score had shown that smokers were more likely to quit compared with a control group whatever risk score they were given [14]. However, these participants were recruited from a hospital in New Zealand. We carried out a similar trial in a UK primary care setting. A surprise finding from our trial was that although all but one of the participants with a very high risk score had stopped smoking at 6 months, participants with an average risk score were more likely to be smoking than controls (**Figure 2**).

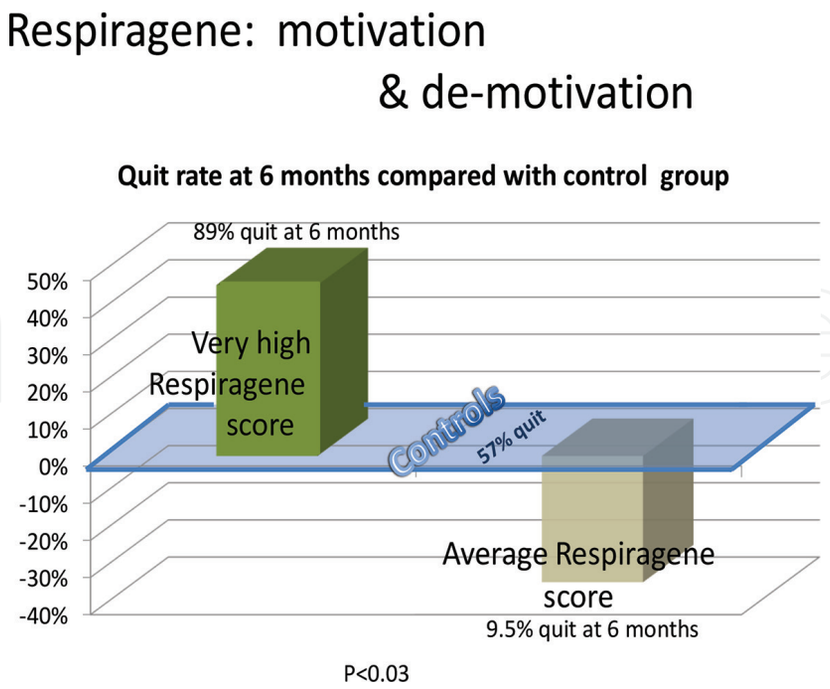

Figure 2. The blue "glass ceiling" represents the quit rate for the control group. Quit rate at 6 months for controls was 57%. Subjects with an average risk score for lung cancer (only non-smokers and ex-smokers are assessed as "low risk score") had a lower quit rate than controls, and a "moderately high" quit rate was no better but difficult to judge due to small numbers (only 4). However, all but one of the nine subjects with a "very high" risk score (equivalent to 50% lifetime risk of lung cancer) had quit at 6 months giving an 89% quit rate.

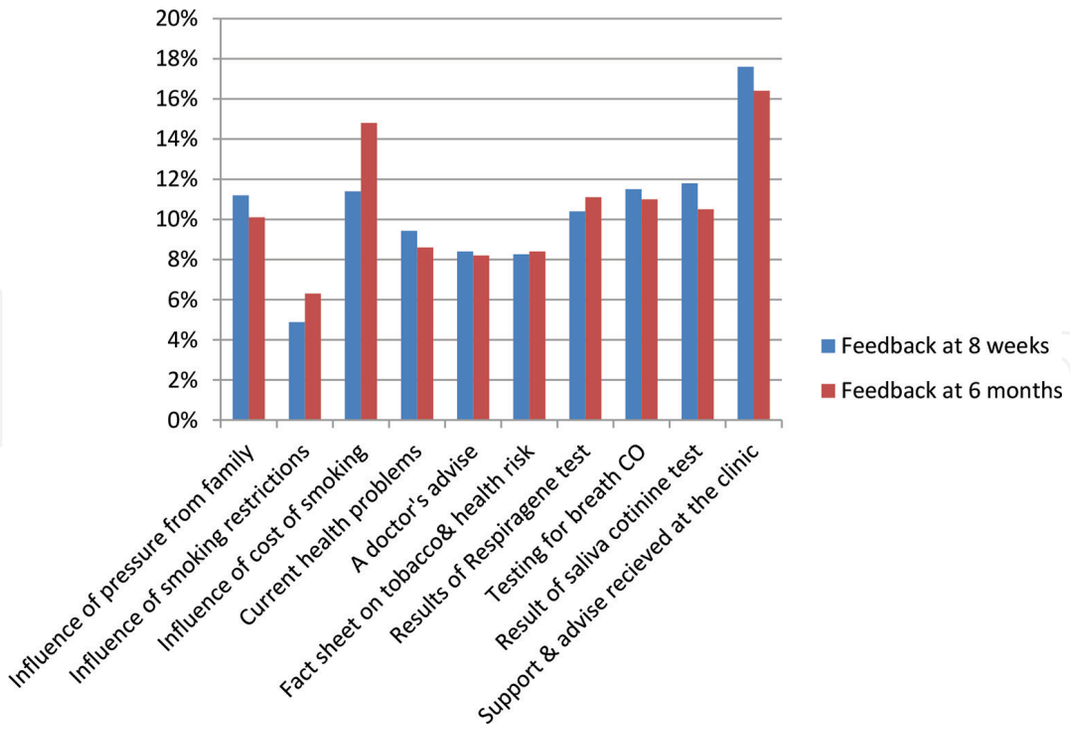

Figure 3. Mean values for motivators and influences that have helped to reduce or stop smoking: "Please score each of the items below according to how strong an influence they have been in helping you to quit smoking". Scores for motivators for individual participants were calculated as percentages of the sum of total scores of the individual and mean values calculated from these percentage scores.

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The test subjects with an average risk score demonstrated a quit rate that was significantly lower than the quit rate in the control group ($p = 0.03$) which suggests that they had been de-motivated and encouraged to think that it was safe to carry on smoking because their lifetime risk was perceived as "not so bad". Or to put it another way, their optimism bias has been reinforced by their average risk score! Psychologists refer to this phenomenon as **(No. (iii)) confirmation bias** [15] and explain that when a subject has two conflicting ideas in their head (i.e., smoking is too risky versus the risk of smoking is exaggerated), this is intolerable—a phenomenon known as cognitive dissonance [16]. This mental discomfort can only be solved by ditching one idea and giving undue prominence to the other. A classic example is the smoker who responds to a challenge about the risks of his habit by saying: "Uncle Charlie smoked like a trouper and lived to be 90". Any evidence to the contrary, such as other smokers in the family who died young, is conveniently ignored.

Other possible factors that make it difficult to quit that we noted in our participants and which have been previously recognized by other researchers in this field were as follows:

1. **Attentional bias** [17, 18]. The smoker is plagued by recurrent thoughts about the pleasures of smoking that serve to increase craving for the next cigarette.

2. **Post-traumatic stress disorder (PTSD)** [19–21]. This is a mental health condition caused by a traumatic event such as rape, warfare experiences, and other near death experiences such as road traffic accidents and industrial accidents. The subjects experience distressing dreams and flashbacks, and they are more likely to become heavily addicted smokers.

3. **Anxieties about smoking cessation and weight gain** [22, 23]. This is an issue for many female smokers who start smoking when they are relatively young to control their weight. Later in life, they may try to quit but revert to smoking when they put on weight.

4. **Side effects of smoking cessation therapy** [24–26]. Patients using pharmaceuticals such as nicotine replacement therapy (NRT) patches or nicotine blocking drugs frequently report side effects. Once they have experienced a side effect, they usually revert to smoking.

5. **Fatalism** [27, 28]. This is the attitude that "What will be will be". These smokers either feel they have little or no control over outcomes such as lung cancer or they simply do not care if they are destined to develop a smoking-related disease.

6. **Peer pressure** [29, 30]. The influence of fellow workers on smoking can be a decisive factor. All the emphasis has been on peer pressure in adolescence and initiation of smoking, but peer pressure can be equally important in the adult work force.

7. **Lack of family cohesion** [31, 32]. Research has shown that family cohesion is associated with concerns about passive smoking and smoking cessation. Conversely, lack of family cohesion is associated with a significantly higher incidence of persistent smoking.

8. **Inadequacy of the risk score as a motivator**. Our own research, as described above, suggests that a risk score for a single disease (lung cancer in this case) is not a powerful enough motivator to cancel out de-motivators in 64% of smokers, especially if the risk score is "low average" when they may be falsely reassured and continue smoking.

2.1. Case histories

To preserve confidentiality, the case histories I present here have been altered (age, gender, and circumstantial details) so that the participants in our research project are unrecognizable. However, basic clinical details have been preserved as far as possible. These cases help to demonstrate why some smokers cannot quit, despite stating that they would like to.

2.1.1. Case no. 1.: lifetime risk of lung cancer = 35%

This participant was a young housewife who was stressed by having to care for two mildly hyperactive small boys aged 3 and 5 and was still smoking 15 cigarettes/day at 6 months. She seemed falsely reassured by the 35% lifetime risk commenting: "only 35% that's not so bad". When I gave her an analogy: "What if I told you that if you carried on living in your present house, you stood a 35% chance of being murdered in your bed, but if you moved to a house in the next road the risk would drop to 1%". She hesitated a moment then said: "But doctor, that's completely different".

2.1.1.1. Commentary

A 35% lifetime risk is less than the risk of tossing a life/death coin but close enough to be worrying. So why wasn't this patient worried? Her hesitation suggests cognitive dissonance [16]. That is two competing ideas buzzing around in your head. For stability and well-being, one of the competing ideas must give way. Her most comforting solution was to accept that the 35% risk of lung cancer was nothing like the risk of being murdered in your bed. Well, of course, it is a different scenario but the risk of death is identical. This is also a good example of confirmation bias [15]. She managed to confirm her feeling that a 35% risk was "not so bad" by rejecting my analogy.

2.1.2. Case no. 2.: lifetime risk of lung cancer = 10%

This participant had been a mature medical student who qualified in his mid 30s. Soon after qualifying, he was at BMA House, Tavistock Square, in 2007, when the suicide bomber detonated on the top deck of a bus in Tavistock Square, and he was the first doctor on the scene. Although he was a non-smoker at the time, he found the only way to cope with flash backs and other PTSD symptoms related to this horrific incident was to become a habitual smoker. He is now a part-time psychiatrist near retirement and was still smoking 10 cigarettes/day at the 6- month follow-up.

2.1.2.1. Commentary

This participant started smoking for the first time aged 40 years, which is unusual. However, the circumstances were also unusual. Although this is obviously linked to post-traumatic stress disorder (PTSD), there may be less dramatic and less obvious versions of PTSD that fuel the smoking habit such as unreported domestic abuse.

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2.1.3. Case no. 3.: lifetime risk of lung cancer = 19%

This participant was a 23-year-old woman who worked as a stable maid. She had quit at 8 weeks and she had always seemed highly motivated. However, she sustained a compound fracture to her right tibia when she was kicked by a horse. As a result, she was stuck at home, off sick, with the injury for some time. All the pain and worry and the boredom of being at home all the time is what started her back on the cigarettes (10/day)—they made it all a bit more bearable.

2.1.3.1. Commentary

Although this participant cites pain and boredom as the reasons for relapsing to smoking, there were also features of PTSD. Her failure to quit was surprising as she was the "leading light" of the test group. She was the first in her group to quit and gently encouraged other participants. Perhaps this case illustrates how PTSD acts as a very powerful de-motivator.

2.1.4. Case no. 4.: control (no risk score)

This 58–year-old woman in the control group did not seem to have much of a problem quitting after a lifetime as a smoker (started aged 14 year) but she told me, at the 6-month follow-up that it was far from easy and described it as being like bereavement. It is, quite literally, as difficult to deal with as the death of someone very close to you. On the other hand, her lead motivator was concern about the affects of side-stream smoke on someone very dear to her—her new baby grandson.

2.1.4.1. Commentary

This participant was remarkably open and honest about her feelings, and it is certainly sobering to think that smoking cessation is as difficult to cope with as suffering a bereavement. However, the fact that her main motivator was concern for her grandchild is very significant. Researchers have shown that family cohesion is associated with a lower incidence of smoking and lack of family cohesion with a very high incidence (70%) of smoking [32]. Family cohesion and awareness and acceptance of the health hazards of side-stream smoke correlated ($p < 0.01$) in a paper from Texas in 2010 [31]. Two other participants mentioned the influence of grandchildren in relation to passive smoking and their decision to quit. Altogether, 8/67 (12%) of our participants mentioned passive smoking and family as a key motivator without prompting (in response to an open-ended question asking for "further comments").

2.1.5. Case no. 5.: lifetime risk of lung cancer >50%

This 48-year-old woman, who had recently been through a stressful divorce, was unable to work due to the debilitating effects of Crohn's disease. She was well aware that smoking cessation would probably improve her Crohn's symptoms. She started on varenicline but had to stop taking it after 3 days due to an acute exacerbation of Crohn's symptoms. She never

returned to the clinic and was still smoking 12/day at the 6-month follow-up saying: “This is my only way of coping with boredom”.

2.1.5.1. Commentary

The impression from this patient was that she had simply “given up”. There are varying degrees of fatalism like this exhibited by smokers [27]. She might have been able to fight back with the help of varenicline, unfortunately she had gastrointestinal side effects that she interpreted as an exacerbation of her Crohn's disease so stopped taking varenicline after 3 days. In her case, the varenicline side effects seemed to a significant de-motivator.

2.1.6. Case no. 6.: lifetime risk of lung cancer 58%

This 35-year-old single man in a high-powered office job had managed to stop smoking for 5 years when his younger brother died of lung cancer. This was the third 1st degree relative to die from lung cancer. However, his current work ethos was one in which “everyone smoked” and now he was back on 15 cigarettes/day. Despite the family history and a high risk score he was still smoking 15 cigarettes/day at the 6-month follow-up. He blamed “work stress and peer pressure” for his inability to quit.

2.1.6.1. Commentary

This subject's inability to quit was really puzzling, and he himself was puzzled by it. There may have been several de-motivating issues but peer pressure at work was certainly very significant in his case.

3. Genetics and smoking behaviour

Nicotine, cannabinoids, and cocaine act as insecticides to protect plants from insect attack. Mammals that eat plants have evolved to tolerate these chemicals but only humans have developed the habit of burning and inhaling plants containing these toxic chemicals. Archaeologists have found evidence for this habit going back into prehistory [33]. There is even evidence of genetic adaptions to nicotine specific to humans [34]. Edward Hagan, professor of Anthropology at Washington State University, argues that there is a balance of benefits and costs to smoking tobacco. Nicotine must have some advantages that outweigh the health costs in some circumstances. Our ancestors may have found the effects of nicotine on the brain beneficial in times of stress and hunger but Hagan argues that nicotine's greatest evolutionary advantage may have been efficacy as an anti-helminth drug, especially in controlling those helminth parasites that migrate through the lungs [35].

It is no surprise, therefore, that there are human genes that relate to smoking behaviour. A recent review estimated that, according to twin studies, 75% of behavioural variation (variation in smoking initiation, persistence, and cessation rates) is genetically determined [36]. However, only about 5% of this variation can currently be explained by known gene variants, mainly single-nucleotide

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polymorphisms (SNPs) but 19% of the variation in smoking initiation can be explained by known SNPs. Research is ongoing in this area with the hope that identification of further SNPs and other gene variants will improve our understanding of smoking behaviour and smoking cessation demotivators leading to new effective treatments to aid smoking cessation [8, 36]. This research includes increasing our understanding of epigenetic off/on gene switching in determining various aspects of smoking behaviour and pathologies associated with smoking [8, 37].

An understanding of the genetics and epigenetics of PTSD is very relevant to helping smokers to quit, especially those who seem to be hardened nicotine addicts. Twin studies have shown that only 20–30% of subjects exposed to severe trauma develop PTSD [38]. Less than 50% of women who experience violent rape develop overt PTSD. Genetic studies have shown that a combination of four or more high-risk alleles (single gene variants) confer a sevenfold increase in the risk of PTSD following trauma [38]. However, lesser degrees of PTSD associated with cigarette smoking [19] may also have a genetic component. Further research in this area seems likely to overlap with research focused on the genetics of smoking behaviour and is likely to lead to new strategies in treatment of both PTSD and in helping to achieve smoking cessation.

4. Discussion

I had been unaware of the possibility that PTSD could be a common barrier to smoking cessation. Beckham et al. [20] showed that there is a significant difference between PTSD and non-PTSD smokers during attempts to quit with the PTSD subjects being more likely to lapse after 1 week (**Figure 4**). There is also a growing body of research that shows that we may only recognize the more obvious instances such as PTSD in war veterans and rape victims. The literature is unclear on the incidence of PTSD in the general population with reports ranging from 1 to 5%. If we take 3% as a median value, it is likely that a sample of lifelong non-smokers would exhibit a lower incidence (approx. 2%) so that the incidence of overt PTSD is 3 times higher in smokers. A paper by Matthews et al. [19] showed that 6.7% of smokers are suffering from overt PTSD but also showed that another 73% of their study group of current smokers (n = 342) had symptom scores suggestive of some degree of stress or as they termed it: "sub-threshold PTSD". There was no correlation between smoking and anhedonia. Only 20% of their sample was completely negative for their PTSD score. Perhaps sub-threshold PTSD includes unreported domestic abuse and bullying at work. Domestic violence has been recorded as a cause of PTSD-related smoking [39]. There is evidence from research by neuropsychiatry that nicotine inhibits negative symptoms experienced in PTSD and that the positive "feel good" effects of nicotine is relatively insignificant [19, 21]. Further research is needed to clarify the differences in PTSD scoring between smokers and non-smokers and to determine what can be done to help this category of refractory smokers.

Smokers who are concerned about weight gain will need special help but sometimes counselling and dietary advice are ineffective. Hurt et al. at The Mayo Clinic, USA, are currently researching the combined pharmacological approach of varenicline and lorcaserin (a new anti-obesity drug) for overweight smokers who want to quit. Early results are encouraging (personal communication from Hurt).

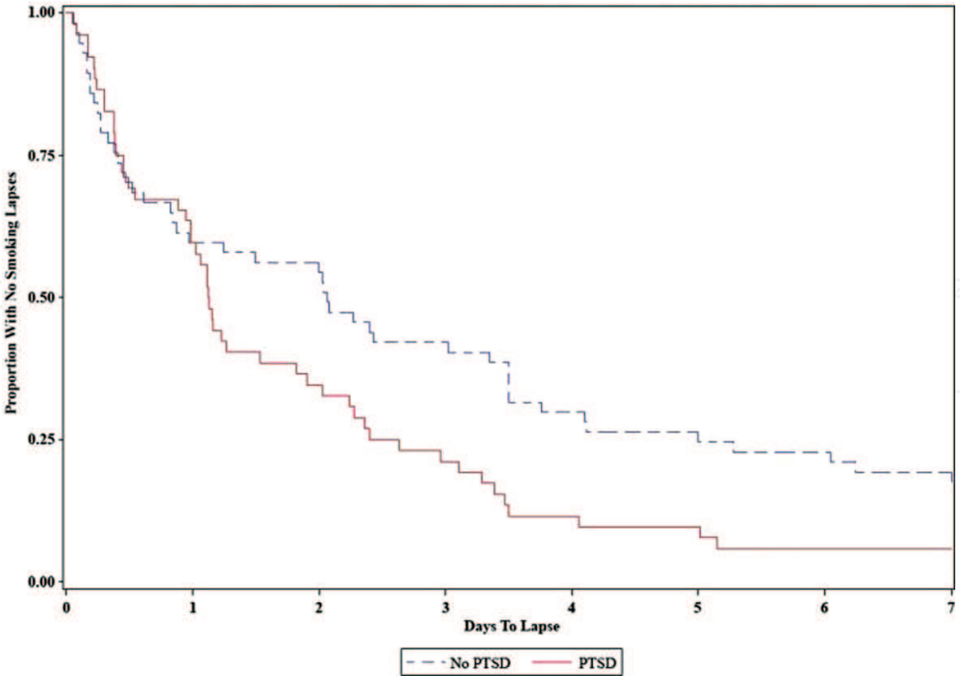

Figure 4. Survival curves for smoking lapse in PTSD (n = 55) versus non-PTSD (n = 52) in first week of a quit attempt showing that PTSD is associated with a higher smoking relapse rate (from Beckham et al. [16]).

Do smokers who experience side effects from smoking cessation drugs tend to give up trying to quit as seemed to be the case with case 5? The literature is unclear on this issue. However, the Respiragene project certainly showed a significant difference between those that had been able to persist with their original smoking cessation prescription (varenicline or nicotine replacement therapy) and those who had stopped due to side effects (**Table 2**) with quit rates at 6 months of 42.6 and 15.3%, respectively (p = 0.01).

	Stopped smoking at 6-month follow-up			**Total**
	Lost to follow-up	**Yes**	**No**	
Prescription history unknown	2	0	5	7
Persisted with first prescription	3	20	24	47
Stopped first prescription	0	2	11	13
Total	5	22	40	67

χ^2 = 6.6, p = 0.01.

Table 2. Smoking cessation outcome for subjects who stopped smoking cessation therapy due to side effects compared with subjects who had persisted with smoking cessation therapy.

Studies linking work stress to smoking are equally balanced between those that do and do not show a link. One of the best studies, however, from Finland shows an odds ratio of 1.28 (p < 0.01) for smoking where there is a high imbalance between effort and reward consistent with work stress [40]. Concerns about passive smoking in the family home have received a

good deal of publicity recently despite attempts by the tobacco industry to play down the risks [41]. Finding that 12% of our participants mentioned this as a key smoking cessation motivator was not, therefore, unexpected. Just as family cohesion is a factor here, conversely lack of family cohesion is emerging as a significant de-motivator [31, 32].

Fatalism and peer pressure are well known as factors that encourage smoking but the precise role of adult peer pressure in the workplace needs further research. A review of smoking cessation in the workplace has outlined strategies for influencing the workplace ethos to improve attitudes and introducing workplace smoking cessation programmes and smoking cessation inducements [42].

The efficacy of a risk score such as the Respiragene risk score as a smoking cessation motivator could, perhaps, be improved if it included cardiovascular risk as well as lung cancer risk. A recent paper estimated that smokers double the risk of an early death from cardiovascular events but that risk reverts to normal after 2 years of smoking cessation [43]. Personalized data on cardiovascular risk could be included in the risk score in future. This might include genetic risk factors such as the apolipoprotein E4 gene but clinical factors such as family history, blood pressure, body mass index, lipid profile, and HbA1C would be equally important.

5. Conclusions

Fear of lung cancer can certainly act as a powerful motivator as demonstrated by the high quit rate for subjects with a very high Respiragene risk score. However, the problem with a personalized risk score is that if the risk is relatively low, it may act as a de-motivator. Including a personalized risk score for life-threatening cardiovascular events (stroke and myocardial infarction) might help to counter this problem, especially as most smokers will be given a risk score round about the mean of 100% increase in risk of a fatal event. However, even the most persuasive smoking cessation motivator is unlikely to overcome powerful de-motivators such as PTSD or weight control issues in about 20% of smokers. If a smoker in this category who may have attempted to quit 2 or 3 times already is still determined to quit, the de-motivator that is standing in the way of success must be addressed and this may need intense one to one counselling and/or a pharmacological intervention. New and better pharmacological approaches are likely to result from genetic studies on smoking behaviour.

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