Smoking, Smoking Cessation, and Lung Cancer Screening in the NELSON Trial

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Smoking, Smoking Cessation, and Lung Cancer Screening in the NELSON Trial

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CHAPTER 1

General introduction

1.1 THE TOBACCO EPIDEMIC

More than one billion people around the world currently smoke tobacco. The use of tobacco kills more than 5 million people yearly. If this trend continues, it is expected that more than 8 million people will die annually from tobacco-related diseases by 2030 and more than 1 billion people during the 21st century.[1-2]

The potential health effects of smoking were predicted as early as the 19th century. Nevertheless, it was not until the 1950s that study results associated smoking with lung cancer.[3-4] Nowadays, it is known that tobacco smoke consists of many chemicals, of which more than 60 are confirmed or suspected carcinogenic substances, and that it affects nearly every organ in the body.[1, 5-6] Smoking is a risk factor for six of the eight leading causes of death worldwide, with the top three: 1) lung cancer, 2) Chronic Obstructive Pulmonary Diseases, and 3) cardiovascular diseases.[5] The chance that a lifelong smoker will die prematurely from a tobacco-related disease is about 50%, and smokers who continued smoking will die on average ten years earlier than lifelong non-smokers.[7] For these reasons, the use of tobacco is the most important cause of preventable disease and premature death worldwide.[2, 5, 7-8] The economic burden of tobacco use has been estimated at US$ 500 billion globally and US$ 98-103 billion for the European Union.[9]

Lung cancer

Of all tobacco-related health problems, lung cancer is the most important disease. Lung cancer is also the leading cause of cancer mortality throughout the world.[10-12] Lung cancer mortality accounts for approximately 28% of all cancer deaths, with an estimated mortality rate of 1.3 million yearly.[10, 12-13]

In the Netherlands, about 18,400 people suffered from lung cancer in 2008. In that year, lung cancer was diagnosed amongst 10,766 people and 9,918 died from lung cancer.[14] Lung cancer is most common in older adults as a result of the historical patterns of smoking behaviour and its average lag time of 20-30 years. In recent years, lung cancer mortality has decreased in men and increased in women due to differences in smoking history between males and females (**Figure 1.1** and **Figure 1.2**). Lung cancer was responsible for the highest number of life years lost (148,284 years) in 2007.[15-16]

Around 80-90% of lung cancer cases are attributable to tobacco smoking, indicating that the most effective way to prevent lung cancer is to abstain from smoking.[2, 5, 7, 17-19] Although the health benefits of smoking cessation at an early age are most effective in terms of life years gained, the benefits of smoking cessation continue after the age of 65.[7, 17, 20-22] Smokers' lifetime risk for developing lung cancer has been estimated at 17.2% and 11.6% for males and females, respectively. This is significantly higher compared to non-smokers (1.3% and 1.4%, respectively).[23] Moreover, the risk for developing lung cancer depends largely on the duration of smoking, as well as the smoking intensity.[24] Currently, despite developments in

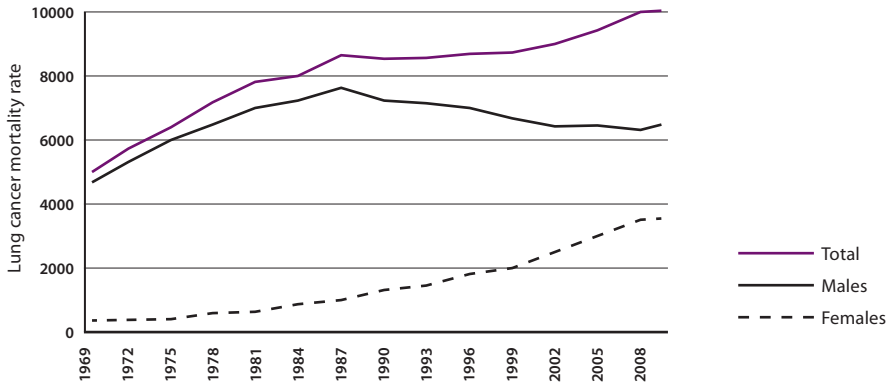

Figure 1.1 Lung cancer mortality rates in the Netherlands from 1969 until 2009.[16]

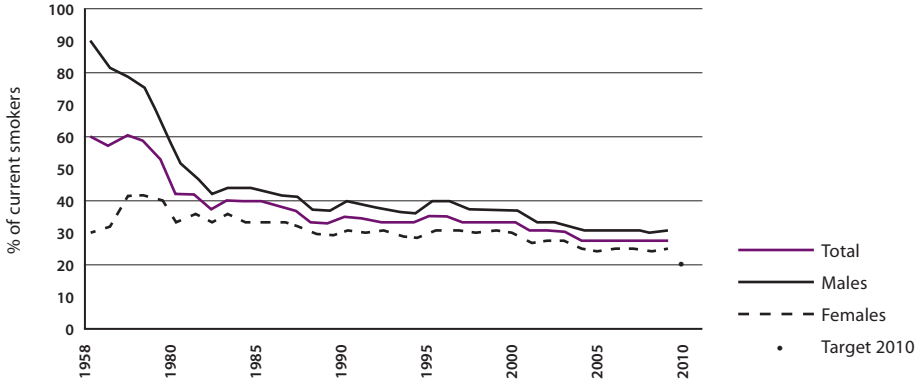

Figure 1.2 Smoking behaviour in the Netherlands.[16]

medical technologies for diagnosis and treatment, the 5-year survival rate of patients diagnosed with lung cancer has not been improved significantly. The most important problem is that clinically-detected lung cancer is often in an advanced and incurable stage. Only 20% of tumours are eligible for surgical resection, but some patients are not even eligible to undergo surgery due to a high risk for morbidity or mortality. The remaining group are treated by chemotherapy, radiation therapy or surgery, depending on the stage.[25] The survival rate depends largely on the stage at diagnosis, but for all stages combined the 5-year survival rate is poor, at only 16%.[26]

Smoking behaviour

At the beginning of the 20th century, the general population was not aware of the health risks of smoking. Smoking was consequently adopted as a new behaviour by higher socio-economic groups and diffused to all other groups. The number of people who smoked was

highest in the '60s, and declined from the '80s onwards in the Netherlands (**Figure 1.2**) and other western countries. The '90s was a period that the proportion of smokers remained stable, followed by further decline in the 21st century.[27] Overall, around 35% of the male populations in high-income countries currently smoke.[1, 27] The Netherlands has a relatively high smoking prevalence of 28% (30% males, 26% females) compared with other European countries.

In order to help eliminate the tobacco epidemic, a comprehensive package of Dutch tobacco control interventions has been implemented for many years now.[28] However, the National Cancer Control Programme (NCCP) for 2005-2010 reported that the aim to reduce the overall prevalence of current smokers to 20% in 2010 was not achieved. In fact, STIVORO – the Dutch expert centre on Tobacco Control – has stated that the observed overall prevalence of current smokers increased by about 1% to 28% between 2008 and 2009.[28-29]

Around 79% of Dutch smokers reported an intention to quit smoking in 2009, but only 27% of them actually made a quit attempt. Approximately 1-7% of those who quit smoking can refrain from smoking without any smoking cessation support.[30]

The available smoking cessation interventions can be divided into several categories, which are 1) self-help interventions (brochures, computer-tailored smoking cessation information (CTSCI), books, Internet sites), 2) behavioural change interventions (quit advice, individual or group therapy), 3) nicotine replacement therapy (nicotine patches, nicotine gum, nicotine lozenges), 4) medication (bupropion, varenicline, nortriptyline) and 5) alternative smoking cessation aids (hypnosis, acupuncture, laser therapy). There is evidence that the three first categories can improve smoking cessation, while the effectiveness of the alternative therapies has not been proven (yet).[31-34] In previous studies, it was found that one single smoking cessation intervention can improve the success rate of a quit attempt to 7-16% and that a combined approach can even increase the success rate to 13-24%.[33]

1.2 LUNG CANCER PREVENTION

Public health promotion has been defined by the World Health Organization as "*the process of enabling people to increase control over and to improve their health*". The major aims of health promotion are the primary, secondary and tertiary prevention of diseases and disability, including lung cancer (**Table 1.1**). **Figure 1.3** shows how each form of lung cancer prevention is targeted at a different phase of its development.[35]

The objective of primary prevention of lung cancer is the prevention of the development of malignancies. Interventions are aimed at people who do not have lung cancer but are at risk for developing it. It is also possible that a person has lung cancer but is not aware of it. Key methods of primary prevention for lung cancer are preventing people from starting to smoking and promoting abstinence from smoking. After the onset of lung cancer, it takes on

Table 1.1 Prevention of lung cancer.

	Aim of prevention	Population
Primary prevention	Inhibition of the development of the cancer	Healthy population/ population at risk for developing lung cancer
Secondary prevention	Identification of people with early stage preclinical malignancy in order to increase opportunities for treating and preventing progression of the cancer	Population at high risk for developing lung cancer
Tertiary prevention	Cancer treatment to improve survival and functionality	Population diagnosed with lung cancer

average 20-30 years before a lung tumour shows obvious signs and symptoms.[5, 13] The entire period up until the manifestation of lung cancer is called the 'preclinical phase'. During this preclinical phase, there is a period in which the cancer can be detected by a screening test (screen-detectable preclinical phase).

The objective of secondary prevention of lung cancer would be the early detection and early treatment of lung cancer in a preclinical phase, with the aim to increase opportunities to treat and prevent further progression. The target population would be those who are at high risk but not already diagnosed with the disease. These people would undergo lung cancer screening. Most would have no screen-detectable lung cancer (yet), but a few could be diagnosed with lung cancer. Without intervention, the tumour would become clinically manifest, entering the 'clinical phase'. In this phase, a diagnosis would be made and followed by treatment, where possible.

Tertiary prevention targets the stage in which lung cancer is diagnosed, with the aim to prevent progression of the disease and thereby improve the survival and quality of life insofar as possible.

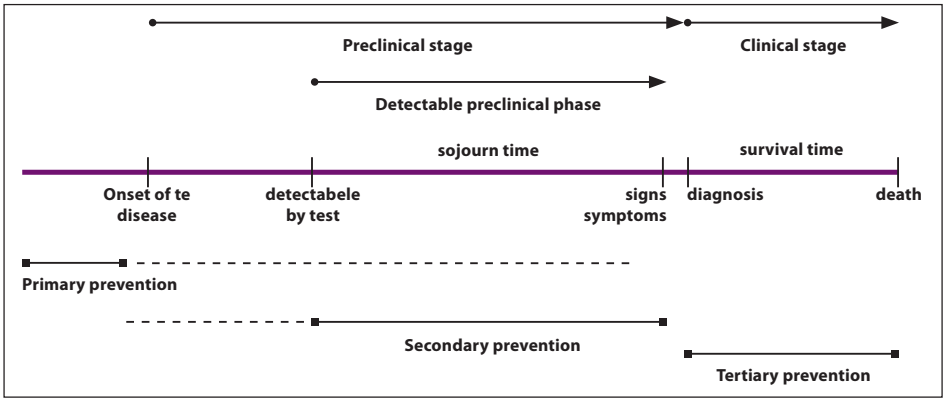

Figure 1.3 Conceptual framework of cancer prevention.

Lung cancer screening

Despite all efforts to eliminate smoking, the smoking population remains large and the number of people who are at high risk for lung cancer remains substantial. The risk of lung cancer mortality among former smokers halves after about ten years compared with continuing smokers, and after 15-20 years this risk is almost comparable to that among non-smokers. However, the extent of the risk reduction depends on the individual smoking history and age of quitting.[5, 36] It will still take a considerable time to further reduce the unacceptable high burden of lung cancer. With the proportion of people who have quit smoking growing, lung cancer is tending to occur more often in former smokers.[24] In view of these factors, attention is being paid to exploring opportunities for the early detection of lung cancer, with the aim to reduce lung cancer mortality.[37]

Since the 1970s, researchers have investigated whether chest radiography, with or without sputum cytology, can be used for the early detection of lung cancer and thereby reduce the lung cancer mortality rate, but all studies so far have failed to demonstrate a lung cancer mortality reduction.[38-42] This might be due to a low sensitivity of the tests in detecting a curable stage of lung cancer,[43] but also the lack of a strong study design, insufficient trial length, lead-time bias, length-time bias and population heterogeneity.[38, 44] Based on this previous research, the existing American College of Chest Physicians guideline continues to recommend no screening for lung cancer.[45] However, rapid developments using such new technologies as low dose multidetector Computer Tomography (CT) have generated renewed interest in opportunities for lung cancer screening. Since the late '90s, several observational studies have investigated the effectiveness of lung cancer CT screening.[46-51] It was found that CT screening detected 48-85% of lung cancers in an earlier and more operable stage (Stage I).[47, 52-53] However, the fraction of participants who received a positive screening test result had a wide range of 5.1-51.4% and the number of false-positive screening test results was considerable. It also remained unknown whether the early detection of lung cancer would result in a lung cancer mortality reduction, because the non-randomised trials used case survival rates. Survival rates do not adjust for the effects of lead-time, length-time or overdiagnosis bias. Lead-time bias refers to the increased time between screen detection of the lung cancer and the time of death, purely as a result of the early diagnosis. Length bias is a form of bias that occurs because screening is more likely to detect slow-growing cancers, which may be less aggressive, giving the appearance that screening prolonged life. In the case of overdiagnosis, participants may be diagnosed with lung cancer that would not be lethal even if it remained undiagnosed. These people do not even benefit from early diagnosis and early treatment. The use of survival rates instead of lung cancer mortality might therefore cause an overestimation of the benefits of screening. Ongoing randomised controlled trials are being conducted to provide evidence about whether lung cancer screening can reduce lung cancer-specific mortality (**Table 1.2**).[35, 54-63] In a recent press release, the National Cancer Institute stated that a 20.3% higher mortality reduction rate was found in high-risk participants in the National

Table 1.2 The main large-scale randomised controlled lung cancer screening trials.

Randomised controlled lung cancer screening trials	N	Comparison	Age group	Nodule measurement	Smoking cessation intervention
NLST [57] USA 2002	53,456	CT vs. chest X-ray	50-74	2D	Written self-help material or Internet sources for smoking cessation (n=171)
NELSON [58] Netherlands/Belgium 2004	15,822	CT vs. usual care	50-75	3D	Standard self-help brochure or CTSCI (1:1) at baseline
DLCST [59] Denmark 2004	4,104	CT vs. usual care	50-70	3D	Smoking cessation counselling specialised nurse (5 minutes) and spirometry yearly
LUSI [60] Germany 2007	4,000	CT vs. usual care	50-69	2D	Quit smoking counselling at baseline
UKLS [61] United Kingdom 2011-2012	4,000 (pilot)	CT vs. usual care	50-75	3D	Unknown
ITALUNG [62] Italy 2003	3,206	CT vs. usual care	55-69	2D	Free access invitation to a smoking cessation programme at baseline
DANTE [63] Italy 2005	2,472	CT vs. clinical review	60-74	2D	Unknown

NLST, National Lung Screening Trial; NELSON, Dutch-Belgian lung cancer screening trial; DLCST, Danish Lung Cancer Screening Trial; CTSCI, Computer-tailored smoking cessation information; UKLS, UK lung cancer screening trial.

Lung Screening Trial (NLST) who were screened with low-dose spiral CT compared with those who were screened by chest X-ray. The trial's independent Data and Safety Monitoring Board (DSMB) recommended ending the trial. The final results are forthcoming.

The NELSON trial

The research described in this thesis was conducted in the NELSON trial – the Dutch-Belgian Lung Cancer Screening trial – which is one of the largest randomised controlled lung cancer screening trials. The NELSON trial started in 2003 with the aim to 1) investigate whether screening for lung cancer by multi-slice low-dose computer tomography in a high-risk population would lead to a reduction in lung cancer mortality of at least 25%, 2) estimate the impact of lung cancer screening on health-related quality of life and smoking cessation and 3) estimate the cost-effectiveness of lung cancer screening for sub-groups.[58]

During two recruitment rounds held between 2003 and 2005, 548,489 people registered in population registries in seven regions in the Netherlands and 17 municipalities in Belgium, all aged between 50 and 75, were sent an initial questionnaire about their general health

and smoking history (Mailing A). A total of 151,346 (27.6%) responded to this questionnaire. Eligible respondents (n=30,047; 19.9%) were sent a second questionnaire (Mailing B), an information brochure about the NELSON trial and an informed consent form in which they were invited to participate in the NELSON trial (**Figure 1.4**).[58]

People eligible to participate in the NELSON trial were aged between 50 and 75 years with a smoking history of >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years, who were current smokers or former smokers who had quit smoking <10 years ago. People with a bad/moderate self-reported perceived health status who were unable to climb two flights of stairs and/or had a body weight over 140 kilograms were excluded, because of the need for sufficient cardiopulmonary capacity to undergo surgery in case of a detected nodule, or for pragmatic reasons (weight). Furthermore, people with current or past renal cancer, melanoma or breast cancer were excluded because of the risk of lung metastases even after a long follow-up. A diagnosis with lung cancer or a treatment related to lung cancer within the last five years was also an exclusion criteria. Finally, people who had received a CT scan of the chest in the year prior to completing the first questionnaire were excluded due to contamination with a medical examination of the lungs.[58, 64]

A total of 15,822 people, mainly males, who were eligible for participation in the NELSON trial and who signed the informed consent (52.7%) were randomised (1:1) to the screen or control arm. Screen arm participants received CT screening for lung cancer in years 1, 2, and 4, whereas participants in the control arm received no screening (usual care). A fourth scan round was recently started 5.5 years after the baseline screening (year 6.5). The CT screening test results used a novel nodule management strategy based on volume and volume doubling time (VDT).[65] The test results could be either negative, indeterminate or positive.[65] An indeterminate or negative screening result was communicated via a standard letter with an explanation in cases where the radiologists had found an abnormality. Those with an indeterminate test result were informed about the follow-up scan. Participants with a positive screening result were informed about their referral to a pulmonologist for a work-up and diagnosis by phone.

At randomisation, all current smokers received a standard brochure or tailoring assessment for tailored smoking cessation information (1:1). The tailoring questionnaire had to be completed and sent back before participants could receive the computer-tailored smoking cessation information (CTSCI). After two and four years of follow-up, subsamples in the screen and control arm received a smoking cessation questionnaire (**Figure 1.4**).

Smoking cessation

Many people who are eligible for lung cancer screening are older adults who currently smoke and who have a long-term smoking history. This highlights the potential opportunities to deliver smoking cessation support to a large population that has not been successful in being abstinent from smoking so far. Current smoking cessation programmes are also less likely

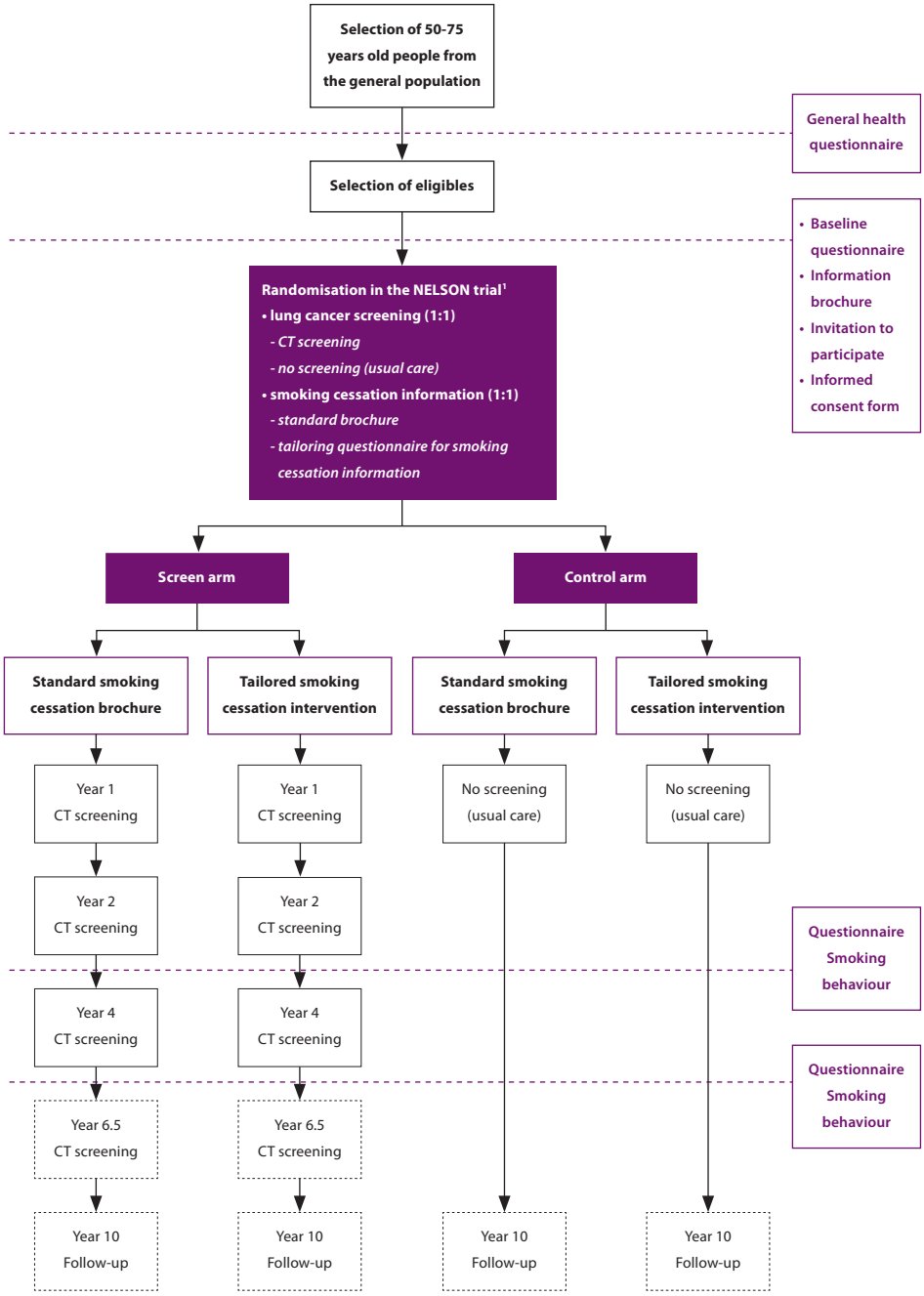

Figure 1.4 Flowchart of the NELSON trial and the smoking cessation sub-study.
[1] NELSON indicates Dutch-Belgian lung cancer screening trial.

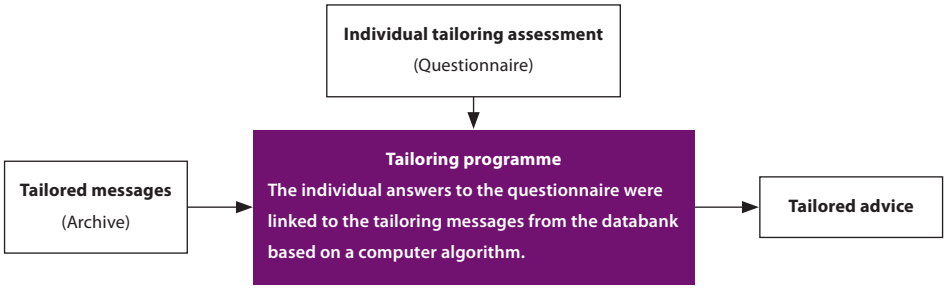

Figure 1.5 The process of computer-tailored advice.[64-66]

to target this specific population. Based on previous research, participants in a lung cancer screening trial are expected to be relatively more motivated to quit smoking and to receive smoking cessation support.[66-67] Observational studies have also shown lung cancer screening to be associated with smoking cessation, although it remains unknown whether this can actually be attributed to lung cancer screening.[68] Combining primary and secondary prevention should be considered in order to optimise tobacco control. In a lung cancer screening setting, the major challenge is to provide a highly individualised smoking cessation intervention with a high effectiveness and broad reach. Alongside existing individual-focussed smoking cessation interventions, computer-tailored advice might provide this opportunity.[69-70]

Computer-tailored health promotion materials are "*any combination of information and behavioural change strategies intended to reach one specific person based on characteristics that are unique to that person, related to the outcome of interest and derived from an individual assessment*".[70] The process of computer-tailored health interventions intends to mimic personal communication.[70-72] The realisation of the tailored advice starts with an individual assessment of the target health behaviour, in this case smoking, and its important (modifiable) determinants (**Figure 1.5**). The results are added into a computer system. The computer system consists of an archive with all possible tailoring messages to fit each possible answer to the tailoring questionnaire. A computer algorithm uses decision rules based on the IF-THEN principle, so that individual answers can be linked to the accompanying tailored feedback messages. The computer programme creates a final tailored advice.

Computer-tailored smoking cessation information (CTSCI) can provide smoking cessation related feedback and advice to participants in a lung cancer screening programme that is tailored to their personal situation, such as their motivation to quit smoking, smoking history, quit attempts, reasons for relapse, attitudes, social support, self-efficacy and so on.

The assumption is that health information that is perceived as personally relevant is more likely to stimulate thoughtful and thorough consideration of a proposed behaviour change.[70] Tailored messages are designed to address the specific concerns, needs and interests of the individual person. In a review, Skinner et al.[73] were the first to publish about the evidence of the effectiveness of tailored health communication in influencing health behaviour. In the

current literature, a large number of studies confirm that CTSCI is usually more effective than standard self-help materials.[31, 33, 74] Process evaluation studies have mainly found that tailored information is more likely, for instance, to catch information, to be read and remembered, saved, discussed with others, and perceived as interesting and more personally relevant.[70] In the NELSON trial, a randomised controlled trial was conducted to investigate whether a computer-tailored smoking cessation advice was more effective at inducing smoking cessation compared with a standard self-help brochure.

Side effects of screening

It is a feature of screening programmes that relatively few of the asymptomatic people who are invited for screening have the benefits from it as a result, while a relatively large number of them will be exposed to minor unfavourable effects. In considering whether screening is justified, it is important to ensure that the favourable effects (reduction in disease-specific mortality, life-years gained etc.) of screening should reasonably balance out the harms (overdiagnosis, overtreatment, false-positive screening result, anxiety, discomfort etc.) caused by screening.[75-76]

As stated before, one important aspect of lung cancer screening that should be considered is the high number of false-positive screening test results. One of the criteria for a screening test is that the test should give a true representation of the condition of the individual.[77] This means that the test should be able to adequately classify the presence or absence of lung cancer (accuracy, sensitivity and specificity). In lung cancer screening, CT screening can detect many lung nodules, but only a few of them may turn out to be malignant. Clinicians are more and more concerned with how to deal with small non-calcified lung nodules. False-positive screening test results may not only unintentionally affect quality of life, but can also lead to unnecessary and sometimes invasive work-up procedures. Until now, nodule management strategies in lung cancer screening trials were mainly based on 2D measurements, and most lung cancer screening trials did not take further actions on the basis of nodule growth, or VDT, despite the fact that nodule growth might differentiate benign and malignant nodules more accurately. With the recent introduction of 3D measurements, new opportunities have arisen for more sensitive nodule management.

Another relatively unknown aspect of screening in general is its impact on future health behaviour. Though a possible positive effect of screening on future health behaviour has been reported in the past,[78] the studies included in that review were characterised by significant methodological limitations. In lung cancer screening, the most important health behaviour is refraining from smoking. Lung cancer screening has been argued to be a teachable moment for smoking cessation.[66, 79-80] A teachable moment can be defined as *"a naturally occurring life transition or health event thought to motivate individuals to adopt risk-reducing health behaviour"*.[79] Lung cancer screening offers several potential teachable moments: when visiting the

health centre, when undergoing CT screening and when receiving the screening test result. These moments could increase people's awareness of their individual risk of developing lung cancer and other tobacco-related diseases, which is a strong predictor of health behaviour. An increased risk perception makes the adaptation of health risk reducing behaviour more likely,[79, 81] especially amongst lung cancer screening participants, since optimistic bias about personal risk is a common occurrence amongst participants in screening trials. The motivation to quit smoking could thus be enhanced when emotional responses are provoked that might attend to and appraise risk reducing behaviour as important.[79] Nevertheless, it is important to realise that screening may also unintentionally give screening participants a feeling that continued or even new unhealthy behaviour is permitted.[82-83] A negative screening test result might increase people's unrealistic feeling of reassurance and invulnerability. This is a so-called "*health certificate effect*". This possible side effect of lung cancer screening was already a subject of speculation in 1989.[84] This phenomenon had also been reported in a colorectal cancer screening trial in 2007, where screened participants were less likely to improve their health behaviour compared with those who received no screening. It remains unknown whether lung cancer screening functions more as a teachable moment or a license to smoke, and the NELSON trial presents an opportunity to investigate the impact of lung cancer screening on smoking behaviour.

Self-selection bias

As stated above, observational lung cancer screening studies are limited by potential lead-time bias, length-time bias and overdiagnosis. In addition, there are several other forms of bias that concern the internal and external validity of study results. Internal validity reflects the extent to which study results are generalizable to the target population. One of the major threats to internal validity is self-selection bias. This form of bias is caused by 'errors' in the selection of the study population. All study participants have their own specific characteristics (age, gender, level of education, smoking history, medical history etc.). These characteristics can also be independent variables related to the outcome of interest. If the characteristics of people who agree to participate and those who are eligible but do not agree are unequally distributed, then the internal validity may be threatened as differences in outcome between the groups may be solely the result of differences in background characteristics. Where lung cancer screening study results show sufficient internal validity, this indicates that the reduction in lung cancer mortality in a high-risk population can indeed be attributed to the screening intervention. Although recruitment in the NELSON trial was based on population registries, which is assumed to limit self-selection as much as possible, it is important to find out whether the study results will ultimately be applicable to the target population or even the general population (external validity). In screening studies, the possibility that the healthy volunteer effect will affect the generalizability of the study results has been postulated previously and should be investigated.

1.3 RESEARCH QUESTIONS

The purpose of this thesis was to investigate smoking and smoking cessation in participants in a randomised lung cancer screening trial and the possible effect of smoking cessation interventions. The following research questions were addressed:

Part 1: The NELSON trial

1) What is the degree of self-selection among a) respondents from the general population who are aged between 50-75 and received a general health questionnaire and b) respondents who are eligible for participating in the NELSON trial compared to the Dutch national reference groups?
2) To what extent is the use of the volume and volume-doubling time of a noncalcified nodule as main criteria for deciding on further action a useful nodule management strategy in lung cancer screening?

Part 2: Lung cancer screening and smoking behaviour

3 What is the current evidence for the effects of cancer screening on lifestyle behaviour and lifestyle-related morbidity, and what opportunities are there for dealing with possible unwanted effects of cancer screening?
4 What is the effect of lung cancer screening (screen arm) on prolonged smoking abstinence compared with no screening (control arm) amongst male smokers randomised in the Dutch-Belgian randomised controlled lung cancer screening trial (NELSON trial) after two and four years of follow-up?
5a) What is the association between the CT screening test result (test negative versus test indeterminate) and future smoking abstinence amongst 50-75-year-old male smokers who received lung cancer CT screening using volume and volume-doubling time in the NELSON trial?
b) Is the number of indeterminate screening test results associated with an increased quit rate?
c) What baseline characteristics are associated with prolonged smoking abstinence after two years of follow-up?

Part 3: Health promotion

6) What is the effect of computer-tailored smoking cessation information (tailored information group) on prolonged smoking abstinence compared with a standard brochure (brochure group) in male smokers who participate in a lung cancer screening trial?

1.4 OUTLINE OF THIS THESIS

The occurrence of self-selection and the degree to which self-selection occurs amongst participants in the NELSON trial is discussed in **Chapter 2**. In the NELSON trial, a novel nodule management strategy based on volume and VDT was developed and used as main criteria for deciding on further action when noncalcified nodules were found by lung cancer screening. An interim evaluation of this nodule management strategy is described in **Chapter 3**.

A systematic review of current knowledge about the impact of cancer screening on future lifestyle is given in **Chapter 4**. In **Chapter 5**, the results of a sub-study concerning the impact of lung cancer screening on future smoking behaviour amongst male smokers participating in the NELSON trial are described. The impact was investigated after a follow-up of two years. Aside from the fact that participating in a lung cancer screening trial may have an impact, more specific attention has also been paid to the impact that the CT screening test result had on participants who underwent CT screening (**Chapter 6**). After a follow-up of four years, the impact of CT screening for lung cancer was investigated again to determine whether the results of the study described in chapter 5 are consistent over time. The results are given in **Chapter 7**. The value of providing NELSON participants with a computer-tailored smoking cessation intervention versus a standard self-help smoking cessation brochure is discussed in **Chapter 8**. Finally, the study results and its interpretation and implications for further research and practice will be discussed in **Chapter 9**.

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PART 1

The NELSON trial

CHAPTER 2

Generalizability of the results of the Dutch-Belgian randomised controlled lung cancer CT screening trial (NELSON): Does self-selection play a role?

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Submitted

ABSTRACT

Objective

The degree of self-selection in the Dutch-Belgian randomised controlled lung cancer screening trial (NELSON) was determined to assess the generalizability of the study results.

Methods

335,441 (mainly) men born in 1928-1953 received a questionnaire. Of the respondents (32%), eligible subjects were invited to participate (19%). Fifty-five percent gave informed consent and were randomised. Background characteristics were compared between male respondents on the first questionnaire (n=92,802), eligible subjects among them (n=18,570) and those randomised (n=10,627) and Statistics Netherlands 2002-2005 (SN) (n=5,289) or GLOBE study-data (Dutch cohort) (n=696).

Results

Initial respondents were less likely to be highly educated (OR_{adj}=0.84; 95% CI: 0.74-0.96) and comprised of significantly less current smokers (OR_{adj}=0.65; 95% CI: 0.61-0.69) compared to the general population. These current smokers smoked more heavily (OR_{adj}=1.23; 95% CI: 1.10-1.37), but for a shorter time-period (respondents: 31, SN: 42 years, p<0.001). Age, general health, BMI, alcohol use and cancer prevalence were comparable. The randomised population was younger (Age 50-65) (randomised subjects: 85.3%, SN: 72% (p<0.01)) comprised of more heavy current smokers (OR=2.08; 95% CI: 1.75-2.44), that smoked for a shorter period of time (randomised subjects: 37, SN_selection: 42 years (p<0.001)).

Conclusions

Both the respondents (32%) of the first questionnaire as well as the randomised population of the NELSON trial appeared to differ slightly on smoking characteristics, but the differences were limited and probably balance each other. Results of the NELSON trial will be applicable to the Dutch and probably other populations that fulfil our selection criteria.

2.1 INTRODUCTION

Lung cancer is the most common cause of cancer-related death in men and the third most common cause of death in women in Europe in 2008.[1] Lung cancer is often in an advanced stage when diagnosed and 5-year-survival is maximally 15%.[2] Ongoing randomised controlled trials are evaluating whether lung cancer screening will result in a cost-effective reduction in lung cancer mortality,[3-7] since it has been reported that lung cancer can be detected in an early stage with low-dose spiral Computed Tomography.[8-9] In a recent press release, the US National Lung cancer Screening Trial (NLST) reported a mortality reduction of 20% in participants who received CT screening for lung cancer compared with screening by chest X ray. A final report is awaited with interest.

In most of these lung cancer screening trials, volunteers are recruited by media. One concern is that this might lead to 'self-selection-bias', because the disease prevalence, general health, socio-economic status, lifestyle and all cause mortality of respondents recruited by several types of media might differ from the average target population. Self-selection bias may influence the validity of the results and the power of the study, which may have important implications for the generalizability of study results and policy-decision making.[10] Such differences may be limited if based on recruitment using population registries. Self-selection in a screening trial has been observed earlier. Trial participants aged 55-69 years in the Rotterdam section of the European Randomised Study of Screening for Prostate Cancer (ERSPC) appeared to have a 13% lower all-cause mortality compared to the average target population.[11] Furthermore, a healthy screenee effect, but a higher lung cancer mortality was observed in participants of the Precode Diagnosi Cancro - Early Diagnosis of cancer (PRECICA) project.[12] Recently, participants of the NLST, who were recruited by media, appeared to be younger, higher educated and less likely to be current smoker, but the smoking history and the distribution of gender are comparable with the general target population.[13] The NLST research team stated that the cohort is roughly representative for the target population in the US. In contrast, researchers showed a substantial socio-demographic and psychosocial participation bias in the Danish Lung Cancer Screening Trial (DLSCT), where the recruitment was also by media.[14]

In the Dutch-Belgian Lung cancer Screening Trial (NELSON), participants were recruited by the use of population registries ("population-based recruitment") with the aim to eliminate the risk of selection-bias. All (mainly) male inhabitants in certain regions aged between 50-75 years were approached and asked to fill in a questionnaire. Although potential participants were non-selectively approached, response could still have been selective and smoking habits could have influenced the willingness to participate.[15] Purpose of this study was to assess the degree of self-selection in the NELSON trial compared to Dutch national data, which will be crucial when outcome results are to be expected in the next future.

2.2 METHODS

The NELSON trial is a randomised controlled trial that aims to determine whether screening for lung cancer with low-dose 16-detector multi-slice Computed Tomography (CT) will reduce lung cancer mortality with ≥25%. A total of 15,822 participants were recruited in two recruitment rounds. This study is restricted to the first recruitment which was described into more detail previously.[16] Briefly, addresses of all men born between 1928 and 1953 were obtained from the population registries in seven Dutch districts and addresses of all men and women of the same age were obtained from the population registries of 14 municipalities in Belgium in 2003. A first questionnaire about general health, lifestyle and smoking history was sent to 335,441 persons. Everybody was asked to respond. Final eligibility criteria for the screening trial were a smoking history >15 cigarettes/day during >25 years, or >10 cigarettes/day during >30 years for both current smokers and former smokers with ≤10 years of smoking cessation. Exclusion criteria were a body weight ≥140 kilogram, a history of renal cancer, melanoma or breast cancer, or lung cancer diagnosed <5 years ago or ≥5 years ago but still under treatment, and a chest CT examination within the previous year. Also, persons with a moderate or bad self-reported health who were unable to climb two flights of stairs were excluded.[16] Respondents on the first questionnaire who met the eligibility criteria received an invitation for participation in the trial, an information leaflet and an informed consent form combined with a short questionnaire. Eligible respondents on the invitation who gave informed consent were randomised (1:1) to the screen or control arm (**Figure 2.1**). The screen arm participants received CT screening in year 1, 2, 4, and 6.5, while the control arm participants received usual care (no screening).

Comparison of population characteristics

Characteristics of the respondents on the first questionnaire (RESP), of eligible subjects (ELIG) and of eligible subjects that gave informed consent and were randomised (RAND) were compared to Dutch national data, mainly provided by Statistics Netherlands (SN). Furthermore, the randomised subjects (RAND) were compared with eligible subjects who were not randomised, because they gave no informed consent (NonRAND).

Statistics Netherlands provided data of subjects that by and large met our selection criteria (SN_selection): current smokers that smoked >15 cigarettes a day during >25 years, or >10 cigarettes a day during >30 years, and former smokers with ≤10 years of cessation, which smoked for >25 years. Subjects with a moderate or bad self-reported health who were unable to climb two flights of stairs, that ever had lung cancer, or with a body weight of >140 kilograms were excluded in their sample.

The age distribution of the NELSON groups was compared to the age distribution of all Dutch inhabitants in 2003/2004. For all other characteristics, except level of education, the national data were provided by Statistics Netherlands, a Dutch institution that extensively collects

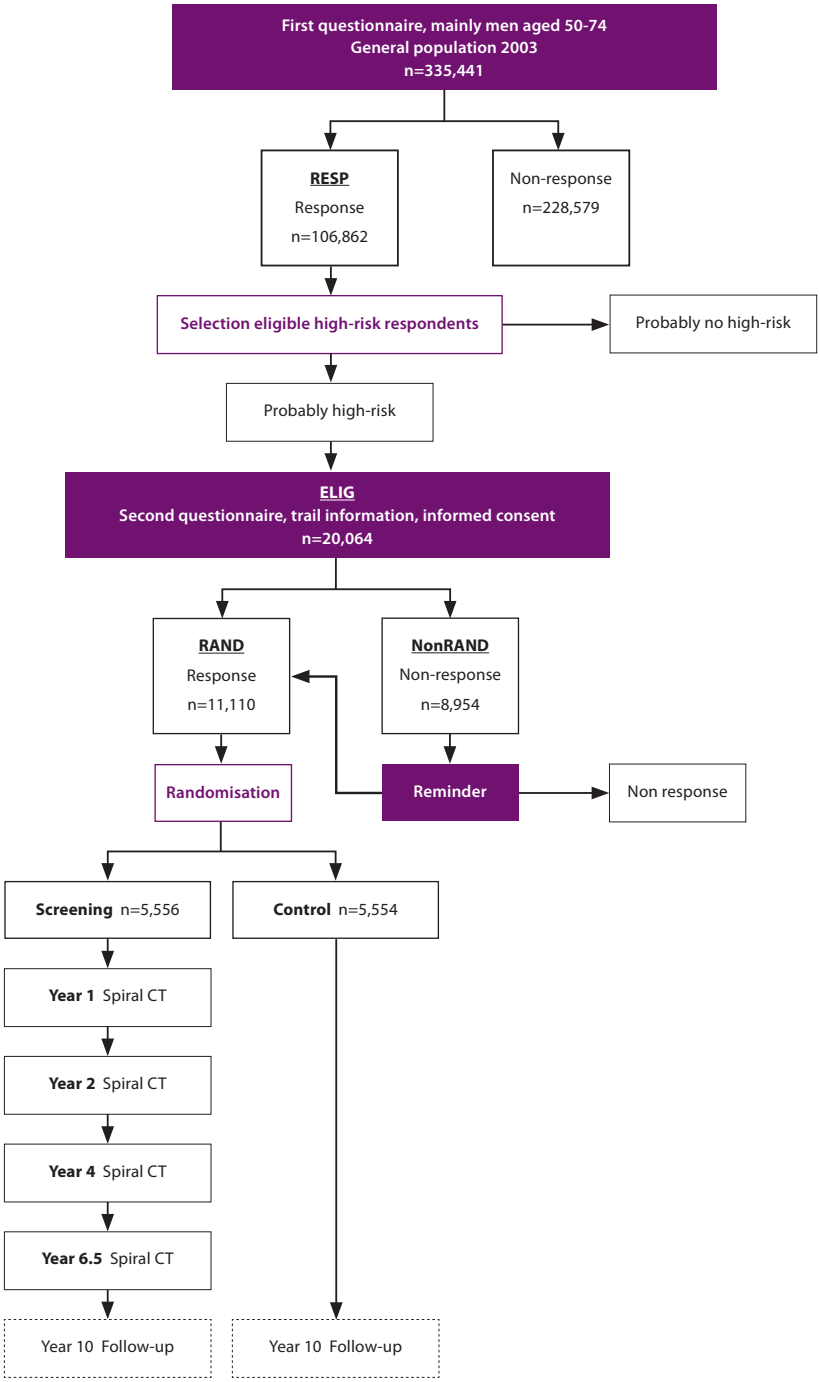

Figure 2.1 Trial design and design of first recruitment of the Dutch-Belgian randomised controlled Lung cancer Screening trial (NELSON).
Purple=questionnaires sent.

and provides national data. Each year Statistics Netherlands invites a representative sample from the Dutch population (the non-institutionalised population) for a Health Interview Survey. Response rate is about 60%. To improve the representation the response is reweighted by age, gender, marital status, and a combination of province and urbanisation. Over the period 2002-2005 the Health Interview Survey contained 41,116 respondents of which 1,364 respondents met the selection criteria. Statistics Netherlands provided frequencies, or means for each 5-year age-group, with corresponding sample sizes and standard errors.

All characteristics of NELSON subjects were retrieved from the first NELSON questionnaire. Only those characteristics were compared where the questions and response items of the NELSON questionnaire were in reasonable correspondence with the questions and response items of the national data. These characteristics included age, life style (smoking and alcohol use (fraction of non-drinkers)) and general health (% of persons with moderate/bad health, % of persons with a Body Mass Index ≥25 (BMI=body weight (kg)/body length $(m)^2$) and the fraction of persons that ever had cancer). Smoking characteristics included the fraction of current, former and never smokers, the fraction of heavy current cigarette-smokers (>20 cig/day), the mean number of cigarettes smoked per day among current cigarette-smokers, the mean duration of smoking among current and former cigarette-smokers (years) and the mean duration of cessation of former cigarette-smokers (years).

Statistics Netherlands used a detailed questionnaire to determine educational level, but in NELSON one single question was used to determine the highest completed education (adapted from the International Standard Classification of Education (ISCED)).[17] We preferred to use a sample that asked educational level in a corresponding way. Therefore data from the GLOBE study were used. GLOBE is a longitudinal study that started in 1991 in the Southeast of the Netherlands (Eindhoven region), aimed at explaining socio-economic inequalities.[18] The total sample of 2004 respondents to the postal survey comprised 6,377 subjects of whom 969 were males aged 50-74.

Ethical and legal approval

The NELSON trial was approved by the Ethics Committees of all participating centres. Furthermore the Health Council of the Netherlands advised the Minister of Health to give permission to start the trial after a positive test of the 'comprehensibility' of the trial information. On December 23, 2003, the Minister of Health of the Netherlands approved randomisation of persons to the NELSON trial.

Statistics

The differences in age distribution for each NELSON group (RESP, ELIG, RAND) were compared to Statistics Netherlands (SN) using Chi-square statistics. Furthermore, logistic regression analyses were performed to determine possible differences in population characteristics

between first, the NELSON groups (RESP, ELIG, RAND) and SN or SN_selection (reference groups) as appropriate, and second between RAND and NonRAND (reference group). All Odds Ratios were adjusted for possible differences in age distribution. The variables "cigarettes/day", "smoking duration" and "duration of smoking cessation" are categorical variables in NELSON. To be able to determine means, each category was recoded to a continue value by using the mid value of each category. Since no individual data were available from SN, we used mean and standard deviation, provided by SN, assuming that the data have a lognormal distribution. ANOVA were performed to check whether the smoking variables differed between NELSON groups and Statistics Netherlands.

2.3 RESULTS

In our first recruitment round 335,441 subjects received the first questionnaire (**Figure 2.1**). Of the 106,931 respondents, we excluded 69 with a blank questionnaire (true response=106,862 (32%)) and 119 subjects because of too many missing values. Of the 20,064 eligible subjects (19%), 11,110 (55%) gave informed consent and were randomised. As mentioned before, analyses were restricted to Dutch males aged 50-74 (RESP: n=92,802, ELIG: n=18,570, RAND: n=10,627, NonRAND: n=7,943, SN: n=5,289, SN_selection: n=1,364 and GLOBE: n=696).

Age

The age distribution of the male respondents on the first NELSON questionnaire (RESP) showed a comparable pattern, although the respondents were statistically different ($p<0.01$) younger compared with the Dutch male population (SN) (**Table 2.1**). Furthermore, younger

Table 2.1 Age distribution of all males, aged 50-74, that responded to the first NELSON questionnaire (RESP), eligible subjects among them (ELIG) and randomised respondents among eligible subjects (RAND) compared to Statistics Netherlands data of Dutch inhabitants 2003/2004 (SN).

	RESP		ELIG		RAND		SN 2003/2004	
Age*	% of population	n	% of population	n	% of population	n	% of population	n
50 to 55	22.8	21,186	28.3	5,261	29.0	3,080	26.6	564,724
55 to 60	27.6	25,582	33.6	6,231	34.6	3,681	26.3	558,590
60 to 65	20.5	19,042	21.8	4,044	21.7	2,311	19.2	408,459
65 to 70	16.6	15,393	11.3	2,094	10.6	1,124	15.4	327,985
70 to 75	12.5	11,599	5.1	940	4.1	431	12.5	266,348
Total	*100.0*	*92,802*	*100.0*	*18,570*	*100.0*	*10,627*	*100.0*	*2,126,106*
χ^2-test**	p<0.01		p<0.01		p<0.01			

* Age at mean date of filling in first NELSON questionnaire (Oct 1, 2003)

** The chi-square test compares each NELSON group (RESP, ELIG, RAND) with Statistics Netherlands (SN)

respondents were more likely to be eligible (ELIG) than older respondents. Age distribution was comparable between RAND and ELIG. Consequently, the male population randomised in the NELSON trial (RAND) is younger than the general male Dutch population of age 50-74.

Health status

The fraction of subjects with a moderate or bad self-reported health was comparable between RESP and SN and between ELIG and SN_selection (**Table 2.2a**). Among RAND significantly more subjects reported a moderate/bad health compared to SN_selection, but the difference was small (17.7% vs. 15.4%; OR_{adj}=1.31, 95% Confidence Interval (CI): 1.10-1.16) (**Table 2.2a** and Appendix).

A modest, but statistically significant difference was observed in the fraction of subjects with overweight or obesity between RESP (60.8%) and SN (62.0%) (OR_{adj}=0.91, 95% CI: 0.86-0.97). No difference was observed between ELIG and RAND compared to SN_selection (**Table 2.2a**). The fraction of subjects that ever had cancer was also modest, but significantly different between RESP (6.6%) and SN (7.4%) (OR_{adj}=0.88, 95% CI: 0.78-0.99). The fraction of subjects that ever had cancer was also statistically significantly different between ELIG and SN_selection (OR=0.59; 95% CI: 0.46-0.75) and RAND and SN_selection (OR=0.62; 95% CI: 0.49-0.79) (**Table 2.2a**).

Table 2.2 Health and life style of all males, aged 50-74, that responded to the first NELSON questionnaire (RESP), eligible subjects among them (ELIG) and randomised respondents among eligible subjects (RAND) compared to Statistics Netherlands (SN) 2002-2005 or selected Statistics Netherlands sample (SN_selection) 2002-2005. Odds Ratios (OR) are adjusted for age.

Table 2.2a Health status.

	RESP		ELIG		RAND		SN	SN selection
	OR age-adj (95% CI)	n	OR age-adj (95% CI)	n	OR age-adj (95% CI)	n	n	n
General health*	1.00 (0.92 - 1.09)	91,246	1.18 (1.00 - 1.39)	18,307	1.31 (1.10 - 1.16)	10,511	4,504	1,143
BMI**	0.91 (0.86 - 0.97)	85,878	1.02 (0.91 - 1.14)	17,640	1.03 (0.92 - 1.16)	10,178	5,203	1,347
Cancer prevalence***	0.88 (0.78 - 0.99)	91,277	0.59 (0.46 - 0.75)	18,347	0.62 (0.49 - 0.79)	10,529	4,514	1,154

* OR General health: OR of having reported a moderate or bad health in RESP/ELIG/RAND compared to having reported a moderate or bad health in SN.

** OR BMI (Body Mass Index): OR of having a BMI ≥ 25.0 (overweight/obesity) in RESP/ELIG/RAND compared to having a BMI ≥ 25.0 in SN/SN_selection.

*** OR Cancer prevalence: OR of ever having had cancer in RESP/ELIG/RAND compared to ever having had cancer in SN/SN_selection.

Table 2.2b Smoking and alcohol use, categorical variables.

	RESP		ELIG		RAND		SN	SN selection
	OR age-adj (95% CI)	n	OR age-adj (95% CI)	n	OR age-adj (95% CI)	n	n	n
Ever smoker*	0.80 (0.74 - 0.86)	92,406	†	18,558	†	10,623	5,281	†
Current smoker**	0.65 (0.61 - 0.69)	72,787	1.00 (0.89 - 1.12)	18,501	0.88 (0.79 - 0.99)	10,604	4,336	1,363
Heavy smokers ***	1.23 (1.10 - 1.37)	21,176	2.13 (1.82 - 2.50)	10,779	2.08 (1.75 - 2.44)	5,897	1,684	778
Alcohol use††	0.91 (0.82 - 1.01)	91,137	0.85 (0.67 - 1.04)	18,291	0.69 (0.55 - 0.86)	10,510	4,509	1,151

* OR of being ever smoker (among all respondents inclusive never smokers) in RESP compared to being ever smoker in SN.
** OR of being current smoker (among all ever smokers inclusive former smokers) in RESP/ELIG/RAND compared to being current smoker in SN/SN_selection.
*** Heavy smokers=current smokers who smoke > 20 cigarettes/day. OR of being heavy smoker in RESP/ELIG/RAND compared to being heavy smoker in SN/SN_selection.
† Only ever smokers were invited for participation among current smokers.
†† OR Alcohol use: OR of being non-drinker (not drunk alcohol in the previous year) in RESP/ELIG/RAND compared to being non-drinker in SN/SN_selection.

Table 2.2c Smoking, continuous variables.

	RESP			ELIG			RAND			SN		SN selection	
	Mean	p	n	Mean	p	n	Mean	p	n	Mean	n	Mean	n
Cigarettes/day in current cigarette smokers	15.6	<0.001	21,064	20.3	<0.001	10,779	20.1	<0.001	5,897	12.3	1,684	21.4	778
Duration of smoking in current cigarette smokers (years)	30.6	<0.001	18,899	37.5	<0.001	10,772	37.4	<0.001	5,891	42.2	1,579	42.3	778
Duration of smoking in former cigarette smokers (years)	23.1	<0.001	46,513	36.7	<0.001	7,551	36.5	<0.001	4,610	24.0	1,341	39.7	586
Duration of cessation in former cigarette smokers (years)	16.6	<0.001	47,623	4.8	0.004	7,496	4.7	0.005	4,584	20.6	1,341	4.4	586

Socio-economic status

Respondents on the first questionnaire (RESP) were more likely to be lower educated (primary, lower vocational or lower secondary general education) compared to GLOBE-participants (OR_{adj}=0.84, 95% CI: 0.74-0.96) (**Table 2.3**). ELIG appeared to be lower educated than RESP (ELIG: 51%, RESP: 45% lower educated) (**Table 2.3**). RAND was higher educated compared to ELIG (RAND: 46%, ELIG: 51% lower educated). The randomised NELSON population includes more subjects in the second (lower) educational level (RAND: 35.1% vs. GLOBE: 29.7%) and less subjects in the fourth (highest) educational level (RAND: 30.3% vs. GLOBE: 36.0%) (OR_{ad}=0.79; 95% CI: 0.68-0.89).

Table 2.3 Educational level of all males, aged 50-75, that responded to the first NELSON questionnaire (RESP), eligible subjects among them (ELIG) and randomised respondents among eligible subjects (RAND) compared to GLOBE (2004). Odds Ratios (OR) are adjusted for age.

	RESP	ELIG	RAND	GLOBE 2004
Educational level*	% of population	% of population	% of population	% of population
1 Low	12.1	13.7	10.8	10.9
2	32.9	37.2	35.1	29.7
3	22.2	22.5	23.8	23.3
4 High	32.9	26.6	30.3	36.0
OR age-adj (95% CI)**	0.84 (0.74 - 0.96)	0.64 (0.56 - 0.73)	0.79 (0.68 - 0.89)	

* 1 = primary education
2 = lower vocational or lower secondary general education
3 = intermediate vocational or higher secondary general education
4 = higher vocational education or university

** OR of being high educated (level 3+4) in RESP/ELIG/RAND compared to being high educated in GLOBE.

Lifestyle

Smoking

The percentage of ever smokers among RESP (78.8%) was slightly lower to SN (82.1%) (OR=0.80; 95% CI: 0.74-0.86) (**Table 2.2b**). The fraction of current smokers among ever smokers was 8-11% lower among the respondents (OR=0.65; 95% CI: 0.61-0.69, **Table 2.2b** and **Figure 2.2**). After applying the selection criteria, the fraction of current smokers amongst ELIG and RAND were comparable to SN_selection, although borderline significantly different caused by the fact that the two highest age groups of RAND contained somewhat less current smokers (**Table 2.2b**, **Figure 2.3**). A lower fraction of current smokers was present among RAND (55.5%) compared to NonRAND (61.8%) (OR=0.85; 95% CI: 0.82-0.88).

Although less current smokers responded on the first questionnaire, they smoked more heavily compared to the Dutch population. The fraction of heavy current smokers among the respondents was 35.1% compared to 15.5% for the Dutch population (OR=1.23; 95% CI: 1.10-1.37) (**Table 2.2b**). Accordingly, the mean number of cigarettes smoked per day of current smokers was also higher among respondents (15.6 cig/day) compared to the Dutch population (12.3 cig/day) ($p<0.001$) (**Table 2.2c** and Appendix). After applying selection criteria, the fraction of heavy current smokers among eligibles and those randomised were still higher compared to the Dutch population (OR=1.68; 95% CI: 1.44-1.97 and OR=1.73; 95% CI: 1.47-2.03, respectively). No significant difference was observed in the fraction of heavy smokers between those randomised and the eligibles who were not randomised in the trial.

Although the RESP contained more heavy current smokers compared to SN, these current smokers smoked for a shorter period of time (30.6 years vs. 42.2 years), especially in

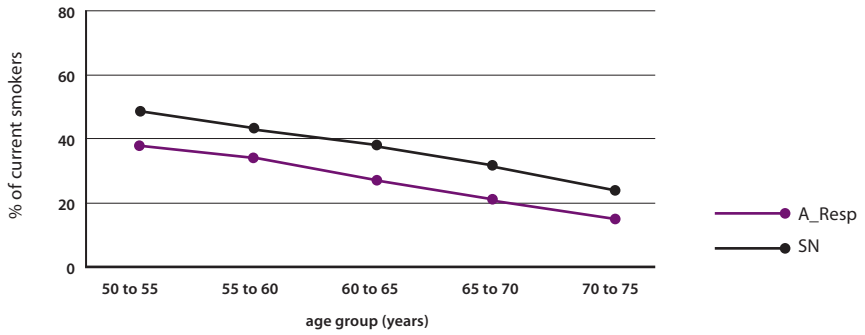

Figure 2.2 Percentage of current smokers of all ever smokers among all males, aged 50-74 that responded to the first NELSON questionnaire (RESP) compared to Statistics Netherlands (SN).

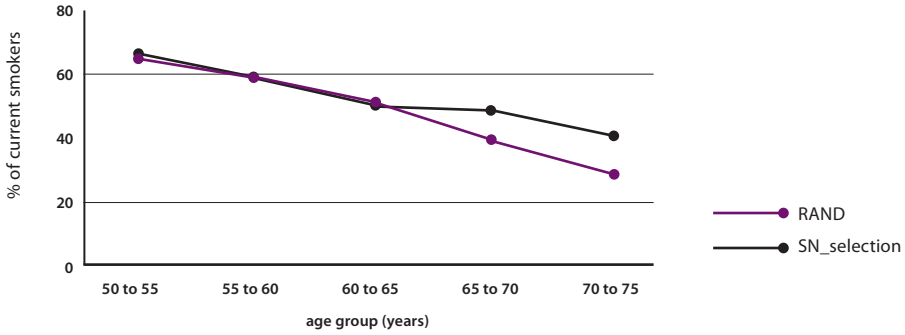

Figure 2.3 Percentage of current smokers of all ever smokers among all males, aged 50-74 that were randomised for the NELSON trial (RAND) compared to the selected Statistics Netherlands group (SN_selection).

the highest age groups (**Table 2.2c** and Appendix). However, the smoking duration was not normally distributed for RESP (median=38 years vs. mean=31 years). Duration of smoking in former smokers among RESP was roughly comparable to SN (23.1 vs. 24.0 years), although significantly different ($p<0.001$) (**Table 2.2c**). Former smokers of RESP had quit smoking for a shorter period of time than the former smokers of SN (16.6 years vs. 20.6 years) (**Table 2.2c** and Appendix). After applying the selection criteria of the trial, the smoking duration of current and former smokers was still lower in ELIG and RAND compared to SN_selection (**Table 2.2c** and Appendix).

Alcohol use

The fraction of persons that did not drink alcoholic beverages in the last year before they filled in the questionnaire was comparable between RESP and SN (OR_{adj}=0.91; 95% CI: 0.82-1.01) and between ELIG and SN_selection (OR_{adj}=0.85, 95% CI: 0.67-1.04). The fraction of non-drinkers was significantly lower among RAND compared to SN_selection (OR_{adj}=0.69,

95% CI: 0.55-0.86). However, this result can be explained by the unusual high percentage of non-drinkers in age group 65-70 for SN_selection (**Table 2.2b** and Appendix).

2.4 DISCUSSION

This study investigates whether selection-bias could play a role in a population-based lung cancer screening trial. In the NELSON trial, respondents on the first questionnaire were more or less comparable to the Dutch population as represented by Statistics Netherlands, with respect to age, health, and lifestyle. The respondents comprised of less current smokers among all ever smokers and these current smokers smoked more heavily for a shorter period of time. The former smoking respondents on the NELSON questionnaire had quit for a shorter period of time compared to the Dutch population. These differences probably balance out in terms of lung cancer risk in general. The respondents were somewhat lower educated compared to the Dutch population (GLOBE). Although some characteristics differed statistically significantly between the respondents and the Dutch population, these differences were negligibly small. Apparently, the modest response on the first questionnaire (32%) did not result in a highly selective group of respondents and did not threat the validity of the results.

Characteristics of the randomised population, consisting of current and former smokers, were in general comparable to a Dutch population that meets our trial selection criteria. However, the randomised population was younger and lower educated compared to the Dutch general population. The fraction of current smokers was comparable, but again these current smokers smoked more heavily, but for a shorter period of time, mainly in the highest age groups. Cancer prevalence was somewhat lower in the randomised population. Again some characteristics differed significantly between RAND and SN, but these differences were negligibly small. It seems to be unlikely that these differences result is important miscalculations.

Should the NELSON trial eventually conclude that lung cancer screening is beneficial, it will be crucial to know to what extent the study results are generalizable to the average target population as well as the general population and whether the study population might affect the outcome measures: lung cancer mortality, especially since the DLSCT reported substantial participation bias.[14, 19-20] Our study results provide the opportunity to correct for the observed differences between the study population and the target or general population through modelling where needed.

The current study gives insight in the degree of self-selection in the NELSON trial. Strength of our study is the large number of subjects that responded. The sample size of the respondents on our first questionnaire is about 18 fold that of four survey years of Statistics Netherlands combined and one might even argue that the NELSON dataset could be considered as the gold standard for the Netherlands.

One limitation is that Statistics Netherlands provided no individual data, but grouped data. Consequently, we were unable to perform an extensive multivariable analysis. Also, we had to simulate a database with individual data from Statistics Netherlands to be able to adjust for age in the statistical comparison of the continuous variables (the means). For the continuous data only means with standard errors and sample sizes were available from SN. Thus, we could not perform a non-parametric test for non-normally distributed variables.

In conclusion, recruitment of the trial population by using population registries resulted in a non-selective response to the first questionnaire, despite this response was low. We can conclude that our selection criteria were applied to a population that was representative of the Dutch population. The NELSON randomised population is roughly representative of the Dutch population that meets our selection criteria and therefore not self-selected. Consequently, the outcomes of the NELSON trial will be applicable for the general Dutch population that fulfils our selection criteria.

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APPENDIX

Detailed data on health and lifestyle. including smoking, for each 5-year age-group of all male respondents on the first questionnaire (RESP), eligible subjects among them (ELIG) and randomised respondents among eligible subjects (RAND), compared to Statistics Netherlands (SN) 2002-2005 or selected Statistics Netherlands sample (SN_selection) 2002-2005.

Appendix: Health

Age	RESP	ELIG	RAND	SN	SN_selection
	% of age group	% of age group	% of age group	% of age group	% of age group
General Health. % moderate or bad health					
50 to 55	13.3	18.3	18.3	12.6	14.4
55 to 60	15.3	18.7	19.0	16.6	14.7
60 to 65	15.2	17.7	17.9	15.3	16.7
65 to 70	15.2	15.1	13.2	14.2	15.2
70 to 75	18.3	15.8	13.1	17.7	18.8
Total	*15.2*	*17.8*	*17.7*	*15.1*	*15.4*
BMI. % BMI ≥ 25.0 (overweight/obesity)					
50 to 55	58.9	59.5	60.2	60.5	59.0
55 to 60	63.5	65.5	65.5	65.9	65.4
60 to 65	61.9	63.6	63.4	63.5	63.7
65 to 70	59.9	62.2	63.0	62.8	56.6
70 to 75	57.4	61.4	61.5	59.8	66.8
Total	*60.8*	*62.8*	*63.1*	*62.7*	*62.0*
Cancer prevalence. % ever had cancer					
50 to 55	3.3	2.7	2.8	3.4	4.7
55 to 60	4.6	3.0	3.2	5.2	5.7
60 to 65	7.2	5.3	5.8	8.9	7.0
65 to 70	9.4	6.5	7.2	11.5	12.5
70 to 75	12.8	9.5	8.5	12.7	12.6
Total	*6.6*	*4.1*	*4.3*	*7.4*	*7.2*

Appendix: Smoking (continuous variables)

Age	RESP	ELIG	RAND	SN	SN_selection
	Mean	Mean	Mean	Mean	Mean
Cigarettes/day in current cigarette smokers					
50 to 55	16.9	21.2	21.0	13.7	21.9
55 to 60	16.0	20.6	20.3	12.7	21.4
60 to 65	15.0	19.7	19.3	11.6	21.9
65 to 70	13.9	17.9	18.1	11.1	20.8
70 to 75	13.7	17.0	16.8	9.4	18.0
Total	*15.6*	*20.3*	*20.1*	*12.3*	*21.4*
Duration of smoking in current cigarette smokers (years)					
50 to 55	29.1	34.3	34.2	35.6	36.3
55 to 60	30.8	37.6	37.4	40.3	41.2
60 to 65	33.0	40.7	40.7	44.3	45.3
65 to 70	30.4	41.4	41.3	51.0	52.3
70 to 75	27.9	42.3	41.3	56.0	56.2
Total	*30.6*	*37.5*	*37.4*	*42.2*	*42.3*
Duration of smoking in former cigarette smokers (years)					
50 to 55	18.8	32.2	32.2	19.0	32.5
55 to 60	21.1	35.3	35.3	20.8	35.6
60 to 65	23.9	38.1	38.2	25.0	41.8
65 to 70	25.9	40.8	40.9	27.8	45.7
70 to 75	27.3	41.7	42.1	30.2	51.2
Total	*23.1*	*36.7*	*36.5*	*24.0*	*39.7*
Duration of cessation in former cigarette smokers (years)					
50 to 55	14.6	3.9	4.0	17.1	3.7
55 to 60	15.8	4.3	4.4	19.4	4.8
60 to 65	16.7	4.9	4.7	20.5	4.0
65 to 70	17.7	5.7	5.8	22.7	4.9
70 to 75	19.0	6.9	6.9	25.2	5.2
Total	*16.6*	*4.8*	*4.7*	*20.6*	*4.4*

Appendix: Smoking and alcohol use (categorical variables)

Age	RESP	ELIG	RAND	SN	SN_selection
	% of age group	% of age group	% of age group	% of age group	% of age group
Smoking status 1. % of ever smokers among all respondents					
50 to 55	75.2			78.9	
55 to 60	76.9			80.6	
60 to 65	79.1			82.3	
65 to 70	81.4			84.8	
70 to 75	85.5			88.7	
Total	*78.8*			*82.1*	
Smoking status 2. % of current smokers. among ever smokers					
50 to 55	38.1	68.7	65.3	47.9	66.9
55 to 60	33.7	62.4	58.5	42.6	59.0
60 to 65	27.3	53.8	51.3	38.1	50.4
65 to 70	22.2	41.8	38.9	31.9	49.2
70 to 75	16.8	28.1	28.2	24.7	41.2
Total	*29.1*	*58.3*	*55.6*	*39.0*	*57.1*
Heavy current smokers. among current smokers					
50 to 55	38.3	48.2	48.2	20.3	37.0
55 to 60	38.2	46.5	46.5	14.2	27.9
60 to 65	34.5	41.3	41.5	13.5	29.8
65 to 70	27.6	33.7	36.5	13.8	32.3
70 to 75	23.5	27.3	32.4	8.3	20.0
Total	*35.1*	*44.6*	*45.1*	*15.5*	*31.6*
Alcohol use. % never drunk alcohol					
50 to 55	7.1	6.9	6.0	6.4	6.6
55 to 60	7.5	7.1	5.8	7.6	6.3
60 to 65	9.0	8.1	6.7	10.5	9.1
65 to 70	10.4	8.6	6.7	13.6	17.1
70 to 75	13.0	9.4	7.2	14.1	11.9
Total	*8.8*	*7.6*	*6.2*	*10.6*	*9.8*

CHAPTER 3

Management of lung nodules detected by volume CT scanning.

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N Engl J Med 2009; 361:2221-2229

ABSTRACT

Background

The use of multidetector computed tomography (CT) in lung-cancer screening trials involving subjects with an increased risk of lung cancer has highlighted the problem for the clinician of deciding on the best course of action when noncalcified pulmonary nodules are detected by CT.

Methods

A total of 7557 participants underwent CT screening in years 1, 2, and 4 of a randomized trial of lung-cancer screening. We used software to evaluate a noncalcified nodule according to its volume or volume-doubling time. Growth was defined as an increase in volume of at least 25% between two scans. The first-round screening test was considered to be negative if the volume of a nodule was less than 50 mm^3, if it was 50 to 500 mm^3 but had not grown by the time of the 3-month follow-up CT, or if, in the case of those that had grown, the volume-doubling time was 400 days or more.

Results

In the first and second rounds of screening, 2.6% and 1.8% of the participants, respectively, had a positive test result. In round one, the sensitivity of the screen was 94.6% (95% confidence interval [CI], 86.5 to 98.0) and the negative predictive value 99.9% (95% CI, 99.9 to 100.0). In the 7361 subjects with a negative screening result in round one, 20 lung cancers were detected after 2 years of follow-up.

Conclusions

Among subjects at high risk for lung cancer who were screened in three rounds of CT scanning and in whom noncalcified pulmonary nodules were evaluated according to volume and volume-doubling time, the chances of finding lung cancer 1 and 2 years after a negative first-round test were 1 in 1000 and 3 in 1000, respectively.

3.1 INTRODUCTION

The use of multidetector computed tomography (CT) has increased the chance of finding noncalcified pulmonary nodules,[1, 2] and as a result, clinicians often face the problem of deciding on the best course of action with respect to such nodules when they are found in asymptomatic subjects who have an increased risk for lung cancer.[3] This difficulty is especially evident in CT-based screening programs for lung cancer. The current practice is to refer participants in these programs for additional diagnostic evaluation if they have a noncalcified nodule that is larger than 5 mm in diameter.[4-9] In designing the Dutch–Belgian randomized lung cancer screening trial (Nederlands-Leuvens Longkanker Screenings Onderzoek [NELSON]), we adopted a strategy that was meant to provide an inexpensive and simple follow-up process without increasing the false negative rate of the screening test.[10] The strategy entailed the use of the volume and volume-doubling time of a noncalcified nodule as main criteria for deciding on further action. In this article, we report an evaluation of this strategy, which involved the tracking of individual nodules and the collection of 2-year follow-up data from the screened population of the NELSON trial.

3.2 METHODS

Participants

We randomly assigned eligible participants in NELSON, who were recruited as described previously,[11] to undergo CT screening at baseline (first round), 1 year later (second round), and 3 years later (third round, 2 years after the second round), or no screening. The purpose of the trial is to determine whether at 10 years after randomization CT screening will have reduced mortality from lung cancer by at least 25%. The trial was approved by the Dutch Minister of Health and the ethics board at each participating centre. All participants gave written informed consent.

Screening Strategy

A 16-detector CT scanner (Somatom Sensation 16, Siemens Medical Solutions or, at the screening site in Utrecht, 1x Mx8000 IDT or Brilliance-16P, Philips Medical Systems) was used at each of the screening sites. Data sets were derived from images of the lung with a thickness of 1 mm that were reconstructed at overlapping 0.7-mm intervals. Isotropic data sets allowed for volume measurements with good reproducibility, even in the case of small lesions.[12] Data acquisition and scanning conditions were standard across screening sites and were the same for all rounds of screening.[10] At each site, CT data were analyzed on one type of digital workstation (Leonardo, Siemens Medical Solutions) with the use of software for semiautomated volume measurements (LungCare, version Somaris/5 VA70C-W, Siemens

Medical Solutions).[13, 14] In the case of inappropriate segmentation (i.e., nodules that were attached to a fissure or to a vessel), the radiologist was allowed to enter manual measurements, which overruled the automatically generated volumes. Data generated by the LungCare software were uploaded into the NELSON Management System, which automatically detected whether a nodule was new or had been present previously and which calculated the percentage change in volume and the volume-doubling time in days (**Figure 1** in the Supplementary Appendix).

A nodule was classified as noncalcified if it did not meet previously specified criteria for a benign lesion.[4] For solid pleural-based and nonsolid pulmonary nodules, the diameter was determined manually, and the volume-doubling time was calculated as described previously (**Figure 1** in the Supplementary Appendix).[10] In the case of pleural-based nodules, the diameter was measured at a point perpendicular to the costal pleura. In the case of partially solid lesions, only the volume of the solid region was used. The diameter was defined as the average of the maximum length and width of the nodule. Growth was defined as a change in volume of at least 25% between the first and second scans or between the second and third scans. The 25% threshold was based on three zero-change data sets in which the variation in volume of individual nodules was assessed between two low-dose CT scans. After the first of these scans, the patient returned to the examining table for the second scan to simulate the condition of a repeat examination for the follow-up of a pulmonary nodule. In these studies, the volume measurement error varied between 20% and 25%.[12, 14, 15] Growing nodules were classified into three growth categories according to their volume-doubling time (<400, 400 to 600, and >600 days).

CT scans were independently read by first and second readers. The experience of the 13 first readers ranged from none to more than 20 years of experience reading thoracic CT scans (median, 6 years); both second readers had 6 years of experience. The second readers matched the nodules they had identified with nodules identified by the first readers according to location and size and compared their results with those of the first readers. If the results were discrepant, the readers reevaluated the scan to reach a consensus. If no consensus was reached, a third radiologist arbitrated the results.

First-Round (Baseline) Scan

A test was considered to be positive if on the CT scan any noncalcified nodule had a solid component that was more than 500 mm^3 (>9.8 mm in diameter) and was considered to be indeterminate if the volume of the largest solid nodule or of the solid component of a partially solid nodule was 50 to 500 mm^3 (4.6 to 9.8 mm in diameter) or if the diameter of a nonsolid nodule was greater than 8 mm.[10] In subjects with an indeterminate result, a follow-up scan was obtained 3 months after the baseline scan to assess the growth of the lesion. If at that time the lesion had a volume-doubling time of less than 400 days, the final result was declared to be positive; otherwise, it was considered to be negative. Subjects with positive

screening tests were referred to a chest physician for workup and diagnosis. If lung cancer was diagnosed, the participant was treated for the disease and left the screening trial; if no lung cancer was found, the regular second-round CT scan was scheduled for 12 months after the baseline scan.

Second-Round Scan

When one or more new nodules were found on the second-round scan, the interpretation (positive or negative result) was based on the size of the nodule, as it had been in round one; if the result was indeterminate, a follow-up scan was obtained 6 weeks later.[10] In the case of nodules that had been detected previously, the second-round result was based on the volume-doubling time. If there was no growth, or if the volume-doubling time was more than 600 days, the screen was classified as negative. If the volume-doubling time was less than 400 days, or if a new solid component had emerged in a previously nonsolid nodule, the scan was considered to be positive. When the volume-doubling time was 400 to 600 days, the test result was considered to be indeterminate and a follow-up scan was obtained 1 year after the second-round scan. At that time, if the volume-doubling time was less than 400 days, the final result was considered to be positive; otherwise it was considered to be negative. If both new and existing nodules were present, the nodule with the largest volume or fastest growth determined the result. All participants with a negative second-round test result were invited to undergo the third round of screening 2 years after the second round. A cancer detected on screening was classified as a first-round or second-round cancer if it was diagnosed after a workup during the first year after a positive first-round or second-round screen, respectively. Lung cancers that were detected during the first year after a negative first-round or second-round screening test were classified as interval cancers. They were identified through linkage with the national pathology database, information from participants and general practitioners, and, in the case of round-one interval cancers, linkage with the National Cancer Registry. The workup, staging, and treatment were standard across all screening sites and were performed according to published guidelines.[10, 16, 17]

All the authors contributed to the data collection and the decision to submit the manuscript for publication, and all the authors vouch for the accuracy and completeness of the data.

Statistical analysis

The diagnostic sensitivity was defined as the ratio between the number of true positive results (participants who were diagnosed with lung cancer during the first year after a positive screening test) and the number of true positive results plus the number of false negative results (interval cancers detected during the same time period). Diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were calculated at the participant level, and 95% confidence intervals were determined with the use of SPSS software, version

15.0 (SPSS). The standard for a negative baseline or second-round test result was based on the retrospective information that lung cancer was absent 2 years after the first round of screening and 1 year after the second round. Normally distributed data are shown as means ± SD. P values of less than 0.05 were considered to indicate statistical significance.

3.3 RESULTS

First Round

The mean (±SD) age of the screened participants was 59 ± 6 years, and the mean number of pack-years smoked was 42 ± 19; a total of 16% of the participants were women. The first round of screening was conducted from April 2004 through December 2006 (**Figure 2** in the Supplementary Appendix). Of the 7557 participants, 50.5% had a total of 8623 noncalcified pulmonary nodules, of which 98.0% were solid. Automated volumetric data were manually adjusted in the case of 6.3% of the nodules. The screening results were determined to be negative in 5987 participants (79.2%), indeterminate in 1451 (19.2%), and positive in 119 (1.6%) (**Figure 3.1**). A total of 1536 follow-up scans were obtained 100 ± 19 days, on average, after the baseline scan in participants with an indeterminate result. Including the outcome of these follow-up scans, the results from round one of the screening were negative in 7361 participants (97.4%) and positive in 196 (2.6%).

Of the 196 participants with a positive scan, 177 were referred for workup; 19 were not referred (9 because of a decision by the tumour board, 3 because of an administrative error, and 7 because they were already receiving treatment from another specialist). Lung cancer was diagnosed in 70 of the 177 participants who had a positive scan (39.5%); the diagnosis was made mainly by means of an invasive procedure (85.7%). These 70 participants had 72 lung cancers, of which 46 (63.9%) were classified as pathological stage I. In three subjects, no tissue for a histologic diagnosis could be obtained. These subjects received high-dose radiotherapy because the lesions were growing and were assessed as positive on a positron-emission tomographic (PET) scan. Of the remaining 107 subjects with a positive scan, 100 had benign disease and 7 had metastases from another cancer. In round one, the proportion of invasive procedures that revealed benign disease was 27.2%.

The lung-cancer detection rate in round one was 0.9% (70 of 7557 subjects). There were four interval cancers, all of which were stage IV adenocarcinomas; three of these were new noncalcified nodules, and one, which had been seen in the first round, had a volume-doubling time of more than 600 days at the 3-month follow-up. The sensitivity of round-one screening was 94.6% (95% confidence interval [CI], 86.5 to 98.0), the specificity 98.3% (95% CI, 98.0 to 98.6), the positive predictive value 35.7% (95% CI, 29.3 to 42.7), and the negative predictive value 99.9% (95% CI, 99.9 to 100.0). Thus, in a subject with a positive CT screening test, the

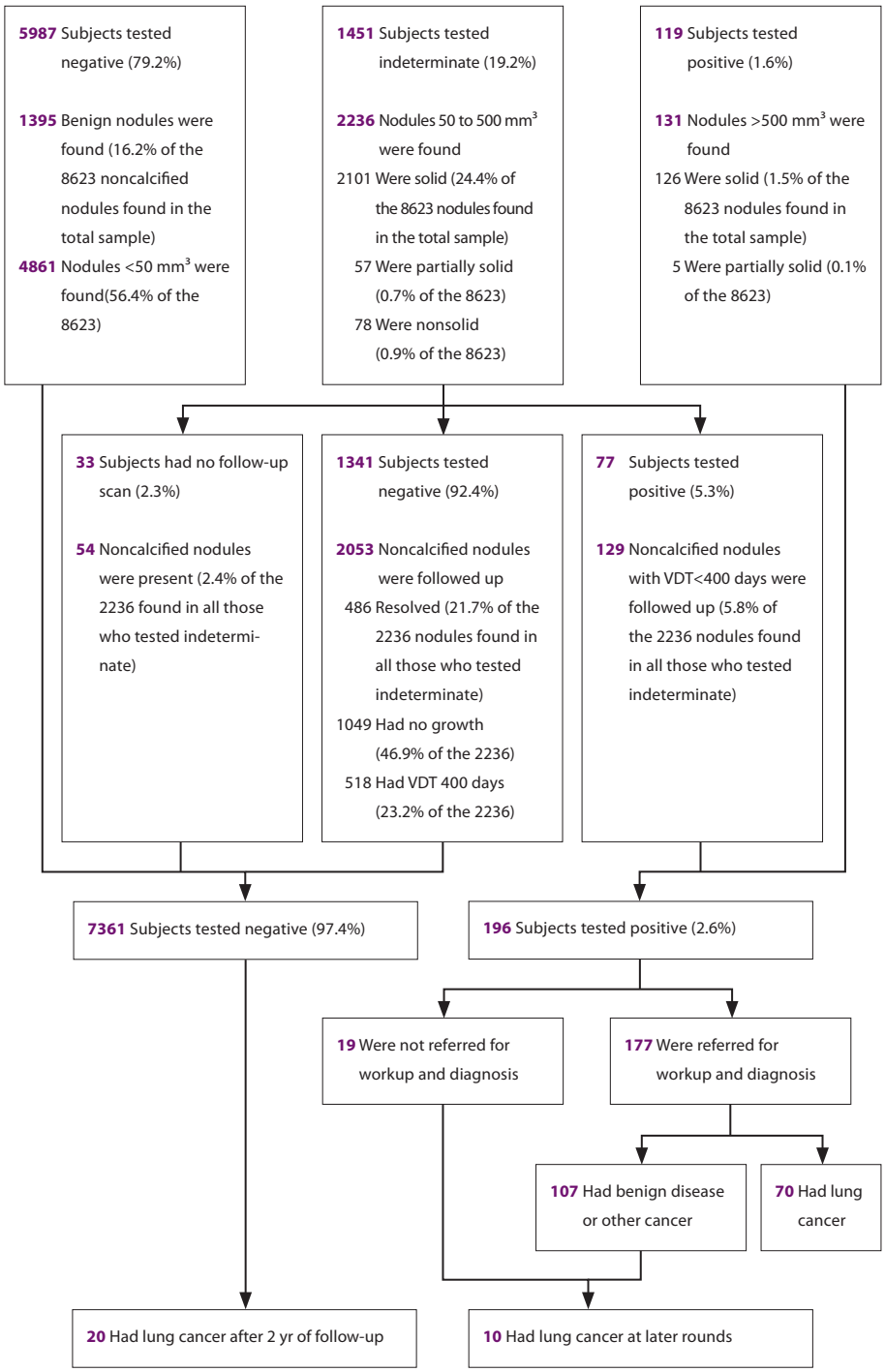

Figure 3.1 Results of the First Round Screening.
Some participants had more than one nodule. VDT denotes volume-doubling time.

probability that the lesion would be malignant was 36%; with a negative screening test, the probability that a participant would not have lung cancer was 99.9%.

Among the 7361 negative CT scans in round one, 20 lung cancers were detected during the 2 years of follow-up: 3 were round-one interval cancers, and 17 were detected in the round-two screening. On the basis of this information, the negative predictive value was 99.7% (95% CI, 99.6 to 99.8). All 126 participants with a positive screening result at round one but with a negative workup returned to the screening program. After a mean follow-up of 785 ± 263 days, 10 of these 126 subjects received the diagnosis of pulmonary adenocarcinoma, which appeared to have originated from a suspicious nodule that was detected in round one (**Table 1** in the Supplementary Appendix).

Second Round

In accordance with the trial's protocol, all the participants in the first round of screening, except those in whom lung cancer had been diagnosed, were invited to undergo screening in the second round,[12] which was conducted from April 2005 through April 2008. A total of 7289 participants underwent screening 384 ± 59 days after the round-one screening (**Figure 1** in the Supplementary Appendix). In 1588 (21.8%) of these participants, a total of 2320 new nodules were detected, 29.2% of which had a volume of less than 15 mm^3 or had been missed in round one. Automated volumetric data were manually adjusted in the case of 5.4% of the new nodules and 1.9% of previously existing nodules. The second-round screening result was negative in 6719 participants (92.2%), indeterminate in 480 (6.6%), and positive in 90 (1.2%) (**Figure 3.2**). Among participants with an indeterminate result, 276 had a follow-up scan 77 ± 36 days after the second-round screening and 231 had a follow-up scan 364 ± 36 days after the second-round screening. The follow-up scans were positive in 38 subjects, and when the results of these positive follow-up scans were added to the results of the 90 positive screening scans, there were 128 subjects (1.8%) with positive second-round scans. Of these 128 participants, 1 patient died as a result of a metastatic colon carcinoma and 118 were referred for workup; 54 of the 118 who were referred for workup (45.8%) received the diagnosis of lung cancer, mainly after undergoing an invasive procedure (88.9%). The nine participants who were not referred for workup (four because of a decision by the tumour board, four because of an administrative error, and one because the patient was already receiving treatment from another specialist) were invited to participate in the third round of screening 2 years later. In one of these nine, lung cancer was found 23 months after the first detection of the nodule in a nodule that had not been seen previously. Of the remaining 64 subjects with a positive scan, 62 had benign disease and 2 had another cancer (1 a thymoma and 1 lymphoma). There were two subjects with suspicious lesions from whom no tissue could be obtained for histological diagnosis. These subjects were treated with high-dose radiotherapy because the lesions were new and growing and were positive on a PET scan. The 54 participants with lung cancer had 57 cancerous nodules, 42 of which (73.7%) were

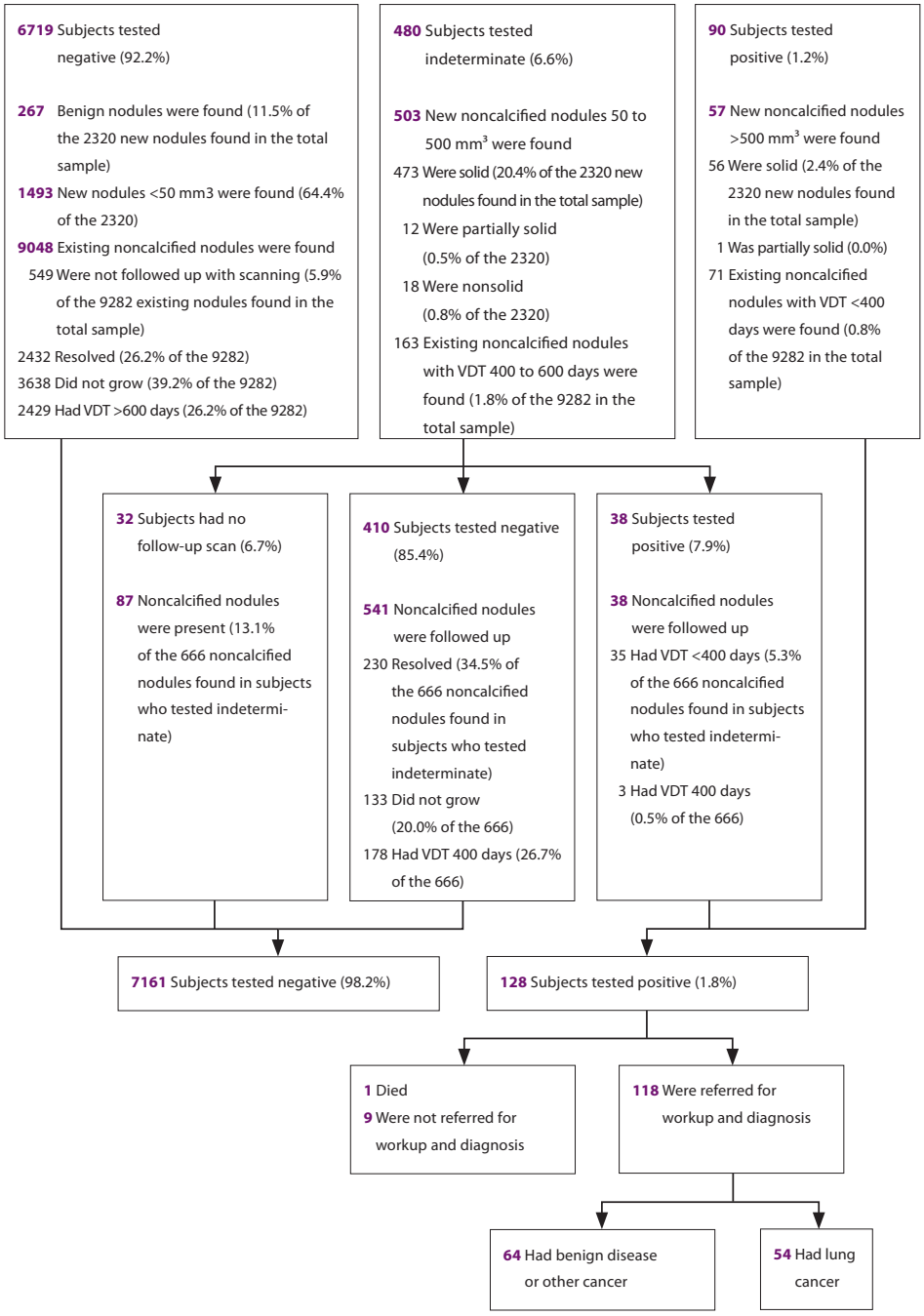

Figure 3.2. Results of the Second Round of Screening.
Some participants had more than one nodule. VDT denotes volume doubling time.

classified as pathological stage I, including 3 that were synchronous double tumours. The lung-cancer detection rate was 0.5% (40 of 7289) during the first year after the second-round screening and 0.8% (57 of 7289) for the entire 2-year period after the second and third rounds of screening. One stage IV small-cell and one stage IV large-cell interval carcinoma, both of which were present in nodules that had been absent at the time of the second-round screening, were diagnosed during the first year after the second-round screening. The sensitivity of the second-round screening was 96.4% (95% CI, 86.8 to 99.1), the specificity was 99.0% (95% CI, 98.7 to 99.2), the positive predictive value was 42.2% (95% CI, 33.9 to 50.9), and the negative predictive value was 99.9% (95% CI, 99.9 to 100.0).

Additional diagnostic investigations

The recall rates for CT scans among participants with indeterminate test results were 19.0% and 3.8% in rounds one and two, respectively (**Table 2** in the Supplementary Appendix). No diagnostic PET or PET–CT scanning was performed in participants with positive test results, and fine-needle biopsy procedures were performed in less than 1% of the subjects. The rate of invasive diagnostic procedures was 1.2% in round one and 0.8% in round two.

3.4 DISCUSSION

In a population that was at an increased risk for lung cancer, our strategy of screening for lung cancer with the use of volume CT diminished the need for follow-up evaluation in participants with an indeterminate test result. This strategy was especially useful during the second-round screening. It reduced the number of follow-up examinations in participants with a positive test result without reducing the overall sensitivity of the technique, as compared with that reported in the literature.[4-8, 18-23] This report concerns itself only with how to deal with an abnormality that has been detected on a CT scan in this population; it does not address the usefulness of screening for lung cancer with the use of CT scanning.

The rate of interval cancers that were found in participants in our trial was similar to that found in participants in other trials.[20] The proportion of early (stage I) lung cancers detected in round one (63.9%) was similar to that found in other randomized trials,[18, 19, 23] but lower than that found in nonrandomized trials (e.g., the proportion in the International Early Lung Cancer Action Program [I-ELCAP] was 86%, and the proportion in a trial performed at the Mayo Clinic was 75%).[6,7,20] The lung-cancer detection rate in round one in I-ELCAP was higher than that in NELSON (1.3% vs. 0.9%),[7] despite similar median ages of the participants and a higher number of pack-years smoked by participants in NELSON. The discrepancy was probably due to the fact that the proportion of women, who tend to have slow-growing cancers,[24,25] was higher in I-ELCAP than in NELSON. Moreover, in I-ELCAP surgeons removed any nonsolid nodule that was larger than 8 mm, instead of waiting for the nodule to grow

before removing it, as was done in NELSON. In our trial of subjects who had an increased risk of lung cancer, we found that the chances of finding lung cancer on a CT scan at 3 months, 1 year, and 2 years after a negative first-round test were 0, 1 in 1000, and 3 in 1000, respectively.

In round one, the proportion of invasive procedures that revealed benign disease was 27.2%, which is similar to that found in other trials.[5, 6, 19, 21, 22, 26-30] The advantages of volumetric measurements become fully apparent when a volumetric comparison can be made with a previous indeterminate CT scan. Because there were no comparative CT scans available at round one, the first-round recall rate was almost as high as that in other trials (**Table 2** in the Supplementary Appendix). The LungCare software version that we used is not proprietary and can be used with any CT data set, regardless of the CT system, for evaluation of solid nodules and the solid component of partially solid noncalcified nodules smaller than 500 mm^3. With manual correction, the mean relative deviation from the true lesion volume was only $-0.3 \pm 6.5\%$ for these types of lesions.[13]

As an absolute standard for negative test results, we used the absence of lung cancer after 2 years of follow-up, a period that is considered to be sufficient for concluding that a nodule is benign.[2] The 400-day threshold for volume-doubling time that we used was based on current opinion that lung cancers with a volume-doubling time of 400 days or more are overdiagnosed cases.[24, 31] A volume-doubling time of 500 days is regarded as the upper limit for lung cancer, even though some tumours may grow more slowly [32-34]; our upper limit was set at 600 days. If a lower upper limit had been used, the rate of false negatives would have increased, but the rate of false positives would have decreased. Therefore, the ranges for volume-doubling time that we used are not definite and could be improved. Finally, before we can make clinically directive recommendations, our strategy requires validation in an independent study.

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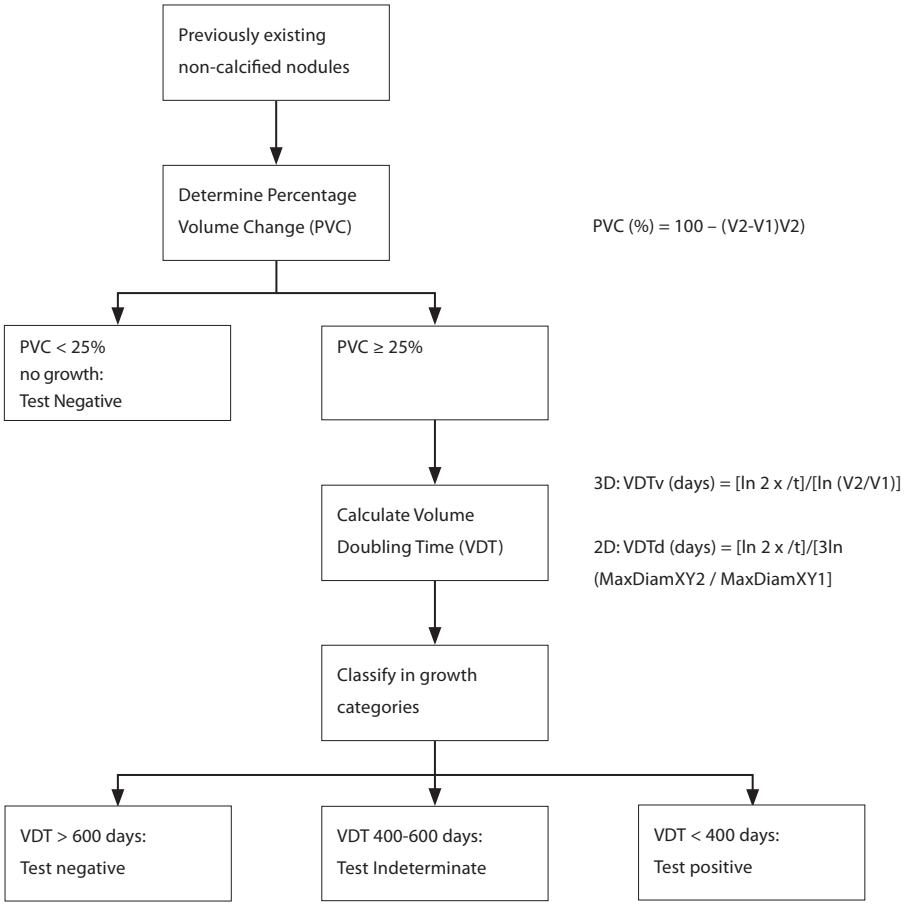
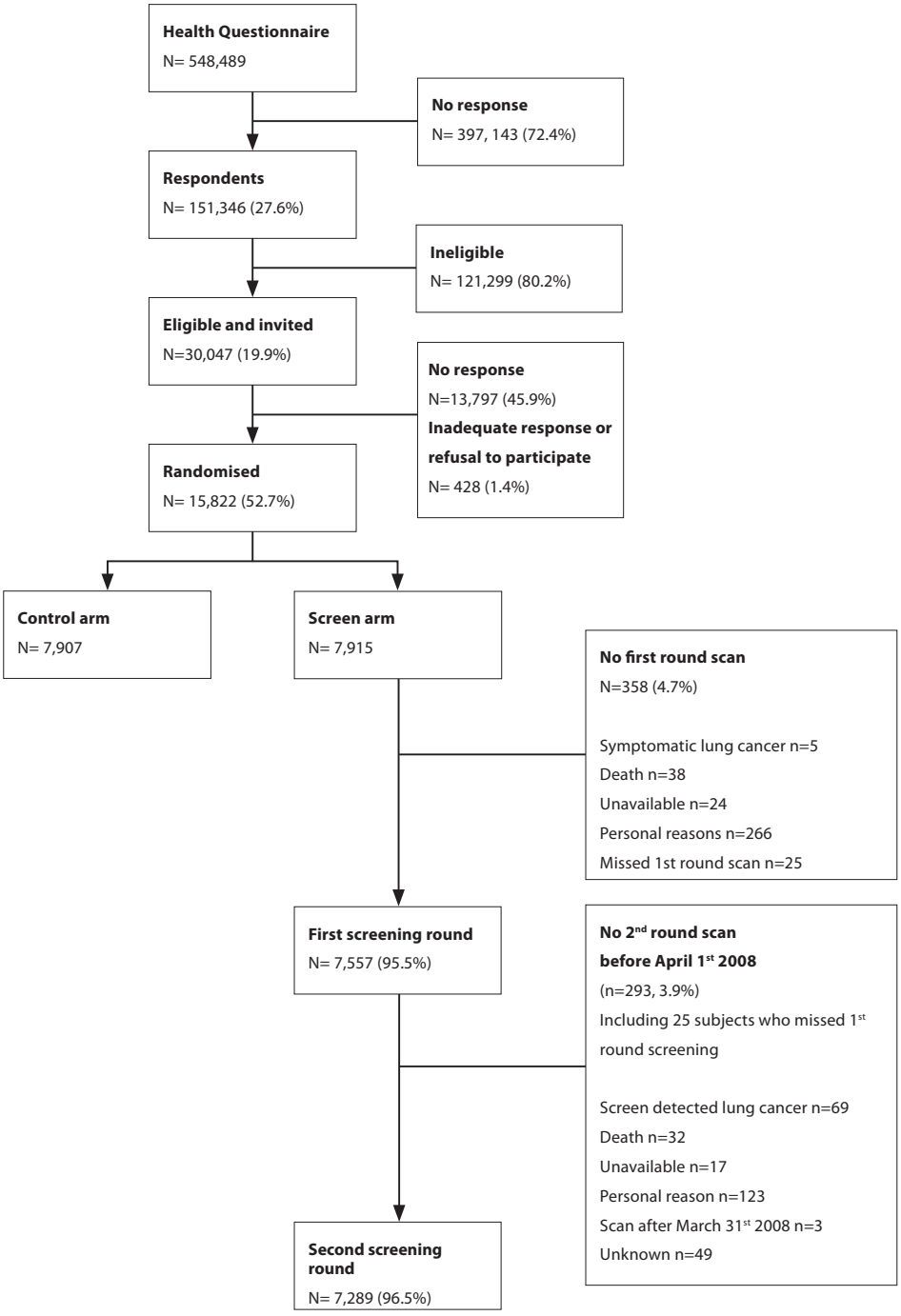
Supplementary Appendix, Figure 1



Definition of abbreviations:
V1: volume of the nodule (mm^3) at first detection on CT
V2: volume of the nodule (mm^3) at subsequent CT evaluation
3D: volume generated by three-dimensional volumetry software (VDTv)
2D: volume estimate based on two-dimensional measurements (VDTd)
MaxDiamXY1: maximum diameter in X/Y-axis at first detection on CT
MaxDiamXY2: maximum diameter in X/Y-axis at subsequent CT evaluation

Supplementary Appendix, Figure 2 CONSORT flowchart.



Supplementary Appendix, Table 1 Subjects with a positive 1st round test result and a false negative work-up in whom lung cancer was diagnosed in the suspicious 1st round nodule at later screening rounds.

	1st round screening						Final lung cancer diagnosis			
	Moment of first detection	Consistency	Size at first detection	VDT (Days)	Highest level procedure	Diagnosis	Interval (Months)	VDT (Days)	Diagnosis	pTNM
Lung cancer detected during 2nd round										
Case 1	3-months FU	Partial-solid	50-500 mm^3	< 400	FBR with washing	No malignancy	23	<400	Adenocarcinoma	T1N0M0
Case 2	3-months FU	Non-Solid	50-500 mm^3	< 400	FBR with washing	Inconclusive	36	< 400	Adenocarcinoma	T1N0M0
Case 3	Baseline	Solid	> 500 mm^3	NA	FNA	Fibrosis	27	< 400	Adenocarcinoma	T1N0M0
Case 4	3-months FU	Solid	50-500 mm^3	< 400	Computer Tomography	Rest of pneumonia	20	< 400	Adenocarcinoma	T1N0M0
Case 5	3-months FU	Solid	50-500 mm^3	400-600	FBR with washing	No malignancy	11	< 400	Adenocarcinoma	T1N1M0
Case 6	Baseline	Solid	> 500 mm^3	NA	FBR with washing	No malignancy	26	> 600	Adenocarcinoma	T1N2M0
Case 7	Baseline	Solid	> 500 mm^3	NA	No work-up*	NA	14	400-600	Adenocarcinoma	T1N0M0
Case 8	3-months FU	Solid	50-500 mm^3	< 400	FBR with washing	No malignancy	24	< 400	Adenocarcinoma	T1N0M0
Lung cancer detected during 3rd round										
Case 9	3-months FU	Non-solid	25 mm	NA	FBR with washing	No malignancy	37	NA	Adenocarcinoma	T2N0M0
Case 10	3-months FU	Solid	> 500 mm^3	NA	FBR with washing	Fibrosis	32	> 600	Adenocarcinoma	T2N0M0

Definition of abbreviations: VDT: volume doubling time; FU: follow-up; FBR: Flexible bronchoscopy; FNA: fine needle aspirate; NA: not applicable; * protocol violation.

Supplementary Appendix, Table 2. Additional diagnostic evaluations in participants with an indeterminate or positive test result following first and second round screening of the NELSON trial in comparison with the literature.

Variable	NELSON [10]			PluSS[21]	Cosmos[22,29,30]	Toronto[28]	LSS [†] [26,27]		
	All No. (%)	No Lung Cancer No. (%)	Lung Cancer No. (%)	All No. (%)	All No. (%)	All No. (%)	All No. (%)	No Lung Cancer No. (%)	Lung Cancer No. (%)
Round one screening	7,557 (100)	7,487 (100)	70 (100)	3,642 (100)	5,203 (100)	3,352 (100)	1,586 (100)	1,556 (100)	30 (100)
Clinical evaluation	181 (2)	111 (2)	70 (100)	1,477 (41)	NA	NA	244 (15)	217 (14)	27 (90)
Recall chest CT scan	1,438 (19)	1,419 (19)	19 (27)	821 (23)[$]	482 (9)	628 (19)	235 (21)	305 (20)	20 (67)
Recall chest CT scans / subject	1.1	1.1	1.2	1.4	NA	NA	1.0	1.0	1.0
Chest X-ray	55 (1)	27 (0)	28 (40)	NA	NA	NA	92 (6)	80 (5)	12 (40)
PET or PET/CT	0 (0)	0 (0)	0 (0)	NA	160 (3)	NA	NA	NA	NA
MRI	5 (0)	2 (0)	3 (0)	NA	NA	NA	NA	NA	NA
Lung function test	147 (2)	78 (1)	69 (99)	NA	NA	NA	73 (5)	55 (4)	18 (60)
Bronchoscopy	149 (2)	84 (1)	65 (93)	NA	NA	NA	29 (2)	16 (1)	13 (43)
FNA	13 (0)	5 (0)	8 (11)	NA	4 (0)	57 (2)	46 (3)	18 (1)	28 (93)
Invasive procedure*	92 (1)	32 (0)	60 (86)	90 (3)	106 (2)	48 (1)	53 (3)	23 (2)	30 (100)
Round two screening	7,289 (100)	7,235 (100)	54 (100)	3,423 (100)	4,867 (100)	2,686 (100)	1,398 (100)	1,390 (100)	8 (100)
Clinical evaluation	125 (2)	71 (1)	54 (100)	1,450 (42)	NA	NA	NA	NA	NA
Recall chest CT scan	275 (4)	267 (4)	8 (15)	1,386 (41) [$]	142 (3)	NA	NA	NA	NA
Recall chest CT scans / subject	1.1	1.1	1.4	1.1	NA	NA	1.0	NA	NA
Chest X-ray	35 (0)	17 (0)	18 (33)	NA	NA	NA	64 (4)	NA	NA
PET or PET/CT	0 (0)	0 (0)	0 (0)	NA	66 (1)	NA	NA	NA	NA
MRI	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA	NA	NA
Lung function test	103 (1)	55 (1)	48 (89)	NA	NA	NA	70 (4)	NA	NA
Bronchoscopy	98 (1)	46 (1)	46 (85)	NA	NA	NA	14 (1)	NA	NA
FNA	3 (0)	3 (0)	0 (0)	NA	NA	16 (1)	18 (1)	NA	NA
Invasive procedure*	61 (1)	13 (0)	48 (89)	NA	NA	NA	NA	NA	NA

Definition of abbreviations: FNA: Fine needle aspirate; PET: Positron emission tomography; CT: computer tomography; MRI: Magnetic resonance imaging; NA: not available; [†] Diagnostic follow-up information available for 316/325 and 351/360 participants with a positive test result at 1st and 2nd round screening, respectively; * includes: lung biopsy or wedge resection, video-assisted thoracotomy, thoracotomy, mediastinoscopy and mediastinotomy; [$]: includes PET and PET-CT.

PART 2

Lung cancer screening and smoking behaviour

CHAPTER 4

Does participation to screening unintentionally influence lifestyle behaviour and thus lifestyle-related morbidity?

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ABSTRACT

Cancer is a leading cause of death worldwide and the burden could be reduced by evidence-based strategies for the primary prevention of cancer, the early detection of malignancies and more adequate treatment of cancer patients.

Previous research has shown that lifestyle factors are associated with common cancers and that several cancer screening programmes are cost-effective in reducing cancer-specific mortality. But, some recent studies reported that participants of screening programs might unintentionally change their lifestyle. Cancer screening might be a teachable moment or, on the other hand, have a false health certificate effect. Despite that the evidence is scarce, cancer screening might have opportunities for lifestyle improvements, although a possible health certificate effect still remains. Integrated approaches to combine primary and secondary prevention have the potential to optimize the efforts to improve cancer prevention and survival. More research is warranted to investigate evidence-based approaches.

4.1 INTRODUCTION

Cancer is a leading cause of death that accounts for more than 8 million (14%) deaths worldwide. The World Health Organization estimated that the global burden of cancer mortality will increase to 12 million deaths in 2030.[1]

Current evidence links several lifestyle factors - nutritional intake, the use of tobacco, the use of alcohol, and performing physical activity - to the main chronic diseases, including the most common cancers – lung, colorectal, prostate, breast, stomach, and liver cancer.[2, 3] The burden of cancer could be reduced by evidence-based strategies based on three major targets, namely the inhibition of the development of cancer (primary prevention), the identification of people with early stage preclinical malignancy to increase the opportunities to treat and prevent progression of the cancer (secondary prevention), and an adequate treatment of cancer patients to improve survival and functionality (tertiary prevention). A variety of studies investigated the efficacy of evidence-based interventions in modifying risk factors of cancer; cancer screening programs in reducing cancer-specific mortality; and new treatment options in increasing the survival of cancer patients. Although all this research contributes to the current evidence, few of them integrate these efforts to optimize the effect, using all evidence in these seemingly separate fields. At the same time, there may be unintended effects of cancer screening. Those with a relatively healthy lifestyle may choose not to attend effective screening programmes, or the other way around, people attending screening programmes might feel they do not need a healthy lifestyle. Relatively less attention has been paid to the impact of cancer screening on future lifestyle and lifestyle-related mortality so far,[4] although the modification of this risk factor can lead to a significant reduction in the burden of cancer, since it has been estimated that more than 30% of the current cancer incidence can be prevented.[1, 5]

The aim of this review is to provide an overview of current knowledge about the effects of cancer screening on lifestyle and lifestyle-related morbidity. Furthermore, we discuss the opportunities on how to deal with possible unwanted effects of cancer screening.

4.2 CANCER SCREENING

Cancer screening is a major component of disease control and aimed at the early detection of malignancies that were not clinically manifest to possibly reduce cancer-specific mortality and to improve survival outcomes amongst asymptomatic people.[6] One characteristic of screening programmes is that relatively few people will have large benefits from screening, whereas relatively many will be exposed to small, unfavourable effects. Important is that the favourable effects (reduction in disease specific mortality, life-years gained) of screening should reasonably outweigh the harms (overdiagnosis, overtreatment, false-positive

screening result e.g.) caused by screening.[7] Relatively new is the question whether cancer screening might have an impact on future health related behaviour. Screening might be a teachable moment for health behavioural change,[8, 9] although screening might also have a health certificate effect to continue or even start unhealthy behaviour.[10, 11]

The impact of cancer screening on lifestyle

The unwanted effects of screening that have been measured are often limited to the direct physical, psychological and social harms, while the impact of cancer screening on lifestyle remains uncertain. A systematic review of studies on the impact of cancer screening on future lifestyle was conducted using two electronic databases (Pubmed, EMbase).[12] Search terms used were related to neoplasm, mass screening, impact, and lifestyle. To be included, articles must have quantified the impact of cancer screening on lifestyle amongst adults in the general population by repeated measurements. The articles must also have been published in English between 2000 and 2010. The initial literature search yielded 3106 articles. After reviewing the titles and abstracts, a total of 13 articles were identified for inclusion at this stage. Three articles were excluded after reviewing the full text. The references of the remaining articles were scanned, but no additional relevant articles have been found. One relevant article that was accepted for publication was added. The characteristics and the results of the reviewed publications are summarized in **Table 4.1 and 4.2**, respectively.

In the next part, we discuss the impact of colorectal and lung cancer screening on lifestyle first. Special attention has been paid to the impact of the screening test result on lifestyle and the possible role of the screening modality.

Colorectal cancer screening

Under-utilization of colorectal cancer screening has been reported regularly, even though the guidelines for colorectal cancer screening. Although there are nationwide differences, there are socio-demographic factors (male gender, marriage, higher socioeconomic status, e.g.), lifestyle factors (smoking history, chronic diseases, family history of colorectal cancer e.g.), and health care related factors (physician recommendation, health insurance coverage e.g.) that are associated with attending colorectal cancer screening.[13] Colorectal cancer screening is also more common amongst people with an increased health motivation who practiced more often other healthy behaviours.[14-16] One should recognize that an impact of cancer screening on future lifestyle choices might be influenced by the previous existing characteristics of attendees that are related to behaviour change.

Colorectal cancer screening and lifestyle changes

One of the leading causes of cancer incidence and death in developed countries is colorectal cancer.[17] Although there are effective screening strategies in reducing mortality from colorectal cancer,[18, 19] Parkin et al. stated that lifestyle modifications will contribute significantly to

Table 4.1. Characteristics of the reviewed articles that have been measured the impact of cancer screening on lifestyle.

First Author Ref No (Year) Country	1. Sample Size 2. Recruitment	Study population	Aim of the (sub) study	1. Screening 2. Screening intervention 3. Smoking cessation intervention
Ashraf et al.[25] (2009) Denmark	1) 2052 screen and 2052 control arm participants (RCT) 2) Recruitment by advertisements in local and regional free newspapers	50-70 years (mean 58 years) 44.8% females Current and former smokers Smoking history: > 20 pack-years, Quit smoking: < 10 years ago (if applicable) No lung cancer related symptoms or no previous treatment for several cancers Ability to climb 2 flights of stairs FEV1 at least 30% of predicted normal Body weight < 130 kg	Evaluation of the effect on smoking habits of screening with low dose CT.	1. Lung cancer screening 2. CT screening or no screening + lung function test 3. Minimal smoking cessation counselling
Anderson et al.[33] (2009) U.S.A.	1) 2078 participants 2) Referral by physician or self-referral by response to advertisements and study announcements in ambulatory health settings	Smoking history: > 10 pack-years Current and former smokers Fit to undergo thoracic surgery Symptom free volunteers No prior history of cancer	Examination whether consistently negative results during long term participation in a lung cancer screening program reduce cessation or increase relapse.	1. Lung cancer screening 2. Chest CT scan 3. Smoking cessation advice + provision of contact information of a telephone quit line
Cox et al.[30] (2003) U.S.A.	1) 901 current smokers and 574 former smokers 2) Recruitment by local and regional television and newspapers	50-85 years (mean 59 years) 48.4% women Current and former smokers Median smoking history: 45 pack-years Quit smoking: < 10 years ago (if applicable) No history of cancer last 5 years Mentally competent Fit enough to undergo surgery	Evaluation of smoking behavioural changes in current and former smokers after CT screening for lung cancer.	1. Lung cancer screening 2. CT screening

Table 4.1 (continued)

First Author Ref No (Year) Country	1. Sample Size 2. Recruitment	Study population	Aim of the (sub) study	1. Screening 2. Screening intervention 3. Smoking cessation intervention
Larsen et al.[20] (2007) Norway	1) 3598 (out of 6961) screen and 3462 (out of 7000) control arm participants (RCT) 2) Recruitment by population registry	50-55 years Males/females	Evaluation of lifestyle changes in a group individuals offered Flexible Sigmoidoscopy (FS) screening compared with a control group and also in relation to the screening outcome.	1. Colorectal cancer screening 2. FS or FS + Faecal Occult Blood Test (FOBT) or control
Hoff et al.[11] (2001) Norway	1) 400 screen and 399 control arm participants 2) Recruitment by population registries	50-59 years Average risk population	Evaluation of the long-term effects of informing participants about findings at FS screening *(RCT)*.	1. Colorectal cancer screening 2. With polyps or without polyps found by screening
MacRedmond et al. [31] (2006) Ireland	1) 449 participants 2) Recruitment by local media advertisements	Median age: 56.4 years (range 50-74) Smoking history: > 10 pack-years No prior history of cancer Fit enough for thoracic surgery	Evaluate whether low dose chest CT scanning (LDCCT) can detect early stage asymptomatic lung cancer in a high-risk urban population.	1. Lung cancer screening 2. CT screening 3. Smoking cessation advice + reinforcement at each follow-up + referral to smoking cessation group (only 1.3% accepted)
Ostroff et al.[27] (2001) U.S.A.	1) 134 smokers 2) Referral by physician or self-referral by response tvo advertisements and study announcements in ambulatory health settings	Mean age: 67 years 59.7% female Current smoker Mean number of cig/day: 25 Mean pack-years: 53 (range: 10-147 PY) No cancer history	Assessment of the impact of lung cancer screening participation on smoking cessation.	1. Lung cancer screening 2. CT screening
Styn et al.[29] (2009) U.S.A.	1) 2094 smokers 2) Recruitment by mass media, physician referral and mass mailings	50-79 years 65.2% heavy smokers 50.7% women No history of lung cancer Smoking history: 36-45 years	Examination of the smoking behaviour in relation to the report of CT abnormalities.	1. Lung cancer screening 2. CT screening

Table 4.1 (continued)

First Author Ref No (Year) Country	1. Sample Size 2. Recruitment	Study population	Aim of the (sub) study	1. Screening 2. Screening intervention 3. Smoking cessation intervention
Taylor et al.[9] (2006) U.S.A.	1) 144 participants from Lung Screening Study and 169 participants from National Lung Screening Trial 2) Recruitment mainly by mass mailings, although also other sources were employed.	55-74 years Current of former smoker Smoking history: > 30 pack-years No chest CT last 1.5-2 years No history of lung cancer No participation in a trial related to cancer	Exploration of the impact of screening on smoking cessation and readiness to stop smoking.	1. Lung cancer screening 2. CT screening
Townsend et al.[28] (2005) U.S.A.	1) 926 current smokers and 594 former smokers 2) Recruitment by local and regional television and newspaper media	> 50 years Current or former smoker Quit smoking: < 10 years (if applicable) Smoking history: > 20 pack-years Asymptomatic men and women No prior history of cancer last 5 years Mentally competent Stable health No serious illness or life expectancy < 5 years	Evaluation of the change in smoking behaviour of current and former smokers who have received three annual low-dose, fast spiral chest CT scan screenings for lung cancer. Identification of factors associated with smoking abstinence at three years of follow-up.	1. Lung cancer screening 2. CT screening
Van der Aalst et al.[26] 2010 The Netherlands	1) 641 and 643 smokers in the screen and control arm 2) Recruitment by population registry	50-75 years Current male smokers Smoking history: > 15 pack-years No current or recent history of cancer (treatment) Ability to climb 2 flights of stairs Body weight < 140 kg No chest CT scan last year	Investigation of the effect of lung cancer screening on smoking abstinence in male smokers.	1. Lung cancer screening 2. CT screening 3. Tailored advice or standard self-help brochure

Table 4.2. Results of the reviewed articles that have investigated the impact of cancer screening on lifestyle.

First Author (Year) Ref No	Follow-up	Results
Ashraf et al.[25] (2009)	1 year	Smoking behaviour: - Comparable smoking cessation (11.9% versus 11.8%; p=0.95) and relapse (10.0% versus 10.5%; p=0.81) rates in the screen and control arm, respectively. Predictors of smoking abstinence in baseline smokers (p<0.05): - Lower FEV1/FVC, lower cigarettes/day, lower pack-years, more time after waking up to the first cigarette (Q1 of FTND), higher motivation. Impact CT findings: - Higher quit rates amongst participants with positive CT result (17.7%) compared with no significant CT findings (11.4%) (p=0.04).
Anderson et al.[33] (2009)	6 years	Smokers with negative results were statistically significant less likely of being point prevalent abstinent compared to positive results. No statistically significant difference in prolonged smoking abstinence.
Cox et al.[30] (2003)	1 year	Smoking behaviour: - Current smokers: 14% smoking abstinent. - Former smokers: 99% smoking abstinent. Predictors smoking cessation: - Lower % FEV1 (OR=1,2/10% decrease; p=0.002). Predictors smoking abstinence: - Longer duration of smoking abstinence at time of baseline visit (OR=1.7/ 3 months of abstinence; p<0.001).
Larsen et al.[20] (2007)	3 years	Smoking behavioural change: - Smokers in the screen arm improved their smoking habits statistically significant less. Change in physical activity: - Control arm participants significantly increased the exercise. Change in nutritional intake: - Screening had only impact in the frequency of chocolate intake. Body weight: - Screen arm participants gained statistically significant more weight. Estimated effect size is moderate (0.77) for BMI and large (0.86) for weight. A negative screening outcome was only statistically significant associated with weight (and BMI) gain. Smoking habits, paid employment, physical exercise, and fruit, berries and vegetable intake remain unaffected. Screening was a statistically significant predictor only for weight gain after Bonferroni correction.
Hoff et al.[11] (2001)	13 years	Behavioural change: - Tendency that participants with polyps tended to reduce their smoking habits better (51% versus 38%; p=0.06) (net improvement). - Participants with polyps tend to have a smaller increase in BMI (0.7 versus 1.2; p=0.07).

First Author (Year) Ref No	Follow-up	Results
MacRedmond et al.[31] (2006)	2 years	Smoking behaviour: - 19.2% have quit smoking. - 1.6% has relapsed to continued smoking.
Ostroff et al.[27] (2001)	6 months	Smoking behaviour: - 23.1% quit smoking, 26.1% decreased smoking, 47.8% no change, and 2.9% increased smoking. Impact screening: - 73.9% stated that screening made them thinking about quitting. - 69% expected a beneficial effect of quitting. - 87% (of the quitters/decreased smokers): undergoing CT-screening had been major influence. Predictors of reduced/quit smoking: - Aged <68 years (OR=2.47, p<0.05), high cancer anxiety (OR=2.40, p<0.05), and perceived benefit (OR=4.02, p<0.01).
Styn et al.[29] (2009)	Median: 353 days after baseline CT scan	Smoking behaviour: - Any quit attempt: 58.5% - Any quit interval: 27.2% - Smoking abstinence for >30 days: 15.5% Impact abnormal CT findings - The quit rate increased after referral because of abnormal CT-findings.
Taylor et al.[9] (2007)	1-month after screening result	Smoking behaviour: - 7% quit smoking - 4% relapsed Stage of change transition: - NLST-sample: become more ready, but no impact of the screening result on smoking behaviour. - LSS-sample: younger participants (<64years) and an abnormal scan result tend to be associated with becoming less ready to stop smoking.
Townsend et al.[28] (2005)	3 years	Impact abnormal CT findings: - 19.8% abstinence after no abnormalities and 24.2%, 28.0%, and 41.9% after respectively 1, 2, or 3 abnormal CT results. Predictors of quit smoking: - Older age, worse pulmonary function, abnormal CT finding.
Van der Aalst et al.[26] (2010)	2 years	Smoking behaviour - Although all trial participants were more than average inclined to stop smoking, screening was associated with a lower prolonged abstinence rate (14.5%) compared to no screening (19.1%) (p<0.05).

further eliminate the incidence of colorectal cancer.[17] The impact of colorectal cancer screening on lifestyle was measured in one randomised controlled trial. The nutritional intake and body weight, physical activity, and smoking behaviour have been measured amongst 3598 screen arm and 3462 control arm participants of a randomised controlled colorectal cancer screening trial at baseline and after three years of follow-up.[20] The participants were invited for colorectal cancer screening by flexible sigmoidoscopy (FS), or FS and Faecal Occult Blood Test, or they received no colorectal cancer screening. Desirable lifestyle changes in dietary, physical activity and smoking behaviour were reported in both groups. However, the control arm participants reported modest, but significant better improved smoking habits ($p<0.05$), physical activity ($p<0.001$), and daily intake of fruits, berries and vegetables ($p<0.001$). The authors concluded that screening for colorectal cancer could possibly have a health certificate effect. There is only one study left in which Hoff et al.[11] evaluated the long term effects of informing participants about the findings at screening. These results will be discussed in the paragraph about the impact of the screening result on lifestyle changes.

Lung cancer screening and lifestyle changes

Lung cancer is the leading cause of cancer death and highly correlates with lifestyle, since 80% of the lung cancers can be attributed to the use of tobacco.[21] Ongoing screening trials are evaluating whether lung cancer screening using low dose Computed Tomography (CT) will reduce lung cancer mortality in a high risk population.[22-24]

Several studies focussed on the impact of lung cancer CT screening on smoking behaviour, although only two RCT were available. In one RCT, Ashraf et al.[25] found a quit rate of 11% amongst all baseline smokers, but the quit rates did not differ between participants in the screen (11.9%) and control (11.8%) arm. Thereby, there was no tendency that former smokers relapsed more often after CT screening for lung cancer. In contrast, Van der Aalst et al. found that, although all trial participants were more than average inclined to stop smoking, the smoking abstinence rate was modest, but significantly lower amongst those who underwent screening (14.5%) compared to the control group (19.1%).[26] In the observational studies,[9, 27-31] supportive quit rates between 7-23% were reported amongst participants 1-6 years after baseline screening. As we refer to the quit rates of 5-7% reported amongst adults in the general population, lung cancer screening seems to be an opportunity to enhance smoking cessation amongst long-term smokers. Encouraging is that almost three-quarter of the participants stated that screening made them thinking about giving up smoking and two-third believed that the abstinence from smoking would have a beneficial effect on their health. Most participants (87%) who had really changed their smoking behaviour reported that undergoing screening had been the major influence of their behavioural change.[27] Although the results suggested that screening for lung cancer could potentially enhance improvements in smoking behaviour, it remains uncertain whether screening might give unrealistic reassurance, because of the lack of randomized controlled trials. Limitations of the

observational studies are related to methodological implications, including different recruitment procedures, heterogeneity of the study population, small sample sizes, different study designs, and different outcome measures, what affects the comparison of the results and the overall level of evidence.

Influence of the screening test result

Whynes et al.[32] found that screening behaviour in a cervical cancer screening programme was driven by a search for reassurance. Receiving a negative screening result might provide a health certificate for participants who seek health control,[10] because participants seem to be falsely reassured. A reduced perceived threat might decrease the motivation for behavioural change after screening. Larsen et al.[20] have found a possible health certificate effect after a negative colorectal cancer screening result, since screened participants improved their lifestyle less compared to participant in the control arm. However, consistently negative screening results were not associated with reduced smoking abstinence amongst 2078 ELCAP participants who underwent CT screening for lung cancer and false reassurance played at most a minor role in health seeking behaviour after breast cancer screening.[33, 34] The other way around, receiving a positive test result might be a teachable moment for health behavioural change, because the personalized health-related feedback might override the optimistic bias and increase the motivation for health behavioural change.[8] Several studies found that a positive test result and referral for work-up and diagnosis were associated with desirable behavioural change. In one study, Hoff et al.[11] evaluated the long-term effects of informing average risk participants about findings after FS screening. Those who were informed about the presence of a polyp tended to improve their smoking habits and had a smaller increase in BMI than those who were informed that no polyps had been found. The impact of a false positives screening result on lifestyle changes has not been investigated so far, although the cumulative probability of a positive screening result after especially FOBT is relatively high and an impact on future lifestyle choices is not inconceivable.[35] After lung cancer screening, the smoking abstinence rate was also higher after referral to the physician because of abnormal CT screening result.[25, 29, 33] Although the screening result had no impact on smoking behaviour amongst ELCAP participants after one year of follow-up, smokers who received multiple positive screening results were significantly more likely to be abstinent from smoking after three screening rounds.[28] No impact of the screening result on future smoking behaviour was found amongst participants of the National Lung Screening Trial, although they became more ready to quit smoking.[9] Despite the inconsistencies, the results would suggest an important (educational) role for physicians and other health care providers. Screened participants seem to be at least more ready for behavioural change and therefore more receptive to health-related feedback and information about behavioural change that might induce risk-reducing health behaviour. Thereby, the psychological impact of screening increased after screening, but returns to baseline values after long term, which highlights the

need for adequate timing of health promotion. Thus far, there is no evidence-based approach to inform participants about the screening test result and the opportunities to combine cancer screening with health promotion interventions.

Could it be modality dependent?

Different modalities for cancer screening are available and one technique is more radical compared to others. Especially in colorectal screening, the burden differs amongst the modalities available, including Faecal Occult Blood Testing, FS, colonoscopy and double-contrast barium enema.[36] Marshal et al. described that modality attributes related to accuracy of the test (sensitivity and specificity) appeared to be more important for screening acceptance than the modality process (preparation, process and pain). On the other hand, the preferred screening test was characterized by a non-invasive process, no required preparation, no pain and a high accuracy of the screening test.[36] Despite that some modalities are uncomfortable and unpleasant, including FS and mammography, these have been well tolerated by screened participants.[37] Although the overall results of the impact of screening on future behaviour are comparable across the several cancer screening studies, there is a gap in current evidence about the possible impact of the screening modality on determinants of behavioural change. Although the exposure to radical technologies might increase the motivation to change unhealthy behaviour to prevent future diseases, one should recognize that the screening modality has most impact on screening (re-)attendance.[38] A screening programme using more radical modalities might reach fewer, but more motivated people.

The impact of screening on lifestyle-related morbidity

In cancer screening evaluation, the cancer specific mortality competes with dying from other diseases. The question is to what extent there is evidence about the side effect of cancer screening on lifestyle-related morbidity and mortality, because of the possible side effects of cancer screening on lifestyle. Studies reported that all-cause mortality was not affected by screening, suggesting that screening had no impact on all cause mortality. However, the review shows that there is insufficient data about the impact of cancer screening on lifestyle-related diseases and death. Further investigation is warranted to explore the impact of cancer screening on lifestyle changes and lifestyle-related diseases.

How to cope with this potential problem?

To understand the possible methods on how to cope with the potential unwanted effects of screening, we should refer to the theoretical concept of participation in a screening programme as described in the Health Belief Model.[39] The assumption is that people are afraid of diseases. Health behavioural change is influenced by the perceived risk and the expected reduction of this risk after risk reducing behaviour. The possible reduction in health risk should outweigh practical and psychological harms. The readiness for behavioural change

is influenced by internal (age, gender e.g.) and external (health education e.g.) factors. The so-called 'cue-to-action' refers to a factor that triggers behavioural change. The screening procedure, receiving the test result as well as the contact with health care providers might be a cue-to-action. These events possibly increase the cognitive availability of risk perceptions that overcome biases, the emotional responses that prompt vigilant attention and it might treat personal control or self-esteem by social stigmatization. However, it remains uncertain what action might be promoted: a healthy lifestyle or an unhealthy lifestyle.

In health promotion, lifestyle is an important determinant, because it is the most important modifiable cause of disease and premature death worldwide.[40] Participants of cancer screening programmes often have a healthier lifestyle compared to the non-participants,[14, 16, 41-46] while the lifestyle characteristics of attendees still require health promotion.[15-16, 47-63] This self selection suggests a potential for health promoting interventions to modify unhealthy behaviour in screening programmes, because participants seem to have a relatively higher health consciousness and motivation for health behavioural changes compared to non-participants. Screening might be a supplement to their health behaviour. However, one concern is that screening still might also be a health check for health risk behaviour.

Health promotion in a cancer screening programme

It might be an opportunity to combine efforts to both modify risk factors as well as the early detection of cancer in asymptomatic individuals to further eliminate the burden of cancer. However, current screening trials were often limited to no intervention, minimal self-help or counselling interventions. The efficacy of the health education intervention was investigated in only few trials (**Table 4.3**).[25, 64-66]

In the context of colorectal cancer screening, Baker and Wardle[64] investigated the efficacy of a short psycho-educational intervention for increasing fruit and vegetable intake that was personalized and tailored to the level of knowledge, attitudes, and individual behaviour. The intervention group (n=742) significantly increased their fruit ($p<0.001$) and vegetable intake ($p<0.001$) compared with the control group (n=309) after 6 weeks of follow-up. The intake increased from 25% to 42% in the intervention group, whereas the intake remained unchanged (26%) in the control group. Part of the efficacy of the intervention was attributed to individuals learning about sufficient nutritional intake, since participants had poor knowledge about the recommended daily intake. Although the study randomized screening participants who volunteered to receive the intervention, so that they are assumed to be more motivated for health risk reducing behaviour, the results suggest a potential for primary prevention measures in addition to cancer screening. However, it was unknown whether the behavioural changes remain over time, because it is well-known that behavioural change is a process rather than a state. The risk of relapse to unhealthy behaviour is reasonable after a short-term follow-up of 6 weeks.

Table 4.3. More detailed information about the reviewed articles that have explored interventions for promoting lifestyle in cancer screening programmes.

First Author (Year) Ref No Country	Sample Size	Characteristics participants	Screening; Screening intervention; Health promotion Intervention	Impact intervention	Follow-up	Relevant results
Baker et al.[64] (2002) UK	742 intervention and 309 control group participants	55-64 years 52% females	Colorectal cancer screening; Flexible sigmoidoscopy; Brief, tailored, psycho-educational intervention or control group	Fruit and vegetable intake, awareness, attitude	6 weeks	Intervention versus control arm: - Daily fruit intake increased with 0.59 servings versus 0.14 servings (p<0.001) - Daily vegetable intake increased with 0.47 servings versus 0.12 servings (p<0.001) - Total daily intake increased with 1.06 servings versus 0.26 servings
Clark et al.[65] (2004) United States	85 intervention and 86 standard group participants	51-74 years 46% females 60% heavy smokers Current smokers	Lung cancer screening; CT-scan; Written self-help materials (control) or internet sources for smoking cessation	Smoking behaviour	1 year	Intervention versus control arm: - Quit attempts: 68% versus 48% (p=0.001) - Point prevalence of smoking: 5% versus 10% (p=0.17) - Readiness to quit smoking: 27% versus 30% (p=0.70) - Review material: standard group is more likely to review all material (p=0.001)
McBride et al.[66] (1999) United States	288 intervention and 292 usual care participants	Mean age: 36.4 years Females Current smokers Participants cervical screening programme	Cervical cancer screening; Pap smear; Usual care or self-help smoking cessation kit	Smoking behaviour	6 and 15 months	Self-help intervention versus usual care: At 6 months; 15 months of follow-up - Point prevalence abstinence: p=0.56; p=0.17 - Quit attempt: p=0.29; p=0.62 Change between the follow-ups - Continuous abstinence: 4.7% versus 5.6%; p=0.38 - Smoking cessation: 12.1% versus 5.6%; p=0.02 - Relapse: 55.2% versus 48.8%; p=0.38

Clark et al.[65] investigated the effectiveness of smoking cessation self-help materials amongst 171 current smokers who underwent lung cancer CT screening. A standard written self-help material was compared with a standard list with internet-based resources about smoking cessation. After one year, participants who received the internet list reported more often a quit attempt, but there were no differences in point prevalence of smoking abstinence or a forward transition in the readiness to quit smoking. Another minimal self-help smoking cessation intervention was also evaluated amongst 288 women who currently smoked following cervical cancer screening.[66] The standard interventions included a self-help booklet, a smoking and reproductive health information card and three telephone counselling calls. Compared to 292 women in the control arm, the cessation rates were comparable after both 6 months as well as 15 months of follow-up.

Despite the few studies published so far, the results suggest an important role for tailoring interventions to promote health behaviour using a cost-effective approach. This had been confirmed by research in the general population before.[64-66] One major limitation of the current knowledge is the lack of evidence for the underlying process of lifestyle changes in cancer screening participants. Insight in the possible success factors and barriers is important for further implications for the development of sufficient interventions. These might also not be restricted to written tailored information. Important is that the cost-effectiveness of other lifestyle-related interventions effective in the general population, such as individual and group counselling or pharmacological interventions, should also be considered.

SUMMARY

Three major targets in cancer control are the prevention of the development of cancer, the early detection of preclinical malignancies and an adequate treatment of cancer patients to improve survival outcomes. The unwanted effects of cancer screening on future lifestyle are uncertain, while lifestyle is a major modifiable cause of cancer and premature death. Although the evidence is limited, this review shows that desirable lifestyle changes have been reported after both colorectal as well as lung cancer screening. However, unwanted effects of screening on lifestyle have also been reported amongst participants of a colorectal cancer screening programme. One should recognize that although cancer screening might be a teachable moment for health behavioural change, screening still might have a false health certificate effect to continue or start unhealthy behaviour. More randomised controlled trials are warranted to investigate the favourable and unfavourable effects of cancer screening on future lifestyle and whether health promotion is feasible in, and complementary to, cancer screening programmes in reducing the burden of cancer.

There is insufficient data to make judgements about the impact of cancer screening on health-related morbidity so far. It should be very important to verify whether the modification

of lifestyle-related behaviour due to screening will reduce or induce lifestyle-related morbidity and to explore the consequences of these lifestyle changes on the cost-effectiveness of cancer screening efforts.

Practice points

- Lifestyle is an important determinant of health, because it is the most important modifiable cause of disease and premature death worldwide.
- Cancer screening might have opportunities for lifestyle improvements, although the concern that remains is that screening provides a possible health certificate effect.
- Cancer screening might be a "teachable moment" for primary prevention measures to modify unhealthy lifestyles.

Research agenda

- The impact of different cancer screening programmes on lifestyle and lifestyle-related morbidity needs to be explored in randomised controlled trials to provide evidence about whether changes are attributable to screening.
- Studies are necessary to investigate cost-effective primary prevention interventions that could be complementary to cancer screening programmes.
- The impact of cancer screening on lifestyle-related morbidity and the effect on the cost-effectiveness of cancer screening programmes need to be clarified.

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CHAPTER 5

Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial.

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ABSTRACT

Background

Lung cancer screening may provide a new opportunity for attempts to quit among smokers or might delay smoking cessation, but studies to date failed to provide evidence for this. This study investigated the effect of lung cancer screening on smoking abstinence in male smokers participating in the Dutch–Belgian randomised controlled lung cancer screening trial (NELSON trial).

Methods

In the NELSON trial, 50- to 75-year-old participants at high risk for developing lung cancer were randomised to either lung cancer screening or no screening. Smoking behaviour was evaluated in two random samples of male smokers in the screen (n=641) and control arm (n=643) before (T0) and 2 years after randomisation (T1). In addition, the data were also analysed by intention-to-treat (ITT) analysis, as recommended in smoking cessation intervention trials, although non-response in screening trials can also be due to reasons other than continued smoking.

Results

Almost 17% (16.6%) of the trial participants quit smoking, which is higher than the 3–7% found in the general adult population. However, screening was associated with a lower prolonged abstinence rate (14.5%) compared with no screening (19.1%) (OR= 1.40, 95% CI: 1.01-1.92; $p<0.05$). No statistically significant difference was found after performing an ITT analysis.

Conclusions

This study showed that all trial participants were inclined to stop smoking more than average, which suggests that screening is a teachable moment to improve smoking behaviour. In those who underwent screening the smoking abstinence rate was significantly lower than for the control group, although the difference was modest. After ITT analysis this difference was no longer observed.

5.1 INTRODUCTION

Smoking is highly correlated with the development of lung cancer, the leading cause of cancer death worldwide.[1, 2] As approximately 80–90% of all cases are attributable to smoking,[2] the most effective way to reduce the risk for developing lung cancer substantially is to refrain from smoking.[3] Clinically diagnosed lung cancer is often in an advanced stage and occurs more often in former than in current smokers today, which highlights the need for further secondary preventive measures in addition to smoking cessation.[4] For that reason, in different randomised trials the cost-effectiveness of lung cancer screening by low-dose CT is being evaluated.[5, 6] Subjects who participated in a lung cancer CT screening trial showed a high interest in smoking cessation-related interventions, which provides new opportunities to approach this population for smoking cessation programmes.[7-10]

People eligible for lung cancer screening usually are of advanced age with a long and intensive smoking history and often smoking-related comorbid diseases.[11, 12] It is well known that these smokers are relatively less motivated to quit smoking and less often seek smoking cessation support,[13, 14] even though smoking cessation could lead to significant health benefits in this population.[15]

In several observational studies, participation in a lung cancer screening programme was found to be associated with smoking abstinence,[3, 9, 16] with cessation rates ranging between 7% and 23%,[7, 9, 17, 18] which is encouraging compared with a quit rate of between of 3% and 7% in the general adult population.[19] Ostroff et al. reported that 87% of the participants who changed their smoking behaviour stated that participation in the screening programme had been a major influence on their motivation to quit smoking.[7] The studies reported on this topic so far are difficult to compare,[7, 9, 10, 18] and one concern that remains is that lung cancer screening may act as a licence to smoke, because of the potential reassuring effect of screening.[7, 9, 18]

Only data from one randomised controlled trial (RCT) for lung cancer screening are available comprising 4104 participants (45% women); in this trial Ashraf et al. reported similar smoking behavioural changes in both trial arms after lung cancer screening.[20]

Our study is the first RCT on lung cancer screening that explored the smoking behaviour in both trial arms and where the control arm participants have never been invited to the screening site. The purpose of the study was to investigate the effect of lung cancer screening (screen arm) on smoking abstinence compared with no screening (control arm) among participants in the Dutch–Belgian randomised controlled lung cancer screening trial (NELSON trial) after 2 years of follow-up, and to identify the baseline characteristics associated with smoking abstinence.

5.2 METHODS

Study design

The study design of the NELSON trial has been described elsewhere.[6, 21] In summary, the volunteers who gave their informed consent (15,822) were randomised (1:1) to either the screen arm or the control arm. Participants in the screen arm received lung cancer screening according to the study protocol and the test result was based on a nodule management protocol.[6, 22] The participants in the control arm received usual care (no screening), without any invitation to the screening site. At randomisation, all current smokers in both study arms received a standard smoking cessation brochure or a questionnaire by which people could ask for tailored smoking cessation information from STIVORO, the Dutch expert centre on tobacco control. The standard brochure contained brief information about the advantages of quitting, the barriers to quitting, tips about how to quit smoking and how to prevent smoking relapse, and the possibilities for smoking cessation support. The questionnaire consisted of questions about smoking history, previous attempts to quit, attitude towards smoking cessation and self-efficacy in smoking abstinence.

The NELSON trial was approved by the Dutch Minister of Health after positive advice from the Dutch Health Council and by the Ethical Boards of the participating centres.

Study population

The NELSON trial

Information regarding the recruitment rounds and selection procedure of the NELSON population has also been described before.[6, 21, 22] In brief, people aged between 50 and 75 years with a smoking history of >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years, and who were current smokers, or former smokers who quit smoking <10 years ago, were invited to participate in the NELSON trial.[21]

The effect of lung cancer screening

The current study was conducted in a random subgroup of current male smokers randomised to the screen (n=641) or control (n=643) arm of the NELSON trial during the first recruitment period (**Figure 5.1**). A current smoker was defined as a participant who had smoked 7 days prior to completing the baseline questionnaire before randomisation (T0). Screened male smokers who received a positive scan result (n=53 (2.1%)) or who were off-study (n=163 (6.3%) in the screen arm and n=7 (0.3%) in the control arm) were excluded from this sample (**Figure 5.1**). The selected population (n=1284) received a second questionnaire to measure smoking behaviour in November 2006, which was 2.2 (SD 0.29) years after randomisation (T1).

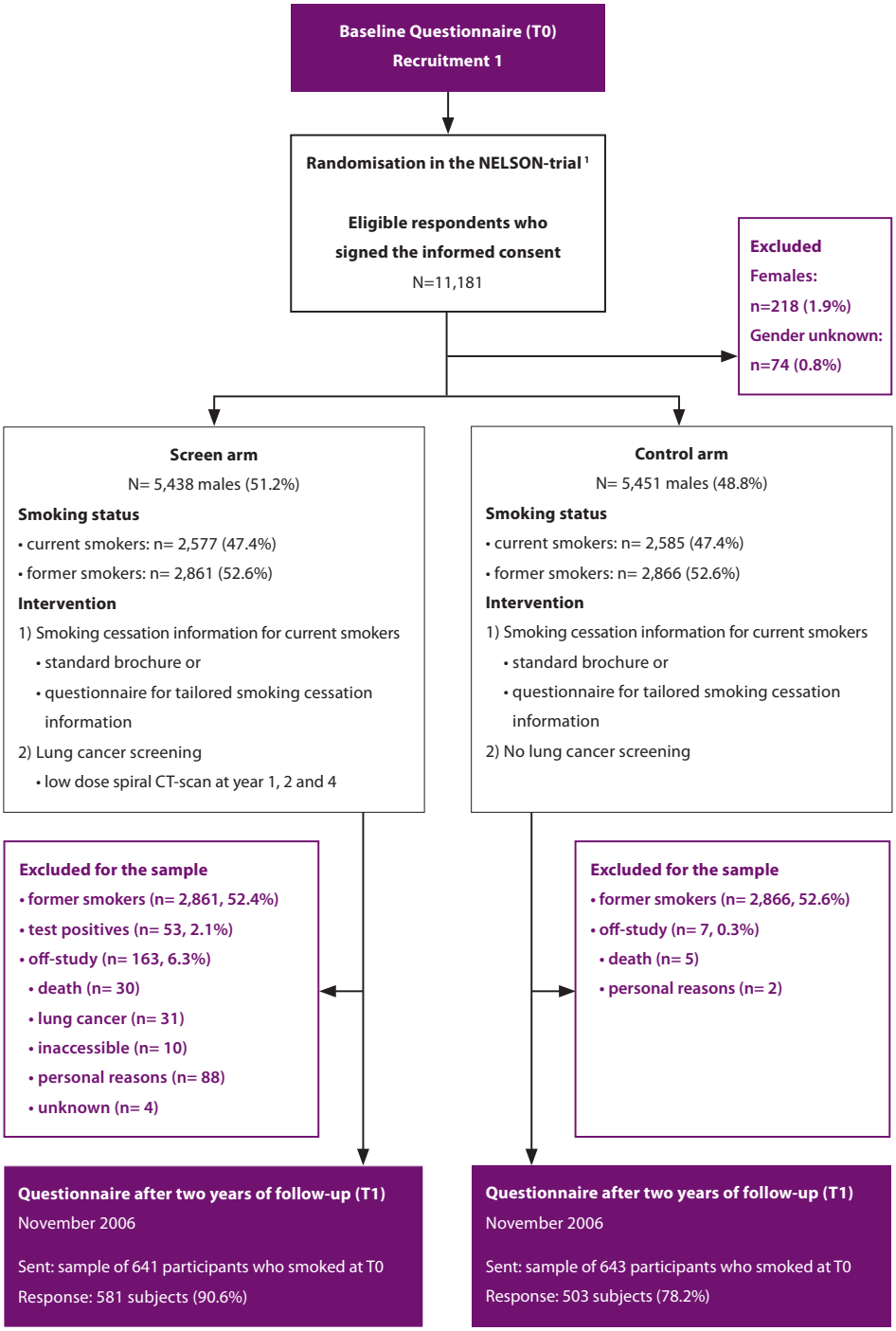

Figure 5.1. Study flow diagram.

[1] NELSON indicates Dutch-Belgian Lung Cancer Screening Trial

General questionnaire (T0)

The general questionnaire included demographic variables (date of birth, gender, level of education) and smoking-related variables.[21] The intention to quit smoking (8-point scale) was adapted from the Transtheoretical Model and recoded according to the stages of change. Respondents with no intention of quitting smoking within 1 year were classified as immotive, whereas precontemplators, contemplators and preparators reported an intention to quit smoking within 6–12 months, 1–6 months or 1 month, respectively.[23, 24] Other smoking-related items were the age of smoking initiation (8-point scale); the average number of cigarettes smoked a day (10-point scale); the number of years of smoking (9-point scale); and the time to the first cigarette after waking up. These last variables were recoded to a variable with 4–5 categories and into a continuous variable based on the mean value of each category. The last item is a measure of nicotine addiction and is adapted from the Fagerström Test for Nicotine Dependence (FTND).[24, 25]

Smoking cessation questionnaire (T1)

In addition to the questions at T0, we asked participants about their marital status/home situation and their smoking behaviour. Current smoking behaviour was measured by questions regarding whether participants still smoked (yes/no); the number of cigarettes, shag (rolling tobacco), cigar/cigarillos and/or pipe smoked a day; and whether they had smoked during the last 24 h (yes/no) and 7 days (yes/no) before completing the questionnaire.[24] Respondents who answered that they still smoked or who smoked in the last 7 days were classified as current smokers. In all other cases, they were regarded as point prevalent smoking abstinent. In addition, these participants were asked the following questions. 'Are you engaged in an attempt to quit at this moment (yes/no)?' 'What was the date of the attempt to quit (day/month/year)?' 'Have you smoked since this quit date (not at all/1–5 cigarettes/>5 cigarettes) and since 2 weeks after this quit date (not at all/1–5 cigarettes/>5 cigarettes)? 'How many attempts to quit lasting for at least 24 h have you made in the past?'[24] Former smokers who had smoked <5 cigarettes since 2 weeks after the quit date were classified as prolonged smoking abstinent, whereas former smokers who had smoked <5 cigarettes since the quit date were classified as continued smoking abstinent. All others were classified as current smokers all the time.[24] Prolonged smoking abstinence was the primary outcome measure of this study.[26] The self-reported smoking status was not biochemically verified.

To calculate the increase or reduction in smoking intensity, the numbers of cigarettes smoked at follow-up were recoded to the categories as measured at T0, which was the least exact measurement. Transitions through the categories were calculated; backward change was classified as reduced smoking, whereas forward change was classified as increased smoking. Otherwise, the smoking behaviour was defined as stable.

Statistical analyses

Power analysis indicated that a sample of 480 participants in the screen arm and 240 participants in the control arm would have 80% power to detect an expected difference in quit rates of 14% in the screen arm and 7% in the control arm. Similarities in distribution of the baseline characteristics in both trial arms were analysed using Pearson χ^2 statistics for categorical variables and the Mann–Whitney U test for continuous variables with a non-normal distribution. These tests were also used to explore differences in smoking behaviour in participants in the screen arm and control arm at T1. Both univariate and multivariate (backward) logistic regression analyses were performed to investigate whether baseline characteristics predict prolonged smoking abstinence at T1. In addition, the association between lung cancer screening and smoking abstinence was calculated by the 'intention-to-treat' (ITT) method (worst-case scenario) as recommended for smoking cessation intervention studies.[26] According to this method, non-responders are considered as current smokers.

The level of significance was set at 0.05 (two-tailed). The statistical package software R was used for the power analysis and all other statistics were performed using SPSS version 15.0.

5.3 RESULTS

Baseline characteristics of the participants

The response rates to the questionnaires were 90.6% (581/641) and 78.2% (503/643) for the screen arm and control arm, respectively (**Figure 5.1**). The median age of the respondents (n=1084) was 58 (IQR 7) years. Moreover, 892 of the 1084 participants (82.3%) lived together and 504 out of 1067 participants (47.2%) had a lower education level. The majority of the respondents had a smoking history of 31–50 pack-years (561/1084; 51.8%) and started smoking at the age of 15–20 years (704/1084; 64.9%). One hundred and seventy-nine smokers (179/1020; 17.5%) reported starting smoking <5 min after waking up, which reflects nicotine addiction. At T0, 40.8% (432/1058) of the smokers did not intend to stop smoking, while 15.6% (165/1058), 28.9% (306/1058) and 14.7% (155/1058) of the smokers had the intention to stop within 1 year (precontemplation stage of quitting), 6 months (contemplation stage) or 1 month (preparation stage), respectively (**Table 5.1**).

The baseline characteristics of the respondents to the subcohort questionnaire were comparable with the baseline characteristics of male smokers in the NELSON trial of the first recruitment round (**Table 5.1**). Furthermore, responders from the screen arm and control arm (**Table 5.1**), and responders and non-responders (data not shown) had similar baseline characteristics (no statistically significant differences).

Table 5.1. Baseline characteristics of the participants.

	Male smokers randomised in the NELSON-trial (1st recruitment)	**Male smokers responded to the smoking cessation questionnaire**	
	Total (n=5161)	**Screen arm** (n=581)	**Control arm** (n=503)
	N (%)[1]	N (%)[1]	N (%)[1]
Median age (IQR) y	58 (7)	57 (7)	58 (8)
Level of Education[2]			
Low educational level	2442 (48.0)	280 (49.3)	224 (44.9)
Medium educational level	1244 (24.5)	136 (23.9)	122 (24.4)
High educational level	1395 (27.5)	152 (26.8)	153 (30.7)
Marital status			
Married or living together	NA	475 (81.8)	417 (82.9)
Pack-years			
≤ 30 PY	1207 (23.4)	186 (32.0)	144 (28.6)
31-40 PY	1810 (35.1)	168 (28.9)	161 (32.0)
41-50 PY	1143 (22.2)	116 (20.0)	116 (23.1)
51-60 PY	540 (10.5)	66 (11.4)	47 (9.3)
> 60 PY	456 (8.8)	45 (7.7)	35 (7.0)
Starting age of smoking			
≤ 15 years	865 (16.8)	87 (15.0)	92 (18.3)
15 - 20 years	3337 (64.7)	392 (67.5)	312 (62.0)
> 20 years	955 (18.5)	102 (17.5)	99 (19.7)
Intention to quit smoking[3] (T0)			
Immotive	2003 (39.9)	229 (40.6)	203 (41.1)
Precontemplator	769 (15.3)	84 (14.9)	81 (16.4)
Contemplator	1504 (30.0)	173 (30.7)	133 (26.9)
Preparator	743 (14.8)	78 (13.8)	77 (15.6)
Time to the first cigarette[4]			
≤ 5 minutes	963 (19.7)	99 (18.1)	80 (16.9)
5 - 30 minutes	2000 (40.8)	206 (37.8)	205 (43.2)
30 minutes - 1 hour	1217 (24.9)	146 (26.7)	120 (25.3)
> 1 hour	717 (14.6)	95 (17.4)	69 (14.6)

IQR = interquartile range; NA = not applicable

[1] Available data were presented N (%) unless described otherwise.

[2] Low educational level indicates primary, lower secondary general or lower vocational education; medium educational level, intermediate vocational education or higher secondary education; high educational level, higher vocational education or university.

[3] Immotive indicates no intention to quit smoking within one year; pre-contemplator, intention to quit smoking within one year, but not within six months; contemplator, intention to quit smoking within six months, but not within one month; preparator, intention to quit smoking within the next month.

[4] First question of the Fagerström test for Nicotine Dependence (FTND).

Lung cancer screening and smoking behaviour

The smoking behaviour of the responders after 2 years of participation in the screening trial (T1) is presented in **Table 5.2**. No difference was found in the number of attempts to quit between the screen arm and control arm participants. At T1, respondents in the control arm reported a significantly higher point prevalence of smoking abstinence (OR=1.38; 95% CI: 1.01-1.90), as well as a higher prolonged (OR=1.40; 95% CI: 1.01-1.92) and continued abstinence rate (OR=1.42; 95% CI: 1.03-1.96) compared with the screen arm.

According to the ITT analysis, assuming that the non-respondents were current smokers, the point prevalence of smoking abstinence was 13.7% (88/641) and 15.5% (99/640) in the screen arm and control arm, respectively, after 2 years of follow-up (p=0.38). The prolonged and continued abstinence rates were, respectively, 13.1% (84/641) and 12.6% (81/641) in the screen arm and 14.9% (96/643) and 14.6% (94/643) in the control arm (p=0.35; p=0.30).

Complete data for the abstinence period were available for 75% (63/84) of the screened participants and 72% (69/96) of the control arm participants (**Table 5.2**). At T1, the median period of prolonged abstinence was 12.0 months in both trial arms. After 2 years of follow-up, the current smokers in the screen (n=497) and control (n=407) arm smoked 20 (IQR: 13–12, respectively) cigarettes a day (p=0.90). A similar proportion of current smokers in the screen (264/497; 53.1%) and control (219/407; 53.8%) arm reported having reduced their smoking intensity (p=0.23). In addition, 17.7% (88/497) and 13.8% (56/407) of the smokers increased their smoking intensity and 29.2% (145/497) and 32.4% (132/407) remained stable in the screen and control arm, respectively.

Table 5.2. Smoking behaviour of male smokers in the screen and control arm after two years of follow-up.

	Screen arm		Control arm		
	%[1]	N	%[1]	N	p value
Median number of quit attempts (IQR)	1 (2)	581	1(2)	503	0.47
Point prevalence of smoking abstinence[2]	15.1	88/581	19.8	99/500	0.04
Prolonged smoking abstinence[3]	14.5	84/581	19.1	96/503	0.04
Continued smoking abstinence[4]	13.9	81/581	18.7	94/503	0.03
Median duration of smoking cessation[5] (IQR) (months)	12.0 (17.0)	63	12.0 (15.5)	69	0.82

IQR = interquartile range

[1] Data is presented in % unless described otherwise.

[2] Point prevalence of smoking abstinence indicates that respondents did not smoke last seven days.

[3] Prolonged smoking abstinence indicates that respondents have smoked <5 cigarettes since two weeks after the quit date.

[4] Continued smoking abstinence indicates that respondents have smoked <5 cigarettes since the quit date.

[5] Results are based on available data of respondents who were former smokers at follow-up (T1).

Predictors of prolonged smoking abstinence

Univariate baseline characteristics associated with prolonged smoking abstinence at T1 were a higher educational level (p=0.01), an intention to quit smoking within 1–6 months and within 1 year (p=0.01), allocation to the control arm (p=0.04) and a time to the first cigarette

Table 5.3. Odds Ratio of baseline characteristics for prolonged smoking abstinence in male smokers two years after randomisation.

	Prolonged smoking abstinence	
	Univariate analysis OR (95% CI)	**Multivariate analysis OR (95% CI)**
Study arm		
Screen arm	1.00	1.00
Control arm	1.40 (1.01-1.92)*	1.45 (1.02-2.04)*
Age (T0)	0.99 (0.96-1.03)	
Level of education[1]		
Lower education	1.00	1.00
Medium education	1.27 (0.83-1.93)	1.29 (0.84-2.00)
Higher education	1.84 (1.26-2.67)*	1.66 (1.12-2.48)*
Starting age of smoking		
< 15 years	1.00	
16-19 years	1.20 (0.77-1.87)	
> 20 years	0.73 (0.41-1.31)	
No of cigarettes smoked a day	0.98 (0.96-1.00)	
Smoking duration (years)	1.00 (0.97-1.03)	
Time to the first cigarette[2]		
< 5 minutes	1.00	
5 - 30 minutes	1.68 (0.97-2.93)	
30 - 60 minutes	1.97 (1.10-3.51)*	
> 60 minutes	2.34 (1.26-4.33)*	
Intention to stop smoking (T0)[3]		
Immotive	1.00	1.00
Pre-contemplator	1.65 (1.02-2.69)*	1.60 (0.98-2.61)
Contemplator	1.93 (1.30-2.87)*	1.81 (1.20-2.73)*
Preparator	1.58 (0.96-2.60)	1.11 (0.61-2.00)

* statistically significant odds ratio (p < 0.05)

[1] Low educational level indicates primary, lower secondary general or lower vocational education; medium educational level, intermediate vocational education or higher secondary education; high educational level, higher vocational education or university.

[2] First question of the Fagerström Test for Nicotine Dependence (FTND).

[3] Immotive indicates no intention to quit smoking within one year; pre-contemplator, intention to quit smoking within one year, but not within six months; contemplator, intention to quit smoking within six months, but not within one month; preparator, intention to quit smoking within the next month.

of >60 min and 30–60 min (p=0.05) (**Table 5.3**). The age, the age at starting smoking, the number of cigarettes smoked a day or the smoking duration were not statistically significant predictors of prolonged smoking abstinence at follow-up (**Table 5.3**).

Multivariate analysis (**Table 5.3**) showed that only an intention to quit smoking within 1–6 months (p=0.03), a higher educational level (p=0.04), and allocation to the control arm (p=0.04) were significantly associated with prolonged smoking abstinence at follow-up.

5.4 DISCUSSION

The high smoking abstinence rate observed among those screened (14.5%) has also been reported in previous observational studies.[7-10, 18, 20] This abstinence rate is positive in comparison with the 3–7% quit rates observed in adults of the general population after a minimal intervention for smoking cessation.[19] This is very encouraging, since screening trial participants are usually elderly people with a long and intense smoking history for whom it is difficult to make an attempt to quit.[11, 14] Despite this high abstinence rate among those screened, control arm participants reported modest but significantly higher smoking abstinence rates.

In contrast to our findings, Ashraf et al. found no effect of the allocation to the screen or control arm on smoking habits,[20] which could probably be explained by the fact that both screen and control arm participants were invited to the screening site for spirometry and minimal smoking cessation counselling offered by a specialised nurse each year. This might have mitigated the effect of CT screening on smoking behaviour, and could explain the lack of any difference in smoking behaviour changes between both trial arms.[10] The strengths of our study are that all smokers in our study received limited written smoking cessation information only once at randomisation, and that control arm participants were never invited to the screening site.

Data analysis according to the ITT method is generally recommended for the evaluation of smoking cessation intervention studies.[26] Ashraf et al. also used this method to analyse their data.[20] When we applied this method, we also found no statistically significant difference in smoking abstinence between the screen and control arm. However, we believe that it is appropriate to exclude non-responders, because non-response of NELSON participants can reasonably also be explained by reasons other than continued smoking, such as loss of interest in screening for lung cancer. Furthermore, people are more likely to under-report their smoking intensity rather than their smoking status.[27] Therefore, we believe that despite the lower response rate observed in the control arm, allocation to the screen arm may lead to lower quit rates as compared with the control arm. Our concern is, therefore, that screening may create some relief among smokers based on false confidence.[7] This unfavourable effect of screening on smoking cessation has not been reported in the context of lung cancer screening before. Only Larsen et al. reported less improvement in smoking habits among

screened individuals in a colorectal cancer screening trial.[28] Furthermore, we found that half of the current smokers reduced their smoking intensity and that the other half did not change or even increased their smoking intensity after lung cancer screening. We should realise, however, that we were able to detect only large changes in smoking intensity, because of the wide categories used and because in reality even more people might have increased their smoking intensity.

These results emphasise the need to improve smoking habits in lung cancer screening programmes. So far, there is no evidence-based approach to how to integrate the promotion of the abstinence from smoking in lung cancer screening programmes. More research is warranted to identify the most cost-effective intervention and the best method to frame the intervention in lung cancer screening programmes. Important issues to explore are the best type of intervention, the optimum teachable moment(s) and whether the test result could be used as biofeedback to enhance quitting smoking.

A limitation of our study is that the data originate from self-completed questionnaires without biochemical verification of the smoking status, with the risk of social desirability response bias. However, self-reports on smoking behaviour appeared to be valid in a lung cancer screening setting.[29] The recruitment was based on population registries, but randomised people volunteered to participate in the lung cancer screening trial. These volunteers were possibly more motivated to quit smoking compared with the general adult population.[13] We excluded male smokers randomised to the screen arm with a positive test result from the sample that was selected for the sub study, because of the low prevalence (2.1%) of this test result in the study population after the introduction of the indeterminate test result by the NELSON trial. This probably may have caused a small underestimation of the smoking cessation rate in participants in the screen arm, because a positive test result might motivate subjects to quit smoking.[10, 18, 20] When we adjust for the exclusion of the people with a positive test result,[20] the prolonged smoking abstinence rate in the screen arm was comparable and had no impact on the results. Another limitation is that this sub study was restricted to men, but, based on past research, we presume that the effect of lung cancer screening is similar for males and females at high risk for developing lung cancer.[10, 18, 20]

Although we demonstrated an association between lung cancer screening participation and smoking abstinence, more research is warranted that explores whether this relationship is causal, because few available studies are available so far.

This study showed that all trial participants were inclined to stop smoking more than average, which suggests a teachable moment to improve smoking behaviour. In those who underwent screening the smoking abstinence rate was significantly lower than for the control group, although the difference was modest. After ITT analysis, this difference was no longer observed.

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CHAPTER 6

The impact of a lung cancer computed tomography screening result on smoking abstinence.

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ABSTRACT

Background

Receiving a lung cancer computed tomography screening result might be a teachable moment for smoking cessation, but it might also unintentionally reassure smokers to continue smoking. The objective of the present study was to investigate whether test results were associated with smoking abstinence in the Dutch–Belgian Randomised Controlled Lung Cancer Screening Trial (NELSON trial).

Methods

Two random samples of male smokers who had received either only negative test results (n=550) or one or more indeterminate test result (n=440) were sent a questionnaire 2 yrs after randomisation.

Results

Smokers with an indeterminate result reported more quit attempts (p=0.02), but the prolonged abstinence rate in smokers receiving a negative test (46 (8.9%) out of 519 subjects) was comparable with the abstinence rate in smokers with one or more indeterminate results (48 (11.5%) out of 419 subjects) (p=0.19). A statistically insignificant increase was found after one or more indeterminate test result (10.9 and 15.0%, respectively) compared with receiving only negative test results (8.9%) (p=0.26).

Conclusions

In conclusion, the outcome of the screening test had no impact on future smoking abstinence in male smokers, although all results suggest more favourable implications after one or more follow-up recommendations. Screening test outcomes could be used as a teachable moment for smoking cessation.

6.1 INTRODUCTION

Lung cancer, the leading cause of cancer deaths, is often diagnosed at an advanced stage and occurs increasingly amongst former smokers,[1] which underline the need for preventive measures. Several randomised screening trials are evaluating the (cost-) effectiveness of lung cancer computed tomography (CT) screening in reducing lung cancer mortality.[2, 3] Even though the population eligible for lung cancer screening usually has a long-term smoking history,[4] significant health benefits might be achieved by smoking cessation, even in this high-risk population.[5, 6] However, resistance to quitting smoking is high in this population[7] and this group of smokers is often underrepresented in smoking cessation interventions.[8]

Healthcare events, such as receiving an abnormal test result or an unfavourable medical diagnosis, might be teachable moments that increase the motivation to quit smoking.[8-11] So far, there is no strong evidence that people at high risk for lung cancer who receive an abnormal lung cancer screening test result will be more prone to quit smoking than those with a normal test result or vice versa. A single baseline CT test result appeared to have no impact on smoking abstinence rates or change in smoking behaviour in studies by Anderson et al.,[12] Cox et al.,[13] Ostroff et al.,[14] and Taylor et al.[15]. In contrast, the number of multiple abnormal lung cancer screening test results was positively associated with smoking cessation in the Mayo Clinic trial after 3 yrs of follow-up.[16] Ashraf et al.[17] and Styn et al.[18] also found a higher quit rate after a positive test result or referral to a physician, and Ostroff et al.[14] concluded that participation in lung cancer screening programmes had a major impact on smoking behavioural changes, and that participants were convinced of the health benefits of smoking cessation.

In most lung cancer CT screening trials, the number of subjects with a positive test result that require referral for work-up and diagnosis is high.[13-16] In the Dutch–Belgian Randomised Controlled Lung Cancer Screening Trial (NELSON trial), we used a novel strategy for the management of lung nodules.[3] After an indeterminate test result, a recall CT scan to assess nodule growth was introduced. This new approach led to a substantial reduction in the number of positive tests and, therefore, fewer referrals to the pulmonologist for work-up, without losing significant diagnostic performance.[3] This novel strategy might also have a different effect on smoking behaviour changes compared with the current nodule management algorithms. Therefore, our objective in the present study was to investigate whether the CT screening test result (negative versus indeterminate) was related to future smoking abstinence amongst 50–75-yr-old male smokers who participated in the NELSON trial. In addition, we investigated whether the number of indeterminate screening test results was associated with an increased quit rate and aimed to identify baseline characteristics associated with prolonged smoking abstinence after 2 yrs of follow-up.

6.2 MATERIALS AND METHODS

Study population

NELSON trial

The recruitment and selection procedure of the NELSON study participants has been described previously.[19] In summary, based on population registries, 15,822 eligible people aged 50–75 yrs, who signed the informed consent, were randomised to the screen or control arm (1:1) in two recruitment rounds. Participants eligible for the NELSON trial were current or former smokers who had smoked >15 cigarettes a day for >25 yrs or >10 cigarettes a day for >30 yrs. Former smokers should have quit smoking for ≤10 yrs.

Participants in the screening arm underwent screening by low-dose, multidetector CT in years 1, 2 and 4, and no screening was offered to control arm participants. The screening results were either positive, indeterminate or negative according to our nodule management strategy.[3] A positive test result was classified as: 1) a solid nodule with a volume >500 mm^3; 2) a solid, pleural-based nodule with a diameter >10 mm; or 3) partially solid, of which the solid component measured >500 mm^3. An indeterminate test result was classified as: 1) a solid nodule with a volume of 50–500 mm^3; 2) a solid, pleural-based nodule with a diameter of 5–10 mm; 3) a partially solid nodule with either a nonsolid component of >8 mm mean dimension or a solid component of 50–500 mm^3; or 4) a nonsolid nodule with a diameter of ≥8 mm. In all other cases, the test result was negative. People with a positive screening result were informed about their referral to a pulmonologist by phone, whereas those with either an indeterminate or a negative screening result received only a standard letter explaining that radiologists had or had not found an abnormality. An indeterminate screening result was not classified as a positive screening result, because participants with an indeterminate test result received a letter which was formulated very carefully to avoid possible psychological consequences often reported after a (false-)positive test result. The letter stated: "We have observed a very small abnormality in your lung (5–10 mm long). Such a small abnormality is often detected in many persons and it usually represents a small scar or a minor inflammation. Therefore, at this moment there is no need for any further investigations. However, in order to see whether there has been any change in this abnormality, a new CT scan of the lungs will be made after 3 to 4 months.".

Smoking cessation information from STIVORO, the Dutch expert centre on tobacco control, was sent to all current smokers at randomisation. Current smokers received a standard brochure with brief information about how to quit smoking or a questionnaire for tailored smoking cessation information.

The NELSON trial was approved by the Ministry of Health, Welfare and Sports after positive advice of the Dutch Health Council, and by the Medical Ethics Committees of the participating centres.

Effect of a CT screening result on smoking cessation

The current study was conducted in a random sub cohort of two samples of male screening arm participants who were current smokers before randomisation and were randomised in the NELSON trial during the first recruitment round. Participants who had smoked in the 7 days before completing the general questionnaire before randomisation (T0) were classified as current smoker. The random samples included only participants who had received either only negative test results ("test negatives"; n=550) or at least one indeterminate test result followed by a recommendation for recall CT screening after 3 months ("test indeterminates"; n=440).

Male screening arm participants with a positive test result at follow-up (n=53, 2.1%) or those who went off-study (because of, for example, unavailability, personal reasons, lung cancer or death; n=163, 6.3%) were excluded from these samples.

The selected population received a second questionnaire about their actual smoking habits (mean ± SD) 2.2 ± 0.29 yrs after trial randomisation (T1) and 1.8 ± 0.35 yrs after receiving their baseline test result (**Figure 6.1**). At follow-up, the test negative group had undergone 2 ± 0.25 (only regular-round) CT scans and the test indeterminate group 3 ± 0.47 (including regular and recall scans) CT scans.

Measures

T0: baseline questionnaire

Participants were asked about their age, sex and level of education. Their smoking history was assessed using questions about: age of smoking onset (8-point scale); average number of cigarettes smoked a day during the years of smoking (10-point scale); and the years of smoking during their lifetime (9-point scale).[19] The last two variables were recoded into variables with five and four categories, respectively, and into a continuous variable based on the mean value of each category. The intention of quitting smoking was adapted from the Transtheoretical Model and classified according to the stages of change.[20, 21] Respondents who had no intention to quit smoking in the near future were defined as immotives, whereas contemplators, pre-contemplators and preparators reported an intention to quit smoking within 6–12 months, 1–6 months or 1 month, respectively.[20, 21] Nicotine addiction was estimated using the first question of the Fagerström Test for Nicotine Dependence (FTND), which asked for the time to the first cigarette after waking up (<5, 5–30, 30–60 or >60 min).[21, 22]

T1: smoking cessation questionnaire

The second questionnaire included additional questions about the smoking habits at 2 yrs of follow-up. Current smoking behaviour was measured by asking the participants whether they usually smoked (yes/no), whether they had smoked during the previous 24 h (yes/no) and/or 7 days (yes/no). Respondents who reported smoking and/or who had smoked in the previous week were defined as current smokers, whereas others were defined as point prevalent abstinent from smoking.[23]

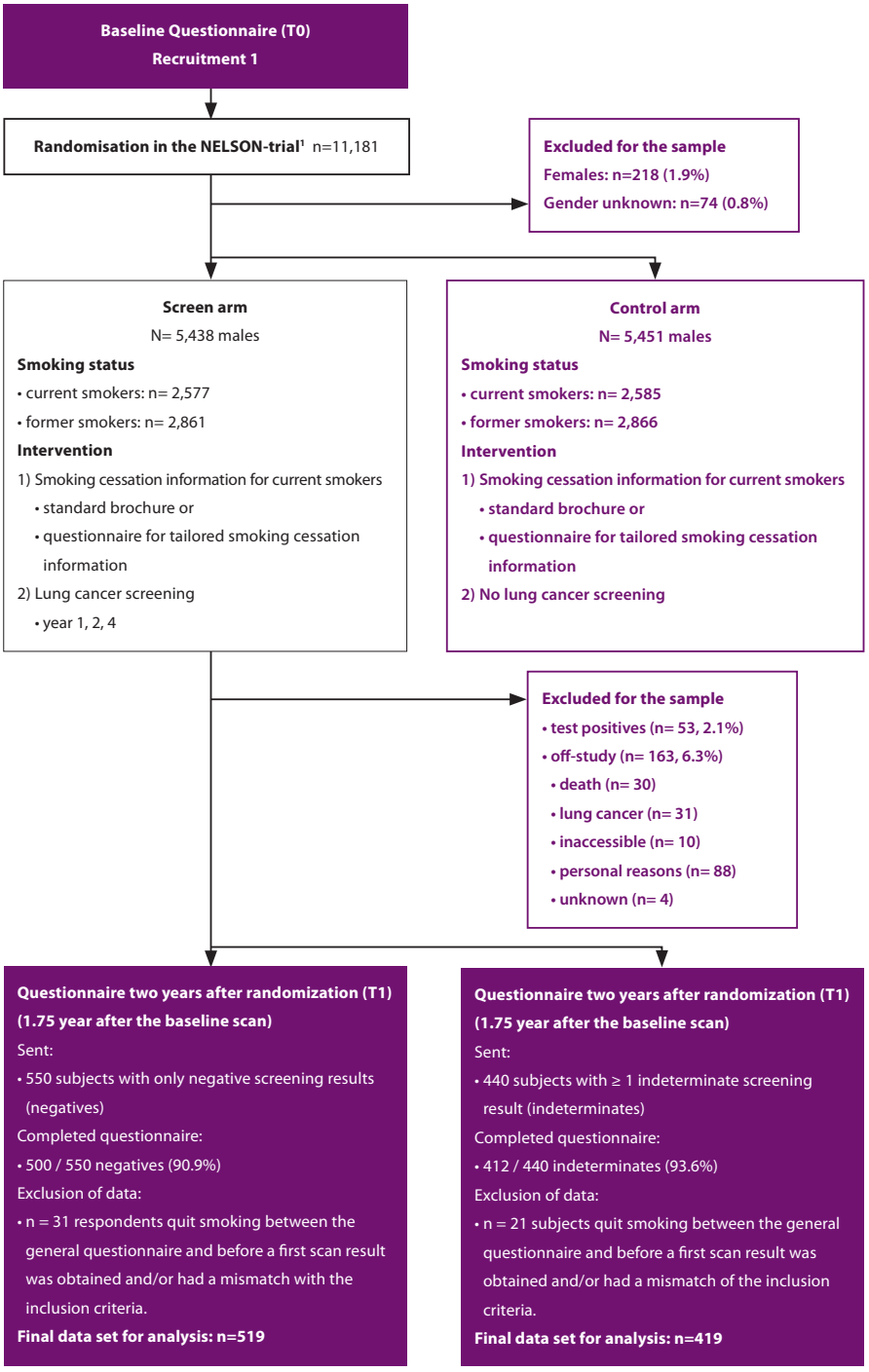

Figure 6.1 Study Flowchart.

[1] NELSON indicates Dutch-Belgian Lung Cancer Screening Trial

To measure smoking abstinence, participants were asked about the number of quit attempts in the last year and whether they were engaged in a quit attempt at that time (yes/no). Former smokers were asked about the date of quitting smoking (day/month/year) and whether they had smoked (not at all, 1–5 cigarettes or >5 cigarettes) since the quit date and 2 weeks after the quit date.[23, 24] Former smokers who had smoked <5 cigarettes since the quit date were classified as continued smoking abstinent, while former smokers who had smoked <5 cigarettes 2 weeks after their quit date were defined as prolonged smoking abstinent. Those who smoked >5 cigarettes were classified as current smokers.[23, 24] The smoking intensity at T1 was recoded into the categories of the number of cigarettes smoked at T0 (least precise). The transition through these categories was calculated and classified as stable, reduced smoking (lower category) or increased smoking intensity (higher category).

Statistical analysis

In order to detect an expected quit rate of 5–7% amongst smokers in the test negative group and 20% amongst smokers in the test indeterminate group[16, 25] with a power of 100%, the required sample size enrolled in each group was 400 participants.

Continuous variables with a normal distribution are presented as mean ± SD and skewed continuous variables are presented as median (interquartile range).

The differences in distributions of baseline characteristics between male smokers of the first recruitment and the subgroups, between the two subgroups and between the respondents and non-respondents of each subgroup were analysed using Pearson's Chi-squared test for nominal or categorical variables and the Mann–Whitney-U test for continuous variables with a non-normal distribution. The non-respondents were classified as current smoker and included in the analysis.[24]

Differences between former smokers in the negative and indeterminate group were analysed using the Mann–Whitney U-test, unpaired t-test or Chi-squared statistics as appropriate. The effect of the screening result on prolonged smoking abstinence was analysed using both univariate as well as multivariate unadjusted backward stepwise logistic regression analyses using the likelihood ratio test. The variables related to the test results, level of education, motivation to quit smoking and the time to the first cigarette (FTND) were included as categorical variables, while the other variables were included as continuous variables.

Results with a p-value ≤ 0.05 were defined as statistically significant. The power analysis was calculated using the statistical software package R (The R Project, Institute for Statistics and Mathematics, Vienna University of Economics and Business, Vienna, Austria). The remaining statistics were performed using the SPSS statistical software package version 15.0 (IBM, Somers, NY, USA).

6.3 RESULTS

Characteristics of the participants

The response rates to the questionnaires were 90.9% (500 out of 550 subjects) and 93.6% (412 out of 440 subjects) for those who received only negative test results and those who received at least one indeterminate test result, respectively (**Figure 6.1**). 52 participants were excluded from all further analyses either because they had quit smoking between completion of the general questionnaire before randomisation and their first CT screening test result (n=31, 3.1%) or because of a mismatch with the inclusion criteria (male current smokers at randomisation) (n=21, 2.1%). The response was higher in the negative group compared with the indeterminate group (7.5 versus 4.3%; p=0.04), although there was no non-response bias (p>0.05).

The baseline characteristics of the subsamples were representative for the male smokers of the first recruitment of the NELSON trial and the participants of both groups were comparable with regard to baseline characteristics (no statistically significant differences) (**Table 6.1**). Mean ± SD age was 57.9 ± 5.0 and 58.6 ± 4.9 yrs in the test negative and indeterminate group, respectively. A total of 49.0% (249 out of 508) of the test negatives and 53.7% (220 out of 410) of the test indeterminates had a low level of education. Participants with and

Table 6.1 Baseline characteristics of the participants of the NELSON trial and the respondents of the sub-cohort.[1]

	Male smokers randomised in the screen arm of the NELSON trial (1st recruitment)	**Male smokers responded to the smoking cessation questionnaire**		
		Total [2]	***Test Negatives***	***Test Indeterminates***
Age	58.0 ± 4.9	58.0 ± 5.0	57.9 ± 5.0	58.6 ± 4.9
Level of education				
Low educational level	48.3 (1223/2532)	49.9 (463/928)	49.0 (249/508)	53.7 (220/410)
Medium educational level	24.3 (615/2532)	23.9 (222/928)	24.0 (122/508)	23.7 (97/410)
High educational level	27.4 (694/2532)	26.2 (227/863)	27.0 (137/508)	22.6 (93/410)
Number of cigarettes a day				
≤ 15 cigarettes	26.1 (673/2576)	29.5 (280/948)	29.7 (154/519)	28.9 (121/419)
16-20 cigarettes	27.2 (701/2576)	26.2 (248/948)	25.4 (132/519)	29.4 (123/419)
21-25 cigarettes	27.0 (696/2576)	27.0 (256/948)	27.9 (145/519)	23.2 (97/419)
> 25 cigarettes	19.6 (506/2576)	17.3 (164/948)v	17.0 (88/519)	18.5 (78/419)
Smoking duration				
≤ 35 years	26.0 (669/2575)	24.9 (236/948)	25.2 (131/519)	23.7 (99/418)
36-40 years	33.9 (874/2575)	34.8 (330/948)	35.3 (183/519)	33.0 (138/418)
41-45 years	28.2 (726/2575)	28.4 (269/948)	27.7 (144/519)	31.1 (130/418)
> 45 years	11.9 (306/2575)	11.8 (112/948)	11.8 (61/519)	12.2 (51/418)

Table 6.1 (continued)

	Male smokers randomised in the screen arm of the NELSON trial (1st recruitment)	Male smokers responded to the smoking cessation questionnaire		
		Total [2]	*Test Negatives*	*Test Indeterminates*
Pack-years				
≤ 30 pack-years	29.7 (766/2575)	31.3 (297/948)	31.4 (163/519)	31.1 (130/418)
31-40 pack-years	28.3 (729/2575)	29.5 (280/948)	29.5 (153/519)	29.7 (124/418)
41-50 pack-years	22.1 (586/2575)	20.5 (194/948)	20.4 (106/519)	20.8 (87/418)
51-60 pack-years	10.8 (277/2575)	10.5 (99/948)	10.8 (56/519)	9.1 (38/418)
> 60 pack-years	9.1 (235/2575)	8.2 (77/948)	7.9 (41/519)	9.3 (39/418)
Starting age of smoking				
< 15 years	17.0 (437/2575)	15.6 (148/948)	15.0 (78/519)	18.1 (76/419)
15-20 years	64.7 (1665/2575)	68.4 (648/948)	69.7 (362/519)	62.3 (261/419)
> 20 years	18.4 (473/2575)	16.0 (152/948)	15.2 (79/519)	19.6 (82/419)
Time to the first cigarette[3]				
< 5 minutes	19.8 (484/2442)	18.8 (169/898)	17.9 (88/492)	22.8 (90/395)
5 - 30 minutes	40.3 (983/2442)	39.0 (350/898)	38.6 (190/492)	40.5 (160/395)
30 minutes -1 hour	25.3 (617/2442)	27.3 (245/898)	28.5 (140/492)	22.5 (89/395)
> 1 hour	14.7 (358/2442)	14.9 (134/898)	15.0 (74/492)	14.2 (56/395)
Motivation to quit smoking				
Immotive	40.0 (993//2485)	40.8 (374/918)	41.4 (208/503)	38.2 (154/403)
Precontemplator	15.6 (388//2485)	14.6 (134/918)	14.7 (74/503)	14.1 (57/403)
Contemplator	30.5 (759//2485)	39.4 (279/918)	29.4 (148/503)	34.8 (140/403)
Preparator	13.9 (345/2485)	14.2 (130/918)	14.5 (73/503)	12.9 (52/403)

Data were presented as % (n/N), mean ± sd, unless stated otherwise.
Test Negatives: male smokers who received only negative test results, Test Indeterminates: male smokers who received at least one indeterminate test result.
Low educational level indicates primary, lower secondary general or lower vocational education; medium educational level, intermediate vocational education or higher secondary education; high educational level, higher vocational education or university.
Immotive indicates no intention to stop smoking within 1 year or later; precontemplator, intention to stop smoking within 6-12 months; contemplator, intention to stop smoking within 1-6 months; preparator, intention to stop smoking within the next month.
[1] No selection and/or non-response bias was found ($p > 0.05$).
[2] Data is weighted to correct for the actual distribution of negative and indeterminate screening results in the screen arm.
[3] First question of the Fagerström Test for Nicotine Dependence (FTND).

without a follow-up recommendation had a comparable smoking history between 31–60 pack-yrs (60.7% (315 out of 519) versus 59.6% (249 out of 418), respectively). 70% (362 out of 519) of the test negatives and 62.3% (261 out of 419) of the test indeterminates started smoking between 15–20 years of age, and 58.6% of the test negatives and 61.8% of the test

indeterminates reported an intention to quit smoking. A high level of nicotine addiction was reported in 17.9% (88 out of 492) of the test negatives and 22.8% (90 out of 395) of the test indeterminates (p=0.04), as estimated by subjects smoking their first cigarette within 5 min after waking up.

Table 6.2. Smoking behaviour of male smokers who have received either only negative screening results (*negatives*) or at least one indeterminate screening result (*indeterminates*).

	Test Negatives	*n*	Test Indeterminates	*n*	*p-value*
Number of quit attempts	1.5 ± 2.0	*376*	1.9 ± 2.7	*312*	*0.016*
Point prevalence of smoking abstinence					*0.39*
Continued smoking	89.6	*465/519*	87.8	*368/419*	
Smoking abstinence	10.4	*54/519*	12.2	*51/419*	
Prolonged smoking abstinence					*0.19*
Continued smoking	91.1	*473/519*	88.5	*371/419*	
Prolonged smoking abstinence	8.9	*46/519*	11.5	*48/419*	
Continued smoking abstinence					*0.23*
Continued smoking	91.1	*473/519*	88.8	*371/419*	
Continued smoking abstinence	8.9	*46/519*	11.2	*47/419*	
Follow-up period after quit date[1] Median (IQR) (in months)	9.0 (10.9)	*40*	7.6 (11.0)	*40*	*0.30*
Time between last regular screening result and quit date[1] Mean (SD) (in months)	7.0 ± 4.2	*40*	6.7 ± 3.8	*40*	*0.74*
Time between baseline scan and quit date[1] Mean (SD) (in months)	12.3 ± 7.2	*40*	13.4 ± 7.8	*40*	*0.50*
Last scan round before quit date[1]					*0.50*
Scan round year 1	50.0	*20/40*	42.5	*17/40*	
Scan round year 2	50.0	*20/40*	57.5	*23/40*	
Number of cigarettes a day[2]		434		*353*	*0.37*
Median (IQR)	20 (13)		20 (12)		
Reduced smoking[2]					
Increased smoking	18.4	*80/434*	14.7	*52/353*	
No change	29.7	*129/434*	30.3	*107/353*	
Reduced smoking	51.8	*225/434*	55.0	*194/353*	

Negatives indicate the group participants who received only negative screening results; Indeterminates indicate the group participants who received at least one indeterminate screening result, NA not applicable.
Data were presented as % (n/N), mean ± sd, or median (interquartile range), unless stated otherwise.
[1] The results are based on data of former smokers with complete data of the quit date.
[2] The results are based on data of respondents who smoked at follow-up.

Screening test results and smoking abstinence

After 2 yrs of follow-up, smokers who received only negative test results had made fewer quit attempts compared with smokers who received at least one follow-up recommendation (1.5 ± 2.0 versus 1.9 ± 2.7 attempts; p=0.016).

No statistically significant differences were found in smoking abstinence rates between the test negative and test indeterminate group.

Point prevalence of smoking abstinence was reported in 54 (10.4%) out of 519 and 51 (12.2%) out of 419 subjects (p=0.39), prolonged smoking abstinence in 46 (8.9%) out of 519 and 48 (11.5%) out of 419 subjects (p=0.19), and continued abstinence in 46 (8.9%) out of 519 and 47 (11.2%) out of 419 subjects (p=0.23) in the negative and indeterminate groups, respectively (**Table 6.2**). Prolonged abstinence rates slightly increased with an increased number of indeterminate test results, from 46 (8.9%) out of 519 subjects after only negative test results to 39 (10.9%) out of 359 subjects after one indeterminate result, and to nine (15%) out of 60 subjects after two or more indeterminate test results, but this did not reach statistical significance (p=0.26) (**Figure 6.2**).

Former smokers had quit smoking for 9.0 (10.9) and 7.6 (11.0) months in the test negative and indeterminate groups, respectively (p=0.30). The time frame between receiving the last regular test result and the quit date was also comparable for both groups (7.0 ± 4.2 and 6.7 ± 3.8 months, respectively; p=0.74) (**Table 6.2**).

Furthermore, we found comparable smoking habits among test negatives and test indeterminates who still smoked after 2 yrs of follow-up (p=0.37) (**Table 6.2**). After multivariate testing, only the addiction to nicotine predicted the prolonged abstinence from smoking significantly (p=0.006) (**Table 6.3**).

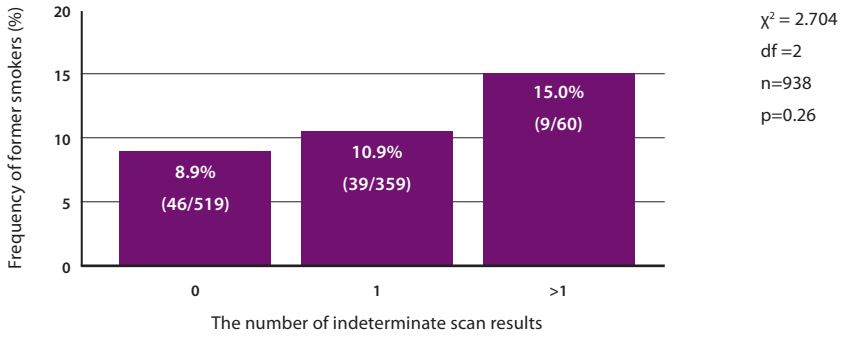

Figure 6.2. The quit rates of male smokers in relation to the number of indeterminate screening result(s) after two years of follow-up.

Table 6.3. The univariate and multivariate predictors of prolonged smoking abstinence.

	Prolonged smoking abstinence			
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Test result				
Only negative test results	1.00			
≥ 1 indeterminate test result	1.33 (0.87 - 2.04)	0.19		
Test result in the last 12 months				
Negative test result	1.00			
Indeterminate test result	1.26 (0.48 - 3.30)	0.64		
Age	1.02 (0.98 - 1.07)	0.31		
Level of education [1]				
Low educational level	1.00	0.09		
Medium educational level	1.14 (0.65 - 1.98)	0.65		
High educational level	1.73 (1.06 - 2.84)	**0.029**		
Cigarettes smoked a day	0.99 (0.96 - 1.02)	0.40		
Smoking duration (years)	1.01 (0.97 - 1.06)	0.53		
Starting age				
< 15 years	1.00	0.09		
15 - 20 years	1.70 (0.88 - 3.29)	0.12		
> 20 years	0.95 (0.40 - 2.27)	0.91		
Time to the first cigarette [2]				
< 5 minutes	1.00	**0.005**	1.00	**0.006**
5 - 30 minutes	1.99 (0.96 - 4.09)	0.06	1.94 (0.94 – 4.00)	0.08
30 - 60 minutes	1.26 (0.56 - 2.85)	0.58	1.28 (0.56 – 2.89)	0.56
> 60 minutes	3.42 (1.56 - 7.51)	**0.002**	3.39 (1.55 – 7.45)	**0.002**
Intention to stop smoking (T0) [3]				
Immotive	1.00	0.55		
Precontemplator	0.80 (0.38 - 1.66)	0.55		
Contemplator	1.25 (0.75 - 2.07)	0.39		
Preparator	1.32 (0.69 - 2.51)	0.40		

[1] Low educational level indicates primary, lower secondary general or lower vocational education; medium educational level, intermediate vocational education or higher secondary education; high educational level, higher vocational education or university.

[2] First question of Fagerström Test for Nicotine Dependence (FTND).

[3] Immotive indicates no intention to stop smoking within one year or later; precontemplator, intention to stop smoking within 6-12 months; contemplator, intention to stop smoking within 1-6 months; preparator, intention to stop smoking within the next month.

6.4 DISCUSSION

The results of our study demonstrated that the lung cancer screening test result (negative or indeterminate) had no statistically significant impact on future smoking abstinence amongst male smokers randomised in the NELSON trial. Nevertheless, all outcome parameters were more favourable for smokers who received at least one indeterminate test result, with a nonsignificant increased quit rate after multiple follow-up recommendations. The findings are supported by the studies of Anderson et al.,[12] Cox et al.,[13] Ostroff et al.,[14] and Taylor et al.,[15] who demonstrated no statistically significant impact of the test result on smoking cessation. The small, but insignificant, increase in the abstinence rates after multiple indeterminate test results was more or less in line with Townsend et al.,[16] who found a positive association between the number of follow-up recommendations and the smoking abstinence rate.

It is expected that this nonsignificant higher quit rate in test indeterminates is a result of the teachable moment of the follow-up procedure. It should be noted that the majority of the smokers who received one or more indeterminate test results also received one or more negative test result during follow-up, which might underestimate the impact of an indeterminate test result as a teachable moment. That aside, we found that, although the overall quit rate amongst all participants of the NELSON trial was higher than we could expect from the quit rate in the general adult population, the proportion of smoker in the control arm who quit smoking was modest, but statistically significantly ($p < 0.05$) higher compared with screen arm participants after logistic regression analysis. This raised some concern that lung cancer screening might have a health certificate effect.[26] This means that lung cancer screening might give some participants an unrealistic feeling of reassurance, which leads to continued smoking or even smoking relapse (licence to smoke). From the present study, we cannot conclude whether the outcome of the test is related to smoking relapse. We expected only a limited effect, because Anderson et al.[12] reported no increase in smoking relapse after consecutive negative test results compared with referral to the pulmonologist.

A combined approach for both primary and secondary prevention efforts to optimise cancer control is a relatively new research area, and evidence-based guidelines have yet to be published. More research is needed to investigate the opportunities for lung cancer screening in current, as well as former, smokers in order to promote health risk-reducing behaviour change and to prevent relapses,[27] and to investigate what the most cost-effective approach is in this screening population.

When interpreting our results, several limitations of the present study should be considered. First, people with a positive test result were excluded from this sample, because of the low prevalence of positive test results in the screening arm (2.6%) as a result of our NELSON nodule management strategy. An indeterminate test result combined with a recommendation for a recall CT scan as a teachable moment is expected to be less powerful compared

with a positive test result, because referral to a pulmonologist for work-up and diagnosis might have more impact on smoking habits compared with receiving our letter with a recommendation for a recall CT scan. This might explain the different outcome of our study compared with the results of Styn et al.,[18] who compared those who were referred because of an abnormal CT screening result with those who were test negative.

Another limitation is that our results were restricted to male smokers, because of the low proportion of females in the NELSON trial (16%). Although there is no evidence that the impact of participation in a lung cancer screening on smoking behaviour is sex-dependent,[13, 16-17] our results can only be generalised to male smokers who have undergone CT screening for lung cancer until there is more evidence that CT screening for lung cancer will have no different impact on smoking habits amongst females.

The data were also based on self-completed questionnaires without the biochemical verification of smoking status. This may introduce a social response bias that could affect the impact of CT screening on smoking habits, although it is unlikely that this bias would differ according to screening result. We also assume a limited risk of social response bias since a valid self-reported smoking status was found in a lung cancer screening programme.[28]

Therefore, our participants were screened for lung cancer instead of participating in a trial that investigated the impact of a smoking cessation intervention. Nevertheless, we would recommend further investigation of whether self-reported smoking behaviour is valid and reliable amongst participants of a lung cancer screening trial.

Finally, our results were based on a small sample of current smokers only with the aim of limiting all possible interventions, besides CT screening for lung cancer, in the first year of the trial. The difference in observed smoking abstinence was substantially lower, so that a significant difference could have been missed due to small sample size. Retrospectively, the required sample size for each group to detect the observed quit rates should be 2,500 for a power of 80%.

In conclusion, the outcome of the screening test had no statistically significant impact on future smoking abstinence in male smokers, although all results suggests more favourable implications after one or more follow-up recommendation.

Lung cancer screening test outcomes might provide a teachable moment for smoking cessation.

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CHAPTER 7

Smoking behavioural change in male smokers of a randomised controlled lung cancer screening (NELSON) trial: 4-year follow-up.

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Submitted

ABSTRACT

Background

Lung cancer screening might be a teachable moment for smoking cessation or a possible health certificate effect. A previous analysis indicated that smokers in the screen arm of the Dutch-Belgian lung cancer screening (NELSON) trial were less likely to refrain from smoking compared with control arm participants after 2 years of follow-up. Aim of the current study is to investigate whether this result persists after 4 years.

Methods

Two random samples were selected of 50-75 years old male smokers randomised to the screen (n=641) or control arm (n=643) of the NELSON trial. Smoking behavioural change was investigated from randomisation (T0) to 4 years of follow-up (T2). Differences in smoking behaviour and predictors of prolonged smoking abstinence were investigated. Data was analyzed according to the intention-to-treat in addition.

Results

Responses were 88.2% and 65.1% in the screen and control arm. Data was weighted for non-response bias in control arm participants. At T2, prolonged smoking abstinence rates were 24.3% (screen arm) and 29.3% (control arm) ($p=0.09$). Multivariate analysis showed that lower baseline nicotine dependency and randomisation to the control arm increased the likelihood of being abstinent from smoking at follow-up ($p<0.05$).

Conclusions

In conclusion, male smokers who received CT screening for lung cancer and who were more addicted to nicotine were less likely to refrain from smoking, although the impact is limited. Adequate treatment of nicotine addiction would be of special importance to maintain the abstinence from smoking to further eliminate tobacco related health problems in male smokers participating in lung cancer screening.

7.1 INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide and at the same time a largely modifiable cause of cancer death.[1-2] Although refraining from smoking is the most effective prevention method,[3-4] the need for the early detection of lung cancer is highlighted by the severe 5-years overall survival rate (16%) in patients with clinically diagnosed lung cancer and the high lung cancer incidence in former smokers.[5-6]

In lung cancer screening trials, it is important to investigate whether the potential benefits of lung cancer screening weight out the potential harms caused by screening.[7] Cancer screening might be a teachable moment for health promotion,[8] but screening might also unintentionally reassure smokers (health certificate effect), which might affect health behaviour negatively.[8-13]

Few observational studies investigated the impact of lung cancer screening on smoking behaviour and supportive abstinence rates (7-23%) were found in this context.[11-12, 14-16] Participants of the Early Lung Cancer Action Program (ELCAP)[8] also reported an increased motivation to quit smoking one month after lung cancer screening and the majority (87%) of the participants of the National Lung Cancer Screening Trial (NLST)[12] stated that screening was an important factor to change their smoking behaviour. In the Danish randomised lung cancer screening trial, one found comparable smoking habits in screen and control arm participants after one year of follow-up (11.9% versus 11.8%; p=0.95).[17] In contrast, a previous evaluation in our trial, the Dutch-Belgian randomised controlled lung cancer screening (NELSON) trial, demonstrated that male smokers who were randomised to CT screening for lung cancer reported lower smoking abstinence rates compared with smokers randomised to no screening (usual care) after two years of follow-up (14.5% versus 19.1%; p=0.04).[10] With the aim to judge whether and what kind of additional smoking related interventions should be offered to screened smokers, it is important to know whether the health certificate effect of screening is consistently over time or whether it was a temporary phenomenon. The current study is the first study that investigates changes in smoking behaviour in male smokers randomised to CT screening for lung cancer (screen arm) or usual care (control arm) (NELSON trial) after 4 years of follow-up. In addition, baseline variables that predict the prolonged abstinence from smoking will be identified.

7.2 METHODS

NELSON trial

This study was conducted in a subsample of participants of the NELSON trial. A more detailed description of the recruitment procedure and the selection of the study participants were described previously.[18-20] In summary, based on population registries, 15,822 mainly males

aged between 50-75 years with a smoking history of >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years, who were current smoker or former smoker who quit smoking <10 years ago, and who signed the informed consent were randomised (1:1) to the screen or control arm in two recruitment rounds. Participants in the screen arm received CT screening for lung cancer, while the participants in the control arm received usual care (no screening). A nodule management strategy was developed based on volume and volume doubling time to decide whether a nodule is suspicious malignancy.[19-20] The CT screening test results could be negative, indeterminate or positive. Those with an indeterminate or a negative screening result received a standard letter explaining that radiologists had or had not found a suspicious abnormality. An indeterminate test result was followed by repeat CT screening. People with a positive screening result were informed about their referral to a pulmonologist by phone. All current smokers were randomised (1:1) to receive a standard brochure or a tailoring questionnaire to provide tailored smoking cessation information at randomisation.

The NELSON trial was approved by the Dutch Minister of Health after a positive advice of the Dutch Health Council as well the Ethical Boards of the participating centres.

Smoking cessation study

Two random subsamples of current smokers randomised in the screen (n=641) and control arm (n=643) of the NELSON trial during the first recruitment round were selected for the smoking cessation study (**Figure 7.1**).[10] A current smoker was defined as someone who had smoked for 7 days prior to completing the questionnaire before randomisation (T0). Male smokers who were off-study (n=163; 6.3% in the screen arm; n=7; 0.3% in the control arm) or who received a positive screening result (n=53; 2.1%) were excluded from this sample (**Figure 7.1**). Two questionnaires about smoking behaviour were sent to both samples (n=1284) 2.0 (IQR=0) years and 4.0 (IQR=1) years after randomisation (T1 and T2, respectively). During the follow-up period, a total of 49 screen arm participants were excluded for follow-up (off study: n=42; positive screening result: n=7). In the control arm, 58 (9.0%) participants were lost to follow-up.

Questionnaires

The general questionnaire (T0) was sent before randomisation and measurements of demographics (date of birth, gender, level of education) and smoking history (starting age of smoking, number of cigarettes smoked, years of smoking, the stage of change, smoking last 7 days and a estimated nicotine dependency) were included, as stated previously.[18]

The follow-up questionnaires (T1, T2) were highly comparable and aimed to measure the actual smoking behaviour.[10] Three types of smoking abstinence were distinguished, namely point prevalence of smoking abstinence, prolonged smoking abstinence and continued smoking abstinence.[21]To determine these concepts, the participants were asked whether they usually smoke (yes/no), and whether they smoked the last 24 hours (yes/no) and the last 7 days (yes/no) before completing the questionnaire.

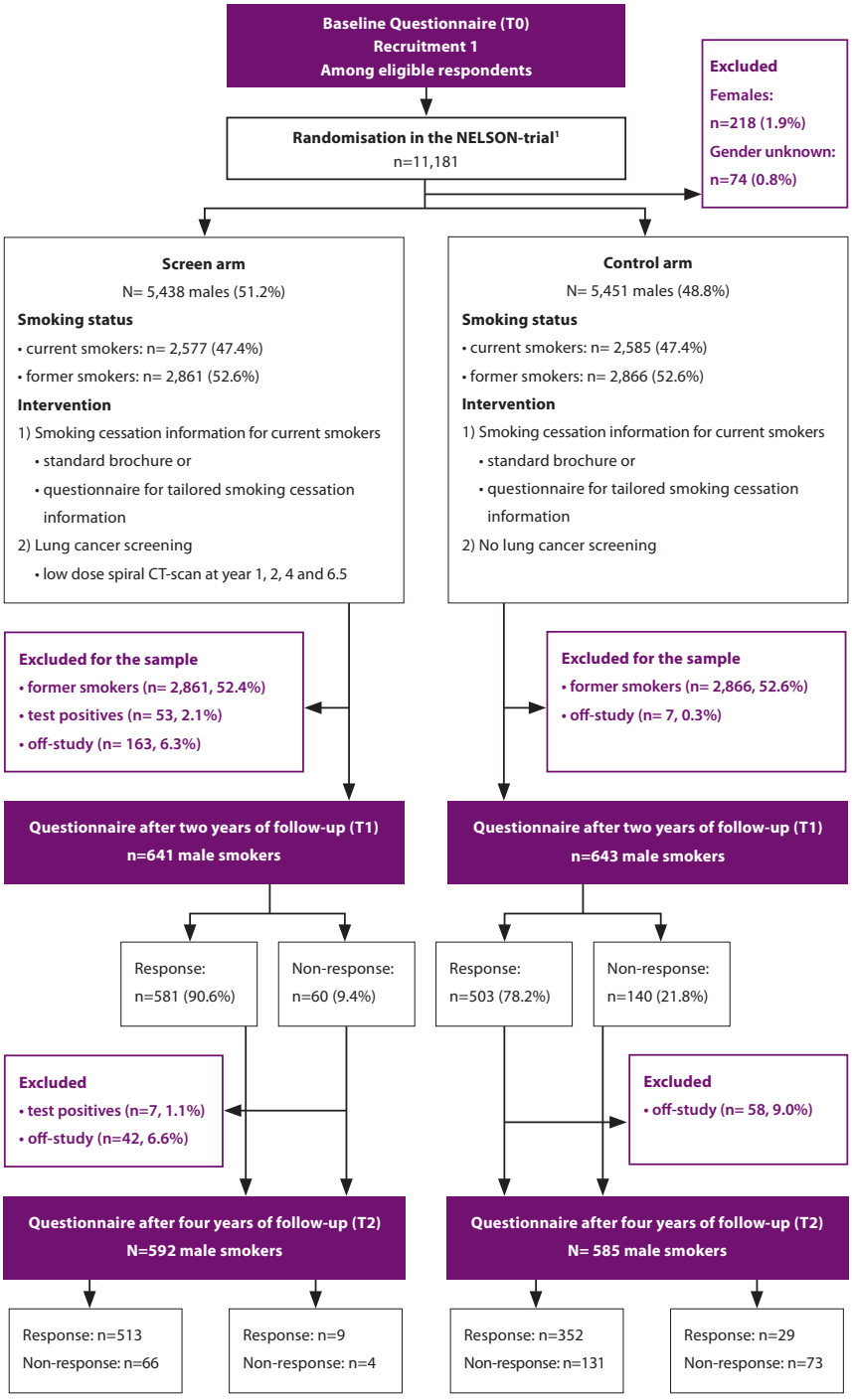

Figure 7.1. Flowchart NELSON participants in the sub-study.

[1] NELSON indicates Dutch-Belgian Lung Cancer Screening Trial

Point prevalence of smoking abstinence was defined when respondents did not usually smoke and when they did not smoke in the past 7 days. These participants were asked: "Are you currently attempting to quit smoking (yes/no)?"; "When did you make your quit attempt? (day/month/year)?", and "Have you smoked since (two weeks after) this quit date (not at all/1-5 cigarettes/> 5 cigarettes)?". Prolonged smoking abstinence was defined as 'having smoked no more than five cigarettes since two weeks after the quit date', whereas continued smoking abstinence required that the participant had smoked no more than five cigarettes in total since the quit date. In all other cases, the respondents were classified as current smoker.[21] The self-reported smoking status was not biochemically verified. Finally, participants were asked to rate the number of quit attempts.

Statistical analysis

Differences in baseline characteristics (T0) and differences in smoking behaviour (T2) between both subsamples were analyzed using Chi-square statistics and non-parametric statistics, as appropriate. Data was weighted for level of education to correct for non-response bias in the control arm. The impact of lung cancer screening was measured by using the intention-to-treat analysis.[21-22] Univariate and multivariate backward logistic regression analysis were performed using maximum likelihood ratio test to investigate the predictors of prolonged smoking abstinence. SPSS version 17.0 was used for all statistical analyses. A p-value of less than 0.05 was considered as statistically significant.

7.3 RESULTS

Study participants

A total of 88.2% (522/592) and 65.1% (381/585) of the male smokers responded to the questionnaire at 4-year follow-up (p<0.01) (**Figure 7.1**). Fewer respondents in the control arm had a lower level of education than non-responders (41.8% versus 53.5%) (p=0.026) and data was weighted. Median ages at randomisation of the participants were 57 and 58 (IQR: 7) years in the screen and control arm. A total of 47.8% of the respondents had a lower education and the median number of pack-years smoked was 38.0 in both trial arms. A total of 41.3% of the responders were not intended to quit smoking in the next future at randomisation. However, 12.2% (62/509) and 16.0% (60/376) were intended to quit smoking within one month in the screen and control arm, respectively. The remaining 44.8% (228/509) and 42.0% (158/376) of the smokers contemplated to quit smoking next year. Furthermore, it was estimated that a comparable part of the participants in the screen (17.8% (88/493)) and control arm (18.8% (68/361)) had a severe nicotine addiction. Control arm participants started smoking at younger age (<15 years) compared to screen arm participants (18.3% versus 14.8%) (p=0.034) (**Table 7.1**).

Table 7.1. Baseline characteristics of the NELSON participants included in the analysis.

	Screen arm		Control arm*		
	(%)	n / N	(%)	n / N	p-value
Median age (IQR) (years)	57 (7)	522	58 (7)	379	0.51
Level of Education[1]					0.94
Low educational level	47.8	245 / 513	47.8	181 / 378	
Medium educational level	25.5	131 / 513	24.7	93 / 378	
High educational level	26.7	137 / 513	27.5	104 / 378	
Cigarettes per day (IQR)	18 (10)	522	18 (10)	381	0.91
Smoking duration (IQR) years	38 (10)	522	38 (5)	381	0.84
Pack-years (IQR)	38 (18)	522	38 (16)	381	0.88
Intention to quit smoking[2] (T0)					0.10
Immotive	41.3	210 / 509	41.3	155 / 376	
Precontemplator	13.9	71 / 509	16.6	62 / 376	
Contemplator	32.6	166 / 509	26.1	98 / 376	
Preparator	12.2	62 / 509	16.0	60 / 376	
Time to the first cigarette[3] (T0)					0.60
≤ 5 minutes	17.8	88 / 493	18.8	68 / 361	
5 - 30 minutes	38.3	189/ 493	42.0	152 / 361	
30 minutes - 1 hour	26.4	130/ 493	23.7	86 / 361	
> 1 hour	17.4	86/ 493	15.5	56 / 361	
Starting age of smoking					**0.034**
< 15 years	14.8	77 / 522	18.3	70 / 381	
15 – 20 years	69.0	360 / 522	60.7	231 / 381	
> 15 years	16.3	85 / 522	21.0	80 / 381	

IQR = interquartile range

* Data is corrected for non-response bias with respect to the level of education.

[1] Low educational level indicates primary, lower secondary general or lower vocational education; medium educational level, intermediate vocational education or higher secondary education; high educational level, higher vocational education or university.

[2] Immotive indicates no intention to quit smoking within one year; pre-contemplator, intention to quit smoking within one year, but not within six months; contemplator, intention to quit smoking within six months, but not within one month; preparator, intention to quit smoking within the next month.

[3] First question of the Fagerström Test for Nicotine Dependence (FTND).

Smoking behaviour

At 4 years of follow-up, the point prevalence of smoking abstinence in the screen arm (24.6%; 127/516) was borderline significant lower compared to the control arm (29.7%; 111/374) (p=0.09) (**Table 7.2**). This trend was also found in the prolonged and continued smoking abstinence rates of 24.3% (126/519) and 29.3% (110/375) in the screen and control arm respectively (p=0.09) (**Table 7.2**).

Table 7.2. Smoking behaviour of male participants at 4-year of follow-up (T2) [1].

	Screen arm		Control arm		
		n/N		n/N	p-value
Point prevalence of smoking abstinence					0.09
Smoking abstinence (%)	24.6	127 / 516	29.7	111 / 374	
Current smoking (%)	75.4	389 / 516	70.3	263 / 374	
Prolonged smoking abstinence					0.09
Prolonged smoking abstinence (%)	24.3	126 / 519	29.3	110 / 375	
Continued smoking (%)	75.7	393 / 519	70.7	265 / 375	
Continued smoking abstinence					0.09
Continued smoking abstinence (%)	24.3	126 / 519	29.3	110 / 375	
Continued smoking (%)	75.7	393 / 519	70.7	265 / 375	
Smoking behaviour change at follow-up *(T1 vs. T2)*					0.67
Quitting (prolonged abstinence) (%)	13.5	70 / 519	12.5	47 / 376	
Stable (%)	84.2	437 / 519	85.9	323 / 376	
Relapse (%)	2.3	12 / 519	1.6	6 / 376	
Number of quit attempts at follow-up mean (sd)	1.6 (2.3)	386	1.8 (3.4)	265	0.58
Period of being abstinent from smoking at 4 years of follow-up Mean (months) (sd)	17.8 (17.1)	122	22.0 (18.5)	108	0.12

[1] Data is weighted for non-response bias.

Between T1 and T2, 13.5% (70/519) and 12.5% (47/376) quit smoking in the screen and control arm. Relapse rates were 2.3% and 1.6% in both groups, whereas the majority of the respondents in the screen and control arm (84.2% and 85.9%) remained stable over time (p=0.67) (**Table 7.2**). The mean period of smoking abstinence was comparable in the control arm (22.0 ± 18.5 months) and the screened population (17.8 ± 17.1 months) (p=0.12).

After receiving only negative screening test results among screen arm participants, the abstinence rate was 24.4% (94/386), which was comparable with the abstinence rates after 1 or ≥ 2 indeterminate scan results of 24.5% (26/106) and 22.2% (6/27) (χ^2=0.067; p=0.97).

According to the intention-to-treat analysis, no statistically significant differences were found in point prevalence of smoking abstinence (21.5% versus 19.0%; χ^2=1.120, p=0.29) and prolonged and continued smoking abstinence (21.3% and 18.8%; χ^2=1.129, p=0.29) between the screen and control arm, respectively.

Predictors of prolonged smoking abstinence

Univariate analysis of the baseline characteristics showed that control arm participants tended to quit smoking more often compared to screened participants (OR=1.29; 95% Confidence Interval (CI): 0.96-1.74). The other way around, screen arm participants were thus less likely to quit smoking with an OR of 0.77 (95% CI: 0.57-1.04). An increase in the average number of cigarettes smoked during the years of smoking decreases the likelihood of

Table 7.3. Odds Ratio of baseline predictors for prolonged smoking abstinence in male smokers after 4 years of follow-up.

	Prolonged smoking abstinence			
	Univariate analysis		Multivariate analysis	
	OR (95%-CI)	n	OR (95%-CI)	n
Study arm		895		832
Screen arm	1.00		1.00	
Control arm	**1.29 (0.96 – 1.74)#**		**1.41 (1.03 – 1.94)***	
Age (T0)	1.01 (0.98 – 1.04)	893		
Level of education[1]		883		
Lower education	1.00			
Medium education	1.08 (0.75 – 1.57)			
Higher education	1.36 (0.95 – 1.93)			
Number of cigarettes smoked	**0.97 (0.95 – 0.99)****	895		
Smoking duration (years)	1.00 (0.97 – 1.03)	895		
Time to first cigarette (T0)[2]		846		832
< 5 minutes	1.00		1.00	
6-30 minutes	1.14 (0.71 – 1.84)		1.14 (0.70 – 1.84)	
31-60 minutes	**1.69 (1.03 – 2.78)***		**1.69 (1.03 – 2.79)***	
> 60 minutes	**2.33 (1.37 – 3.94)****		**2.35 (1.38 – 4.01)****	
Stages of smoking cessation self change (T0)[3]		878		
Immotive	1.00			
Pre-contemplation	**1.67 (1.07 – 2.60)***			
Contemplation	**1.41 (0.98 – 2.03)#**			
Preparation	**1.58 (1.00 – 2.50)#**			
Age of smoking oneset		895		
< 15 years	1.00			
15-20 years	1.53 (0.99 – 2.38)			
> 20 years	1.22 (0.71 – 2.09)			

# $p < 0.10$, * $p < 0.05$, ** $p < 0.01$; Data is weighted for non-response bias.

[1] Low educational level indicates primary, lower secondary general or lower vocational education; medium educational level, intermediate vocational education or higher secondary education; high educational level, higher vocational education or university.

[2] First question of the Fagerström Test for Nicotine Dependence.

[3] Immotive indicates no intention to quit smoking within one year; pre-contemplator, intention to quit smoking within one year, but not within six months; contemplator, intention to quit smoking within six months, but not within one month; preparator, intention to quit smoking within the next month.

reporting abstinence from smoking at 4-year follow-up (OR=0.97; 95% CI: 0.95–0.99) (**Table 7.3**). Furthermore, a lower level of nicotine dependency increased the likelihood of smoking abstinence at follow-up, with an OR of 1.69 (95% CI: 1.03–2.78) and 2.33 (95% CI: 1.37-3.94)

for starting smoking between 31-60 minutes and after more than 60 minutes after waking, respectively. Finally, smokers who reported an intention to quit smoking within one year, but not within the next 6 months were most likely to be abstinent from smoking at follow-up (OR=1.67; 95% CI: 1.07–2.60). No interaction with the trial arm was found in the univariate analyses (p>0.05). After multivariate testing, both the allocation to the control arm (OR=1.41; 95% CI: 1.03–1.94) and a lower level of nicotine dependency (OR=1.69, 95% CI: 1.03–2.79 and OR=2.35; 95% CI: 1.38–4.01) predicted statistically significant the likelihood of being prolonged abstinent from smoking after 4 years of follow-up.

7.4 DISCUSSION

The results of the current study support the idea that lung cancer screening might be a teachable moment for smoking cessation in older adults with a long-term smoking history, who are eligible for lung cancer screening. The overall quit rates are promising and comparable with other observational lung cancer screening studies.[8-10, 14-16]

However, even after 4 years of follow-up, CT screening for lung cancer might falsely reassure cancer-free participants, since screenees tended to report lower smoking abstinence and for a shorter period compared with participants who received no screening (usual care), although the differences were limited. This phenomenon of a possible health certificate effect after cancer screening was only reported in a colorectal cancer screening trial (RCT) before, where smoking behaviour improved less amongst screened participants.[9] Results of the Danish lung cancer screening trial were contradictory to our results.[17] The difference might be explained by the fact that, in contrast to the NELSON trial, the control arm participants of the Danish trial were invited to the screening site for spirometry and smoking cessation counselling.[17] This might unintentionally had a false reassurance effect in control arm participants or the smoking cessation programme was more effective than ours.[10, 23]

The vast majority of the NELSON participants reported nicotine dependency. Nicotine dependency fulfils the criteria of addiction.[4, 24] The importance of nicotine addiction in the process of smoking cessation is also highlighted by our results. A higher baseline level of nicotine addiction, combined with the allocation to the screen arm, predicts continued smoking better than other smoking related variables after long-term follow-up. In line with this, nicotine replacement therapy was of high interest among screened participants of the Lung Screening Study and the NLST.[8] Nicotine addiction often hinders smoking cessation, which might be reflected by the long-term smoking history of the participants in which they move through the stages of change continuously. This long-term exposure to tobacco is responsible for their eligibility for lung cancer screening. Evidence about health promotion in cancer screening settings is scarce and a best-practice smoking cessation intervention that is complementary to cancer screening should still be developed.[25-26] Promising is that

screening participants reported interest in such programmes.[25] To prevent tobacco related health problems in screened smokers,[27-29] where significant health improvements can still be reached,[30] it would be recommendable to investigate a cost-effective smoking cessation intervention. Opportunities for adequate treatment of nicotine addiction would be of special interest to increase successful smoking abstinence.

As reported previously,[31] the CT scan result (indeterminate versus negative) has no statistically significant impact on future smoking behaviour, which is also supported by a recent report of Anderson et al.,[14] who found that the reassurance by consistently negative screening results might not influence long term smoking abstinence compared with a positive, but non-cancer, screening test result amongst ELCAP-participants over a 6-year follow-up. One implication of the NELSON trial is that the nodule management strategy reduces the number of positive screening test results enormously.[19] Therefore, participants who were referred to the pulmonologist because of an abnormal screening result were excluded for these samples, although this group is more likely to refrain from smoking.[8, 12, 15-17] Because of the small number of test positives, a possible underestimation of the impact of screening among screen arm participants would be limited. Control arm participants started smoking at younger age compared to screen arm participants, but additional analysis showed comparable results after adjusting the data.

Other limitations of this study, as the selection of volunteers for lung cancer screening, the lack of the biochemical verification of the smoking status and the use of the intention-to-treat method for data analysis have been debated before.[10] In addition, the high and also selective non-response in the control arm might always affect data by differences between respondents and non-respondents, although we corrected for the non-response bias statistically.

In conclusion, male smokers who voluntary participate in a lung cancer screening trial reported positive smoking abstinence rates. Nevertheless, CT screening for lung cancer potentially reassures long-term male smokers compared with no screening (usual care) after 4 years of follow-up, although the impact is limited. Adequate smoking cessation interventions, with an emphasis on the treatment of nicotine addiction, would be recommended to increase maintained smoking abstinence to further eliminate tobacco related health problems in this high-risk population.

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PART 3

Health promotion

CHAPTER 8

The effectiveness of a computer-tailored smoking cessation intervention for participants in lung cancer screening: A randomised controlled trial.

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Submitted

ABSTRACT

Background

Lung cancer screening might be a teachable moment for smoking cessation intervention. The objective was to investigate whether a tailored self-help smoking cessation intervention is more effective in inducing smoking cessation compared to a standard brochure in male smokers who participate in the Dutch-Belgian randomised controlled lung cancer screening trial (NELSON trial).

Methods

Two random samples of male smokers who had received either a standard brochure (n=642) or a tailoring questionnaire for computer-tailored smoking cessation information (n=642) were sent a questionnaire to measure smoking behaviour two years after randomisation.

Results

Twenty-three percent of the male smokers in the tailored information group returned a completed tailoring questionnaire and thus received the tailored advice. The prolonged smoking abstinence was slightly, but not statistically significant, lower amongst those randomised in the tailored information group compared with the brochure group. The level of education and intention to quit smoking significantly predicted smoking cessation at follow-up ($p<0.05$). The majority of the respondents did not recall which smoking cessation intervention they had received at randomisation after 2-years of follow-up.

Conclusions

The smoking abstinence rates of male smokers with a long term smoking history who participate in a lung cancer screening trial and who received either standard self-help information or tailored smoking cessation information were comparable after two years of follow-up.

8.1 INTRODUCTION

Lung cancer is most important tobacco related health problem worldwide.[1] About 80-90% of the lung cancers is attributable to the use of tobacco, so that smoking cessation is the most effective way to reduce the risk for developing lung cancer among smokers.[2]

Health education is one of the strategies to combat the growing tobacco epidemic. One of the forms of health education is the self-help materials.[3] Standard health education materials are characterized by large and identical messages to reach a broad and undifferentiated group. A major disadvantage of standardized information is the lack of individualization of this information.[4] Tailored health educational information may close this gap. It tries to imitate interpersonal communication on a mass scale by *"combining information and behavioural change strategies with the intention to reach an individual, based on the unique characteristics of that person, related to the behaviour of interest, which derived from an individual assessment"*.[5-7] Previous studies showed evidence for the effectiveness of tailored self-help smoking cessation information in the general population.[3, 8-12]

A substantial high proportion of the lung cancer screening population is a smoker (46%), which highlights the need for smoking cessation as well as the opportunities to reach a large population.[13-15] Smokers who are subjected to lung cancer screening seem to be more interested in receiving smoking cessation information.[13] However, Clark et al.[16] found no statistically significant difference in smoking abstinence or the readiness to quit smoking amongst participants of a randomised lung cancer screening trial who received standard smoking cessation information or a list of internet resources for smoking cessation. The authors argued that this might be due to the lack of tailoring of both interventions. Lung cancer screening might be a so-called teachable moment for smoking cessation, although a possible health certificate effect of cancer screening remains.[13-14, 17]

This is the first study that investigates whether a tailored smoking cessation intervention is more effective in inducing smoking cessation than a standard brochure in male smokers who participate in a lung cancer screening trial.

8.2 METHODS

NELSON trial

This study was conducted in a subgroup of the participants enrolled in the Dutch-Belgian lung cancer screening trial (NELSON trial). A more detailed description of the recruitment procedure and the selection of the study participants were described previously.[18-19] In summary, based on population registries, 15,822 mainly males aged between 50-75 years were randomised (1:1) to the screen or control arm. They smoked >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years, and they were current smoker or former smoker who quit smoking <10 years

ago. All gave their written informed consent. Participants in the screen arm received CT screening for lung cancer in year 1, 2, 4, and 6.5 while the participants in the control arm received usual care (no screening).[18] The CT screening test results were based on a novel nodule management strategy based on volume and volume doubling time and could be negative, indeterminate or positive.[20] Those with an indeterminate or a negative screening result received a standard letter explaining that radiologists had or had not found an abnormality, whereas people with a positive screening result were informed about their referral to a pulmonologist by phone.

All current smokers were randomised (1:1) to receive a standard brochure or a tailoring questionnaire necessary to provide individualized smoking cessation information. Those who received the tailoring questionnaire were asked to complete and return the questionnaire before they received the tailored smoking cessation advice.

The NELSON trial was approved by both the Dutch Minister of Health after a positive advice of the Dutch Health Council as well the Ethical Boards of the participating centres.

Smoking cessation study

This study was conducted in a sub cohort of the NELSON trial. Two random samples of current smokers received either the standard brochure (n=642) (*brochure group*) or a tailoring questionnaire (n=642) (*tailored information group*).

A current smoker was defined as a participant who had smoked for 7 days prior to completing the questionnaire before randomisation (T0). Male smokers who were off-study (n=163; 6.3% in the screen arm and n=7; 0.3% in the control arm) or male smokers in the screen arm who received a positive screening result (n=53; 2.1%) were excluded from this sample (**Figure 8.1**). A second questionnaire that measured actual smoking behaviour was sent to both samples of male smokers (n=1,284) 2.2 (SD 0.29) years after randomisation (T1).

First questionnaire (T0)

Demographics (date of birth, gender, level of education) and smoking related variables were assessed by the first general questionnaire.[18] The smoking history was measured by the starting age of smoking (8-point scale), the average number of cigarettes they smoked a day (10-point-scale), and the years of smoking (9-point scale). The variables were recoded into categorical variables with 4-5 categories and into a mean value based on the median value of each category.

The motivation to quit smoking (8-point scale) was adapted from the Transtheoretical Model and recoded into four stages of change. Smokers who reported no intention to quit smoking were classified as immotive, whereas pre-contemplators, contemplators and preparators were considered to be motivated to quit smoking in respectively 6-12 months, 1-6 months and within a month.[21-22] Finally, level of addiction to nicotine was estimated by the time to the first cigarette after waking-up as adapted from the first question of Fagerström Test for Nicotine Dependence (FTND).[21-23]

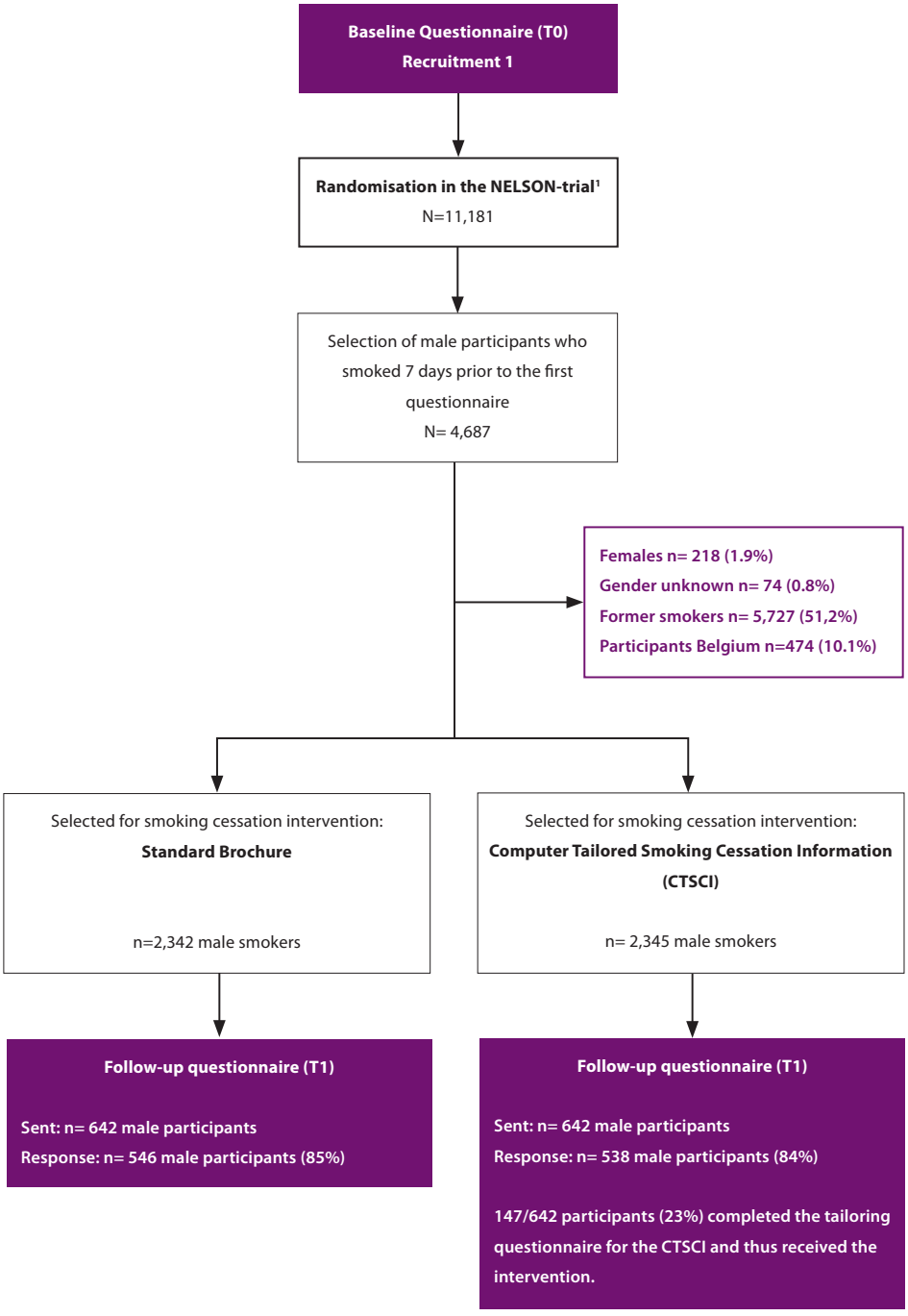

Figure 8.1. Flowchart of the study population.
[1] NELSON indicates Dutch-Belgian Lung Cancer Screening Trial

Second questionnaire (T1)

After two years of follow-up, smoking behaviour was assessed again. Three types of smoking abstinence were defined, i.e. point prevalence of smoking abstinence, prolonged smoking abstinence and continued smoking abstinence.[21] The participants were asked whether they usually smoke (yes/no), and whether they smoked the last 24 hours (yes/no) and the last 7 days (yes/no) before completing the questionnaire. The respondents who answered that they did not usually smoke and that they did not smoke in the last 7 days were classified as point prevalent abstinent from smoking. In the next step, those who were point prevalent abstinent from smoking were asked: "Have you been engaged in a quit attempt at this moment (yes/no)?"; "When did you quit smoking? (day/month/year)?"; and "Have you smoked since this quit date (not at all/1-5 cigarettes/> 5 cigarettes)?". Those who reported that they smoked <5 cigarettes since two weeks after the quit date were classified as prolonged smoking abstinent and those who reported that they had smoked <5 cigarettes since the quit date were classified as continued smoking abstinent. All other respondents were classified as continued smoker.[21]

Several questions about the smoking cessation tailoring intervention were added to this follow-up questionnaire. Participants were asked whether they had received a smoking cessation intervention (yes/no/do not know) and what intervention they had received (brochure/ tailoring assessment).

The smoking cessation intervention

Standard brochure

The brochure "Smoking cessation, why and how" is a 35 paged standard self-help brochure of STIVORO – the Dutch expert centre on tobacco control – that is subdivided in four parts. Each part focuses on another group of smokers with differences in their intention to stop smoking, but who want more health education about smoking and smoking cessation. The first part of this brochure focuses on those who want additional information concerning the advantages of smoking cessation. In the second part, the focus is to handle experiences of doubts among smokers who intend to quit smoking. Central in the third part is providing information about methods for smoking cessation. The fourth part focuses on the group of smokers who have successfully quit, but who experience the need for information about how to prevent relapse to smoking.

Computer Tailored Smoking Cessation Intervention

The computer tailored smoking cessation intervention was also provided by STIVORO. The individual tailoring questionnaire consists of questions regarding the actual smoking behaviour, the level of addiction to smoking, the quit smoking history, the opinion regarding smoking cessation methods, smoking in the direct environment, the perceived advantages and disadvantages of smoking and the presence of the most frequent occurring tobacco

related diseases (heart disease and chronic lung diseases).[24] With the aim to increase the individualization of the messages, the outcomes of the tailoring questionnaire directed the development of the tailored smoking cessation advice. STIVORO sent the tailored smoking cessation advice to the home addresses of only those participants who completed the tailoring questionnaire.

Statistical analysis

Differences in baseline characteristics between 1) the male smokers of the first recruitment who received a smoking cessation intervention (n=4,687), 2) the two samples (n=1,284), and 3) between those who completed and who did not completed the tailored questionnaire were tested using Chi-square statistics and non-parametric statistics as appropriate.

The analyses were performed using an intention-to-treat analysis, unless otherwise specified. Non-respondents were classified as current smoker and included in the analysis, because the assumption is that non-response is highly correlated with continued smoking.[25] To determine whether there is a different impact of the brochure or tailored smoking cessation information on prolonged smoking abstinence both univariate as well as multivariate backward logistic regression analyses using the likelihood test ratio were performed. The level of significance was set on 0.05 (two-tailed). For the power analysis the statistical package software R was used, while all other statistics were performed by using SPSS version 17.0.

8.3 RESULTS

The study population

Of the brochure and tailored information group 85% (546/642) and 84% (538/642) responded to both the first and the second questionnaire, respectively (**Figure 8.1**). Both samples were representative for the male smokers randomised in the first recruitment of the NELSON trial (**Table 8.1**). The median age in both groups was 57 (IQR: 7) years and they smoked on average 18 (IQR: 10) cigarettes a day for 38 (IQR: 19) years. A large proportion of the participants - 47.6% (301/633) of the brochure group and 48.8% (309/633) of the tailored information group - were lower educated (primary, lower secondary general or lower vocational education). About 40% (40.3% (253/628) and 40.9% (254/621)) of the male smokers reported that they did not consider quitting smoking. Approximately 20% (18.9% (114/603) and 17.9% (108/603)) of the participants were categorized as being highly nicotine dependent. Participants in the tailored group started smoking at younger age (p=0.012) (**Table 8.1**). No further statistically significant differences were found in the baseline characteristics between male smokers of the first recruitment and the samples, between both samples, or between the respondents and respondents and non-respondents (p>0.10).

Table 8.1. Baseline characteristics of the male smokers.

	Male smokers randomised in the first recruitment period of the NELSON trial		Total sample of male smokers		Brochure group		Tailored group	
		Total n=4687		Total n=1284		Total n=642		Total n=642
	%[1]	n	%[1]	n	%[1]	n	%[1]	n
Age (years): median (IQR)	57 (7)	4661	57 (7)	1283	57 (7)	641	57 (7)	642
No of cigarettes smoked/ day: median (IQR)	18 (10)	4684	18 (10)	1284	18 (10)	642	18 (10)	642
Smoking duration (years): median (IQR)	38 (10)	4684	38 (10)	1284	38 (10)	642	38 (10)	642
Pack-years: median (IQR)	38 (20)	4684	38 (19)	1284	38 (17)	642	38 (20)	642
Educational level[2]								
lower educational level	49.1	2264 / 4612	48.1	610 / 1266	47.6	301 / 633	48.8	309 / 633
medium educational level	24.2	1116 / 4612	23.9	302 / 1266	25.4	161 / 633	22.3	141 / 633
higher educational level	26.7	1232 / 4612	28.0	354 / 1266	27.0	171 / 633	28.9	183 / 633
Motivation to quit smoking[3]								
immotive	40.3	1841 / 4566	40.6	507 / 1249	40.3	253 / 628	40.9	254 / 621
precontemplator	15.3	698 / 4566	15.5	194 / 1249	16.7	105 / 628	14.3	89 / 621
contemplator	30.1	1372 / 4566	29.5	368 / 1249	28.0	176 / 628	30.9	192 / 621
preparator	14.3	655 / 4566	14.4	180 / 1249	15.0	94 / 628	13.9	86 / 621
Time to first cigarette[4]								
< 5 minutes	19.2	857 / 4453	18.4	222 / 1206	18.9	114 / 603	17.9	108 / 603
5 - 30 minutes	41.2	1833 / 4453	40.4	487 / 1206	40.3	243 / 603	40.4	244 / 603
30 - 60 minutes	25.0	1114/ 4453	25.5	308 / 1206	25.2	152 / 603	25.9	156 / 603
>= 60 minutes	14.6	649 / 4453	15.7	189 / 1206	15.6	94 / 603	15.8	95 / 603
Age of start smoking								
< 15 years	16.5	775 / 4684	17.1	220 / 1284	14.8	95 / 642	19.5	125 / 642
15-20 years	65.2	3053 / 4684	65.1	836 / 1284	69.0	443 / 642	61.2	393 / 642
> 20 years	18.3	856 / 4684	17.8	228 / 1284	16.2	104 / 642	19.3	124 / 642
Trial arm								
screen arm	49.5	2321 / 4687	49.9	641 / 1284	50.6	325 / 642	49.2	316 / 642
control arm	50.5	2366 / 4687	50.1	643 / 1284	49.4	317 / 642	50.8	326 / 642

IQR = interquartile range

[1] Available data were presented N (%) unless described otherwise.

[2] Low educational level indicates primary, lower secondary general or lower vocational education; medium educational level, intermediate vocational education or higher secondary education; high educational level, higher vocational education or university.

[3] Immotive indicates no intention to quit smoking within one year; pre-contemplator, intention to quit smoking within one year, but not within six months; contemplator, intention to quit smoking within six months, but not within one month; preparator, intention to quit smoking within the next month.

[4] First question of the Fagerström test for Nicotine Dependence (FTND).

No statistically significant differences ($p > 0.10$) were found between male smokers of the first recruitment and the samples.

The smoking cessation information

All participants of the brochure group received a standard brochure as described before.

Those who were randomised to the tailored information group had to complete a tailoring questionnaire before they could receive the tailored smoking cessation advice. Twenty-three percent (147/642) have been self-selected to receive a tailored advice (**Figure 8.1**).

Those who completed the tailoring questionnaire were statistically significant more often randomised to the screen arm of the lung cancer screening trial (OR=2.27; 95% CI: 1.55-3.32), but there were no statistically significant differences in age, level of education, motivation to quit smoking, smoking history, or the level of addiction between the two groups (p>0.10).

Smoking cessation

Of those male smokers who received the standard brochure, 15.9% (102/642) reported that they have not smoked during the 7 days prior to completing the questionnaire, which was somewhat higher, but not statistically significant different from the point prevalence of smoking abstinence amongst those who were randomised to the tailored information group (13.2% (85/642) (OR=0.81; 95% CI: 0.59-1.10) (**Table 8.2**).

Subsequently, the prolonged (12.5% (80/642); OR=0.77; 95% CI: 0.56-1.06) and continued (12.1%; (78/642); OR=0.78; 95% CI: 0.56-1.07) smoking abstinence were also slightly lower amongst those randomised in the tailored information group compared to the brochure

Table 8.2. Smoking behaviour of male smokers in the brochure group compared with the tailored intervention group.

A: INTENTION-TO-TREAT ANALYSIS						
	Brochure group		Tailored information group			
	%	N	%	N	OR (95%-Confidence Interval)	p-value
quit attempts: mean (sd)	1.6 (2.4)	348 / 642	1.6 (2.3)	354 / 642		0.62
point prevalent smoking abstinence	15.9	102 / 642	13.2	85 / 642	0.81 (0.59 - 1.10)	0.18
prolonged smoking abstinence	15.6	100 / 642	12.5	80 / 642	0.77 (0.56 - 1.06)	0.11
continued smoking abstinence	15.1	97 / 642	12.1	78 / 642	0.78 (0.56 - 1.07)	0.12
B: ANALYSIS WITH MALE SMOKERS WHO RECEIVED THE INTERVENTION IN PRACTICE						
	Brochure group		Tailored information group			
	%	N	%	N	OR (95%-Confidence Interval)	p-value
point prevalent smoking abstinence	15.9	102 / 642	14.3	21 / 147	0.88 (0.53 – 1.47)	0.63
prolonged smoking abstinence	15.6	100 / 642	14.3	21 / 147	0.90 (0.54 – 1.50)	0.70
continued smoking abstinence	15.1	97 / 642	14.3	21 / 147	0.94 (0.56 – 1.56)	0.80

Table 8.3 Univariate and multivariate logistic regression analysis.

	Prolonged smoking abstinence					
	Univariate analysis			Multivariate analysis		
	OR (95% CI)	p-value	n	OR (95% CI)	p-value	n
Smoking cessation intervention group			1284			
Standard brochure	1.00					
Tailored information	0.77 (0.56 - 1.06)	0.109				
NELSON trial			1284			
Screen arm	1.00	0.346				
Control arm	1.16 (0.85 - 1.60)					
Age	0.99 (0.96 - 1.03)	0.716	1283			
Level of education [1]		**0.003**	1266		**0.018**	1161
Low	1.00			1.00		
Medium	1.31 (0.87 - 1.98)			1.33 (0.87 – 2.05)		
High	1.89 (1.31 - 2.73)			1.76 (1.19 - 2.61)		
Cig/day	0.98 (0.96 - 1.01)	0.136	1284			
Smoking duration	1.00 (0.97 - 1.03)	0.937	1284			
Pack-years	0.99 (0.98 - 1.00)	0.146	1284			
Motivation to quit smoking [2]		**0.018**	1249		**0.036**	1161
Immotive	1.00			1.00		
Pre-contemplator	1.63 (1.01 - 2.63)			1.61 (0.99 - 2.62)		
Contemplator	1.84 (1.24 - 2.72)			1.74 (1.16 - 2.60)		
Preparator	1.58 (0.96 - 2.58)			1.12 (0.62 - 2.01)		
Age of start smoking		0.155	1284			
< 15 years	1.00					
15-20 years	1.24 (0.80 - 1.92)					
> 20 years	0.81 (0.45 - 1.44)					
Time to first cigarette [3]		**0.023**	1206			
< 5 minutes	1.00					
5 - 30 minutes	1.75 (1.01 – 3.02)					
30 - 60 minutes	2.09 (1.18 – 3.71)					
>= 60 minutes	2.49 (1.35 – 4.57)					

[1] Low educational level indicates primary, lower secondary general or lower vocational education; medium educational level, intermediate vocational education or higher secondary education; high educational level, higher vocational education or university.

[2] Immotive indicates no intention to quit smoking within one year; pre-contemplator, intention to quit smoking within one year, but not within six months; contemplator, intention to quit smoking within six months, but not within one month; preparator, intention to quit smoking within the next month.

[3] First question of the Fagerström test for Nicotine Dependence (FTND).

group (15.6% (100/642) and 15.1% (97/642) respectively), but the differences were not statistically significant (**Table 8.2**).

Participants in the tailored information group had to complete an individual assessment before the smoking cessation advice could be tailored and send out. The tailored information was delivered to 23%, because only this part of the participants sent the tailored questionnaire back to STIVORO (**Figure 8.1**). The participants who received the tailored smoking cessation information quit smoking slightly more often compared with those who did not receive the tailored smoking cessation information (14.3% (21/147) versus 11.9% (59/495); p=0.45), although the difference was not statistically significant. When only those who actually received the standard or tailored smoking cessation information advice were included in the analysis, the prolonged smoking abstinence in the tailored information group (14.3%; (21/147)) and brochure group (15.6% (100/642)) was comparable (OR=0.90; 95% CI: 0.54-1.50; p=0.70) (**Table 8.2**). This did not modify the interpretation of the study results.

Analysis shows that in both groups the time of being abstinent from smoking was comparable with a median period of 18 (IQR: 18) months in the brochure group and 15 (IQR: 17.5) months in the tailored information group. Furthermore, multivariate analysis showed that those who were higher educated and motivated to quit smoking were more likely to quit smoking at follow-up (p<0.05) (**Table 8.3**).

Process evaluation

In both groups, less than a half of the respondents (42.7% (233/546) and 47.4% (255/538) in the brochure group and tailored information group recalled that they had received smoking cessation information, 17.6% (96/546) and 17.5% (94/538) reported that they did not receive any smoking cessation intervention, and 39.7% (217/546) and 35.1% (189/538) did not remember whether they received smoking cessation information, respectively (p=0.236).

Furthermore, participants were asked what intervention they received (**Figure 8.2**). Of the respondents in the brochure group, 38.8% (212/546) remember that they received this brochure, 2.7% (15/546) reported this erroneously and 58.4% (319/546) did not know that they received a brochure. In the tailored information group, respondents remembered the type of intervention significantly less often (p<0.001). Only 25.1% (135/538) recognized the intervention correctly, 20.6% (111/538)) answered the question incorrectly by stating that they received the standard brochure, although many of them received no information at all. Just like the brochure group, 54.3% (292/538) reported that they did not know what information they had received.

In the tailored group, many respondents did not know whether they completed the assessment for tailored smoking cessation information and received the tailored advice (**Figure 8.3**); 25% (134/538) of the respondents received the tailored advice, but only 5.6% (30/538) remembered this. Thirteen respondents (2.4%) reported that they did not receive the tailored advice, although the observed that 75.1% (404/538) did not return the tailoring

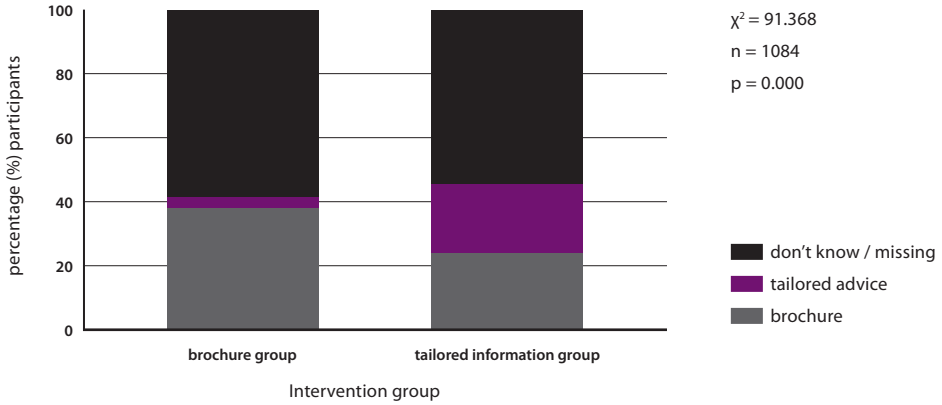

Figure 8.2. The smoking cessation information as remembered by the respondents of the brochure group and the tailored information group.

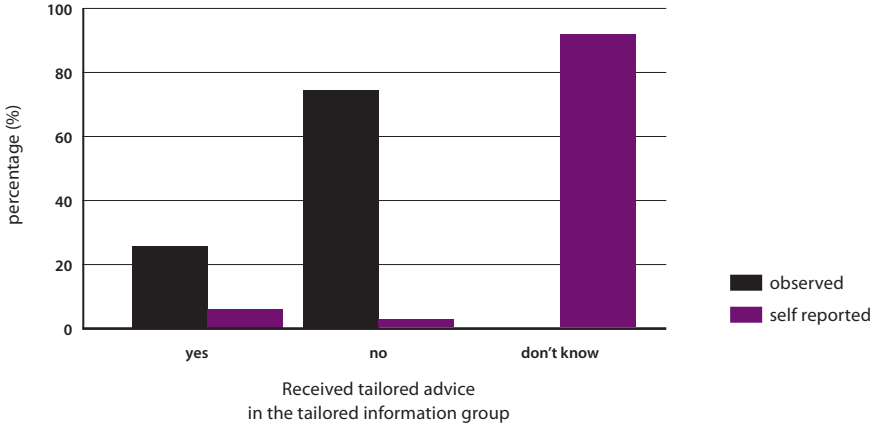

Figure 8.3. The difference in self-reported and observed received tailored advice among respondents in the tailored information group.

questionnaire. The majority (92.0% (495/538)) did not know whether they had completed the assessment and received the tailored advice.

8.4 DISCUSSION

The current study shows that computer tailored self-help smoking cessation information has no advantage compared with a standard self-help brochure on prolonged smoking abstinence amongst male smokers who participate in a lung cancer screening trial after two years of follow-up. Nevertheless, the overall quit rate in lung cancer screening participants (14%) was higher than we could expect from the quit rates in the general adult population (3-7%).[17]

The results indicate that a single tailored smoking cessation intervention at the beginning of a lung cancer screening programme might not be sufficient enough to reach long-term effects in smoking behavioural change. The fact that many respondents did not remember the intervention has major implications for the usefulness of this intervention in this specific population.

Previous studies often lack a long-term follow-up (>6-12 months), despite that smoking behavioural change should have to be maintained over time. Only few of those who make a quit attempt (3-5%) can prevent relapse to smoking within the first year of cessation.[26-27] In the current study, a long-term impact of tailored smoking cessation information compared with a standard brochure on future smoking behaviour was not observed, but a short-term effect of the smoking cessation intervention could have been missed due to the follow-up period of two years. Although the lack of statistically significant differences in smoking abstinence, one should recognize that, from a public health rationale, even interventions that cause small changes can result in significant health benefits when large populations can be reached.[7]

Several studies on tailored smoking cessation information show favourable outcomes on smoking behaviour.[3, 8-9] Kreuter et al. concluded in line with this that tailored health educational interventions are effective in many, but not in all cases.[7] In the current study, the standard brochure was even slightly more effective compared with the tailored smoking cessation advice. An important question is whether the tailored advices adequately meet the individual information needs of this specific population.[28] In line with many previous studies, the intention to quit smoking was a strong predictor for smoking cessation in our study, as were a higher level of education and a high level of nicotine addiction. Schumann et al. demonstrated that tailored information for those with a lower intention to quit smoking needs further improvement.[29] More research is recommended to investigate whether the tailoring process should be adapted more sufficiently to a population who were screened for lung cancer, because of their high risk for developing lung cancer, and who are lower educated, less motivated to quit smoking, and more addicted to nicotine. The facts that the overall quit rate was high and that statistically significant more screen arm participants completed the assessment for the tailored smoking cessation information compared to the control arm participants, implicate that a smoking cessation intervention has an opportunity to be attractive in this setting. A more detailed effect and process evaluation is recommended to further develop and improve the smoking cessation intervention for a high risk population who receive lung cancer screening that can be used in such a screening programme.

In interpreting the results, one should recognize that only 23% of the participants in the tailored information group completed the tailoring questionnaire and thus received the tailored smoking cessation information, what could have underestimated the potential impact of tailored smoking cessation information in this group.[3, 8] Prolonged smoking abstinence was higher amongst those who completed the tailoring questionnaire compared to those

who did not, although the difference was not statistically significant. A difference might be missed here due to an effect of the tailoring questionnaire, because this assessment might also cause a reconsideration of the smoking habits, what might induce smoking cessation.[28] A second limitation of our study is that participants who received a positive screening result (2.6%) were excluded, because of the low percentage of positive screening results as result of the novel nodule management protocol that was used in the NELSON trial.[19] Another limitation of this study is that we have not biochemically verified the smoking status at follow-up. We expected that this has not biased the responses of the participants. One reason is that one previous study reported valid self-reported smoking data amongst participants of a lung cancer screening trial.[30] Additionally, the respondents participate in a lung cancer screening trial instead of a smoking cessation intervention trial. None of the participants were expected to quit smoking explicitly. The intention-to-treat analysis was also a conservative method of data analysis that corrects for possible non-response bias. Furthermore, the sample size was limited, because the difference in observed quit rates was smaller than expected. Retrospectively, a larger sample size (n=1,355 in each group) was required to be able to detect a difference with a power of 80%. Finally, this study is restricted to male smokers aged between 50-75 years who are at high risk for developing lung cancer, so that the study results are only generalizable to this population. Tailored smoking cessation interventions might be slightly more attractive to females,[31-32] although there is no evidence about the impact of such an intervention amongst females who were screened for lung cancer so far.

In conclusion, male smokers who participate in a lung cancer screening trial stopped smoking more than expected, although tailored smoking cessation advice had no advantage over standard smoking cessation information after two years of follow-up.

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CHAPTER 9

General discussion

9. GENERAL DISCUSSION

The answers to the research questions will be summarized and interpreted in the first paragraph. In the next section, several methodological issues of the studies are discussed. Finally, the main conclusions and the implications for further research and practice are given.

9.1 RESEARCH QUESTIONS

This paragraph is divided in the three parts that are central in this thesis; 1) the NELSON trial, 2) the impact of lung cancer screening on smoking cessation, and 3) health education.

PART 1: THE NELSON TRIAL

9.1.1 Generalizability of the study results

Population-based recruitment of study participants is preferred over volunteer-based recruitment, because of the risk of self-selection that might threat study's validity. The aim of the first research question was to explore whether the population-based selection of the participants of the NELSON trial introduced important (biased) self-selection (**Chapter 2**):

What is the degree of self-selection among a) respondents from the general population who are aged between 50-75 and received a general health questionnaire and b) respondents who are eligible for participating in the NELSON trial compared to the Dutch national reference groups?

Main findings

More than 335,000 people aged between 50-75 years received a first questionnaire about demographics, general health, and lifestyle in the first recruitment round. A total of 106,862 (32%) people responded to this questionnaire. Of these respondents, 20,064 people were eligible to participate in the NELSON trial and 11,110 (55%) of them gave their informed consent and were randomised.

In general, the respondents should be comparable to the general Dutch population. Fewer respondents to the first questionnaire were current smokers, but the smokers smoked more heavily and for a shorter period. The former smokers had quit smoking for a shorter time than the general population. It is expected that these differences might not strongly impact lung cancer risk. Finally, respondents were somewhat lower educated compared to the general Dutch population. More or less the same results were found when the randomised study population was compared with the Dutch population who meets

the inclusion and exclusion criteria as used in the NELSON trial. The comparison showed that the participants were younger and lower educated. A comparable proportion of the participants were current smokers, although the smoking participants smoked more heavily for a shorter period. The differences found between the respondents and the Dutch population and between those randomised in the NELSON trial and the Dutch population that meets our inclusion- and exclusion criteria were, although statistically significant, negligibly small.

Interpretation of the results

The findings imply that the final results of the NELSON study will be roughly applicable to both the target population of high-risk individuals as well as to the Dutch population. It was expected that a substantial part (± 15-25%) of the general Dutch population aged between 50 and 75 years could be targeted for routine lung cancer screening.[1-2] Thus, it may be possible to generalize study results more or less to a relative large part of the general population. One should however recognize that the NELSON study results might be less generalizable to females, because of the low proportion of females in the study. Gender-related factors might have an impact on the effectiveness of lung cancer screening.[1, 3-5]

People who are included in studies by volunteer-based recruitment might differ in important aspects as the general health status, disease prevalence, and all-cause mortality compared with a population-based recruitment.[6-11] Although this self-selection might threat the validity of the study results, a limited number of cancer screening trials investigated whether selection-bias might play a role so far.[6-8, 11-12] The National Lung Screening Trial (NLST) used a volunteer-based recruitment method by media, although they paid special attention to reach minority groups who are assumed to be less likely to participate voluntarily in cancer screening trials. It was found that the NLST cohort was also roughly representative for the general population of (former) smokers in the US.[13] The study population was somewhat healthier, although this was not expected to influence the generalizability of the study results of this lung cancer screening trial.[7] Researchers of the volunteer-based Danish lung cancer screening trial (DLCST) reported a substantial participation bias due to differences in socio-demographic and psychosocial aspects recently.[11] The previous studies relied on a comparison of risk factors and no data was available about mortality rates amongst both participants and non-participants, although comparing all-cause and specific mortality rates between these groups is considered to give the highest level of evidence about whether self-selection bias might affect the generalizability of the study results. Previously, it was found that the trial cohorts of the Swedish breast cancer screening trials were representative for the general population in terms of total mortality.[12] Some self-selection was observed in the volunteer-based randomised controlled European Study for Prostate Cancer Screening.[8] In a population-based colorectal cancer-screening programme, non-participants had a higher risk for developing colorectal cancer compared with participants. Population-based recruit-

ment is preferable over volunteer-based recruitment, although the results show that this is no guarantee that self-selection bias would not occur.

9.1.2 Nodule management strategy

A nodule management strategy for lung cancer screening based on volume and volume-doubling time (VDT) was developed and used in the NELSON trial. The nodule management protocol was described previously.[14] The research question (**Chapter 3**) related to the evaluation of this strategy was:

To what extent is the use of the volume and volume-doubling time of a noncalcified nodule as main criteria for deciding on further action a useful nodule management strategy in lung cancer screening?

Main findings

A total of 7,557 and 7,289 participants received a first and second scan in the NELSON trial. In the screen arm, 19.2% and 6.6% participants received an indeterminate screening test result and 2.6% and 1.8% of the screen arm participants received a positive screening test result at the first and second screening round, respectively. The proportion of invasive procedures amongst test-positives that revealed benign disease was 27.2% after the first screening round. Lung cancer was diagnosed amongst 70 out of the 7557 and 54 out of the 7289 screen arm participants in the first and second screening round, respectively. Early stage lung cancer (stage I) was found in 63.9%. The sensitivity – the ability to classify participants with lung cancer correctly as having the disease – and specificity – the correct classification of the abstinence of lung cancer in screened participants, were 94.6% and 98.3% in the first screening round. Of those who received a positive screening result, the chance of having lung cancer would be 36%. After receiving a negative screening result, it was almost for sure (99.7%) that the participant indeed had no lung cancer at time of screening. The sensitivity and specificity were 96.4% and 99.0% after second round screening. The positive and negative predictive values were 42.2% and 99.0% in this round, respectively.

Interpretation of the results

The use of the volume and VDT (growth) of a non-calcified nodule as main criteria for deciding on further action seems to be a useful nodule management strategy in lung cancer screening amongst asymptomatic people at high risk for developing lung cancer so far. The strategy reduced the need for follow-up evaluation substantially, which is a major concern of lung cancer screening, while the strategy did not interfere in the sensitivity and specificity of CT scanning.[15-16] Previous reported rates of test-positives varied between 8-30% and 18-26% after one and two screening rounds, respectively.[17] Now it is important to investigate whether the use of this management protocol might facilitate (teachable moment) or hinder

(health certificate effect) future abstinence from smoking with the aim to explore possible (un)favourable effects of screening.

The detected number of lung cancers in stage I was also in line with other randomised controlled trials, but somewhat lower compared to observational studies, which was attributed to differences in the study population and the protocol in case of a detected lung nodule in the observational studies.[16-17]

However, despite the good performance results obtained by the use of volume and VDT in lung cancer screening so far, there is no evidence about the (cost)effectiveness of reducing lung cancer mortality by lung cancer screening using this nodule management strategy. One disadvantage of a sensitive screening test is that it might lead to more overdiagnosis should the person fail to have benefitted from the early detection in terms of life years gained. This highlights the need to use the mortality reduction as an endpoint in establishing any conclusions about the (cost-)effectiveness of lung cancer screening using volume and VDT.

The nodule management strategy should also be validated in other large-scale lung cancer screening programmes. The UK lung cancer screening trial started in early 2011 and the investigators based their nodule management strategy on the NELSON trial.[18] This might provide additional opportunities to gain more insight in lung cancer screening based on volume and VDT.

PART 2: LUNG CANCER SCREENING AND SMOKING CESSATION

9.1.3 Impact of screening on lifestyle

In **Chapter 4**, the current evidence about the impact of cancer screening on lifestyle was investigated in a systematic review. The research question that was addressed is:

What is the current evidence for the effects of cancer screening on lifestyle behaviour and lifestyle-related morbidity, and what opportunities are there for dealing with possible unwanted effects of cancer screening?

Main findings

Only 11 studies, which included both a pre-test as well as a post-test, were published about lifestyle changes after cancer screening. Desirable lifestyle changes have been reported after both colorectal as well as lung cancer screening. This suggested that cancer screening might be useful as a teachable moment for health promotion. However, one should recognize that cancer screening might also have a false health certificate effect that permits the continuation or even the initiation of unhealthy behaviour. This phenomenon was reported in two randomised controlled trials where screen arm participants reported less desirable lifestyle changes (smoking behaviour, nutritional intake, and physical activity) compared with control

arm participants after lung and colorectal cancer screening. None of the studies found by the literature search aimed at exploring the impact of cancer screening on future lifestyle-related morbidity. Furthermore, three studies were found that investigated whether a combined approach of primary and secondary prevention is complementary in reducing the burden of cancer. The studies aimed to improve the intake of fruits and vegetables or to promote smoking cessation by self-help materials and were conducted in a colorectal, lung and cervical cancer screening setting. The results suggest a potential role for health promotion, although all studies had to deal with important methodological issues such as a small sample size or short follow-up that makes it hard to draw conclusions.

Interpretation of the results

After reviewing the literature, one major conclusion that could be drawn is that the evidence about the impact of cancer screening on future lifestyle and how to deal with a possible unwanted effect is almost lacking. This is remarkable, because an unhealthy lifestyle is an important modifiable cause of cancer and premature death. A screened population might be useful in reaching a large target group for health improvement.

The limited evidence about the (cost-)effectiveness of primary prevention interventions in a screened population and the underlying working mechanism of a combined approach of primary and secondary prevention emphasize the need for further investigation. Previous studies mostly investigated the impact of screening on future changes in health behaviour ((intended or actual) screening attendance, use of health services) or health beliefs (susceptibility of the disease, seriousness of the disease, benefits of screening, knowledge, barriers) instead of lifestyle changes (smoking behaviour, nutritional intake, physical activity and alcohol use).[19] Most studies also lack the use of repeated measurements, so that it remains unknown whether the behaviour could be attributed to screening. In general, cholesterol screening seems to positively affect health behaviours, but it remains unknown whether breast cancer screening or cervical cancer screening affect future health behaviour.[19] Another review, which explored the evidence about whether screening affects health behaviour, was published in the meanwhile.[20] Based on the available literature, the authors also concluded in general that risk factor screening might have a positive effect on health behaviour, but the lack of evidence about the impact of the early detection of diseases on lifestyle changes makes it hard to draw reliable conclusions.

The consequences of lifestyle changes in screened participants on lifestyle-related morbidity seem to be a complete new area of interest in (cancer) screening research. Lifestyle changes might have an impressive impact on lifestyle-related morbidity when small effects can be reached in a large (screened) population. Changes in lifestyle-related morbidity might thus have impact on cancer screening programmes' effectiveness.

9.1.4 Impact of lung cancer screening on smoking cessation

As stated before, one of the possible (un)favourable effects of lung cancer screening is that screening might influence further smoking behaviour, positively (as teachable moment) or negatively (as health certificate). The following research question (**Chapters 5** and **7**) was formulated:

What is the effect of lung cancer screening (screen arm) on prolonged smoking abstinence compared with no screening (control arm) amongst male smokers randomised in the Dutch-Belgian randomised controlled lung cancer screening trial (NELSON trial) after two and four years of follow-up?

Main findings

The results of the sub-studies amongst 1284 participants showed that 16.6% and 26.4% of the male smokers were abstinent from smoking after 2 and 4 years of follow-up, respectively. Unfortunately, screen arm participants in the NELSON trial were modest but less likely to quit smoking compared with control arm participants. After 2 years of follow-up, the abstinence rate in screen arm participants (14.5%) was statistically significantly lower than in control arm participants (19.1%) (p= 0.04). However, after performing an intention-to-treat analysis, no statistically significant difference was found (13.1% versus 14.9%; p= 0.35). After 4 years of follow-up, the difference was smaller, but screen arm participants still tended to be less likely to refrain from smoking compared to control arm participants (24.3% versus 29.3%) (p= 0.09).

Multivariate analysis showed that the allocation to the control arm, a higher level of education and being more motivated to quit smoking at start of the study predicted the abstinence from smoking best after 2 years of follow-up. However, after 4 years of follow-up, most important predictors of being abstinent from smoking were a lower estimated baseline level of nicotine addiction (OR= 1.69; 95% CI, 1.03–2.79 and OR= 2.35; 95% CI, 1.38–4.01 for 31-60 minutes and >60 minutes to smoking the first cigarette after waking-up, respectively) and the allocation to the control arm (OR= 1.41; 95% CI, 1.03–1.94).

Interpretation of the results

The self-reported quit rate of NELSON participants in the screen arm (14.5%) was in line with previous lung cancer screening studies that investigated the association between lung cancer screening and smoking behaviour. However, most studies were observational studies,[21-23] so that it remains unknown whether the quit rates can be attributable to receiving lung cancer screening or to the selection of smokers who might be more prone to quit smoking.[24-25] For that reason, we compared the smoking behaviour in screen and control arm participants. The overall quit rates are supportive if we notice that only 3-7% of the general adult population quit smoking successfully each year.[26-27] Relapse is also a huge problem amongst smokers who make a quit attempt, even after being abstinent from smoking for one year,[27-30] although

older adult smokers are assumed to be more successful in their quit attempt.[31-32] From this perspective, lung cancer screening might be a teachable moment for smoking cessation.[23-33] However, the phenomenon that the screen arm participants tended to be less likely to quit smoking compared to the control arm participants remained over time. One possible explanation for this result is a health certificate effect amongst screen arm participants. Following screening, most participants experience less distress and fewer health-related concerns,[34-35] and a health concern alone is argued to be a primary motive for smoking cessation.[36] Although unintended and unrealistic, screening might cause a feeling of reassurance that reduces their perceived risk and so their motivation to change their lifestyle.[37]

In the Danish randomised controlled lung cancer screening trial,[38] no differences in smoking habits were found between screen and control arm participants after one year of follow-up. Important differences in their study design (smoking cessation counselling and lung function test for control arm participants, intention-to-treat analysis) might explain the difference with our study results.[25, 39] Recently, one compared differences in smoking status and smoking behaviour amongst participants in the screen (chest X-ray) and control arm (usual care) in the Mayo Lung Project. There was no difference in smoking status, although screened participants reported a lower reduction in cigarette consumption compared with controls.[40] Only one colorectal cancer screening trial also demonstrated that, although all participants showed desirable lifestyle changes, future healthy lifestyle choices had been unintentionally limited in those who received cancer screening compared with the controls.[41] Until now, our study is the first randomised controlled lung cancer screening trial in which it was demonstrated that lung cancer screening might be a teachable moment, but that it also might falsely reassure some participants. Adequate smoking cessation assistance should be seen as a required addition to lung cancer screening.

In developing adequate interventions, one should be aware of differences in smoking cessation behaviour amongst participants. At both follow-ups, screen arm participants were less likely to quit smoking than control arm participants. Besides this, the analysis with the available baseline characteristics showed that participants who reported a higher baseline motivation to quit smoking were more likely to quit smoking at 2 years of follow-up. This is in line with several widely accepted behavioural models as the Health Belief Model, Theory of planned behaviour, Protection Motivation Theory, or ASE-model.[42-46] Furthermore, participants with a higher level of education were also more likely to quit smoking, which was expected from previous research that showed a socioeconomic status gradient in smoking behaviour.[47] However, only the baseline level of nicotine addiction predicted smoking abstinence after 4 years of follow-up. Nicotine dependence is a well-known predictor of the success or failure in continuing abstinence from smoking.[31, 48-49] Smoking has been regarded as purely a habit for many years, but the World Health Organisation introduced an international classification of disease code for tobacco dependence recently.[50] Nicotine has been compared to other

addictive drugs previously and in a report of the US Surgeon General, it was stated that "*the pharmacologic and behavioural processes that determine the addiction are similar to those that determine the addiction to drugs such as heroin and cocaine*".[51] The importance of nicotine addiction and its treatment is supported by the increased success rate of quitting smoking by the treatment of nicotine addiction.[27, 30, 52-53] One of the opportunities in tobacco control is the wide recognition and treatment of nicotine dependence as an addiction rather than a lifestyle.[54]

9.1.5 Impact of CT screening test results

The impact of CT screening test results on smoking behaviour was investigated amongst 990 male smokers participating in the NELSON trial. The following research questions were formulated (**Chapter 6**):

a What is the association between the CT screening test result (test negative versus test indeterminate) and future smoking abstinence amongst 50-75-year-old male smokers who received lung cancer CT screening using volume and volume-doubling time in the NELSON trial?

b Is the number of indeterminate screening test results associated with an increased quit rate?

c What baseline characteristics are associated with prolonged smoking abstinence after two years of follow-up?

Main findings

Smokers who received at least one indeterminate screening test result made statistically significantly more quit attempts compared to smokers who received only negative screening test results (1.5 ± 2.0 versus 1.9 ± 2.7 attempts; p= 0.016). Nevertheless, smoking abstinence rates were quite comparable in male smokers who received either only negative screening test results (8.9%) or at least one indeterminate screening test result (11.5%) after two years of follow-up. An increase in the number of indeterminate screening test results (0, 1, and ≥2) was accompanied by an increased smoking abstinence rate (8.9%, 10.9%, and 15.0% respectively), although statistically insignificant (p= 0.26). Furthermore, smokers who reported lowest estimated levels of nicotine dependency were most likely to refrain from smoking at follow-up.

Interpretation of the results

It was concluded that the outcome of the screening test result had no influence on smoking abstinence in male smokers who received either only negative screening test results or at least one indeterminate screening test result. Other lung cancer screening trials reported more or less comparable patterns of smoking abstinence after negative and positive find-

ings.[21-23, 33] However, in both the Danish lung cancer screening trial as well as the Pittsburgh Lung Screening Study,[38, 55] a higher smoking abstinence rate was found in participants with significant CT findings. One possible explanation of the difference in our results might be that the NELSON participants were carefully informed about the indeterminate screening result to avoid possible negative psychological consequences. The letter to inform this group of participants about the lung nodule found stated: *"We have observed a very small abnormality in your lung (5–10 mm long). Such a small abnormality is often detected in many persons and it usually represents a small scar or a minor inflammation. Therefore, at this moment there is no need for any further investigations. However, in order to see whether there has been any change in this abnormality, a new CT scan of the lungs will be made after 3 to 4 months."* This letter, combined with a follow-up scan, is expected to produce a very different experience in comparison to the experience of referral to a specialist for work-up and diagnosis after a positive screening test result. Additionally, all participants who received at least one indeterminate screening test result also received a recall CT scan resulting in a final negative screening test result. Furthermore, the smoking questionnaire had not been sent immediately after receiving the screening test result. This all might have diminished an immediate impact of the screening result at the time of completing the questionnaire. A temporary increased lung-cancer specific distress was also found after an indeterminate screening test result, but the long-term health-related quality of life was not affected by the screening test result.[56] This pattern was also seen with the perceived risk.[57]

Another finding was that an increase in the number of indeterminate screening test results was accompanied by an increase in quit rate, although statistically insignificant. A similar pattern was found at the Mayo Clinic, where the number of follow-up recommendations was positively associated with the smoking abstinence rate after three CT screening results.[58] This phenomenon might be explained by an accumulative increased or decreased perceived risk for developing lung cancer after indeterminate or negative test results each time.[25, 40] The risk perception is assumed to affect risk-reducing behaviour.[59-60]

As a consequence of the NELSON nodule management strategy, the number of test-positives decreased drastically after the introduction of an indeterminate screening test result. Consequently, the remaining group of test positives was too small for a sample. For these reasons, we decided to include only people with a negative or indeterminate screening test result in the sub-studies described in this thesis. However, within the context of the impact of lung cancer screening on smoking behaviour, we excluded a population that was expected to be more motivated to quit smoking. It had been reported previously that participants who were referred to the pulmonologist after lung cancer screening remained more often abstinent from smoking at follow-up.[55-58] The exclusion of test-positives from the sub-studies might thus underestimate the impact of screening on smoking cessation. However, additional analysis indicated that conclusions would not change when the study results were controlled for the inclusion of test-positives.

PART 3: HEALTH PROMOTION

9.1.6 Lung cancer screening and tailored health education

In the NELSON trial, the long-term impact on smoking abstinence of a standard self-help smoking cessation brochure was compared with tailored smoking cessation advice (**Chapter 8**). The next research question was addressed:

What is the effect of computer-tailored smoking cessation information (tailored information group) on prolonged smoking abstinence compared with a standard brochure (brochure group) in male smokers who participate in a lung cancer screening trial?

Main findings

All participants of the brochure group (n=642) received the standard self-help information. Only 23% of those who received the tailoring questionnaire (n=642) completed the questionnaire and thus received tailored smoking cessation advice. Screen arm participants were more likely to complete the tailoring questionnaire (OR= 2.27; 95% CI: 1.55-3.32) and thus to receive tailored smoking cessation advice.

After two years of follow-up, 15.6% of smokers who received the standard brochure were abstinent from smoking and a comparable proportion of 12.5% of the smokers who received the tailored smoking cessation advice quit smoking. In the tailored group, the quit rate was comparable between those who received the tailored advice and those who did not receive tailored advice (14.3% versus 11.9%) (p=0.45). Participants with a higher level of education and who were more motivated to quit smoking were more likely to quit smoking. Furthermore, only few participants of both groups were able to recall what kind of intervention they received.

Interpretation of the results

We found that a computer-tailored smoking cessation advice has no advantage over a standard self-help brochure on smoking abstinence amongst baseline smokers after two years of follow-up. Nevertheless, the overall quit rate in lung cancer screening participants (14%) was supportive compared to quit rates after self-help materials in the general adult population.[27] However, only few people (23%) received tailored smoking cessation advice because they completed the tailoring questionnaire, despite the expectation that lung cancer screening participants were highly interested in smoking cessation interventions.[23,61]

A smoking cessation intervention that might be feasible in a lung cancer screening setting should be individualized as much as possible and should reach a large population. Computer-tailored smoking cessation advice seemed to be best suited to this population taking into account the intention to contribute to the prevention of undesirable effects of the

screening strategy on smoking behaviour. The supportive overall quit rates in general might be explained by the expectation that smokers who volunteer to participate in a lung cancer screening trial are more aware of smoking-related disease which may result in a higher motivation to change their smoking behaviour due to some kind of vulnerability compared with the general high-risk population.[23-24] A possible explanation for the failure of the tailored advice might be that the individualization of the tailored information was not sufficient enough for such a specific population as included in the NELSON trial. In a meta-analysis of Noar et al.,[62] it was found that there are many aspects (e.g. type of information, type of comparison condition, type material, number of contacts, length of follow-up) that can moderate its success. Kreuter et al.[63] stated that to be effective, customization of information of a tailored intervention is essential. A lack of individualization might also explain why Clark et al.[64] found that the smoking abstinence or motivation to quit smoking did not differ amongst current smokers who underwent CT screening for lung cancer and who received either a standard written self-help material or a written list of internet resources for smoking cessation at one year of follow-up. To our best knowledge, the effectiveness of a smoking cessation intervention in a lung cancer screening trial has not been investigated in other studies, despite that the specific population of older adult smokers with a long-term smoking history who receive lung cancer screening might be an interesting target group. A wide range of (cost-)effective smoking cessation interventions are available at the moment.[27, 53, 65] Now, attention should be paid to adequately integrate cancer screening with health promotion interventions. There is a need for using a planned approach, such as intervention mapping, that can contribute to create a feasible theory- and evidence-based programme that is likely to be (cost-)effective in promoting smoking cessation in high-risk smokers who will be exposed to (cancer) screening.[66]

9.2 METHODOLOGICAL CONSIDERATIONS

In interpreting the results of the studies described in this thesis, some strengths as well as limitations should be considered. The main methodological issues that are discussed in the previous chapters will be mentioned in this paragraph first. Then, some methodological issues will be discussed into more detail.

Main methodological issues

One of the strengths is that all participants who volunteer in the NELSON trial were randomly allocated to either the screen or control arm. The use of such a study design is methodologically most preferable. The assumption of randomisation is that potential confounding factors are distributed evenly throughout both trial arms. This is highly desirable, especially in the sub-studies with respect to the impact of lung cancer screening on smoking behaviour,

because this health behaviour will be determined by many psychological and social factors. Another major strength for these sub-studies is that the control arm participants had never been invited to the screening site. This might be crucial, since for example hospital visits and contacts with health care providers might influence smoking behaviour.[25] Although the participants are randomised into a screen and control arm, one should recognize that the participants were possibly more motivated to quit smoking than the general adult population. This might overestimate the impact of screening. Another advantage of the studies is that the long-term effect of lung cancer screening on smoking behaviour has been measured using a longitudinal design with a pre-test and two post-tests. Abstinence from smoking should be maintained over time and it is well known that many people who make a quit attempt relapse within 12 months. Therefore, a long-term follow-up was necessary to find out whether lung cancer screening might induce smoking cessation that can be sustained over time. Regardless of this strength, there was no available data about relapse behaviour or any short-term follow-up data that might cause that an immediate effect of lung cancer screening on smoking behaviour to be missed. The power calculations were based on smoking abstinence rates as found in previous research about smoking in a lung cancer screening setting.[27, 58] The observed differences between the screen and control arm were smaller than we could expect from these publications. This caused a reduced power of some of the studies described in this thesis. Several existing health behavioural change theories, as the Health Belief Model, Theory of Planned Behaviour, or the concept of a teachable moment might give more insight in the process of smoking cessation in lung cancer screening participants.[60] Unfortunately, there was no data available related to these concepts from pre-screening to post-screening. Only a small number of demographical characteristics and the smoking history have been measured at randomisation. Consequently, our opportunities to provide more insight in the process of behavioural change were limited.[25] Furthermore, as a consequence of a risk-based selection that was used to make a large-scale trial feasible, mainly males were included in the study.[1-2] For this reason, only males were selected for the NELSON trial sub-samples described in this thesis. Our results are therefore applicable to males in general, although there are no indications so far to suggest that the impact of lung cancer screening on smoking behaviour is gender-dependent.[22, 38-58]

Biochemical verification of the self-reported smoking behaviour

Data about the individuals' current and past smoking behaviour provides useful information to construct lifetime histories of the exposure to tobacco, which is essential from the inclusion of the study participants until the final analysis of the cost-effectiveness of lung cancer screening. Self-reported data is a commonly used method for data collection concerning smoking behaviour. Despite the wide use of self-reported data, the practical usefulness is often under discussion, because it depends on how accurately the (retrospective) data is reported by the individual.[67-68] Self-completed reports can be affected by factors such as

socially desirable response bias,[69] which is especially of concern within disease prevention or health promotion programmes, where social pressure or medical criticism is higher.[70] The increased attention to the harmful effects of smoking may induce the misclassification of their smoking behaviour.[71-72] Moreover, questions about their own smoking history may also be subject to recognition bias, because the time frame often implies many years.[67] Besides the convincible disadvantages, self-reported data is one of the most easiest and affordable methods for data collection within a large population.[73] For the reason that self-reported smoking behaviour might be imprecise, it is recommended to biochemically verify the self-reported smoking behaviour in smoking cessation intervention studies.[39]

Although we are aware of potential bias, however, we have not biochemically verified the self-reported smoking behaviour in the NELSON trial. One reason for this is that there is a major difference between the NELSON trial and smoking cessation intervention trials in general. The participants of the NELSON trial participate in a lung cancer screening trial instead of a smoking cessation intervention trial. None of the participants were aware of the inclusion and exclusion criteria used in the NELSON trial due to the population-based recruitment procedure, so that participants were less likely to misclassify their smoking behaviour to increase their chances of being invited. Participants were also unaware of the aim to explore the impact of lung cancer screening on smoking behaviour as well. It is less likely that the participants of our lung cancer screening trial were subjected to social pressure or that they tried to increase the chances of being invited for screening or smoking cessation support. Our expectation that participants have valid self-reports in general was confirmed by Studts et al.,[74] who found that self-reported smoking status was highly consistent with urinary cotinine test results in participants of the Jewish Hospital Lung Cancer Screening and Early Detection Study. Thereby, biochemical verification should be done in both the screen arm as well as the control arm. Because of the aim to minimize intervening in the control arm, a biochemically verification of the self-reported smoking behaviour was not performed.

Intention-to-treat analysis

In addition to the recommended biochemical verification of self-reported data, the evaluation of smoking cessation intervention studies should also be done according to the intention-to-treat analysis (ITT).[39] The main analysis of two of our studies was not in conformity with the ITT-analysis. Although this method is widely used, there are some major differences between our study and other studies that investigate the impact of a particular intervention on smoking behaviour that cause that an intention-to-treat analysis might be too conservative and therefore it might not be most appropriate type of data analysis here. The most important reason to deviate from the recommendation is that the NELSON participants were invited to participate in a lung cancer screening trial. The study population was selected on the basis of their smoking history, but participants have not been aware of this inclusion criterion. Thus, from the participants' perspective, even despite their impressive self-reported smoking

history, they were invited to participate in the trial. Neither were participants told that they were expected to quit smoking. They only received self-help smoking cessation information, without any expectations from the investigators. Participants were also not informed about the real aim of the smoking cessation questionnaires. The questionnaire contained questions about general health, quality of life, smoking behaviour, family history of lung cancer and so on, with the aim to prevent social responses. With all this in mind, an intention-to-treat analysis might be too conservative. The results of an additional intention-to-treat analysis were provided continuously.

Non-response bias

In our sub-samples, the response rate decreased over time. The decrease in the control arm was consistently higher than in the screen arm. Control arm participants were less likely to respond to questionnaires. Several reasons may ground this phenomenon. Control arm participants were possibly lost to follow-up when they moved to another place without informing us because of the passive involvement. Control arm participants were willing to participate in the trial and to undergo CT screening for lung cancer. The result of the randomisation has been disappointing for some of these control arm participants. The motivation to participate as a control arm participant might decrease. Non-response might become selective and in that case, study results might be affected. In all sub-studies, a possible non-response bias was investigated by comparing baseline characteristics of respondents with baseline characteristics of non-respondents. After four years of follow-up, we found some non-response bias in the control arm: higher educated participants were more likely to respond on the follow-up questionnaire. The data were controlled for differences in non-response, because of the concern that non-response bias might influence the internal validity, although the outcomes of the corrected and uncorrected analysis of the data were comparable.

Relapse to smoking

While smoking abstinence was the primary outcome in the sub-studies described in this thesis, smoking cessation is a process in which people go through the stages of change repeatedly. Many of the smokers want to quit smoking, but most of them fail to persevere in abstaining from smoking.[29-30, 75] Within one year, about 95% of those who tried to stop smoking on their own and 75% of those who quit smoking using evidence-based smoking cessation intervention relapsed to continue smoking.[29, 76] Most people need multiple quit attempts before they are able to be successfully abstain from smoking. In the NELSON study, we have only data about continued smoking or the abstinence of smoking at two fixed time points, completed with data about quit attempts in a fixed time period. When combining the data, it was obvious that people transfer throughout the stages of change. However, detailed data about all quit attempts, periods of abstinence and relapse to smoking were unfortunately lacking, although this information might give much more insight in the process of smoking

and smoking cessation in high-risk smokers who participate in a lung cancer screening trial. Since the follow-up periods were two years, this makes it hard to adequately and completely measure all relevant data about smoking, quit attempts, smoking abstinence and relapse by self-reports. Additionally, we included only participants who smoked at randomisation. Thus, information about whether lung cancer screening might play a role in relapse to smoking in long-term former smokers is uncertain. Nevertheless, although that detailed information about relapse might be relevant, no increased relapse rates were found after lung cancer screening in observational studies to date.[21-22, 58]

9.3 GENERAL CONCLUSIONS

- The self-selection of NELSON study participants is limited, so that the study results should be applicable to both the future target as well as the general populations.
- The novel nodule management strategy that measured volume and VDT is a good screening instrument for deciding further action, should a lung nodule be found in asymptomatic high-risk persons based on primarily findings of the first and second screening rounds.
- The novel nodule management strategy reduced the number of test positives substantially by introducing a new screening test result: the indeterminate screening test result. It was found that receiving one or more indeterminate test results had no different impact on smoking behaviour compared with receiving only negative screening test results. After two years of follow-up, the smoking behaviour seemed to be more favourable after an increased number of indeterminate screening test results, although this finding diminished after four years of follow-up.
- There is a considerable lack of evidence about the impact of cancer screening on future lifestyle. Based on the studies published so far, cancer screening might be a teachable moment for lifestyle improvement, although the risk of a health certificate effect remains.
- Supportive quit rates (14.5% and 24.3%) were found in screen arm participants after two and four years of participating in the NELSON trial. Lung cancer screening is a teachable moment for smoking cessation. However, screen arm participants were less likely to quit smoking (to a modest extent however) compared to control arm participants (19.1% and 29.3%), which raised the concern of a feeling of false reassurance.
- A computer-tailored smoking cessation advice had no advantages over a standard self-help brochure on smoking behaviour after two years of follow-up.

9.4 RECOMMENDATIONS FOR RESEARCH AND PRACTICE

- Although the analysis suggests that selection bias might not play a major role in the NELSON trial, future analysis of differences in all-cause mortality between study participants and eligible non-participants is recommended to demonstrate further to what extent the study results are representative of the target and general population and whether self-selection bias plays a role in interpreting results about the cost-effectiveness of lung cancer screening.
- Analysis in which the screen and control arm will be compared will be crucial in order to determine whether a potential lung cancer mortality reduction might be attributable to screening. The National Cancer Institute reported a mortality reduction in the NLST recently and ending of the study was recommended. Interim analysis in the NELSON trial is recommended to investigate the lung cancer mortality rate in both trial arms.
- The nodule management strategy as used in the NELSON trial performed well as a screening protocol in a high-risk population during the first and second round screening. Further optimization of the protocol to avoid unfavourable effects as false-positives, overdiagnosis, and overtreatment is still recommended.
- This thesis shows that lung cancer screening might be a teachable moment for smoking cessation, although the concern of a possible health certificate effect remains. It is important that health care providers recognize that the contact with subjects who were invited for lung cancer screening might have opportunities to help smokers to change their behaviour by increasing their motivation to quit smoking.

  Special attention should be given to the use of potential teachable moments, such as undergoing CT screening or receiving the screening test result.
- Smoking cessation is most effective way to prevent lung cancer. Therefore, there is an urgent need for the development of a smoking cessation intervention that is feasible in a lung cancer screening programme in a cost-effective way with the aim to increase the magnitude of the overall impact of screening on health. Such a best-practice smoking cessation intervention requires the use of a model for planned health promotion to guide the development of a theory and evidence-based intervention that can be proved to be effective, implemented successfully and likely to be sustainable.
- Health care providers should be aware that lung cancer screening might act as a health certificate effect by providing a feeling of false reassurance.
- The impact of cancer screening on lifestyle and lifestyle-related morbidity should be proposed in all new cancer screening trials and investigated in current cancer screening programmes to get more insight in the underlying process.
- A nation wide implementation of lung cancer screening in its present form cannot be recommended until a cost-effective smoking cessation intervention is integrated in the screening programme, although the cost-effectiveness of lung cancer screening should be clear first.

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SUMMARY

SAMENVATTING

SUMMARY

Lung cancer is the leading cause of cancer mortality throughout the world. About 80-90% of all lung cancer cases can be attributed to smoking, so that refraining from smoking is the most effective way to prevent lung cancer. Unfortunately, current interventions aimed at preventing people to start smoking and promoting smoking cessation were not able to eliminate the tobacco epidemic.

Lung cancer is often in an advanced stage at time of diagnosis and despite the advances in medical treatment, the 5-year survival rate of less than 16% is still very poor. Nowadays, lung cancer is also more common in former smokers than in current smokers. This all emphasizes the need for the early detection and treatment of lung cancer. CT screening for lung cancer proved to detect lung cancer at an earlier stage, but evidence about the reduction in lung cancer mortality after CT screening for lung cancer from current lung cancer screening trials is still awaited. Thereby, many people may be exposed to the possible (minor) side effects of screening, while only few people may benefit from screening. The purpose of this thesis was to investigate the impact of lung cancer screening, using volume and volume-doubling time (VDT), on future smoking behaviour in smokers at high risk for developing lung cancer and the possible effect of smoking cessation interventions.

Part 1: The NELSON trial

The aim of the first research question was to investigate the degree of self-selection of the NELSON participants (**Chapter 2**). Characteristics (age, general health, lifestyle and level of education) of respondents to the first general questionnaire, those eligible to participate in the NELSON trial, and those randomised in the NELSON trial, were compared to national reference groups. The differences that have been found were negligibly small, which implicates that the study results of the NELSON trial will be roughly applicable to both the target population as well as the Dutch general population.

In **Chapter 3**, the novel management strategy that was introduced in the NELSON trial was evaluated with primary data obtained from the first and second screening round. The strategy reduced the need for follow-up evaluation substantially, without interfering the sensitivity and specificity of CT screening. After one screening round, the percentage of early lung cancer (stage I) detected by CT screening was comparable to other randomised controlled trials. Based on the study results so far, the use of the volume and growth (VDT) of lung nodules as main criteria for deciding on further action is a useful nodule management strategy in lung cancer CT screening amongst asymptomatic people at high risk for developing lung cancer. Subsequently it is important to investigate whether the use of this management protocol might facilitate (teachable moment) or hinder (health certificate effect) future abstinence from smoking with the aim of exploring possible (un)favourable effects of screening.

Part 2: Lung cancer screening and smoking cessation

The (un)wanted effects of cancer screening on the lifestyle are uncertain, although lifestyle is a major modifiable cause of cancer and premature death. Current evidence about the effects of cancer screening on lifestyle and lifestyle-related morbidity, and how to deal with possible unwanted effect of cancer screening, was examined by means of a systematic review (**Chapter 4**). After reviewing the literature, one major conclusion that could be drawn was that the evidence about the impact of cancer screening on lifestyle is very limited and evidence about the impact on lifestyle-related morbidity is lacking. There is also a lack of evidence about the opportunities of lifestyle interventions in a screened population. However, the available evidence suggested a possible teachable moment for desirable lifestyle changes after cancer screening, although one should realize that cancer screening might also have an unintended health certificate effect that might contribute to the continuation or even initiation of unhealthy behaviour. Randomised controlled trials are needed to further investigate the possible (un)wanted effects of cancer screening on lifestyle and whether health promotion interventions are feasible in and complementary to cancer screening programmes.

The impact of lung cancer screening on smoking abstinence was investigated amongst male smokers randomised in the NELSON trial after both two (**Chapter 5**) and four (**Chapter 7**) years of follow-up. Two sub samples of screen (n=641) and control (n=643) arm participants were sent a follow-up questionnaire to measure their actual smoking behaviour twice. The quit rates in screen arm participants were encouraging when we compare this with the quit rate in the general adult population, which suggested a potential teachable moment for lung cancer screening for smoking cessation. However, screen arm participants were less likely to quit smoking than control arm participants, although the differences were modest. As such, there is a remaining concern that participants may experience a false feeling of reassurance after lung cancer screening.

In the NELSON trial, a new screening test result was introduced: the indeterminate screening test result. We explored whether the CT screening test result (negative versus indeterminate) was associated with smoking abstinence (**Chapter 6**). A questionnaire was sent to screen arm male smokers who received either negative screening test results (n=550) or at least one indeterminate screening test result (n=440). Those participants who received at least one indeterminate reported more quit attempts, although the smoking abstinence rate was comparable with participants who received only negative screening test results. An increase in the number of indeterminate screening test results was accompanied with a slightly, but statistically non-significant, increase in smoking abstinence. In conclusion, the CT screening test result had no impact on future smoking abstinence in male smokers at a high risk for developing lung cancer who received lung cancer screening.

Part 3: Health promotion

The purpose of the study described in **Chapter 8** was to investigate whether a computer-tailored smoking cessation intervention was more effective in inducing smoking cessation compared with a standard self-help brochure. All participants received either a tailoring questionnaire to generate the tailored advice or a standard self-help brochure. The results indicated that only 23% of those who received the tailoring questionnaire actually returned a completed form and thus received tailored advice. This has major implications on the usefulness of this intervention for this specific population. Two sub-samples of 642 male smokers randomised in the NELSON trial subsequently received subsequently a questionnaire to measure their smoking behaviour after two years of follow-up. The computer-tailored smoking cessation advice did not achieve better results in inducing smoking abstinence than a self-help brochure and might not be a sufficient intervention to reduce smoking behaviour in the way it was provided to this specific population of participants in a lung cancer screening trial.

Discussion

The answers to the research questions and its implications were discussed in **Chapter 9**. Furthermore, attention had been paid to methodological issues (as study design, sample size, study population, non-response bias, the intention-to-treat method, and the biochemical verification of the self-reported smoking status) that should be considered in interpreting the study results.

The research described in the first part of this thesis showed that the self-selection of NELSON study participants is limited, but future analysis of all-cause mortality is recommended to demonstrate the extent to which the study results are representative of the target and general population. Furthermore, the nodule management strategy as used in the NELSON trial performed well as a screening protocol for a high-risk population during the first and second screening rounds. Nevertheless, further optimization of the protocol is still recommended to avoid unfavourable effects. Finally, interim analysis in which the screen and control arm will be compared is crucial to investigate whether a potential lung cancer mortality reduction might be attributable to lung cancer screening.

In the second part, a considerable lack of evidence was discovered about the possible impact of cancer screening on lifestyle and lifestyle-related morbidity and more research is warranted. The available studies suggested that cancer screening might be a teachable moment for lifestyle improvement, although the risk of a health certificate effect caused by a false feeling of reassurance remains. This was also found in the NELSON trial, where screen arm participants appeared to be more likely to quit smoking than control arm participants, although the differences were modest. Receiving at least one indeterminate test result – the extra test result introduced in the NELSON trial introduced – had no different impact on

future smoking behaviour compared to receiving only negative screening test results. Finally, we found that a single computer-tailored smoking cessation advice had no advantages over a standard self-help brochure on smoking behaviour. These results strongly emphasized the need to develop a cost-effective approach to promote smoking abstinence in a lung cancer screening setting with the aim of increasing the magnitude of the overall impact on health.

It is also important that health care providers recognize that the contact with subjects who were invited for lung cancer screening might have opportunities to help smokers to change their behaviour, but that lung cancer screening might act as a license to smoke.

A nation wide implementation of lung cancer screening in its present form cannot be recommended until a cost-effective smoking cessation intervention is integrated in the screening programme, although the cost-effectiveness of lung cancer screening should be clear first.

SAMENVATTING

Longkanker is wereldwijd de voornaamste aan kanker gerelateerde doodsoorzaak. Van alle longkanker is ongeveer 80-90% primair te wijten aan roken, waardoor niet roken de meest effectieve manier is om longkanker te voorkomen. Helaas zijn de huidige interventies, die zijn gericht op zowel het voorkomen dat mensen beginnen met roken als het bevorderen dat mensen stoppen met roken, niet in staat geweest om de tabaksepidemie terug te dringen.

Longkanker is op het moment van de diagnose veelal in een vergevorderd stadium en ondanks de ontwikkelingen in medische behandelmogelijkheden is de 5-jaars overlevingskans van minder dan 16% nog steeds erg laag. Tevens komt longkanker tegenwoordig vaker voor bij ex-rokers dan bij huidige rokers. Dit alles benadrukt het belang van de vroege opsporing en behandeling van longkanker. Het is bewezen dat CT screening op longkanker de kanker in een eerder stadium kan opsporen, maar het is nog altijd wachten op het wetenschappelijke bewijs of dit ook de sterfte aan longkanker omlaag kan brengen. Daarnaast zal een grote groep mensen worden blootgesteld aan potentiële (kleine) neveneffecten, terwijl slechts een kleine groep mensen zal profiteren van vroegopsporing. Het doel van dit proefschrift was dan ook om na te gaan wat de impact is van longkankerscreening, gebruik makend van het volume en de volume verdubbelingstijd (VDT), op het toekomstige rookgedrag van rokers met een hoog risico op longkanker en het mogelijke effect van interventies gericht op stoppen met roken.

Deel 1: De NELSON studie

Het doel van de eerste onderzoeksvraag was om de mate waarin sprake is van zelfselectie van de NELSON studiedeelnemers te onderzoeken (**Hoofdstuk 2**). Kenmerken (leeftijd, algemene gezondheid, leefstijl en opleidingsniveau) van mensen die hebben gereageerd op een eerste vragenlijst, degenen die in aanmerking kwamen voor deelname aan de NELSON studie en degenen die in de NELSON studie werden gerandomiseerd werden vergeleken met nationale referentiegroepen. De gevonden verschillen waren te verwaarlozen, wat impliceert dat de resultaten van de NELSON studie grofweg toe te passen zijn op zowel de doelpopulatie als de algemene Nederlandse bevolking.

In **Hoofdstuk 3** werd de nieuwe nodule management strategie die was geïntroduceerd in de NELSON studie geëvalueerd op basis van de eerste resultaten uit de eerste en tweede screeningsronden. De strategie verlaagde de noodzaak tot doorverwijzing substantieel, zonder daarbij de sensitiviteit en specificiteit van CT screening aan te tasten. Na de eerste screeningsronde was het percentage longkanker dat in een vroeg stadium (stadium I) werd ontdekt vergelijkbaar met andere gerandomiseerd gecontroleerde studies. Als we kijken naar de huidige studieresultaten kunnen we concluderen dat het gebruik van het volume en groei (VDT) als richtlijn voor het bepalen van de vervolgstrategie bij het vinden van long

nodules een goede methode is voor longkanker CT screening bij asymptomatische personen met een hoog risico op het ontwikkelen van longkanker. Nu is het nog van belang om uit te zoeken of dit screeningsprotocol stoppen met roken bevordert (*teachable moment*) of hindert (*health certificate effect*) met als doel om mogelijke (on)gewenste effecten van screening te achterhalen.

Deel 2: Longkankerscreening en stoppen met roken

De (on)gewenste effecten van kankerscreening op de leefstijl zijn onbekend, ondanks dat leefstijl een belangrijk modificeerbare oorzaak is van kanker en vroegtijdige sterfte. Door middel van een literatuuronderzoek werd gezocht naar huidig wetenschappelijk bewijs over de effecten van kankerscreening op leefstijl en leefstijlgerelateerde aandoeningen en hoe met mogelijke ongewenste effecten van kankerscreening kan worden omgegaan **(Hoofdstuk 4)**. Na het doornemen van de literatuur kon vooral worden geconcludeerd dat er een schaarste is aan wetenschappelijk bewijs met betrekking tot het effect van kankerscreening op leefstijl en dat literatuur over het mogelijke effect van kankerscreening op leefstijlgerelateerde aandoeningen ontbreekt. Tevens is er weinig bekend over de mogelijkheden van leefstijlinterventies in een gescreende populatie. Uit de beschikbare literatuur kwam echter naar voren dat kankerscreening mogelijk een leermoment is voor gewenste leefstijlveranderingen, maar dat men zich wel moeten realiseren dat kankerscreening mogelijk ook een onbedoeld gezondheidscertificaat geeft dat er toe kan bijdragen dat ongezond gedrag wordt voortgezet of zelfs wordt gestart. Gerandomiseerd gecontroleerde onderzoeken zijn noodzakelijk om te achterhalen wat de mogelijke (on)gewenste effecten zijn van kankerscreening op leefstijl en of gezondheidsbevorderende interventies haalbaar zijn in en een toevoeging zijn aan kankerscreeningsprogramma's.

De impact van longkankerscreening op het stoppen met roken werd onderzocht onder mannelijke rokers die waren gerandomiseerd in de NELSON studie na een follow-up van zowel twee (**Hoofdstuk 5**) als vier (**Hoofdstuk 7**) jaar. Twee steekproeven van screen- (n=641) en controlegroep (n=643) deelnemers kregen twee keer een vragenlijst toegezonden om hun actuele rookgedrag te meten. De stoppercentages onder deelnemers in de screengroep waren aanmoedigend wanneer we deze vergelijken met het stoppercentage onder de algemene bevolking, wat suggereert dat longkankerscreening een mogelijk leermoment is om te stoppen met roken. Deelnemers in de screengroep waren echter minder geneigd om te stoppen met roken dan deelnemers in de controlegroep, al zijn de verschillen gering, waardoor toch de zorg bestaat dat longkankerscreening voor een onterecht gevoel van geruststelling zorgt.

In de NELSON studie werd een nieuwe screeningstestuitslag geïntroduceerd: de twijfelachtige screeningstestuitslag. We hebben onderzocht of de CT screeningtestuitslag (negatief versus twijfelachtig) was geassocieerd met stoppen met roken (**Hoofdstuk 6**). Een vragenlijst

werd verzonden naar mannelijke rokers in de screengroep die of enkel negatieve testuitslagen (n=550) of tenminste één twijfelachtige testuitslag (n=440) hadden ontvangen. De deelnemers met tenminste één twijfelachtige testuitslag rapporteerden vaker een stoppoging, ondanks dat het stoppercentage vergelijkbaar was met de deelnemers die enkel negatieve testuitslagen ontvingen. Een toename in het aantal twijfelachtige testuitslagen ging gepaard met een lichte toename in het stoppercentage, al was de toename niet statistisch significant. Concluderend kunnen we stellen dat de CT screeningstestuitslag niet van invloed is geweest op het toekomstige rookgedrag bij mannelijke rokers met een hoog risico op longkanker die werden gescreend op longkanker.

Deel 3: Gezondheidsbevordering

Het doel van de studie beschreven in **Hoofdstuk 8** was het onderzoeken of een advies-op-maat effectiever was in het bevorderen van stoppen met roken vergeleken met een standaard zelfhulp brochure. Alle deelnemers ontvingen of een vragenlijst om daarmee een advies-op-maat te kunnen maken of de standaard zelf-hulp brochure. Uit de resultaten bleek dat slechts 23% van de deelnemers die de vragenlijst ontvingen voor een advies-op-maat, een ingevulde vragenlijst terugstuurden en daarmee het advies-op-maat hebben ontvangen. Dit is een belangrijk gegeven wanneer we kijken naar de bruikbaarheid van deze interventie binnen deze specifieke populatie. Twee steekproeven van 642 mannelijke rokers die zijn gerandomiseerd in de NELSON studie kregen vervolgens na twee jaar een vragenlijst om daarmee hun rookgedrag te meten. Een advies-op-maat behaalde geen betere resultaten met betrekking tot het stoppen met roken vergeleken met de standaard brochure, waardoor een advies-op-maat zoals deze is aangeboden vooralsnog onvoldoende blijkt bij te dragen aan het terugbrengen van het aantal rokers dat deelneemt aan een longkankerscreeningsprogramma.

Discussie

De antwoorden op de onderzoeksvragen en de daarbij behorende implicaties werden besproken in **Hoofdstuk 9**. Tevens kwamen methodologische aspecten (zoals studie design, steekproefgrootte, studiepopulatie, non-response bias, de intention-to-treat methode en de biochemische verificatie van de zelfgerapporteerde rookstatus) aan bod die moeten worden meegenomen in de interpretatie van de studiegegevens.

Het onderzoek dat werd omschreven in het eerste deel van dit proefschrift toonde aan dat de mate van zelfselectie in de NELSON studiepopulatie beperkt is, maar dat aanvullende analyse van de doodsoorzaken wordt aanbevolen om daarmee aan te tonen in welke mate de studieresultaten representatief zijn ten opzichte van de doelpopulatie en de algemene populatie. Verder blijkt de nodule management strategie die wordt gebruikt in de NELSON

studie een goed screeningsprotocol te zijn in een hoogrisico populatie tijdens de eerste en tweede screeningsronden. Desondanks verdient het nog altijd de aanbeveling om het protocol te optimaliseren om ongewenste effecten te voorkomen. Tot slot is het cruciaal om voorlopige analyses te doen waarin de screen- en controlegroep zullen worden vergeleken om na te gaan of een potentiële verlaging in longkankersterfte toe te schrijven is aan longkankerscreening.

In het tweede gedeelte van dit proefschrift werd een duidelijk gebrek aan wetenschappelijk bewijs gevonden voor de mogelijke impact van kankerscreening op leefstijl en leefstijlgerelateerde aandoeningen en meer onderzoek is dan ook noodzakelijk. Gebaseerd op de enkele studies die tot nu toe zijn gepubliceerd blijkt dat screening op kanker mogelijk een leermoment is voor verbeteringen van de leefstijl, maar dat er ook een risico is dat kankerscreening ongewenst een gezondheidsverklaring is door een onterecht gevoel van geruststelling. Dit werd ook gevonden in de NELSON studie, waarin deelnemers in de screengroep minder geneigd bleken te zijn om te stoppen met roken dan deelnemers in de controlegroep, al waren de verschillen klein. Het ontvangen van tenminste één twijfelachtige screeningstestuitslag – de in NELSON geïntroduceerde extra testuitslag – had geen verschillend effect op het toekomstige rookgedrag vergeleken met het ontvangen van enkel negatieve testresultaten. Tot slot vonden we dat het geven van advies-op-maat geen voordelen had op het rookgedrag ten opzichte van een standaard zelfhulpbrochure. Al deze resultaten benadrukken de noodzaak om een kosteneffectieve methode te ontwikkelen die het mogelijk maakt om in een longkankerscreening setting het stoppen met roken te bevorderen om daarmee het totale effect op de gezondheid te vergroten. Het is tevens van belang dat zorgverleners zich realiseren dat het contact met mensen die worden gescreend op longkanker mogelijkheden biedt om rokers te ondersteunen bij gedragsverandering, maar dat longkankerscreening ook kan werken als een onbedoelde vrijbrief om te roken. Een landelijke invoering van longkankerscreening zoals het op dit moment wordt aangeboden kan niet worden aanbevolen totdat er een kosteneffectieve rookstopinterventie is geïntegreerd in het screeningsprogramma, al zal eerst nog de kosteneffectiviteit van longkankerscreening duidelijk moet worden.

DANKWOORD

Nu sta ik voor de laatste uitdaging bij het schrijven van een proefschrift: het schrijven van het dankwoord, het meest gelezen onderdeel van het proefschrift. Ook ik wil nu graag iedereen, en een aantal mensen in het bijzonder, bedanken voor alle steun die ik heb gekregen. Zonder die steun was dit proefschrift er niet gekomen.

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ABOUT THE AUTHOR

Carlijn van der Aalst was born on August 7, 1983 in Eindhoven, the Netherlands. She completed her Bachelor of Nursing at the Fontys Hogeschool Verpleegkunde in Eindhoven in 2005. In that year, she started studying Health Care Sciences at the Maastricht University. After graduating the entrance examination for the Master of Health Care Sciences, she continued with the Master of Public Health, with the differentiation Health Care Studies. She graduated in Health Care Sciences in March 2008. Since November 2007, she has been appointed as junior researcher at the department of Public Health and the department of Pulmonology at the Erasmus University Medical Centre in Rotterdam. During this period, she performed researches in the Dutch-Belgian randomised controlled lung cancer screening (NELSON) trial, as described in this thesis.

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Van der Aalst CM, de Koning HJ, van den Bergh KAM, Willemsen MC, van Klaveren RJ. The effectiveness of a computer-tailored smoking cessation intervention for participants in lung cancer screening: a randomised controlled trial. *Submitted*

Van der Aalst CM, van Klaveren RJ, van den Bergh KAM, Groen HJM, Weenink C, Lammers J-WJ, Willemsen MC, de Koning HJ. Smoking behavioural change in male smokers of a randomised controlled lung cancer screening (NELSON) trial: 4-year follow-up. *Submitted*

PHD PORTFOLIO

Summary of PhD training

Name PhD student:	Carlijn M. van der Aalst
Erasmus MC Department:	Public Health/ Pulmonology
PhD period:	2007-2011
Promotors:	prof.dr. H.J. de Koning
	prof.dr. H.C. Hoogsteden

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
- Scientific writing course	2009	15 hours
- Computer courses/ literature search Department of Public Health, Erasmus MC Rotterdam, The Netherlands	2008/2009	16 hours
Specific courses (e.g. Research school, Medical Training)		
- *Planning and Evaluation of Screening*	2008	1.4 ECTS
- *Methods of Health Services Research*	2010	0.7 ECTS
- *Primary and Secondary Prevention Research* Summer Courses Netherlands Institute for Health Sciences Rotterdam, The Netherlands	2010	0.7 ECTS
- *Best Practices of Health Education and Promotion* Master of Public Health, Health Education and Promotion Maastricht University Maastricht, The Netherlands	2010	6.0 ECTS
Seminars, meetings and workshops at the department of Public health/ Erasmus MC		
- Seminars / workshops / meetings / PhD-days	2007-2011	140 hours
- Risk perception – Informed decision making – Quality of life (RIQ) meetings	2009/2011	10 hours
- Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen	2011	6 hours

Presentations

-	'The impact of the CT-scan results in a lung cancer screening trial on smoking abstinence.' *(Oral presentation)* World Conference of Tobacco Or Health Mumbai, India	2009	28 hours
-	*'The Long-term Effects of Participating in a Lung Cancer Screening Trial on Smoking Cessation.'* *(Poster presentation)* World Conference of Tobacco Or Health Mumbai, India	2009	20 hours
-	*'Impact of CT-scanning on quality of life and smoking behaviour.' (Oral presentation)* Cancer and screening: trials and modelling to guide public health policies Rotterdam, The Netherlands	2009	28 hours
-	*'Effects of CT screening on smoking habits: NELSON results.'* *(Oral presentation)* NELSON symposium Utrecht, The Netherlands	2009	28 hours
-	*'Quality of Life assessment in the NELSON trial.'* *(Oral presentation)* NELSON symposium Utrecht, The Netherlands	2009	28 hours
-	*'Impact of cancer screening on lifestyle.'* *(Oral presentation)* International Conference of CT screening on lung cancer Copenhagen, Denmark	2010	28 hours
-	*'Smoking behavioural change in male smokers of a randomised controlled lung cancer screening (NELSON) trial: 4-year follow-up.' (Poster presentation)* World Conference on Lung Cancer Amsterdam, The Netherlands	2011	15 hours

(Inter)national conferences		
- *1+1 = SUCCES!* Oestgeest, The Netherlands	2008	8 hours
- World Conference of Tobacco Or Health Mumbai, India	2009	40 hours
- *Cancer and Screening: trials and modelling to guide public health policies* Rotterdam, The Netherlands	2009	8 hours
- *NELSON symposium* Utrecht, The Netherlands	2009	8 hours
- *International Conference of CT screening on Lung Cancer* Copenhagen, Denmark	2010	16 hours
- European Conference on Tobacco or Health Amsterdam, The Netherlands	2011	24 hours
- Post-doc retreat 2011 Post-doc Career Development Initiative Heeze, The Netherlands	2011	24 hours
- World Conference on Lung Cancer Amsterdam, The Netherlands	2011	32 hours
2. Teaching	**Year**	**Workload (Hours/ECTS)**
Supervising practices and excursions, Tutoring, Lecturing		
- Theme 4.2: The population as a patient	2009-2010	6 hours
- Theme 3.c: Physician and public health	2011	10 hours
- Theme 3.c: Medication safety (training)	2011	8 hours
- Guest lecturer nursing (Care Academy)	2011	28 hours