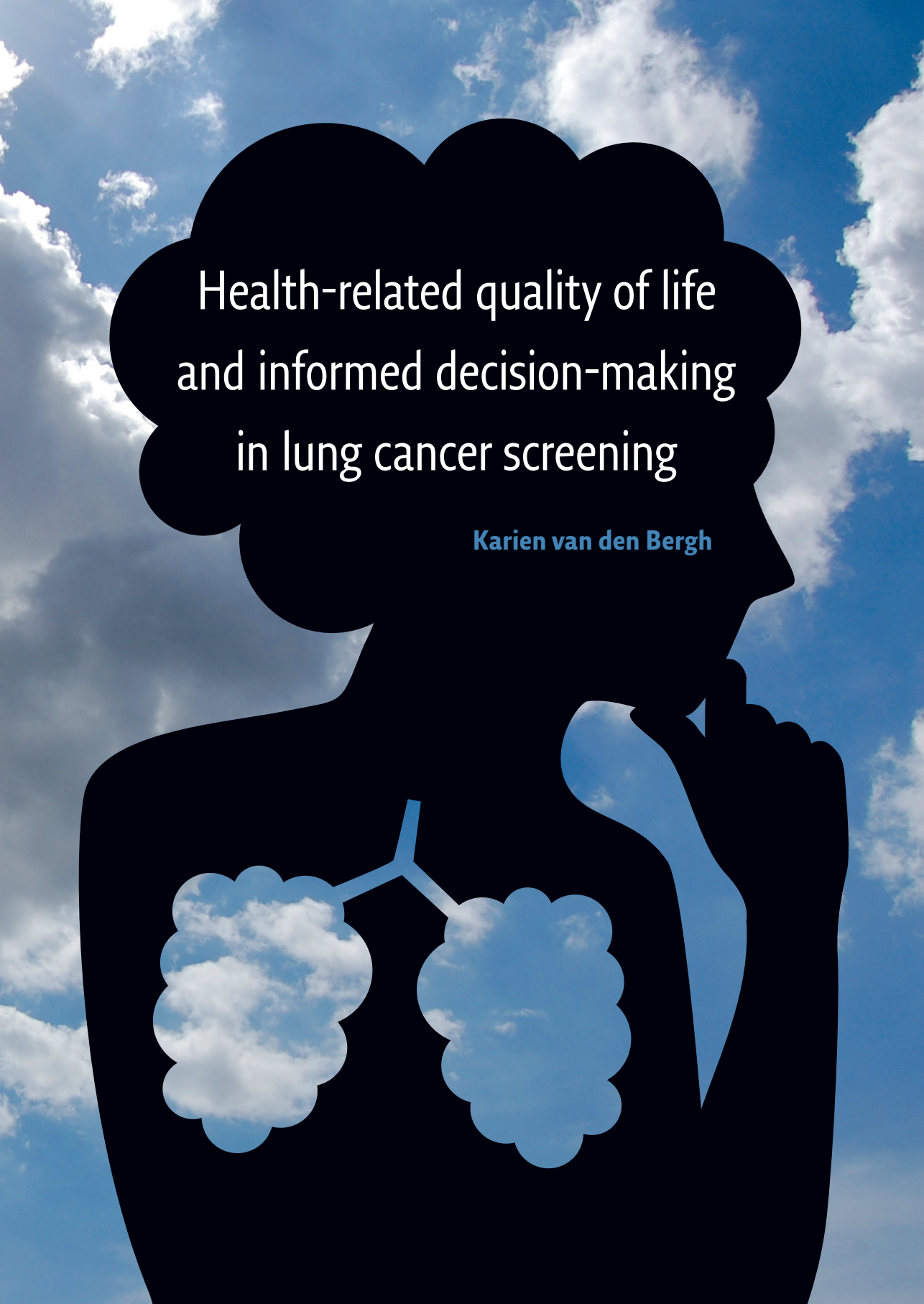

Health-related quality of life and informed decision-making in lung cancer screening

Karien van den Bergh

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Health-related Quality of Life and Informed Decision-making in Lung Cancer Screening

Gezondheidsgerelateerde kwaliteit van leven en geïnformeerde besluitvorming bij longkankerscreening

Proefschrift

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Introduction

Chapter 1

General introduction

Lung cancer

Lung cancer is worldwide the most common form of cancer and the most common cause of death from cancer (1, 2). It accounts for approximately 28% of all cancer deaths (2). World-wide 1.2 million people die from lung cancer each year (3). In the Netherlands, 9,918 people died from lung cancer in 2008 (4). Lung cancer is often diagnosed in an advanced incurable stage. Despites advances in treatment, 85% or more patients will die within 5 years after diagnosis (5, 6). In the Netherlands, the mortality-incidence ratio is 95% (7). Total costs of lung cancer in the Netherlands were estimated to be 193 million euro in 2005 (8).

Lung cancer prevention: primary and secondary

Smoking causes 80-90% of all lung cancer cases (2). Lung cancer risk increases with the number of cigarettes smoked and the years of smoking (9). Therefore, theoretically, primary prevention, quitting smoking or, more importantly, measures to reduce starting smoking may almost totally eliminate the disease. However, although several such measures have been successful, the number of lung cancer deaths is still unacceptably high (9, 10). Although the risk of subjects with a heavy smoking history who quit smoking decreases after quitting, they remain at increased risk for lung cancer during their life and their risk will probably not become as low as in never smokers (11, 12). Moreover, despite the decreasing number of smokers, the incidence of lung cancer is decreasing only slightly in men and is still increasing in women, due to the 'lag time' (i.e. the time period between smoking and incidence) (13). It is expected to see a growing proportion of lung cancer patients who are former smokers and not current smokers (9).

An additional, alternative approach to reduce lung cancer mortality could be secondary prevention or screening. In the 1960-1980s, several randomised trials studied the effect of chest radiography (X-ray), but found no differences in lung cancer mortality between screened and unscreened groups, despite detection of more early stage cancers in the screening group (i.e. 31-38% was stage 1)(14, 15). Reasons why the trials found no statistical significant mortality reduction were the low sensitivity of X-ray for lung cancer (i.e. only 23%) and, possibly the lack of power (16). Insufficient numbers of lung cancers were detected at a curable stage (17). In contrast to X-ray, multidetector spiral Computed Tomography (CT) can detect lung cancer at a smaller size (17, 18) and with a higher sensitivity (16, 19). Therefore, lung cancer screening by CT may result in earlier detection and possibly more effective treatment. If early detection is shown to reduce mortality from lung cancer, this would offer an enormous public health benefit.

Lung cancer CT screening studies

Since 1999 several observational lung cancer CT screening studies have been conducted (16, 20). These studies showed that 55-85% of the CT-detected lung cancers at baseline were detected in a surgically removable stage I, and at annual repeat screening this was 60-100% (21). The five-year survival for stage I lung cancer was high (60-80%) (22). Data from the I-ELCAP group showed 10-year survival rates as high as 88% among screen-detected stage I lung cancer cases (23). However, it is unknown whether an increase in the detection of early-stage disease will lead to a reduction in lung cancer mortality. Although these survival data seem promising, they are subject to lead time bias (i.e. earlier diagnosis of disease but no postponement of death), length time bias (i.e. screening will give an overrepresentation of slow-growing tumours because these are more likely to be detected), over-diagnosis bias (i.e. the diagnosis would not have been made clinically - if not detected by screening - because of competing causes of mortality), and selection bias (i.e. subjects volunteering for cancer screening studies may differ from the general population resulting in a better outcome for their cancers). Therefore several randomised controlled trials (RCT) with CT screening for lung cancer were initiated: the National Lung Study Trial (NLST) that compares CT screening with X-ray, the Dutch-Belgian lung cancer screening trial (NELSON trial), the Danish Lung Cancer Screening Trial (DSCST), the Italian ITALUNG trial, and the German Heidelberg trial that compares CT screening with no screening (Table 1.1). The results of the CT screening trials on lung cancer specific mortality are eagerly awaited (24-28).

Table 1.1. Overview of current randomised lung cancer CT screening trials.

Trial, country	Screen/control group	Total no. of subjects	Quality of life assessment
National Lung Screening Trial (NLST) (US)(29)	CT vs X-ray	53,000	Yes
Dutch-Belgian randomised lung cancer screening trial (NELSON) (19, 30, 31)	CT vs no screening	15,822	yes
Danish Lung Cancer ScreeningTrial (DSCST)(32)	CT vs no screening	4,104	yes
ITALUNG (33)	CT vs no screening	3,206	no
Heidelberg (Germany)(34)	CT vs no screening	4,000	unknown

An unfavourable effect of CT screening is the frequent finding of small nodules for which the best management is uncertain. Approximately 50% of screened high-risk subjects have at least one lung nodule at first screening (19, 35), whereas the lung cancer detection rate is 0.4-2.7% at first screening (16, 19). Hence, many of the nodules are benign. Follow-up of these nodules should be effective in decreasing mortality, but should not be too burdensome for participants or reduce cost-effectiveness due to invasive work-up, surgery and morbidity due to diagnostic procedures. Ongoing studies are exploring the best follow-up protocol is for these nodules, e.g. diagnostic follow-up or repeat screening (19, 35-37).

NELSON trial

The research in this thesis is conducted within the Dutch-Belgian randomized controlled trial for lung cancer screening: the NELSON trial. 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% (27). A selection of Dutch and Belgian subjects, registered in population registries and aged 50 to 75 years, were sent a letter with an information leaflet and a first NELSON questionnaire (Figure 1.1). This questionnaire contained questions on smoking history and health. Respondents who had smoked >15 cigarettes per day for >25 years or >10 cigarettes per day for >30 years, those who still smoked, or those who had quit 10 or less years ago were invited to participate in the trial (27). Exclusion criteria were a self-reported moderate or bad health status in combination with the inability to climb two stairs; a history of renal cancer, melanoma or breast cancer; a history of lung cancer diagnosed less than 5 years ago, or more than 5 years ago but still under treatment; a chest CT examination <1 year before recruitment; a body weight ≥140 kilograms (27). Subjects eligible for trial participation received a second letter with an information brochure and a second NELSON questionnaire, including the informed consent form. Informed consent was obtained from 15,822 high-risk subjects, who were subsequently randomized (1:1) either to a screen group with three subsequent CT screening rounds in year 1, year 2 and year 4, or to a control group that received no screening. Participants in the screening group could receive either a positive, indeterminate, or negative test result within 3 weeks after the baseline CT scan was performed (19, 38). A positive test result required a referral to a pulmonologist for work-up and diagnosis. Participants with an indeterminate result were scheduled to undergo a follow-up CT scan to evaluate whether the nodule had grown. The follow-up period for an indeterminate result was on average 3 months after baseline screening; after the 2nd year screening, follow-up was at 6-8 weeks or 1 year depending on the volume doubling time of the previously existing nodules (38). If there was significant nodule growth, a histological diagnosis was obtained. Participants with a negative result were invited for a (bi)annual repeat scan (38).

Health-related quality of life considerations in cancer screening

If a cancer screening trial indeed shows a decrease in cancer-specific mortality it seems worthwhile to consider a population-based cancer screening program. However, a cancer screening program will incur costs due to screening and these costs should be reasonable in relation to the benefits of screening. Moreover, every cancer screening program has favourable and unfavourable side-effects on health-related quality of life

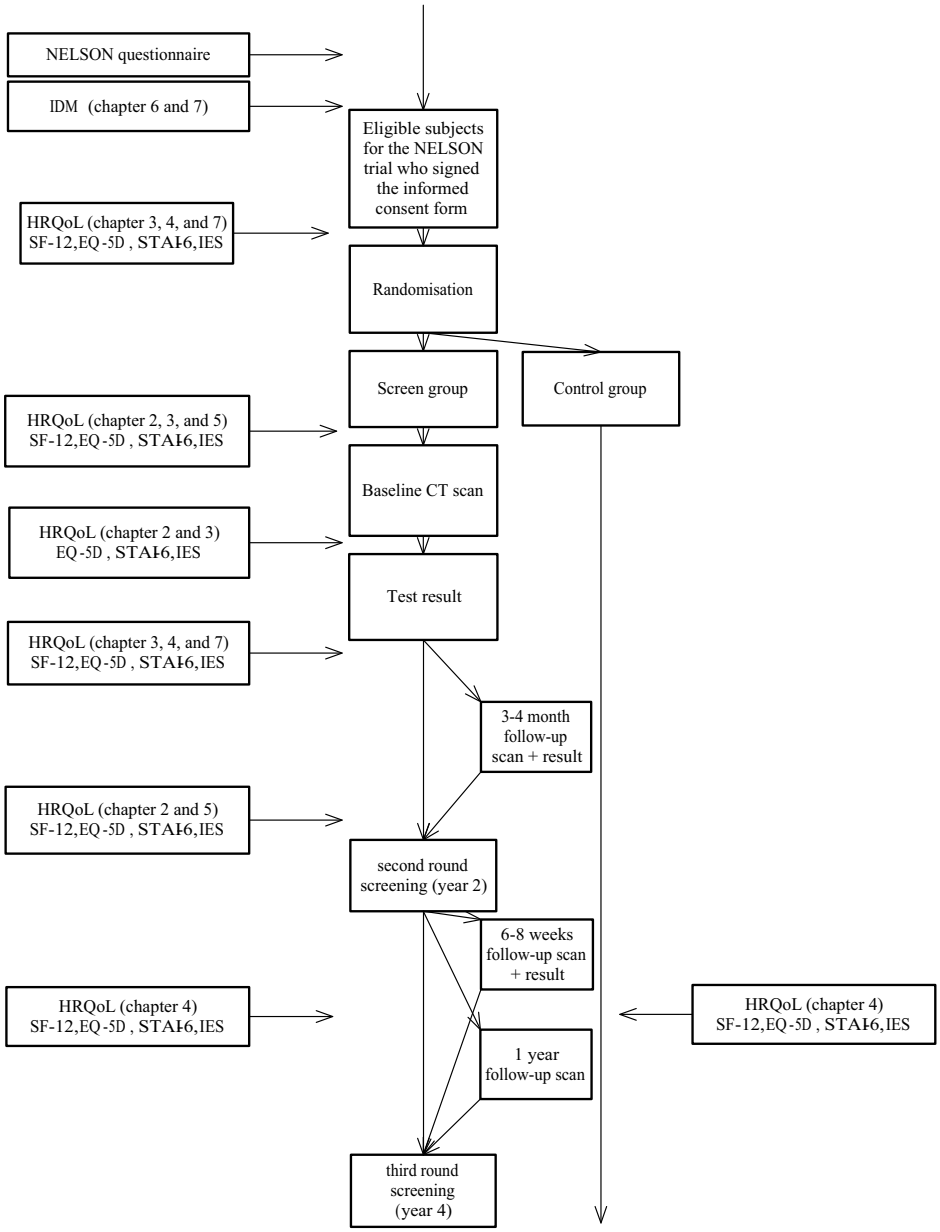

Figure 1.1. Flow-chart of the Nelson trial, showing the questionnaires used.
NELSON = Dutch-Belgian randomized controlled trial for lung cancer screening; IDM = informed decision making; HRQoL = Health-related quality of life; SF-12 = 12-item Short Form; EQ-5D = EuroQol questionnaire; STAI-6 = State-Trait Anxiety Inventory; IES = Impact of Event Scale; CT = Computed Tomography.

(HRQoL) (39). HRQoL, commonly defined as the subject's functioning and well-being in the physical, psychological, and social domains in relation to disease and treatment (40), can be affected during different phases of the screening process, both in the short and the long term (39, 41, 42). HRQoL evaluation is particularly important because asymptomatic persons are the target population.

Firstly, the process of screening: being invited and screened can cause anxiety and distress. Undergoing screening may induce a decrease in HRQoL due to the effects of the test, including pain, discomfort and anxiety whilst undergoing the test, and also the anxiety and distress whilst waiting the test result. For example, endoscopy as a screening test for adenocarcinoma of the esophagus was reported burdensome for 60% of patients with a Barrett's esophagus (43). Also, many women experienced discomfort or pain during mammography or MRI screening for breast cancer (44).

Secondly, during the screening process, some screened subjects will be confronted with abnormal results. Receiving such results is expected to have an unfavourable effect on HRQoL. Subjects face the possibility of having cancer and will have extra tests or even invasive follow-up procedures. Additionally, cancer screening tests are not perfect and a substantial proportion of screenees will get a false-positive result. However it is reported that the unfavourable HRQoL effects of a false-positive result in cancer screening are generally transient, especially after subsequently receiving a normal result (45).

Thirdly, because screening detects cancer in an early phase of the disease subjects will undergo primary treatment. Consequently, participants may experience unfavourable side-effects of treatment. For example, in prostate cancer screening, subjects who received primary treatment reported significant decreases in urinary and erectile function (41).

Lastly, screening will also result in fewer subjects experiencing advanced stages of the disease. This will lead to a decrease in the proportion of patients receiving palliative chemotherapy and radiotherapy, and as such screening may diminish the unfavourable HRQoL effects and costs of advanced lung cancer treatment (39, 41, 42).

In general, the potential health benefits of screening will only apply to a small group of participants, whereas the majority of the participants is subjected to potential unfavourable side-effects. For a thorough evaluation of a screening program (including HRQoL and costs), Miller et al. recommended evaluation in 21 different phases of the screening process in a RCT, most of them described above (39). An RCT is the best research design to evaluate the favourable and unfavourable HRQoL effects of screening. In most observational screening evaluation studies, HRQoL of screening participants is compared with the general population. However, screenees are a (healthy) selection from the general population (healthy screenee effect) (39, 46, 47). Therefore, unbiased evaluation requires a comparison of screenees with a control group. Both the screen group and the control group are selected from the subjects eligible to participation in

screening by randomization across screening or no screening. In such a design both groups share the same characteristics, which makes an evaluation justifiable.

Health-related quality of life in lung cancer screening

For each specific (cancer) screening some specific problems are at stake. In this section the HRQoL issues of lung cancer screening are discussed in relation to the phase of screening itself. The phases of primary treatment and advanced disease will be left out of consideration in this thesis. Here we discuss the positive and indeterminate results, and the subgroups.

In lung cancer CT screening unfavourable HRQoL effects are expected, because nodules requiring further evaluation are found in a large proportion of the participants (19, 35). This evaluation includes either repeat CT scans or an evaluation by a pulmonologist (19, 36). If participants are referred to a pulmonologist for evaluation of the nodules, the CT screening test result is called 'positive'. In studies that advise a repeat screening after several months in case of small nodules, the CT screening test result is often called 'indeterminate'. Most CT screening studies report baseline screening result rates of 14-43% of non-calcified nodules requiring repeat screening to assess nodule growth (19, 36, 48). Receiving a positive result and being referred to a pulmonologist will probably reduce HRQoL. However, receiving an indeterminate result and being advised to go for a repeat screening may also cause unfavourable HRQoL effects. Since indeterminate screening test results are relatively common, a large proportion of all screened participants may be subjected to a reduced HRQoL.

If a nodule requires invasive follow-up, there are potential risks associated with lung biopsy and surgery (21, 49). These risks must be considered when evaluating the risks and benefits of screening. Some of these diagnostic evaluations can have serious morbidity and a low but real, risk of death (20, 49).

Specific subgroups in lung cancer CT screening may experience more psychological distress than the average participant (45, 50, 51). For example, subjects who perceive their risk of developing lung cancer as high probably experience more distress during lung cancer screening than subjects who perceive their risk as low.

Informed decision-making in cancer screening

In general, the public demand and enthusiasm for cancer screening are high (52, 53). Developments in the field of screening are moving fast (54). If research shows that a screening program can detect cancer in an early stage, can reduce disease-specific

mortality, results in a gain of quality-adjusted life years, and is cost-effective, then it is worthwhile to consider its introduction as a population-based screening program. In that case, the benefits of a screening program outweigh the disadvantageous side-effects at the *population* level. However, at the *individual* level not all subjects will experience health gains from screening. Participants have only a relatively small chance of deriving a large advantage (e.g. if cancer is found earlier by screening, and treated, and prognosis improves), but are at much higher risk to experience smaller unfavourable side-effects of screening (55, 56). Many subjects eligible for screening are not fully aware of this low chance of considerable success and the high risk of small disadvantages. Moreover, each individual may value the balance between these chances and risks differently. Therefore, it is important that potential screenees are well informed about the benefits and harms of both screening participation and non-participation. Subjects who are offered screening should be able and supported to make an autonomous informed decision to accept or decline the screening offer (57-59).

An informed decision (or informed choice) (IDM) is defined as a decision based on adequate decision-relevant information (knowledge), and the ultimate screening behaviour is consistent with the decision-maker's values (uptake-attitude consistency) (60, 61). Using this definition, screening participants and non-participants can be classified into eight categories (Figure 1.2).

According to this box, an informed decision to participate is characterised by adequate knowledge, a positive attitude towards lung cancer screening, and actual participation (cell 1, Figure 1.2). An informed decision to decline participation is characterised by adequate decision-relevant knowledge, a negative attitude towards lung cancer screening, and actual nonparticipation (cell 4, Figure 1.2). All other combinations are defined as uninformed decisions. Decisions based on inadequate decision-relevant knowledge are by definition uninformed. Cells 2 and 3 (uniformed decisions based on adequate decision-relevant knowledge) may be analysed for either external barriers to participation (cell 3) or pressure to participate (cell 20). Ideally, subjects make an informed decision as to whether or not to participate in a cancer screening program (55).

It is believed that IDM can have a positive effect on psychological and health outcomes and reduce decisional conflicts (60-63). For instance, someone who receives a positive test result is assumed to be less anxious or distressed if participation was based on an informed decision. An informed participant probably knows the consequences of the test results and has anticipated on this possibility, while an uninformed participant may not have thought about this option. Although it is expected that IDM has favourable effects on HRQoL, it remains an unexplored area of investigation that is limited to prenatal screening (61, 64).

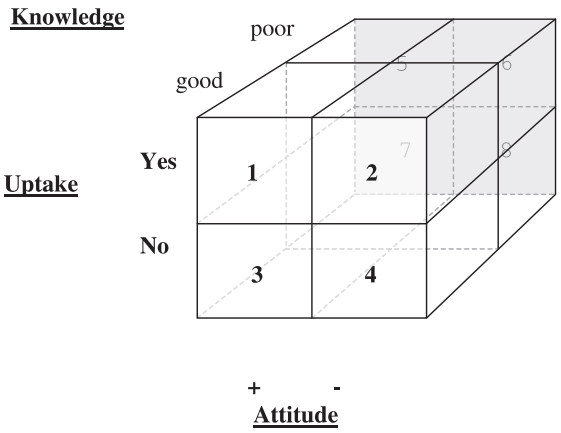

Figure 1.2. Classifying choices, based on three dimensions of knowledge (good, poor), attitudes (positive, negative) and uptake (yes, no) (60).

Informed decision-making in lung cancer screening

Knowledge about cancer screening is often limited among screening invitees (65-67). For lung cancer screening, only few data are available concerning IDM issues. A low perceived risk for lung cancer and limited understanding about the fact that someone can have lung cancer without the appearance of symptoms were associated with less interest in screening (68, 69). However, these studies only examined associations between a few knowledge items and the perceived risk for lung cancer with interest, intention or willingness to be screened and no actual participation.

Until now, no studies have examined the association of knowledge with actual lung cancer screening participation, or showed levels of informed decision making, knowledge, or attitudes towards undergoing lung cancer screening. Such information will give insights in the decision making process for lung cancer screening. If lung cancer screening provides evidence for a reduction in lung cancer mortality and population-based screening is subsequently considered, the results will be important for development of strategies to increase knowledge and understanding of lung cancer screening. If knowledge is limited, additional strategies should improve knowledge of potential screenees, and if attitudes are not consistent with their behaviour potential barriers and/or reasons to participate should be evaluated.

Research questions of this thesis

The objective of this thesis is to investigate the health-related quality of life issues and informed decision-making in lung cancer CT screening.

Research question 1 (HRQoL)

What are the effects, both in size and extent, of lung cancer CT screening in high risk subjects on health-related quality of life?

a. To what extent do screened subjects experience discomfort before and during CT scanning and while waiting for the baseline scan results?
b. To what extent does the course of HRQoL change in the short- and in the long-term? Does the course of HRQoL differ between participants with an indeterminate result and a negative result, received both after the baseline scan or second-round scan?
c. To what extent does the course of HRQoL change over time and differ in the long-term between the screen and control group?
d. Is a high perceived risk of lung cancer associated with more lung cancer-specific distress prior to screening and does perceived risk of lung cancer decrease after CT screening?

Research question 2 (IDM)

How do high-risk subjects decide about lung cancer screening and does informed decision-making affect their HRQoL?

a. Among (non-) participants in the NELSON trial, what is their level of knowledge about lung cancer (screening), their attitudes, lung cancer perceived risk, and their reasons to participate or not in lung cancer screening, when making their decision about participation?
b. To what extent is decision-making regarding participation in the NELSON trial based on an informed decision?
c. Do participants who make an informed decision about lung cancer screening have a better HRQoL than participants who do not make an informed decision, especially those who received an indeterminate test result requiring a follow-up CT scan?

Structure of this thesis

Part II of this thesis (Chapter 2-5) deals with the first research question regarding the effect of lung cancer CT screening on HRQoL.

Chapter 2 addresses research question 1a. Both the experienced discomfort of CT scanning and the subsequent waiting for results are evaluated. Then, HRQoL changes are addressed before and after the CT scan, and again after 6 months when all participants have received a negative final CT result.

Chapters 3 and 4 explore research questions 1b and 1c. Chapter 3 examines whether HRQoL changes in the short-term and whether it differs between subjects with either an indeterminate or a negative baseline CT result. Chapter 4 assesses the long-term effects of lung cancer screening on HRQoL. The screen and control group are compared up to 2 years of follow-up. In addition, the effects on HRQoL of an indeterminate CT result at baseline, and of indeterminate second-round scan, are evaluated.

Chapter 5 evaluates differences between subgroups with a high and a low perceived risk for lung cancer (affective risk perception). Subgroup differences of experienced lung cancer specific distress are assessed before the baseline CT scan and after 6 months, when all had received a negative final CT result. Changes in perceived risk for lung cancer over time are also evaluated.

Part III of this thesis addresses the second research question. Chapter 6 provides an answer to research questions 2a and 2b by determining the knowledge on lung cancer (screening), the attitudes, lung cancer risk perceptions, and the reasons for participating or declining to participate in the lung cancer screening trial. In addition, the extent to which subjects made an informed decision about their participation was also determined. Chapter 7 the IDM study is extended by comparing subjects who did and did not make an informed decision. Generic and lung cancer screening specific HRQoL differences are evaluated during screening and after receiving CT results (research question 2c).

Finally, part IV of this thesis (chapter 8) discusses the results of the studies and presents recommendations for further research.

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Part 2
Health-related quality of life

Chapter 2

Impact of computed tomography screening for lung cancer on participants in a randomized controlled trial (NELSON trial)

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Abstract

Background: Computed tomography (CT) screening is an important new tool for the early detection of lung cancer. In the current study, the authors assessed the discomfort associated with CT scanning and the subsequent wait for results and health related quality of life (HRQoL) over time.

Methods: A total of 351 participants in the Dutch-Belgian randomized controlled trial for lung cancer screening in high-risk subjects (the NELSON-trial) who had an appointment for a baseline CT scan were asked to complete questionnaires regarding their experienced discomfort and HRQoL before, 1 day after, and CT scanning, 1 day after, and approximately 6 months after the CT scan. HRQoL was measured as generic HRQoL (12-item Short Form [SF-12] and EuroQol questionnaire [EQ-5D]), generic anxiety (State-Trait Anxiety Inventory [STAI-6]), and lung cancer-specific distress (Impact of Event Scale [IES]). Approximately 76.9% of the participants completed all 3 questionnaires.

Results: Approximately 87% to 99% of participants reported experiencing no discomfort related to the CT scan. The median SF-12, EQ-5D, STAI-6 and IES scores did not appear to change relevantly over time. Approximately 46.0% and 51.3%, respectively, of the participants reported discomfort in connection with having to wait for the results of the CT scan and dreading those results. These patients had relevantly higher STAI-6 and IES scores ($P<.01$) (unfavorable) at all 3 assessments.

Conclusions: The current evaluation of the potential adverse effects of CT screening for lung cancer on HRQoL demonstrated no negative effects. However, waiting for the CT scan results was reported to be discomforting by approximately half of the participants. Minimizing the waiting time for the test results is therefore recommended.

Introduction

Lung cancer is the most common cancer worldwide and the most common cause of death from cancer (1, 2). Recent research has indicated that lung cancer can now be diagnosed at an earlier stage if high-risk subjects are screened with computed tomography (CT)(3). However, there is debate regarding whether CT screening for lung cancer reduces mortality from the disease. Therefore, the results of ongoing randomized controlled studies are eagerly awaited (4-7).

In general, the health benefits of CT screening for lung cancer to the general population should outweigh the physical and psychologic harm caused by the test, diagnostic follow-up, and possible overtreatment (8, 9). At the individual level, relatively few subjects will benefit from screening, whereas all subjects who participate in screening are subjected to (unfavorable) side effects, including the discomfort, anxiety, and distress associated with lung cancer CT screening. In particular, the percentage of subjects with lung nodules detected by screening (approximately 15—20%) who are advised to undergo a repeat CT scan after 3 months may experience a decrease in their health-related quality of life (HRQoL). The impact of CT screening on HRQoL can be taken into account in the overall balance of the favorable and unfavorable effects of lung cancer screening and cost-effectiveness analysis when screening has been proven to reduce lung cancer mortality (9, 10). To our knowledge, no empiric data regarding the discomfort of CT scanning and the impact of CT screening lung cancer on HRQoL have been published to date. The objective of the current study was to explore the potentially adverse side effects of CT screening lung cancer. We assessed the discomfort experienced by subjects during CT scanning and the discomfort associated with waiting for the results in addition to exploring the impact of CT screening on HRQoL over time, in a subsample of the screening group of the Dutch-Belgian randomized controlled trial for lung cancer screening in high-risk subjects (the NELSON-trial).

Materials and methods

Study population

NELSON trial

The recruitment procedure for and selection criteria of the NELSON trial have been reported in a previous study (6). In brief, a selection of Dutch and Belgian subjects registered in population registries and aged between 50 and 75 years was sent a questionnaire containing questions regarding smoking history and health. Subjects who had smoked >15 cigarettes per day for >25 years or >10 cigarettes per day for >30 years,

those who still smoked, or those who had quit ≤10 years ago were invited to the trial. Exclusion criteria were self-reported moderate or bad health status in combination with an inability to climb 2 stairs; a history of renal cancer, melanoma or breast cancer; a history of lung cancer diagnosed <5 years previously or >5 years previously but for which the person was still under medical treatment; a chest CT scan performed <1 year before study recruitment; and a body weight ≥140 kg (6). Informed consent was obtained from 15,822 high-risk subjects, who were subsequently randomized (at a ratio of 1:1) to either a screening group or a control group that received no screening.

Participants in the CT screening group could receive a positive, indeterminate, or negative test result within 3 weeks after the baseline CT scan was performed. A positive test result was obtained in the case of a nodule that was solid and measured >500 mm^3 solid, pleural based, and measured >10 mm minimum dimension (d_{min});or partially solid, with a solid component that measured >500 mm^3 and required referral to a pulmonologist for work-up and diagnosis. An indeterminate test result was obtained in the case of a nodule that was solid and measured between 50-500 mm^3; solid, pleural based, and measured between 5 and 10 mm d_{min}; partially solid, with a nonsolid component that measured ≥8 mm mean dimension (d_{mean}); partially solid, with a solid component that measured between 50-500 mm^3; or nonsolid and measured ≥8 mm d_{mean}. These participants were advised to undergo a repeat CT scan in another 3 to 4 months to assess possible nodule growth. If there was significant nodule growth, a histological diagnosis was obtained. Participants with a negative CT result were invited to an annual repeat scan (first incidence screening) (11). The trial (including the HRQoL study) was approved by the Dutch Ministry of Health and by the ethics committee of Rotterdam, Haarlem and Utrecht in The Netherlands. Informed consent was obtained from all participants.

HRQoL study

We selected a consecutive sample of 351 participants randomized to the screening arm who had an appointment for a CT scan between June 2005 and November 2005 at the screening centers in Haarlem and Utrecht. These participants were sent a questionnaire 1 week before the baseline CT scan was performed (Time 1 or [T1]), and asked to complete the questionnaire before the CT scan was performed. One day after this baseline CT scan, participants received a second questionnaire (Time 2 or [T2]). They were asked them to complete this questionnaire within 1 week to assess the HRQoL impact while waiting for the results of the baseline CT scan. Finally, a third questionnaire was sent approximately 6 months after the baseline CT was performed (Time 3 or [T3]). This questionnaire was not sent to participants who did not undergo baseline CT screening (n = 10), those with a positive test result at baseline (n = 15) or significant growth noted at the time of the repeat scan (n = 5), or those who indicated that they did not wish to receive any further questionnaires (n = 1) (Figure 2.1). T1 questionnaires completed after

baseline CT screening and T2 questionnaires completed after receiving the baseline CT result were excluded from analysis. T3 questionnaires that were completed by participants with an indeterminate result who had not yet undergone their repeat CT scan or who were still waiting for the result of the repeat scan, were also excluded.

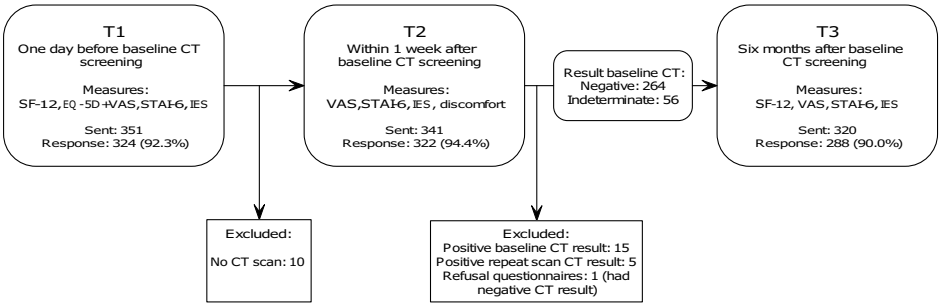

Figure 2.1. Flowchart data collection and response.
CT = computed tomography; SF-12 = 12-item Short Form questionnaire; EQ-5D = EuroQol questionnaire; VAS = visual analogue scale; STAI-6 = State-Trait Anxiety Inventory; IES = Impact of Event Scale.

Measures

Discomfort of CT scanning and waiting for the CT results

Respondents were asked to rate the discomfort experienced during the CT scanning procedure at T2. Items on the questionnaire were adapted from earlier studies assessing the impact of cancer screening tests (12-14). Items to assess the discomfort of the test procedure included lying in the short tunnel, lying on the CT table as it moves through the arch of the CT scanner, lying still without breathing, having to remove metal objects, taking 3 breaths, coughing on command, and being alone during CT scanning. Two items related to waiting for the CT results included "discomfort of waiting for the CT scan result" and "dreading the CT scan result". All items had 5 response options ranging from "no discomfort at all" to "extreme discomfort". Respondents were also asked to identify the most discomforting part of CT scanning (the prospect of CT scanning, undergoing CT scanning or waiting for the CT scan result).

HRQoL

HRQoL is commonly defined as the subjects' functioning and well-being in the physical, psychological and social domains in relation to disease and treatment (15). It can be measured with generic, disease-specific and domain–specific questionnaires. Generally, the empirical evaluation of lung cancer screening can serve 2 different purposes (16). One is to measure HRQoL for use in cost-effectiveness analysis of lung cancer screening and to compare the results with other (cancer screening) studies (9, 10). Another purpose

is to provide a more detailed description of all (negative) psychosocial consequences with measures specifically developed for that purpose. The results of such studies can be used, for example, for counseling and the development of informational brochures in the event that lung cancer screening is indeed introduced. Data from generic measures are both necessary and important for equation and calibration against other adverse health outcomes. The focus of the current study was on the first purpose, and therefore we directed our attention toward the effect of lung cancer screening on generic HRQoL.

The participants' generic HRQoL was measured with the 12-item Short Form (SF-12) and the EuroQol questionnaire (EQ-5D) (17-20). The SF-12 is a shorter alternative to the SF-36 and consist of a Physical Component Summary (PCS) and a Mental Component Summary (MCS) (20). We used the acute (1-week recall) form of Version 1. Each participant completed the SF-12 at T1 and T3. A higher score indicates a better HRQoL. One missing item was allowed and was imputed by the median.

The EQ-5D classifies generic HRQoL in 5 items: mobility, self-care, usual activities, pain/discomfort and anxiety/depression with 3 response options (no, some/moderate, and unable/extreme) (19). Furthermore, respondents were asked to rate their own health directly on the visual analogue scale (VAS) of the EQ-5D ranging from 0 (labeled as "worst imaginable health status") to 100 (labeled as "best imaginable health status"). Utility scores were based on the UK EQ-5D tariff (21). One missing item was allowed. Participants completed all items of the EQ-5D at T1 and rated their own health at all 3 assessments.

Generic anxiety was measured using the Dutch translation of the short form of the Spielberger State Trait Anxiety Inventory (STAI-6) (22). Six items related to anxiety (calm, tense, upset, relaxed, content and worried) were rated on a 4-point scale. The total summary score was calculated in subjects without missing values and could range from 20-80, with higher scores indicating more anxiety. The STAI-6 is reported to have a good reliability and validity and was found to be useful for the evaluation of the effectiveness of screening programs on anxiety levels (22) STAI-6 was measured at all three assessments.

Lung cancer specific distress was measured using the Impact of Event Scale (IES) (23, 24). The 15 IES-items were tailored to the specific event: "lung cancer". Each item was scored on a 4-point scale: not at all (score of 0), rarely (score of 1), sometimes (score of3), and often (score of 5). Total score and subscales (avoidance and intrusion) were calculated for those subjects who completed ≥75% of the questions on each subscale and were corrected for the total number of questions of the subscale. The summary score of the total scale could range between 0 to 75, with a higher score indicating more lung cancer-specific distress. IES was measured at all 3 assessments.

Demographic and other data

At T1, the questionnaire contained items regarding sex, age, marital status and smoking status. Participants who answered the question "Do you smoke?" with "yes, daily" or "yes, sometimes" were defined as current smokers (25). All other participants were therefore former smokers, because all NELSON trial participants are ever-smokers. At T2, participants were asked whether they had ever undergone a CT scan before (of their lungs or otherwise), because participants who had a prior CT scan may experience CT scanning differently.

Statistical analyses

Respondents were divided into 2 age groups based on their age at T1. Responses to the discomfort items used as single item and were recategorized by combining the responses "rather", "very", or "extremely", because these answers were endorsed by only few participants. The Cronbach α for the SF-12, STAI-6, and IES were 0.77 or higher. Non-parametric, 2-sided tests were used for the analysis, because the score distribution of all continuous data was not normal.

Differences in the distribution of background characteristics between various subgroups (men vs women, those aged <60 years vs those aged ≥60 years, education, current vs former smokers) were analyzed by chi-square for nominal/ordinal variables and Mann-Whitney *U* test for continuous variables. We used the chi-square test to test for differences in the distribution of reported discomfort between participants who had previously undergone a CT scan and those who had not. Chi-square and Kruskal-Wallis tests were used to determine whether the reported discomfort of CT scanning and HRQoL scores (the SF-12, VAS, STAI-6, and IES) at T1 and T2 were associated with the "most discomforting part of CT scanning" as reported by the respondents at T2.

Dutch age- and sex-adjusted reference scores of the SF-12 and STAI-6 were used to compare respondents' scores at T1 (26, 27).

We used Mann-Whitney *U* tests to test the significance of differences in the mean HRQoL scores (SF-12, VAS, STAI-6, IES) by sex, age, smoking history, and screening result, and whether discomfort was experienced while waiting for the results. To test for differences in HRQoL over time, paired Wilcoxon signed rank tests were conducted. To determine the clinical relevance of the significant differences between means at 2 assessments or sub groups, we used the minimal important difference (MID), which is defined as half of a standard deviation (28). The MID can serve as a default value for important patient-perceived changes on HRQoL. HRQoL questionnaires were found to be sufficiently reliable (Cronbach α>0.70), as to allow these analyses to be performed.

Results

Response and Respondent characteristics

The response rate of each questionnaire was ≥90.0% or higher (Figure 2.1). The mean time between baseline CT scan and completion of the T3 questionnaire was 6.4 months (standard deviation (SD) of 0.8 months: range, 3.8-9.4 months). At least 1 of the 3 questionnaires was returned by 336 participants (95.7%); 270 completed all 3 questionnaires (76.9%).

Approximately 51% of the respondents to the T1 questionnaire were aged <60 years. Men were more often married/living with a partner than women (P<0.01) and current smokers were younger than former smokers (P<.01). No other significant differences between background characteristics and subgroups (men vs women, age < 60 years vs age ≥60 years, education, current vs former smokers) were found (Table 2.1). The results of the CT scan for the to T3 respondents were negative for 83.0% of subjects (n = 239) and indeterminate for 17.0% (n = 49) for their baseline CT scan and all were negative for their most recent CT scan when completing the T3 questionnaire.

Table 2.1. Respondent characteristics.

Characteristics	% (Except where indicated)	Response
Sex: male	50.9	165/324
Age, years	Mean: 60.3 (SD 6.4), Median 59.3	323
Education		
1 primary education	17.6	57/324
2 lower vocational or lower secondary general education	40.4	131/324
3 intermediate vocational or higher secondary general education	22.5	73/324
4 Higher vocational education or university	19.4	63/324
Marital status: married/ living with partner	64.2	201/313
Smoking: current smokers*	74.7	236/316

SD = standard deviation.

*All participants were ever smokers. A current smoker was defined by report of "daily" or "sometimes" smoking.

Discomfort

The vast majority of the respondents (87.8-98.7%) did not report any discomfort related to the various aspects of the CT scan (Table 2.2). Approximately half of the respondents

reported at least some discomfort from waiting for the results (46.4%) and dreading the results (50.5%). One hundred nine respondents (34.1%) had undergone CT scan before participating in this trial (4 of whom had undergone CT scans of their lungs). These respondents reported neither significantly more nor significantly less discomfort in connection with the CT scan than respondents who never undergone a CT scan (data not shown).

Table 2.2. Discomfort of CT scanning.

Measure		Total item response	Not at all		Some		Rather, very or extremely	
		n	n	%	n	%	n	%
Discomfort CT scan	Lying in the short tunnel	322	290	90.1	30	9.3	2	0.6
	Lying on the CT-table as it moves through the arch of the CT scan	321	285	88.8	32	10.0	4	1.2
	Lying still without breathing during CT scanning	319	280	87.0	36	11.3	3	0.9
	Having to take off metal objects	307	303	98.7	4	1.3	0	
	Taking three breaths	313	282	90.1	25	8.0	6	1.9
	Coughing on command	230	217	94.3	10	4.3	3	1.3
	Being alone during CT scanning	319	301	94.4	15	4.7	3	0.9
Result CT scan	Discomfort from waiting for CT scan result	319	171	53.6	124	38.9	24	7.5
	Dreading the CT scan result	321	159	49.5	138	43.0	24	7.5

CT = computed tomography

HRQoL

Baseline HRQoL scores and comparison with reference groups

At T1, the average PCS and MCS scores of the SF-12 were 48.2 (SD of 9.1) and 51.3 (SD of 10.5), respectively. These scores were in the same range as age- and sex-adjusted Dutch reference scores (data not shown).

Approximately 62% of the respondents reported general health problems on at least 1 of the items on the EQ-5D self classifier (Table 2.3). Approximately 15% reported experiencing some pain or discomfort only. Generic anxiety scores (STAI-6) (mean score of 34.1 [SD 7.7]) were comparable to the Dutch general population.

Table 2.3. Generic health-related quality of life scores (EQ-5D) one day before screening.

	Total item response	n	%
Mobility problems	324	94	29.0
Self-care problems	323	6	1.9
Daily activities problems	324	85	26.2
Pain or discomfort	324	169	52.2
Anxiety or depression	321	73	22.7
			Mean (SD), median
VAS	323	323	76.3 (13.5), 79.0
Utility score *	324	324	0.82 (0.19), 0,80

SD = standard deviation; VAS = self-reported health on a visual analogue scale.
* EQ-5D index value based on the UK EQ-5D tariff (21).

HRQoL over time

The median SF-12 scores did not change significantly over time during screening (Table 2.4). The EQ-5D VAS, STAI-6 and IES scores were found to differ significantly over time, but the scores were low (favorable) and the reported changes were smaller than the MID (Table 2.4). Dropout participants could have influenced the results of the HRQoL analyses over time. Using the same analyses but only taking the HRQoL assessments of subjects who responded to all three questionnaires (270 subjects [76.9%]), into account, we noted similar results (data not shown).

Determinants of HRQoL

At the time of all assessments, some differences in HRQoL were found between men and women. HRQoL changes over time were somewhat different between men and women (Table 2.4). Overall, these differences all were smaller than the MID. No relevant differences were found between current and former smokers and no significant differences in HRQoL scores were noted between respondents in the high or the low age category. In addition, no differences were found at T3 between respondents with a negative baseline CT scan result and respondents with an indeterminate baseline CT scan result but a negative repeat CT scan result.

Correlation between the most discomforting part of CT scanning and reported discomfort and HRQoL

"Waiting for the CT scan result" was rated by 76.0% (n = 196) as the most discomforting part of CT scanning. The "prospect of CT scanning" was rated as the worst part by 17.8% (n =46), and "undergoing CT scanning" was rated as the worst part by 6.2% (n = 16). These 3 groups differed significantly with regard to the amount of reported discomfort in 4 aspects of CT scanning.

These aspects were lying in the short tunnel and on the table as it moves through the arch of the CT scan, lying still without breathing and being alone (*P*=.005, .001, .019, .050

Table 2.4. HRQoL one day before screening, within 1 week after screening, six months after screening.

	(T1) One day before screening		(T2) Within 1 week after screening		(T3) Six months after screening		T1 vs. T2	T1 vs. T3	T2 vs. T3
N	324		322		288		313	279	276
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Significant difference		
SF12 (PCS)									
total group	48.2 (9.1)	51.3			48.7 (9.4)	51.9			
Men	48.5 (9.2)	51.6			49.5 (8.8)	52.4			
Women	47.9 (9.1)	51.3			48.0 (10.1)	50.6			
SF12 (MCS)									
total group	51.3 (10.5)	54.2			50.6 (12.0)	55.4			
men	52.5 (10.6)	55.9*			51.5 (11.0)	55.8			
women	50.1 (10.4)	52.2*			49.6 (12.9)	55.1			
EQ-5D, VAS									
total group	76.3 (13.5)	79.0	76.8 (12.6)	80.0	75.8 (13.7)	80.0			§
Men	76.5 (13.9)	79.0	76.9 (13.2)	80.0	77.6 (14.1)	80.0‡			
Women	76.1 (13.2)	76.0	76.8 (11.7)	80.0	73.9 (13.0)	78.0‡		§	†
STAI-6									
total group	34.1 (7.7)	33.3	32.7 (8.4)	30.0	34.3 (9.1)	33.3	†		†
men	33.3 (7.5)	33.3	31.9 (7.8)	30.0	33.3 (8.5)	33.3	†		§
women	34.9 (7.8)	33.3	33.6 (8.9)	33.3	35.2 (9.8)	33.3	§		§
IES total									
total group	6.9 (9.6)	3.0	5.6 (8.8)	1.0	5.1 (8.0)	2.0	†	†	
men	5.9 (7.7)	3.0	5.0 (7.8)	1.0‡	4.8 (7.1)	2.0	†	§	
women	7.9 (11.2)	3.0	6.5 (9.9)	2.0‡	5.6 (9.0)	1.0		†	
IES intrusive									
total group	2.8 (4.3)	1.0	2.1 (3.9)	0.0	2.1 (3.7)	0.0	†	†	
men	2.5 (3.4)	1.0	1.7 (2.9)	0.0	1.9 (3.2)	0.0	†	§	
women	3.2 (5.0)	1.0	2.6 (4.7)	1.0	2.5 (4.3)	0.0	§		
IES avoidance									
total group	4.1 (6.2)	1.0	3.5 (5.9)	0.0	3.0 (4.7)	1.0	§	†	
men	3.4 (5.1)	1.0	3.3 (5.7)	0.0	2.9 (4.5)	1.0			
women	4.8 (7.0)	1.5	4.0 (6.2)	1.0	3.1 (5.1)	1.0		†	

HRQoL = health-related quality of life; SD = standard deviation; SF-12 = 12 item Short Form (generic HRQoL); PCS = physical component summary; MCS = mental component summary; EQ-5D = EuroQol questionnaire; VAS = visual analogue scale: Self-reported health status; STAI-6 = State-Trait Anxiety Inventory; IES = Impact of Event Scale (lung cancer specific distress).

* Differences between men and women, $p < 0.01$.

† $P \leq 0.05$.

‡ Differences between men and women, $p < 0.05$.

§ $P < 0.01$.

All significantly differences were less than half a SD.

respectively). The group who rated "undergoing CT scanning" as the most discomforting part of screening more frequently reported at least some discomfort with regard to these items compared to the other 2 groups.

The STAI-6 score ($P < .05$) and IES score (sub scales) scores ($P < 0.01$) measured while waiting for the CT scan result (T2), were found to differ significantly between the 3 groups ("prospect of CT scanning", "waiting for the CT scan result", and "undergoing CT scanning") The group who rated "waiting for the CT scan result" as the most discomforting part of screening had worse STAI-6 and IES scores than the other 2 groups. These differences were smaller than the MID.

One week before the baseline CT scan (T1), the three groups ("prospect of CT scanning", "waiting for the CT scan result", and "undergoing CT scanning") differed significantly with regard to IES score (subscales) ($P<.05$). Contrary to our expectations, the group who rated "waiting for the CT scan result" as the most discomforting part of screening had the worst IES scores at T1. This difference was smaller than the MID.

Because the analyses to test differences among the 3 groups (196 respondents, 46 respondents and 16 respondents) of the most discomforting part of the CT screening and HRQoL was comprised of 2 small groups, we also performed a number of extra analyses. Approximately half of the respondents reported at least some "discomfort of waiting for the CT scan result" and/or "dreading the CT scan result". This group had significantly higher scores on STAI-6 and IES ($P < 0.01$) but not on the SF-12, VAS, or EQ-5D compared

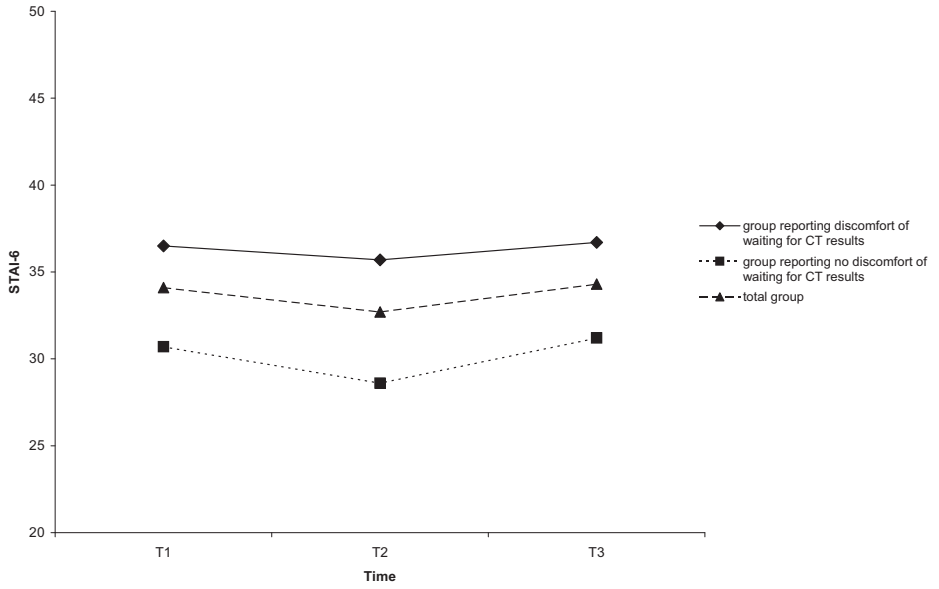

Figure 2.2. Anxiety scores over time for total group, and separated for respondents who reported at least some "discomfort of waiting for the CT scan result" and/or "dreading the CT scan result" and those who did not. STAI-6 = State-Trait Anxiety Inventory; CT = computed tomography.

with those reporting no discomfort or dread at the time of all 3 assessments (Figure 2.2 and 2.3). The differences found were significant and exceeded the MID. The HRQoL did not appear to change relevantly over time in either group (data not shown).

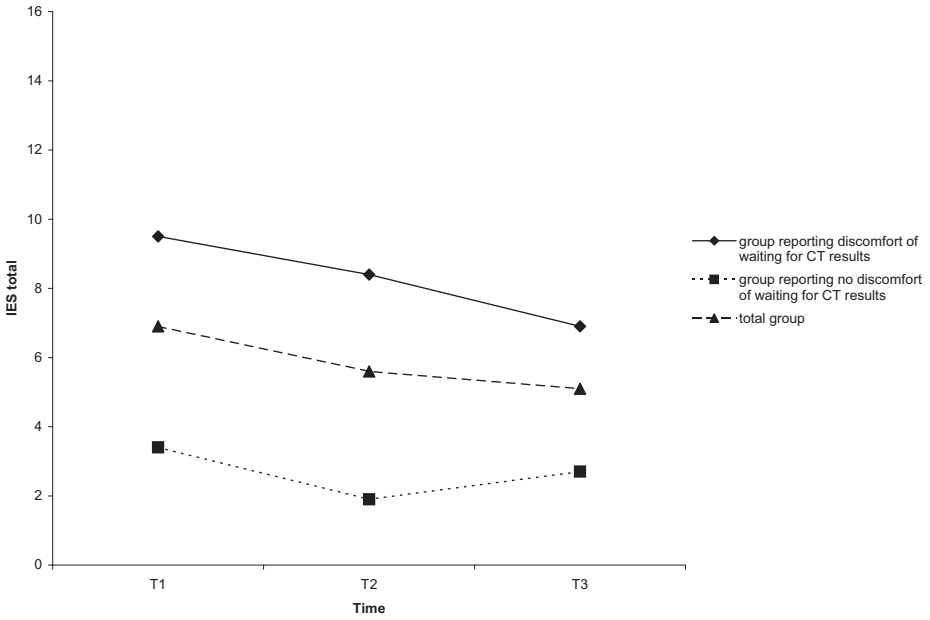

Figure 2.3.
Lung cancer specific distress scores (IES total) over time for total group, and separated into respondents who reported at least some "discomfort of waiting for the CT scan result" and/or "dreading the CT scan result" and those who did not.
IES = Impact of Event Scale; CT = computed tomography.

Discussion

To our knowledge, the current study is the first empiric report of the potential adverse side effects of CT screening for lung cancer. The results demonstrated that screening for lung cancer with CT caused little discomfort and appeared to have no major impact on HRQoL. Nevertheless, approximately half of the respondents reported a negative impact of waiting for the CT scan results. Compared with the prospect of undergoing CT scanning or undergoing the CT scan, this part was also rated as the most discomforting part of CT screening.

The CT scan itself caused almost no discomfort. The reported discomfort was less than that from magnetic resonance imaging (MRI) scanning for breast cancer screening (12). This is credible because a CT scan has a shorter and more open tunnel, makes less noise and subjects are not required to lie still for a period of 20 minutes because the entire procedure takes only approximately 5 minutes.

Somewhat surprisingly, on the basis of these results respondents' HRQoL was found to be comparable to that of the age-adjusted/sex-adjusted reference population. This does not concur with other studies regarding the impact of screening, in which the study population often demonstrated a better HRQoL, compared with the age-adjusted/sex-adjusted reference population (14, 29-31). This does not suggest that the study population in the current study may be assumed to accurately reflect the general population; our respondents were all heavy smokers or former heavy smokers and smokers generally have a worse HRQoL than non-smokers (32). Nevertheless, the HRQoL of the respondents was comparable, not worse than, that of the reference population. This may be accounted for by the finding that, due to the application of the NELSON trial selection criteria, subjects with a moderate or bad health status combined with an inability to climb 2 stairs were excluded from participating in the study. Moreover, participants in screening studies tend to be comprised of the healthier subjects in a population (33). Hence, the respondents in the current study may belong to the group of healthy (former) smokers.

A review of the impact of cancer prevention and screening on QoL demonstrated indications for negative effects, which were most often transient (29). The results of the current study demonstrated no evidence for adverse effects on anxiety and distress due to CT screening for lung cancer. In addition, no negative impact was found after 6 months in subjects whose repeat scan results came back negative (after an indeterminate baseline CT result) compared with subjects with a negative CT result at baseline. Several explanations are possible for not finding changes in HRQoL over time, and for remaining within the normal limits. First, CT screening for lung cancer may simply not have a negative impact on average HRQoL. We did not find any effect on the IES, a HRQoL-specific instrument. Many subjects may have held the belief that they took action to deal with their lung cancer risk. Second, subjects' coping methods can generate and sustain positive psychologic states in the context of screening, thereby minimizing or avoiding the adverse mental and physical health effects of distress (34). Last, as was discussed in the literature, HRQoL measures used in screening (SF-12, STAI-6, and VAS) are possibly insensitive with regard to measurement of the impact of screening in great detail. The specific questionnaire we used was not primarily developed for measuring HRQoL changes in screening (15, 16, 35). However, evaluating screening with generic questionnaires is important because it can be equated to and calibrated against other adverse health outcomes and screening programs (16). Moreover, it is necessary to balance the positive and negative effects of screening with cost (9, 10). It is doubtful whether insensitivity was an issue in the current study because we observed both significant and relevant differences in generic anxiety and lung cancer-specific distress between subgroups (eg. between the group of participants who reported "at least some discomfort of waiting for the CT scan result and/or dreading the CT scan result" and the

group who did not). Although these average anxiety and lung cancer-specific distress remained within normal limits, this subgroup of half of the respondents was identified that had relevantly worse anxiety and lung cancer-specific distress scores during CT screening. Because anxiety and lung cancer-specific distress did not change over time in either group, this indicates, for example, that these respondents might have a higher predisposition toward anxiety

Limitations

Some selection bias in the current study cohort is possible because we chose only the first 351 participants with an appointment to undergo for a CT scan between June 2005 and November 2005. These individuals were easy to approach and willing to participate. However, we have no reason to believe that they constitute a specific group.

Our first assessment was performed just before the baseline CT scan. It might be possible that the HRQoL was already affected by this event. An assessment made earlier in time than T1 would have measured the participants' baseline HRQoL.

An extra assessment after receiving the result of the baseline CT scan is recommended to determine whether HRQoL is affected by receiving a result and whether there are relevant differences between receiving a negative or indeterminate result. Waiting for a follow-up screening can increase anxiety (36). The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial included chest x-ray screening for lung cancer and found that there was a negative impact on HRQoL after receiving an abnormal result, but not after the follow-up result indicated no cancer (31). When we initiated the current study, the best method with which to measure specific HRQoL was the IES. Recently, a new instrument was developed to measure the psychological consequences of screening, which is a study that is currently being performed (37).

In conclusion, the results of the current study did not demonstrate unfavorable side effects of CT screening on HRQoL. However, approximately half of the respondents reported at least some "discomfort of waiting for the CT scan result" and/or "dreading the CT scan result". Minimizing the waiting time for the test result is recommended.

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Chapter 3

Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON)

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Abstract

Background: In lung cancer CT screening, participants often have an indeterminate screening result at baseline requiring a follow-up CT. In subjects with either an indeterminate or a negative result after screening, we investigated whether health-related quality of life (HRQoL) changed over time and differed between groups in the short-term.
Methods: A total of 733 participants in the NELSON trial received 4 questionnaires: T0, before randomisation; T1, 1 week before the baseline screening; T2, 1 day after the screening results; and T3, 2 months after the screening results but before the 3-month follow-up CT. HRQoL was measured as generic HRQoL (SF-12, EQ-5D), anxiety (STAI-6), and lung cancer-specific distress (IES). For analyses, repeated measures ANOVA was used, adjusted for covariates.
Results: Response to each questionnaire was 88% or higher. Scores on SF-12, EQ-5D, STAI-6 showed no clinically relevant changes over time. At T3, IES scores that were clinically relevant increased after an indeterminate result, whereas these scores showed a significant decrease after a negative result. At T3, differences in IES scores between the two baseline result groups were both significant and clinically relevant ($p<0.01$).
Conclusion: This longitudinal study among participants of a lung cancer-screening program showed that in the short-term recipients of an indeterminate result experienced increased lung cancer-specific distress, whereas the HRQoL changes after a negative baseline screening result may be interpreted as a relief.

Introduction

Lung cancer is the main cause of cancer-related deaths worldwide among men and women (1, 2). Although cancer can be detected in an early stage by computed tomography (CT) screening (3), results from randomised controlled trials are needed before deciding whether CT screening will reduce lung cancer mortality, and whether implementation of large-scale lung cancer CT screenings programmes should be recommended (4-7).

Most CT screening studies report baseline rates of 14-43% of non-calcified nodules (5-10 mm in diameter); this relatively large range is attributed to geographic differences in nodule prevalence and the slice thickness used (8, 9). Subjects with this type of nodule usually receive a recommendation to undergo a follow-up CT 3-4 months later to assess whether a nodule has grown, because nodule growth is associated with increased cancer risk (10).

In the Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects (the NELSON trial), subjects could receive either a negative, an indeterminate, or a positive scan result (11). Subjects receiving an indeterminate scan result at baseline were invited to undergo a follow-up scan 3 months later; however, receiving such a result and waiting for this scan might have an unfavourable effect on health-related quality of life (HRQoL), compared with receiving a negative result. For example, in the PLuSS study, a significant increase of generic anxiety was found 1-2 weeks after communication of an indeterminate baseline screening result (12). However, the latter authors used HRQoL instruments that precluded detailed evaluation of the psychological consequences of lung cancer screening; moreover, possible changes in HRQoL between the baseline test result and the 3-month follow-up scan result were not reported. Furthermore, a study on breast cancer screening showed that anxiety was higher just before screening, compared to basic HRQoL unrelated to screening (13). So, to determine the whole effect of screening, it is important to establish whether HRQoL is already negatively affected just before baseline screening.

In this study we assessed changes in generic and lung cancer-specific HRQoL changes over time among participants undergoing lung cancer screening in the short-term. Therefore, we addressed the following questions: 1) To what extent does HRQoL decrease just before baseline screening? 2) Is there a difference in HRQoL between those with an indeterminate baseline result and those with a negative result? We hypothesised that lung cancer-specific distress scores just before baseline CT screening would be higher compared with scores acquired a few months before screening (13). Also, in subjects who received an indeterminate baseline result we expected higher levels of lung cancer-specific distress 2 months after screening (but before the 3-month follow-up scan) compared to those who received a negative result.

Material and Methods

NELSON Study Population

A random sample of Dutch and Belgian subjects (aged 50-75 years) registered in population registries received a questionnaire containing items about health and smoking history. Current and former smokers were asked to complete this 'first' NELSON questionnaire. Respondents who had smoked >15 cigarettes per day for >25 years or >10 cigarettes per day for >30 years, those who still smoked, or those who had quit 10 or less years ago were invited to participate in the trial (6).

Informed consent was obtained from 15,822 high-risk subjects who were subsequently randomised (1:1) to either a screening group, or to a control group that received no screening. Participants in the screening group could receive either a positive, indeterminate, or negative test result within 3 weeks after the baseline CT scan was performed (11). A positive test result required referral to a pulmonologist for work-up and diagnosis.

Participants with an indeterminate result were scheduled to undergo a follow-up CT scan 3 months later to evaluate whether the nodule had grown. The letter to participants with an indeterminate result stated: " … w*e have observed a very small abnormality in your lung (5 to 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...*" The letter also explains the possible results and related work-up after this follow-up CT scan: "*… participants with an abnormality showing no growth will receive a negative test result and will be invited for a CT scan 1 year after the baseline screening. Those with an abnormality showing some growth will be referred to a pulmonologist for further investigations"* (11).

The NELSON trial, including the current HRQoL study, was approved by the Dutch Ministry of Health and by the local ethics committees of the participating centres. Informed consent was obtained from all participants. The NELSON trial is registered at www.trialregister.nl with number ISRCTN63545820

HRQoL study

A consecutive sample of 1466 participants was taken from the screening centres in Haarlem and Utrecht, randomised in August 2005 (n=977), September 2005 (n=390) and November 2005 (n=99). All participants received a questionnaire after eligibility check, after sending the information brochure, and signing of the informed consent form, but before trial randomisation (Time 0, T0, baseline HRQoL assessment). Subjects randomised to the screen arm received a second questionnaire 1 week before the baseline scan (Time 1, T1); they were asked to complete the questionnaire before the

baseline scan was made. At 1 day after this baseline scan, they received a third questionnaire (Time 2, T2) and were asked to complete this questionnaire within 1 week. At T2, subjects did not receive the scan result of the baseline scan. Finally, for subjects who had a negative or an indeterminate test result, a questionnaire was sent about 2 months after the baseline scan was made (Time 3, T3). For subjects with an indeterminate scan result this was about 1 month before the 3-month follow-up scan.

In the present study, the response of those who did not undergo baseline screening, or who had a positive test result, was excluded from the analyses. The questionnaire responses of those who completed T1 after the CT scan (n=12), who completed T2 before the CT scan (n=0) or after the baseline test result (n=6), and who completed T3 after the result of the follow-up scan (n=1) were excluded. These were not counted as responses.

Measures

Generic HRQoL

The participant's generic HRQoL was measured with the 12-item Short Form (SF-12) and the EuroQol questionnaire (EQ-5D) (14-17). The SF-12 is a shorter version of the SF-36 and consists of a Physical Component Summary (PCS) and a Mental Component Summary (MCS) (17). We used the acute (1-week recall) form of Version 1. Each participant completed the SF-12 at T0 and T3. A higher score indicates a better HRQoL.

Respondents were also asked to rate their own health on the visual analogue scale (VAS) of the EQ-5D, ranging from 0 (worst imaginable health status) to 100 (best imaginable health status) (14, 16). Participants completed the EQ-5D VAS at all four assessment points (i.e. T0, T1, T2 and T3).

Generic anxiety

Generic anxiety was measured using the short form of the Spielberger State-Trait Anxiety Inventory (STAI-6) (18). Six items related to anxiety (calm, tense, upset, relaxed, content, and worried) were rated on a four-point scale. The total summary score was calculated in subjects with a maximum of three missing values and could range from 20-80, with higher scores indicating more anxiety (19). The STAI-6 is reported to have good reliability and validity, and was found useful to evaluate the effectiveness of screening programmes on subjective anxiety levels (18). The STAI-6 was used at all four assessment points.

Lung cancer-specific distress

Lung cancer-specific distress was measured using the Impact of Event Scale (IES) (20, 21). The 15 IES items were tailored to lung cancer as the specific stressor. Each item was scored on a four-point scale: not at all (score of 0), rarely (score of 1), sometimes (score of

3), and often (score of 5). The total score and subscales (avoidance and intrusion) were calculated for those who completed 75% of the questions on each subscale, and were corrected for the total number of questions on the subscale. The total summary score could range from 0-75 (intrusive scale 0-35, avoidance scale 0-40), with a higher score indicating more lung cancer-specific distress. The IES was used at all four assessment points.

Demographic and other data

At T0, the questionnaire had items on marital and smoking status. Educational level and smoking pack-years were derived from the first NELSON questionnaire.

Statistical Analyses

Differences in respondent characteristics between those with a negative or indeterminate baseline scan result were tested with Mann-Whitney U tests (in case of non-normally distributed continuous variables) and Chi-square tests (for discrete variables). Then, we first analysed differences in HRQol over time, focusing on differences between the two baseline result groups. Second, the changes in HRQoL before and after the baseline scan result were analysed. For the latter analyses, we started by using data of the total group in the period before the CT scan result (T0, T1, T2), because all subjects were still unaware of the baseline CT result. After the CT scan result (T0-T3 and T2-T3) the data from the two result groups were analysed separately. For all analyses repeated-measures analysis of variance (ANOVA) was applied, using 'proc mixed' from the SAS system version 9.1; this allowed use of all available data, including the incomplete records. For the subjects, we used models with a random intercept to allow for dependence between the repeated measurements:

Effect of baseline result on HRQoL over time

Differences in HRQoL between the negative and indeterminate result groups were analysed at the four assessment points. The models included a main effect for time, and for an interaction between group and time. Time was included as a factor with four levels (one for each assessment) to account for possible non-linearity in the change in HRQoL scores. The following fixed covariates were added to the model: age (because older people are reported to show less anxiety and better mental health) (12, 22), gender (because women are reported to show a different fear of cancer and have worse generic HRQoL compared with men)(22), education (because higher-educated lung cancer screening participants are reported to be less anxious, have less fear of cancer and less distress) (12), smoking status (because current smokers generally have a worse HRQoL than non-smokers, and more anxiety and fear of cancer) (23), and smoking pack-years

(because we expected subjects with more pack-years to be more anxious and to have worse health).

The IES scores were highly skewed. However, as a logistic regression model using a generalised linear mixed models approach analysis would limit the data, and because choosing a cut-off point is arbitrary and use of the model in fact produced the same results as with the repeated measures ANOVA, we considered repeated measures ANOVA to be appropriate for the IES scores.

Change in HRQoL before and after receipt of baseline scan result

Before the receipt of the baseline result (T0, T1 and T2), the same repeated measures models as described above (adjusting for covariates) were used for the total group, but this time including contrasts to test differences in scores of the total group between specific assessment points (i.e. T0 versus T1, and T1 versus T2, and a model with T0 versus T2). In these models, the main effect for group, and the interaction between group and time, were no longer necessary and were thus excluded. After receipt of the baseline result (T3) changes in HRQoL between T2 and T3 and changes between T0 and T3 were analysed separately for the groups with a negative and with an indeterminate baseline result. The same repeated-measures model was used as for the analyses between T0, T1, and, T2.

A p-value <0.05 was considered statistically significant. To provide a clue to the meaningfulness of statistically significant differences between means at two assessments or between subgroups, we used the minimal important difference (MID), which is defined as half of a standard deviation (SD) of the mean (24). The MID can serve as a default value for meaningful changes in HRQoL. For changes over time the SD at the first assessment of the two compared assessment points was used, and for differences between groups the pooled SD of the two groups at a specific time point was used.

Results

Response and respondent characteristics

In total, 41 screen arm participants (5.6%) were excluded from the HRQoL study because they either did not undergo baseline screening (n=30) or had a positive baseline result (n=11). In the screen group, the response to the questionnaires was 91.0% (630/692) at T0, 93.6% (641/685) at T1, 93.0% (620/667) at T2, and 87.7% (600/684) at T3 (Figure 3.1). At least one of the four questionnaires was returned by 99.6% (689/692) of the subjects, and 71.4% (494/692) completed all four questionnaires. The T0 questionnaire was completed 164.8 (SD 107.5) days before baseline screening, and the T1 questionnaire 2.5 (SD 6.5) days before baseline screening. The T2 questionnaire was completed

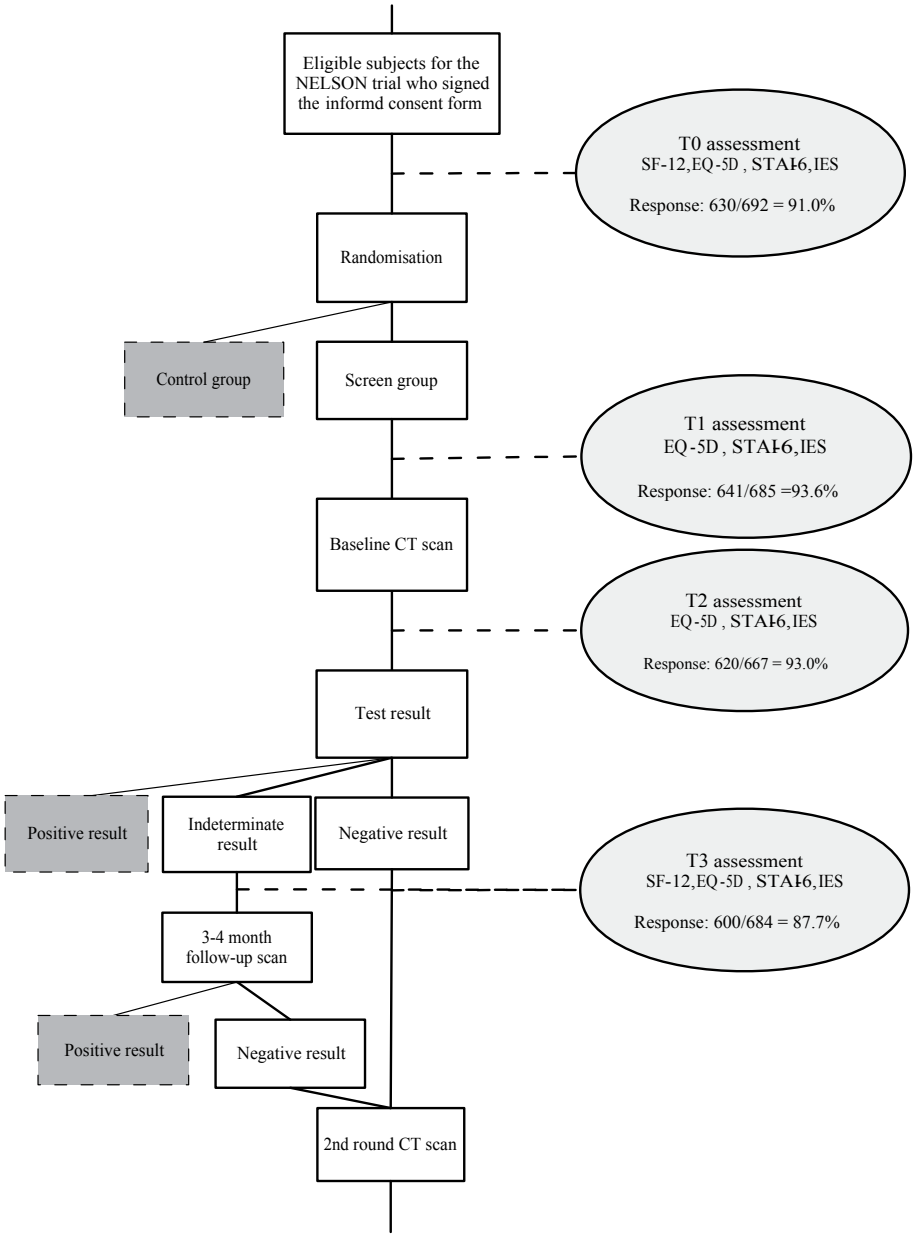

Figure 3.1. Flow chart of the HRQoL study.

* 41 subjects of the screen group were excluded from the HRQoL study: 30 had no baseline CT scan, and 11 had a positive CT result at baseline.

At T1, T2 and T3 a total of 7, 25 and 8 questionnaires, respectively, were not sent due to administrative failures. Responses at T1, T2 and T3 were excluded for 1, 2 and 2 questionnaires, respectively, due to more than 50% missing items. Also excluded were: T1 questionnaires (n-10) completed after the baseline CT scan, T2 questionnaires (n=6) completed after the baseline CT scan result, and T3 questionnaires (n=1) completed after the follow-up scan result

4.0 (SD 3.3) days after baseline screening, and the T3 questionnaire 80.2 (SD 20.1) days after baseline screening. The T3 questionnaire was completed 59.4 (SD 24.1) days after the baseline screening result. For subjects with an indeterminate result this was 20.1 (SD 16.3) days before the follow-up scan.

Almost 50% of the respondents were male and the mean age was about 58 years (Table 3.1). No statistically significant differences in background characteristics were found between subjects with a negative and indeterminate baseline screening result.

Table 3.1. Characteristics of the respondents at T0.

		Baseline scan result		
	Total group (n=630)	**Negative (n=489)**	**Indeterminate (n=141)**	**P differences Negative/ Indeterminate result**
Sex: male (%)	47.1	46.2	50.4	0.386[a]
Age in years: mean (SD), median	57.8 (5.5), 56.7	57.7 (5.5), 56.6	58.3 (5.6), 57.5	0.225[b]
Education				0.150[a]
1 Primary education (%)	9.3	8.9	10.8	
2 Lower vocational or lower secondary general education (%)	37.9	38.3	36.7	
3 Intermediate vocational or higher secondary general education (%)	25.1	23.4	30.9	
4 Higher vocational education or university (%)	27.7	29.4	21.6	
Marital status: Married/living with partner (%)	74.9	75.1	74.5	0.888[a]
Smoking				
Current smokers (%)	54.6	53.6	58.2	0.336[a]
Pack-years mean (SD), median	40.1 (17.8), 34.2	40.1 (18.2), 34.2	39.9 (16.3), 34.2	0.732[b]

SD = standard deviation.
[a] Chi-square test.
[b] Mann-Whitney U-test.

Effect of baseline result on HRQoL over time

At each assessment, subjects with a negative test result had better HRQoL scores on all scales than subjects with an indeterminate result (Table 3.2., Figures 3.2A-G). Results of the repeated measures analysis (adjusted for gender, age, education, smoking status and smoking pack-years) showed no statistically significant differences in the SF-12

Table 3.2. Unadjusted mean (SD) HRQoL scores at the four assessment times, by baseline CT scan result (negative or indeterminate).

	T0	T1	T2	T3
N	630	641	620	600
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
SF12 (PCS)				
Total group	49.5 (8.7)			50.0 (8.2)
Negative	49.7 (8.4)			50.3 (8.3)
Indeterminate	48.5 (9.6)			48.9 (7.8)
SF12 (MCS)				
Total group	51.9 (10.3)			51.6 (11.1)
Negative	51.9 (10.2)			51.6 (11.1)
Indeterminate	51.8 (10.6)			51.9 (11.0)
EQ-5D, VAS				
Total group	79.3 (13.7)	78.3 (12.9)	79.1 (12.3)	78.4 (13.7)
Negative	79.4 (13.8)	78.7 (12.6)	79.4 (12.2)	79.2 (13.4)
Indeterminate	79.1 (13.4)	76.8 (13.8)	78.3 (12.5)	75.0 (14.5)
STAI-6				
Total group	33.2 (8.6)	34.6 (8.6)	32.7 (8.8)	33.0 (9.2)
Negative	33.1 (8.4)	34.4 (8.5)	32.5 (8.8)	32.6 (9.2)
Indeterminate	33.6 (9.3)	35.2 (8.9)	33.5 (8.9)	34.8 (9.2)
IES total score				
Total group	4.2 (7.2)	5.9 (9.1)	4.5 (7.8)	3.6 (7.5)
Negative	4.1 (7.4)	5.8 (9.1)	4.5 (7.7)	2.4 (5.5)
Indeterminate	4.5 (6.5)	6.3 (9.1)	4.9 (8.4)	8.3 (11.3)
IES intrusive				
Total group	1.8 (3.4)	2.5 (4.0)	1.8 (3.6)	1.4 (3.3)
Negative	1.7 (3.5)	2.4 (4.0)	1.8 (3.5)	0.8 (2.4)
Indeterminate	2.0 (3.0)	2.7 (4.0)	2.0 (3.8)	3.5 (5.2)
IES avoidance				
Total group	2.4 (4.5)	3.5 (5.6)	2.7 (4.7)	2.2 (4.7)
Negative	2.4 (4.7)	3.4 (5.6)	2.7 (4.7)	1.5 (3.7)
Indeterminate	2.5 (4.1)	3.6 (5.7)	2.9 (4.9)	4.8 (6.9)

T0 = before trial randomisation, i.e. baseline HRQoL assessment; T1 = one week before the baseline CT scan; T2 = one day after the baseline CT scan; T3 = two months after the baseline CT scan; SD = standard deviation; SF-12 = Short Form 12 (generic HRQoL); PCS = physical component summary; MCS = mental component summary; EQ-5D VAS = self-reported health status; STAI-6 = anxiety; IES = lung cancer-specific distress.

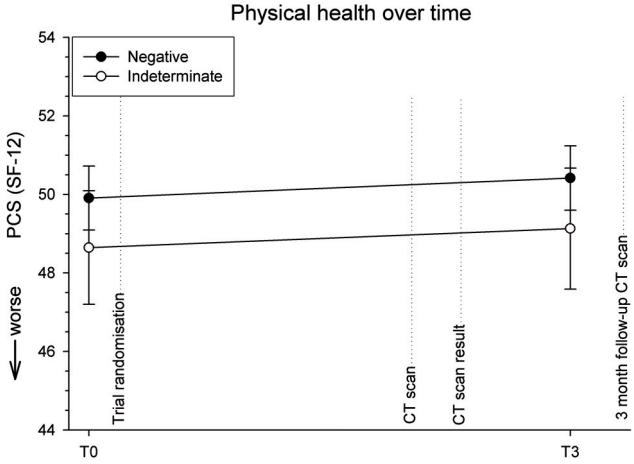

Figure 3.2A

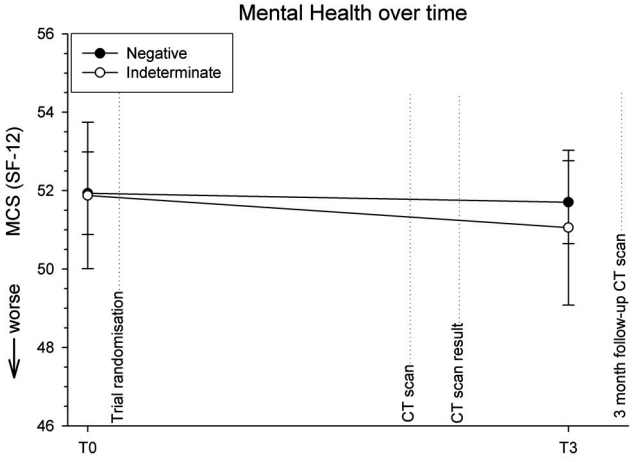

Figure 3.2B

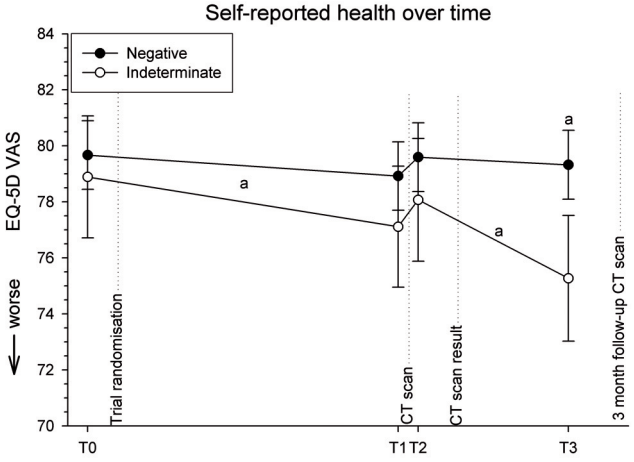

Figure 3.2C

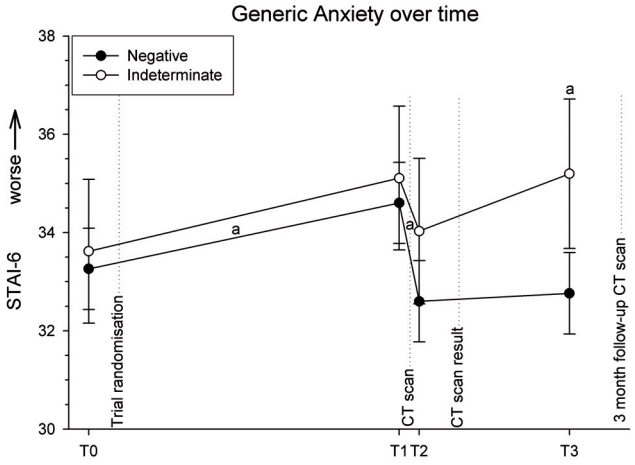

Figure 3.2D

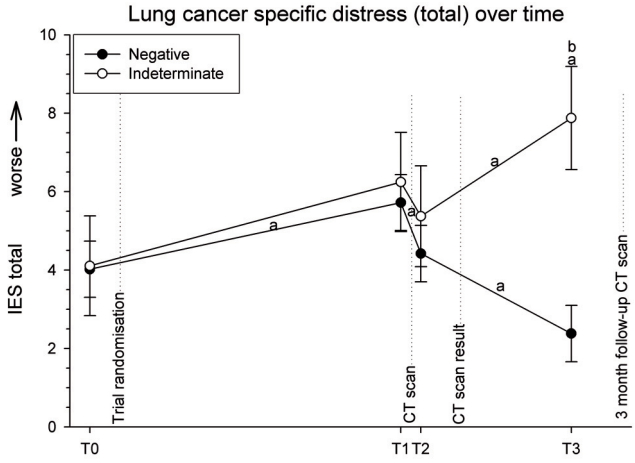

Figure 3.2E

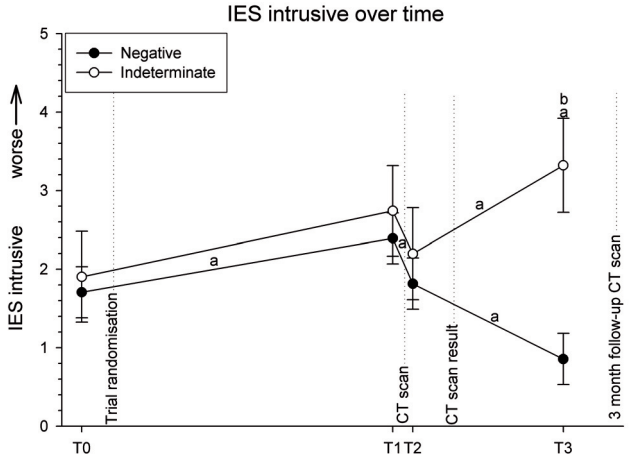

Figure 3.2F

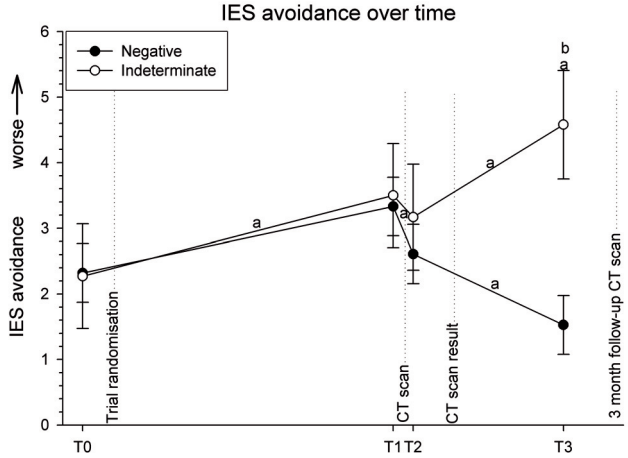

Figure 3.2G

Figure 3.2A-G. Average scale scores and 95% confidence intervals per result group (negative or indeterminate baseline result) adjusted for gender, age, education, smoking status and smoking pack-years: SF-12 (PCS and MCS) (A and B); EQ-5D VAS (C), STAI-6 (D) and IES (total, intrusive, avoidance) (E-G). T0 = before trial randomisation; T1 = just before baseline CT scan; T2 = 1 day after baseline CT scan; T3 = about 2 months after baseline CT scan.
a Significant difference.
b Clinically-relevant difference.
Figure A, B, C: A higher score indicates better HRQoL.
Figure D, E, F, G: A lower score indicates better HRQoL.

scores (MCS and PCS) between subjects with a negative and an indeterminate result at the two assessment points (Figure 3.2A+B). Also, at T0, T1 and T2 no statistically significant differences were found in EQ-5D-VAS and STAI-6 scores between subjects with a negative and an indeterminate test result (Figure 3.2C+D). At T3, compared to subjects with a negative result, those with an indeterminate result had statistically significantly lower scores on the EQ-5D-VAS and higher scores on the STAI-6 (i.e. both worse), but the difference was not clinically relevant (both $p<0.01$). At T0, T1 and T2 the IES total score showed no statistically significant inter-group difference, whereas at T3 the IES scores in the indeterminate result group were statistically significant and clinically relevant higher (i.e. worse) than in the negative result group ($p<0.01$) (Figure 3.2E+F+G).

In women and current smokers, scores on the PCS, EQ-5D VAS, STAI-6 and IES showed a statistically significant difference, but were not clinically relevant worse (i.e. they did not exceed the MID), compared with men and former smokers (data not shown).

Change in HRQoL before and after receipt of baseline scan result

Before the receipt of the baseline scan result, HRQoL scores on the EQ-5D VAS, STAI-6 and IES for the total group of respondents, were statistically significantly worse at T1

(just before the baseline CT scan) compared with those at T0 ($p < 0.05$ for EQ-5D, rest < 0.01) (Figure 3.2A-G). Between T1 and T2, there was no statistically significant change in EQ-5D VAS scores. Average scores on the STAI-6 and IES were statistically significantly better at T2 (just after the CT scan) compared with T1 (all $p<0.01$). IES total scores and the IES avoidance scores did not revert to baseline levels, as they were statistically significantly worse at T2 compared with T0 (both $p<0.05$). In the total group, none of the statistically significant changes over time exceeded the MID, thus none of them were clinically relevant.

In the negative result group, the EQ-5D VAS and STAI-6 scores remained unchanged between T2 and T3, and between T0 and T3. The IES scores were statistically significantly lower (i.e. better) at T3 compared with T2 (all $p<0.01$) and also compared with T0 ($p<0.01$). In the indeterminate result group, the EQ-5D and the IES scores were worse at T3 compared with T2 ($p<0.01$), and compared with T0 ($p<0.01$). The STAI-6 scores remained unchanged between T2 and T3, but were worse at T3 compared with T0 ($p<0.05$). For all statistically significant differences in HRQoL over time, only the changes in IES scores between T0 and T3 in the indeterminate result group were also clinically relevant.

Impact of covariates on HRQoL

In general, the HRQoL scores were worse for women than for men ($p<0.05$). Subjects with more pack-years had a worse self-reported health (EQ-5D VAS) and had worse physical health scores (PCS) than subjects with less pack-years ($p<0.05$). Current smokers had worse HRQoL scores at all scales ($p<0.05$) except for the mental health scores (MCS) than former smokers.

Discussion

Lung cancer-specific distress increased in a clinically relevant manner two months after receipt of an indeterminate result of baseline screening. After receiving the baseline CT result, subjects with an indeterminate screening result had clinically relevant higher lung cancer-specific distress than subjects with a negative result. In the groups with a negative or indeterminate result, no clinically relevant differences over time within or between groups were found for physical/mental/self-reported health and generic anxiety.

In this study, the statistically significantly worse HRQoL just before the CT scan, compared with HRQoL at a neutral point of time before screening (T0), is similar to an earlier report on breast cancer screening (13); however, in the latter study it is unknown whether the self-reported health change exceeded the MID of half a SD. As a result of a slightly unfavourable effect of CT scanning on HRQoL, we did not find any clinically

relevant changes between the assessment points (T0 to T1 to T2 to T3). Nevertheless, in the indeterminate result group there was a clinically relevant increase in lung cancer-specific distress when comparing T0 with T3. This implies that performing a HRQoL assessment at a neutral point in time is important.

In our indeterminate result group, the STAI anxiety scores showed a statistically significant increase from the baseline HRQoL assessment up to 2 months after receipt of the baseline screening result. Byrne et al. also found also a statistically significant increase in anxiety 1-2 weeks after an indeterminate baseline result compared with before the CT scan (12). However, the size of the change was below our criterion for clinical relevance. Re-evaluation of the reported unadjusted means in the study of Byrne et al. revealed that anxiety scores for indeterminates were not clinically relevantly worse, which is similar to our results. However, comparison of the results of the PLuSS study and ours is difficult because the details of their result letter to the participants are unknown, and the follow-up time for the indeterminate results also differed (9, 11, 12).

Using a more specific HRQoL instrument (i.e. the IES) we could demonstrate both a statistically significant and clinically relevant change from the baseline HRQoL assessment up to 2 months after the receipt of the result, as well as a difference between our two result groups. This implies that an indeterminate test result had at least some negative impact on HRQoL in the period between receipt of the test result and the follow-up scan 3-4 months later. Nevertheless, the effect was small because the average IES total score in the indeterminate group was only 8.3 (SD 11.3) on a scale with an upper limit of 75. The IES scales were also highly skewed; even in the indeterminate result group 30% did not experience any lung cancer-specific distress at 2 months after screening (i.e. IES total score = 0).

The HRQoL decrement should be very low in a screening situation, because even a small HRQoL decrement due to screening at the individual level will accumulate to a large burden at population level due to the large numbers of subjects involved. By using the MID criterion we intended to provide a clue to the meaningfulness of a statistically significant change in mean scores. An additional reason for using the MID was the fact that this study included large numbers of subjects and that HRQoL scale scores do not have an intuitive interpretation. It is situation-dependent whether a statistically significant change in mean scores from e.g. 12.1 to 11.7 is to be regarded as a meaningful difference.

Remarkably, in the indeterminate result group, at all assessment points the HRQoL scores were worse than those in the group with negative results. This was the case before the screening result was known, and even before screening took place; however, these differences were not statistically significant. Subjects who had a positive baseline CT scan who completed the T0 questionnaire (n=8) reported even worse HRQoL scores before screening (data not shown). Previous studies showed a prognostic effect of

HRQoL on survival (of lung cancer) or disease onset (25). Our results suggest that worse HRQoL scores before screening may serve as a weak indicator of an indeterminate or positive baseline scan result.

In the indeterminate group we did not assess HRQoL after they had received the result of the 3-month follow-up scan. This would have provided additional information on the further evolution of the unfavourable HRQoL scores in test indeterminates, especially because the majority would have received a negative result based on this follow-up scan. However, in our previous study on HRQoL we found no differences between subjects with a negative baseline CT scan and subjects with an indeterminate follow-up scan that had a negative follow-up CT scan (26). It would have been interesting to evaluate the HRQoL effects in subjects who received a positive test result; however, because only 11 subjects received a positive result at baseline, this would not provide sufficient power to give reliable results. Moreover, because this will be a false-positive result for some subjects, further studies are needed to determine the impact of such a result on HRQoL.

Implications

Following the baseline scan, this led to a clinically relevant increase in lung cancer-specific distress in a substantial number of persons who underwent baseline screening, although the letter to participants clearly explained the meaning of an indeterminate test result (i.e. a very common small abnormality). Based on recent data from the NELSON trial and other lung cancer screening trials, the risk of lung cancer in this group is estimated to be <2.5% (5). Because distress levels may remain elevated until the result of the follow-up CT scan is known (e.g. 3 months in the NELSON), we recommend that the screening program should be improved. For example, providing information about the small risk of having lung cancer in the letter might lead to a reduction in the lung cancer-specific distress. Another approach could be to reduce the number of indeterminate test results by identifying certain subgroup of nodules with an increased cancer risk, or by a combination of imaging and proteomic or genomic biomarkers.

Conclusions

This longitudinal study among participants of a lung cancer-screening program showed in the short-term that recipients of an indeterminate baseline screening result requiring a follow-up CT experience an increase in lung cancer-specific distress, whereas the scores of recipients of a negative baseline screening result may be interpreted as a relief.

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Chapter 4

Long-term effects of lung cancer CT screening on health-related quality of life (NELSON trial)

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Submitted

Abstract

Background: Lung cancer CT screening trials continue to evaluate the effects on mortality reduction. However, screening may result in unfavorable effects on health-related quality of life (HRQoL), especially after abnormal test results. The long-term effects on HRQoL (including second-round screening and screen-control group comparisons) have not yet been investigated.

Methods: In a population-based lung cancer CT screening trial (NELSON), 733 participants of the screen group and 733 of the control group received 3 and 2 HRQoL questionnaires, respectively: before randomization (T0), 2 months after baseline screening (the screen group only) (T1), and at 2-years follow-up (T2). Repeated measures ANOVA, adjusted for covariates, were used to analyze differences between screen and control group, and between indeterminate (requiring a follow-up CT) and negative screening result groups. All statistical tests were two-sided.

Results: At T0 and T2 there were no significant differences in HRQoL scores over time between the screen and control group, or between the indeterminate or negative second round screening result group. There was a temporary but significant increase in lung cancer-specific distress after an indeterminate baseline result: mean (95% CI) at T0: 4.0 (2.8-5.3), T1: 7.8 (6.5-9.0), and T2: 4.5 (3.3-5.8).

Conclusions: Lung cancer CT screening had no negative effects on HRQoL. At 2-years follow-up the HRQoL of screened subjects was similar to that of control subjects, the unfavorable short-term effects of an indeterminate baseline screening result had resolved, and an indeterminate result at the second screening round requiring a one-year follow-up CT had no impact on HRQoL 6 months later.

Introduction

Lung cancer is the most important cause of cancer-related deaths worldwide among men and women (1, 2). Although, lung cancer can be detected more often in an early stage by computed tomography (CT) screening (3, 4), it is unknown whether CT screening for lung cancer reduces lung cancer mortality. Possible screening benefits will apply to a small group of participants only, whereas the majority is subjected to potential unfavorable side-effects. Effective policy decisions regarding cancer screening programs require data on the effects of screening on mortality, health-related quality of life (HRQoL) and their cost-effectiveness (5). Few studies have examined the HRQoL effects of lung cancer screening with CT (6-9). Subjects receiving an indeterminate or positive result for a baseline CT screening reported increased anxiety or fear of cancer (6) and more lung cancer-specific distress than subjects with a negative result (7). At short-term follow-up, when all subjects had negative CT results, these unfavorable effects on HRQoL had decreased and the differences between subjects with initially negative or positive/indeterminate results were no longer observed (6, 8, 9). CT scanning itself caused only little discomfort and had no major impact on HRQoL (8).

However, within a screened cohort, comparisons of HRQoL are of limited value due to the possible effects of reassurance and selection. The best method to evaluate the long-term impact of screening is to compare a group of screen participants with a control group in a randomized controlled trial (RCT) (5). The rationale for this is, firstly, because a study population is often a selective group who is healthier than the general population (10, 11), and secondly because subjects invited for lung cancer screening differ from the general population in that they are usually heavy current or former smokers. The Dutch-Belgian randomized controlled trial for CT screening (the NELSON trial) allows to evaluate the long-term impact of screening on HRQoL (12).

An indeterminate result at baseline (i.e. first, or prevalence screening) has an unfavorable effect on HRQoL, but it is unknown whether subjects experience a similar decrease in HRQoL after second-round screening (i.e. incidence screening).

The aims of the present study are to: 1) compare HRQoL in a screen and control group over 2 years, 2) explore the short-term effects on HRQoL of an indeterminate result at second-round screening, 3) evaluate the long-term effects of an indeterminate baseline result, and 4) evaluate differences between getting a negative follow-up scan and getting at least one indeterminate or positive result at follow-up.

Methods

NELSON Study Population

The selection criteria for the NELSON trial have been described in detail elsewhere (13). Subjects randomized to the screen group could receive either a positive, indeterminate, or negative test result at each screening round (14). A positive test result required referral to a pulmonologist for work-up and diagnosis. Participants with an indeterminate result were scheduled to undergo a follow-up CT scan to evaluate whether the lung nodule had grown (Figure 4.1). The follow-up period for an indeterminate result was 3 months after baseline screening; after the second screening round, the follow-up period was 6-8 weeks for subjects with new nodules and 1 year for subjects with previously existing nodules with a volume doubling time of 400-600 days (14). Participants with an indeterminate test result received a letter stating that: a very small abnormality in the lung (5-10 mm in diameter) has been found, that this is a common finding that usually represents a small scar or minor inflammation only, and that at this moment there is no need for any further investigations.

The entire NELSON trial, including this HRQoL study, was approved by the Dutch Ministry of Health and by the local Ethics Committees of the participating centers. Informed consent was obtained from all participants. The NELSON trial is registered at www.trialregister.nl with number ISRCTN63545820.

HRQoL study

A consecutive sample of 1466 subjects participating in the NELSON trial was taken from the screening centers in Haarlem and Utrecht; the subjects were randomized in 2005 (n=733 screen group, n=733 control group) (Figure 4.1). All participants received a questionnaire before trial randomization (Time 0 [T0], baseline HRQoL assessment). A second questionnaire (Time 1 [T1]) was sent 2 months after baseline screening to 684 screen participants with either a negative baseline result (n=541) or an indeterminate baseline result (n=143). The final questionnaire was sent at 2-year assessment to 682 screen participants and a random sample of 498 control participants out of 726 eligible participants (Time 2 [T2]): for the screen participants this was approximately 1.5 years after baseline screening, i.e. 0.5 years after the second-round screening. The T2 questionnaire was not sent to 51 screen participants (7.0%) who did not undergo CT scans (n=28) for various reasons, or went 'off-screening' (n=23). Reasons for being 'off-screening' were screen-detected lung cancer (n=9), no longer wishing to participate (n=10), died (n=2), or could not be contacted (n=2). Also, of the 733 control group participants, 7 were not eligible for the T2 questionnaire because they had died (n=4) or no longer wished to participate in the trial (n=3).

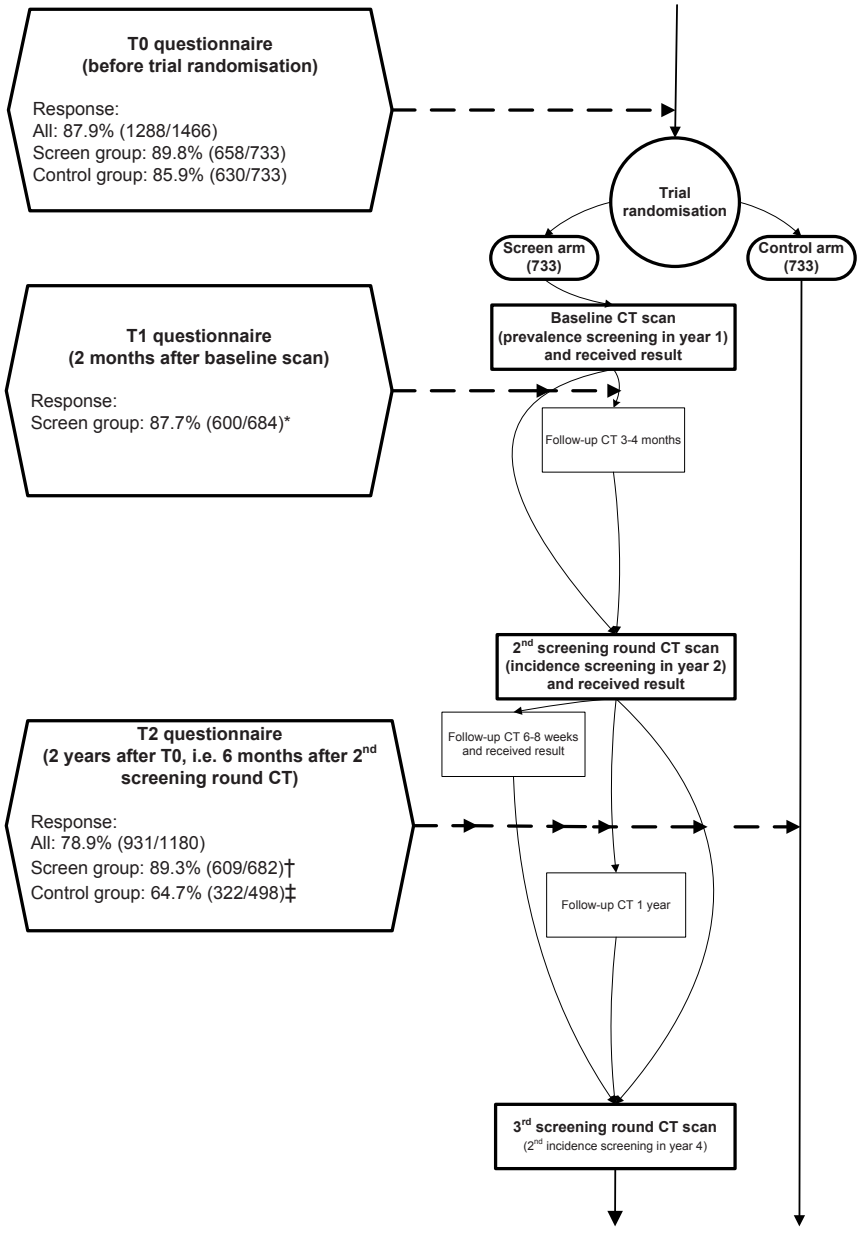

Figure 4.1. Flowchart of the Health-related Quality of Life study in the screen and control arm.
* This questionnaire was sent to participants with either a negative (n=541) or an indeterminate (n=143) baseline scan result.
† The T2 questionnaire was not sent to 51 screen group participants (7.0%) who did not undergo CT scans (n=28) for various reasons, or were 'off-screening' (n=23).
‡ The T2 questionnaire was sent to a random sample of 498 control group participants out of 726 eligible participants. 7 participants were not eligible for the T2 questionnaire.

Measures

Generic HRQoL

The participant's generic HRQoL was measured with the 12-item Short Form (SF-12) and the EuroQol questionnaire (EQ-5D) (15-18). The SF-12 is a shorter version of the SF-36 and consists of a Physical Component Summary (PCS) and a Mental Component Summary (MCS) (18). We used the acute (1-week recall) form of Version 1 in which a higher score indicates a better HRQoL. Respondents were also asked to rate their own health on the visual analog scale (VAS) of the EQ-5D, ranging from 0 (worst imaginable health status) to 100 (best imaginable health status) (15, 17).

Generic anxiety

Generic anxiety was measured using the short form of the Spielberger State-Trait Anxiety Inventory (STAI-6) (19). Six items related to anxiety (calm, tense, upset, relaxed, content, and worried) were rated on a 4-point scale. The total summary score was calculated in subjects with a maximum of 3 missing values and could range from 20-80, with higher scores indicating more anxiety (20). The STAI-6 is reported to have good reliability and validity, and was found useful to evaluate the effectiveness of screening programs on subjective anxiety levels (19).

Lung cancer-specific distress

Lung cancer-specific distress was measured using the Impact of Event Scale (IES) (21, 22). The 15 IES items were tailored to lung cancer as the specific stressor. Each item was scored on a 4-point scale: not at all (score of 0), rarely (score of 1), sometimes (score of 3), and often (score of 5). The total score and subscales (avoidance and intrusion) were calculated for those who completed 75% of the questions on each subscale, and were corrected for the total number of questions on the subscale. The total summary score could range from 0-75 (intrusive scale 0-35, avoidance scale 0-40), with a higher score indicating more lung cancer-specific distress.

Demographic and other data

At T0, the questionnaire included items on marital and smoking status. Educational level and smoking pack-years were derived from the first NELSON questionnaire that was used for selection of the Nelson trial participants (13).

Statistical analysis

Differences in respondent characteristics between the screen and control arm were analyzed with Chi-square tests and Mann-Whitney U tests, because these data were not normally distributed.

Analyses of each research question required different datasets. For the first research question, data were used of participants in the NELSON trial who received both T0 and T2 questionnaires and returned at least one questionnaire (screen arm: n=665, control arm: n=460). For the second question, screen group participants were included who received both T0 and T2 questionnaires, returned at least one questionnaire, and had an indeterminate (n=49) or a negative (n=585) result at the second screening round. For the third question, data were used of screen participants who received T0, T1 and T2 questionnaires, who returned at least one questionnaire and who at baseline screening had either a negative result (n=521) or an indeterminate result (n=135). Furthermore, for the subgroup analyses of subjects with an indeterminate baseline result, two subgroups were analyzed: subjects with at least one indeterminate result (n=28) or positive result (n=7), and subjects with only negative results (n=100).

HRQoL changes over time and between groups

To analyze the HRQoL changes over time and differences between groups, random effects analysis of variance (ANOVA) was used to account for the repeated measurements of each subject. The 'proc mixed' procedure in the SAS system version 9.1 was used that allowed use of all available data, including the incomplete records. The models included a main effect for time, and the interaction between group and time. This parameterization entailed that the separate components in the interaction term tested the group differences at the consecutive measurement moments.

The following fixed covariates were added to the model: age (because older people are reported to show less anxiety and better mental health) (6, 23), gender (because women are reported to show a different fear of cancer and have worse generic HRQoL compared with men) (23), education (because higher-educated lung cancer screening participants are reported to be less anxious, have less fear of cancer and less distress) (6), smoking status (because current smokers generally have a worse HRQoL than non-smokers, and more anxiety and fear of cancer) (24), and smoking pack-years (because we expected subjects with more pack-years to be more anxious and to have worse health). If the interaction term was not significant, models with the main effects for time and group were used, adjusted for covariates.

The IES scores were highly skewed. We considered repeated measures ANOVA to be appropriate for the IES scores because a logistic regression model using a generalized linear mixed models approach analysis would 1) reduce information content of the data, 2) the cut-off point is arbitrarily chosen, and 3) the results are comparable to those of repeated measures ANOVA.

All statistical tests were two-tailed. A p-value <0.05 was considered statistically significant. To determine a clinically-relevant difference between means at two assessment

points or between the two subgroups, the minimal important difference (MID) was used; this is defined as half a standard deviation (SD). The MID can serve as a default value for important patient-perceived changes in HRQoL (25, 26). For changes over time the SD at the first assessment of the two compared assessment points was used, and for differences between groups the pooled SD of the two groups at a specific time point was used.

Results

The questionnaire response at T0 was 89.8% in the screen arm and 85.9% in the control arm, at T1 87.7% (screen arm only), and at T2 89.3% in the screen arm and 64.7% in the control arm (Figure 4.1). Screen group participants completed T0 on average 4.9 (SD 3.6) months before baseline screening, T1 at 1.3 (SD 0.8) months after the baseline result, and T2 on average 5.6 (SD 1.2) months after the second screening round. For the screen and control group together, the time interval between T0 and T2 was on average 23.3 (SD 3.7) months. No significant differences in gender, age, education and smoking characteristics were found between responders in the screen (n=665) and control group (n=460) (Table 4.1).

1. HRQoL differences between screen and control arm

No statistically significant differences were found in HRQoL scores over time between the screen and control group (Table 4.2; Appendix 4.1 and 2). None of the parameters for time or the trial arm, nor the interaction between time*trial arm was significant for any of the HRQOL outcome measures.

2. Short-term impact of an indeterminate 2nd screening round result

No statistically significant differences were found in HRQoL scores from baseline to 6 months after the second-round screening between subjects with an indeterminate or negative second-round screening result (Table 4.2; Appendix 4.1 and 4.2). None of the parameters for time or result, nor the interaction between time*result was significant for any of the HRQOL outcome measures.

3. Long-term HRQoL differences between indeterminate and negative baseline results

Subjects with a negative (n=521) or indeterminate test result (n=135) at baseline had received on average 1.0 (SD 0.3) and 2.0 (SD 0.4) new CT scans with results, respectively, when they had completed the T2 questionnaire.

For the group with a negative result at baseline, the result of the last follow-up CT at T2 was: 0.2% 'positive' (n=1), 6.5% 'indeterminate' (n=34), and 93.3% 'negative' (n=486).

Table 4.1. Baseline characteristics of the screen group (n=665) and control group responders (n=460), included in the health-related quality of life study of the NELSON trial.

	Screen group responders* n=665	Control group responders† n=460
Sex: male %	46.2	50.0
Age, years mean (SD)	57.8 (5.5)	57.8 (5.7)
Education		
1 primary education %	9.8	11.5
2 lower vocational or lower secondary general education %	38.0	37.6
3 intermediate vocational or higher secondary general education %	25.2	23.3
4 Higher vocational education or university %	27.1	27.6
Smoking		
Current smokers %	53.7	52.4
Pack-years mean (SD)	39.7 (17.4)	39.4 (16.2)

SD = standard deviation; T0 = before trial randomisation; T2 = 1.5 years after baseline screening.
* Subjects received both the T0 and T2 questionnaire, and responded to at least one. Excluded subjects: 17 did not respond to the T0 and T2 questionnaire, 23 had CT scans but were off-study at T2, and 28 did not undergo CT scans.
† Subjects received both the T0 and T2 questionnaire and responded to at least one. Excluded subjects: 38 did not respond to T0 and T2, 7 were off-study at T2, and 228 were not selected in the random sample.
No significant differences between the screen and control group (Chi-square and Mann-Whitney U-tests).

For the group with an indeterminate result at baseline, the result of the last follow-up CT at T2 was 'indeterminate' for 15 (11.1%) subjects and 'negative' for 120 subjects (88.9%).

The course of IES (total, intrusive, and avoidance) scores over time differed between the groups with a negative and an indeterminate baseline result (p interaction time*result for all <0.01) (Table 4.2, Figure 4.2A-C; Appendix 4.1 and 4.2). In the indeterminate group the total IES scores changed from on average 4.0 (95% CI 2.8-5.3), to 7.8 (6.5-9.0), to 4.5 (3.3-5.8), whereas the negative group changed from 4.1 (3.4-4.8), to 2.6 (2.0-3.3), to 3.5 (2.9-4.2) at T0, T1, T2, respectively (Appendix 4.2). No statistically significant differences in IES between result groups were found at T0 or T2. The course of the EQ-5D VAS and the MCS scores did not differ between the two result groups over time, but the group as a whole had worse scores at T1 compared with T2 (-1.3 and -0.8; p<0.01 and p=0.05, respectively) (Table 4.2). Although PCS scores did not change over time, the indeterminate result group had worse PCS scores than the negative result group (-1.4, p=0.04) (Table 4.2). For all these analyses, only the differences between the result groups of the IES scores exceeded the MID at T1, and only these were therefore clinically relevant.

Table 4.2. Main parameter estimates (Beta (SE))* in mixed effect models of health-related quality of life scores over time during lung cancer screening.

Research questions with main parameters	PCS	MCS	EQ-5D VAS	STAI-6	IES-intrusive	IES-avoidance	IES-total
1. HRQoL differences from baseline to 2-years follow-up in the screen and control group†							
Intercept	54.84 (2.55)	49.19 (3.06)	79.78 (4.11)	33.27 (2.68)	-0.14 (0.92)	-2.23 (1.25)	-2.40 (2.02)
Time (T0) ‡	-0.07 (0.30)	-0.52 (0.35)	0.16 (0.43)	0.50 (0.28)	0.20 (0.12)	-0.00(0.16)	0.21 (0.25)
Trial arm (Screen) §	0.28 (0.48)	0.31 (0.58)	1.28 (0.78)	-0.59 (0.51)	-0.08 (0.17)	-0.06 (0.24)	-0.12 (0.38)
2. HRQoL differences from baseline to 2-years follow-up (i.e. 6 months after second-round screening) in negative and indeterminate *second-round* result group†							
Intercept	54.84 (3.38)	49.73 (4.03)	76.86(5.34)	37.16 (3.55)	-0.39 (1.20)	-1.26 (1.72)	-1.71 (2.71)
Time (T0) ‡	-0.44 (0.39)	-0.76 (0.41)	-0.46 (0.52)	0.61 (0.33)	0.25 (0.14)	0.06 (0.21)	0.33 (0.31)
Second-round screening result (indeterminate) ‖	0.19 (1.14)	-1.29 (1.36)	-0.94 (1.81)	-0.12 (1.20)	0.59 (0.41)	0.97 (0.58)	1.53 (0.92)
3. Long-term HRQoL follow-up (i.e. 2 years) in negative and indeterminate *baseline* result group¶							
Intercept	55.77(3,02)	48.57 (3,91)	78.85 (5,00)	37.43 (3.41)	-0.20 (1.11)	-1.15(1.60)	-1.36 (2.52)
Time (T0) ‡	-0.53 (0,37)	-0.57 (0,42)	-0.19 (0,52)	0.53 (0.32)	-0.27 (0.15)	0.26 (0.22)	0.56 (0.33)
Time (T1) ‡	0.02 (0,37)	**-0.85 (0,42)#**	**-1.28 (0,52)#**	0.54 (0.32)	**-0.49 (0.15)****	-0.39 (0.22)	**-0.90 (0.33)****
Baseline result (indeterminate) ††	**-1.40 (0,69)#**	0.78 (0,89)	-1.92 (1,14)	0.87 (0.77)	N.a.	N.a.	N.a.
Time*result (T0,indet) ‡‡	N.a.	N.a.	N.a.	N.a.	0.17 (0.31)	-0.17 (0.45)	-0.06 (0.70)
Time*result (T1, indet) ‡‡	N.a.	N.a.	N.a.	N.a.	**2.40 (0.32)****	**2.72 (0.46)****	**5.12 (0.72)****
Time*result (T2, indet) ‡‡	N.a.	N.a.	N.a.	N.a.	0.30 (0.32)	0.72 (0.46)	1.01 (0.71)

3.a. Long-term HRQoL follow-up (i.e. 2 years) in the indeterminate *baseline* result subgroup: a group with at least one indeterminate/positive and a group with only negative follow-up results†							
Intercept	51.62 (7.05)	47.90 (8.94)	74.56 (11.50)	39.62 (8.02)	-2.96 (2.68)	-2.26 (3.86)	-5.27 (6.16)
Time (T0) ‡	-0.08 (0.84)	**-1.79 (0.76)#**	-0.08 (1.19)	0.01 (0.68)	0.16 (0.41)	-0.61 (0.53)	-0.46 (0.85)
Time (T1) ‡	0.63 (0.87)	**-1.88 (0.79)#**	**-2.78 (1.22)#**	1.28 (0.69)	1.62 (0.42)	**1.61 (0.55)****	**3.22 (0.87)****
Follow-up results after the indeterminate baseline result (at least one indeterminate/positive) §§	-0.71 (1.47)	1.98 (1.87)	2.09 (2.42)	-1.37 (1.69)	-0.63 (0.56)	-0.91 (0.81)	-1.54 (1.29)

HRQoL = health-related quality of life; SE = Standard Error; PCS = Physical Component Summary of SF-12; MCS = Mental Component Summary of SF-12; EQ-5D VAS = EuroQol questionnaire Visual Analog Scale; STAI-6 = State-Trait Anxiety Inventory; IES = Impact of Event Scale; T0 = before trial randomisation; T1 = 2 months after baseline screening; T2 = 1.5 years after baseline screening; N.a. not applicable.

* The main estimates are adjusted for gender, age, education, pack-years and smoking status (see Appendix 1 for betas).

†For research questions 1, 2, and 3 subgroups, the interaction term was not significant.

‡ Reference category for time is T2.

§ Reference category for the trial arm is the control arm.

|| Reference category for the second-round result is a negative result.

¶ For research question 3, outcome measure IES, the interaction term was significant and therefore the parameters are presented in this table.

# $p<0.05$.

** $p<0.01$.

†† Reference category for the baseline result is a negative result.

‡‡ Reference category for the interaction term is the same assessment point for the negative result group.

§§ Reference category for the results after an indeterminate baseline result is all negative follow-up results.

EQ-5D, PCS, MCS: higher scores indicate better scores; STAI-6 and IES: lower scores indicate better scores.

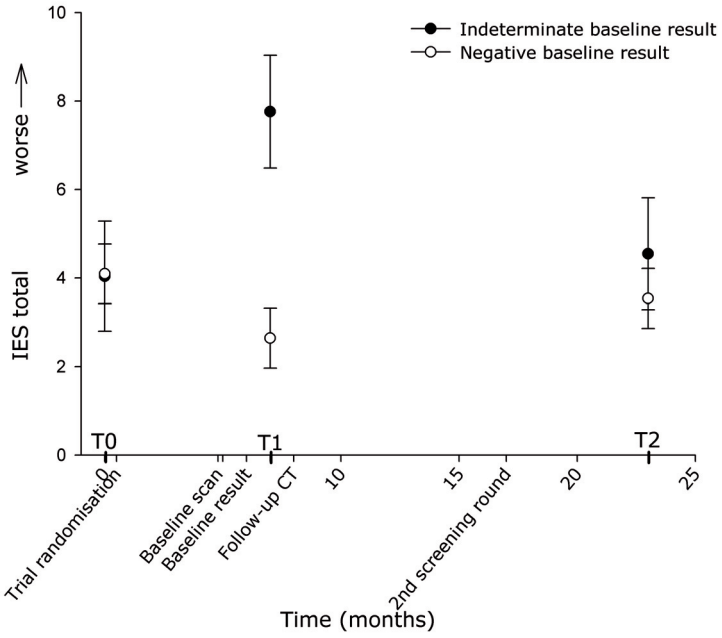

Figure 4.2A

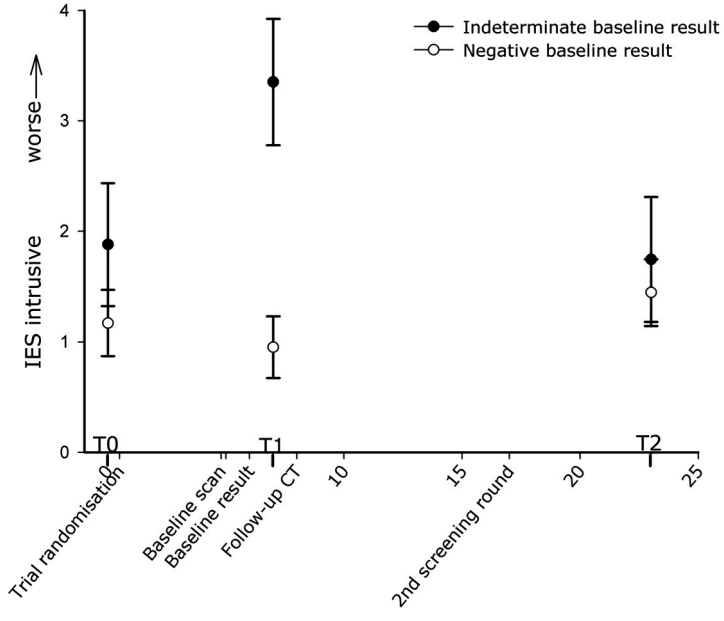

Figure 4.2B

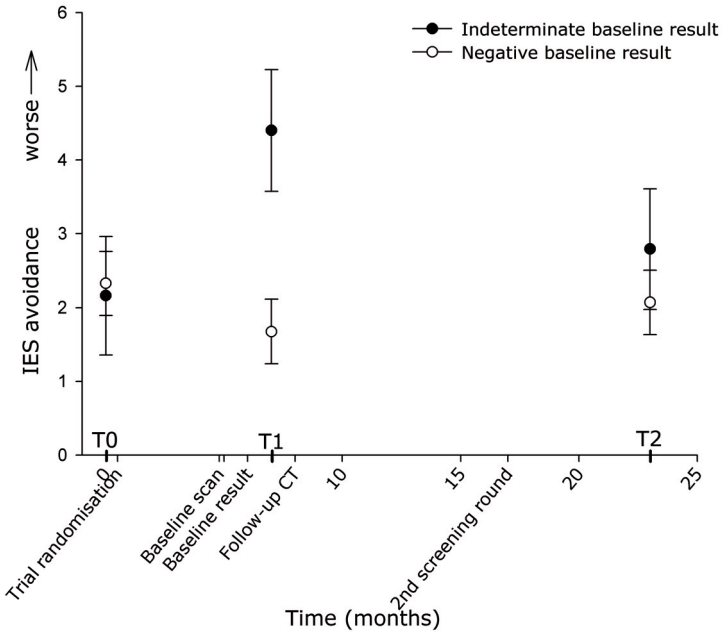

Figure 4.2C

Figure 4.2A-C. Average lung cancer-specific distress scale scores (least squares means) and 95% confidence intervals (Impact of Event Scale, IES): IES total (A), IES intrusive (B) and IES avoidance (C). The scores were adjusted for gender, age, education, smoking status and smoking pack-years. T0 = before trial randomisation; T1 = 2 months after baseline screening; T2 = 2 years follow-up.

In the subgroup analyses of the indeterminate baseline result group (i.e. subgroups with subjects with at least one indeterminate/positive result at follow-up (n=35) and subjects with only negative results at follow-up (n=100)), no statistically significant differences in HRQoL were found between the groups (Table 4.2, Appendix 4.1). The EQ-5D VAS and IES total, intrusive, and avoidance scores were worse at T1 compared with T2 (-2.8, 1.6, 1.6 and 3.2, respectively; p=0.02, <0.01, <0.01 and <0.01, respectively) and MCS scores were also better at T2 compared with T0 (-1.8) and T1 (-1.9) (both p=<0.02). None of these statistically significant differences exceeded the MID.

Impact of covariates on HRQoL

In general, the HRQoL scores were worse for women than for men (p<0.05) (Appendix 4.1). Subjects with more pack-years and/or current smokers had a statistically significantly worse self-reported health (EQ-5D VAS) and had statistically significant worse physical health scores (PCS) than subjects with less pack-years and former smokers

($p<0.05$). Smoking status and pack-years were not associated with MCS and STAI-6. A current smoking status was negatively associated with IES ($p<0.01$).

Discussion

Within a randomized design, the present study showed no long-term negative effects of lung cancer screening on HRQoL at 2-years follow-up. Firstly, HRQoL was the same in both the screen group and control group before trial randomization and at 2-years follow-up. Secondly, HRQoL was the same in subjects with an indeterminate and a negative second-screening round result, both before randomization and 6 months after the second screening. Thirdly, the negative effects on HRQoL after an indeterminate baseline result did not persist on the long term, even if an indeterminate baseline test result was followed by one or more positive or indeterminate test results.

Evaluating the HRQoL effects of lung cancer screening is ideal when including a randomized comparison of changes in HRQoL between those who underwent screening and those who did not. As far as we know, no other cancer screening studies have investigated HRQoL using a randomized screening design. Only Taylor et al. in their prostate, lung, colorectal and ovarian cancer screening trial reported baseline and 1-year HRQoL average scale scores of the SF-12 in a screen and control arm (19). In their study, according to the MID, no clinically relevant differences existed between the screen and control arm, and their scores were similar to our scores.

Until now, an unfavorable HRQoL effect of lung cancer screening was only found after an indeterminate or positive baseline scan result (6, 7, 9). In the present study we found no unfavorable HRQoL effects 6 months after an indeterminate second-screening round result requiring a 1-year follow-up CT. This is remarkable because subjects with an indeterminate second-round screening received a result letter similar to that received after baseline screening. An explanation may be that many subjects become accustomed to such a result. About 40% of the subjects had already received an indeterminate baseline result. Also, participants may become reassured after a follow-up period of one year. However, several participants and general practitioners telephoned the research centers after receiving the 1-year follow-up recommendation. Therefore, a more plausible explanation for this finding is the timing of the HRQoL measurement after the second-round screening: i.e. 6 months after screening, which was also 6 months before the follow-up scan. A temporary negative impact on HRQoL may have occurred just after receiving the result of the second-round screening and/or just before the extra follow-up screening; however, this was not specifically assessed in the present study. Nevertheless, if HRQoL was negatively affected by the indeterminate second-round screening result, this effect diminished over time since no unfavorable effect was found after 6 months.

Women showed a worse HRQoL than men. Byrne et al. also found significantly more anxiety in women than in men in a lung cancer screening trial (6) and Taylor et al. found higher IES intrusive scores and MCS scores in women than in men in their screening trial (23). Similar to Byrne et al. who found a higher fear of cancer in current smokers, we found more lung cancer-specific distress in current smokers (6).

Study limitations

Differences in response rates between the screen and control groups may limit the validity of comparisons because of possible selection bias. The response rate at T2 was 89% in the screen group and 65% in the control group. However, the lower rate in the control group was estimated too low. We had less opportunity to correct the denominator in the control group for changes in address, and serious events associated with being 'off-screen'. Furthermore, because comparison of respondents and non-respondents in the control group showed no significant differences in demographic characteristics, there is no evidence for selective response in the control group.

Unfortunately, we could not measure the HRQoL effects of false-positive results. The group with a positive screening result was too small to provide sufficient power for reliable comparisons. Studies are needed to estimate the effect on HRQoL in this latter group, because the negative impact on HRQoL is likely to be greater than after receiving an indeterminate result.

Implications

The only negative effect on HRQoL of lung cancer screening was a temporary increase in lung cancer-specific distress scores after an indeterminate baseline result; this does not seem to be an obstacle to the introduction of a lung cancer screening program.

Conclusions

In the present study, lung cancer screening had no negative impact on HRQoL on the long term. At 1.5 years after baseline screening, subjects who did not have (screen-detected) lung cancer had a HRQoL similar to that in control subjects, the negative short-term effects of an indeterminate baseline screening result was resolved, and an indeterminate second-round screening result had no negative impact on HRQoL 6 months later.

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Appendix 4.1. Parameter estimates (Beta (SE)) in mixed effect models of health-related quality of life scores over time during lung cancer screening.

Research questions with parameters	PCS	MCS	EQ-5D VAS	STAI-6	IES-intrusive	IES-avoidance	IES-total
1. HRQoL differences from baseline to 2-years follow-up in the screen and control group*							
Intercept	54.84 (2.55)	49.19 (3.06)	79.78 (4.11)	33.27 (2.68)	-0.14 (0.92)	-2.23 (1.25)	-2.40 (2.02)
Time (T0)†	-0.07 (0.30)	-0.52 (0.35)	0.16 (0.43)	0.50 (0.28)	0.20 (0.12)	-0.00(0.16)	0.21 (0.25)
Trial arm (Screen)‡	0.28 (0.48)	0.31 (0.58)	1.28 (0.78)	-0.59 (0.51)	-0.08 (0.17)	-0.06 (0.24)	-0.12 (0.38)
Sex (male)	**1.13 (0.48)§**	**1.63 (0.58)‖**	1.00 (0.77)	**-1.11 (0.50)§**	**-0.63 (0.17)‖**	**-0.74 (0.24)‖**	**-1.37 (0.38)‖**
Age	-0.02 (0.04)	0.04 (0.05)	0.04 (0.07)	-0.01 (0.05)	0.02 (0.02)	**0.06 (0.02)‖**	**0.08 (0.03)§**
Primary education ¶	**-2.76 (0.89)‖**	-0.76 (1.06)	-2.15 (1.40)	**2.02 (0.91)§**	**0.81 (0.32)§**	0.70 (0.43)	**1.59 (0.70)§**
Lower vocational or lower secondary general education ¶	**-2.56 (0.59)‖**	0.93 (0.71)	0.34 (0,96)	0.09 (0.62)	0.18 (0.21)	0.26 (0.29)	0.45 (0.47)
Intermediate vocational or higher secondary general education ¶	-0.93 (0.65)	**1.61 (0.78)§**	1.18 (1.05)	-0.93 (0.69)	-0.14 (0.24)	0.09 (0.32)	-0.05 (0.52)
Pack-years	**-0.06 (0.01)‖**	-0.01 (0.02)	**-0.08 (0.02)‖**	0.02 (0.02)	0.00 (0.01)	0.00 (0.01)	0.01 (0.01)
Smoking status (current)	-0.89 (0.48)	-0.42 (0.57)	**-1.86 (0.77)§**	0.54 (0.50)	**1.18 (0.17)‖**	**2.08 (0.23)‖**	**3.25 (0.38)‖**
2. HRQoL differences from baseline to 2-years follow-up (i.e. 6 months after second-round screening) in the negative and indeterminate *second-round* result group*							
Intercept	54.84 (3.38)	49.73 (4.03)	76.86(5.34)	37.16 (3.55)	-0.39 (1.20)	-1.26 (1.72)	-1.71 (2.71)
Time (T0) †	-0.44 (0.39)	-0.76 (0.41)	-0.46 (0.52)	0.61 (0.33)	0.20 (0.12)	0.06 (0.21)	0.33 (0.31)
Second-round screening result (indeterminate) #	0.19 (1.14)	-1.29 (1.36)	-0.94 (1.81)	-0.12 (1.20)	0.59 (0.41)	0.97 (0.58)	1.53 (0.92)
Sex (male)	**1.59 (0.63)§**	**2.73 (0.75)‖**	**2.06 (0,99)§**	**-1.99 (0.66)‖**	**-0.62 (0.22)‖**	**-0.77 (0.32)§**	**-1.39 (0.50)‖**
Age	-0.01 (0.06)	0.03 (0.07)	0.11 (0.09)	-0.08 (0.06)	0.02 (0.02)	0.04 (0.03)	0.06 (0.05)
Primary education ¶	-1.41 (1.17)	-0.73 (1.40)	-0.42 (1.83)	1.49 (1.22)	1.05 (0.41)§	0.83(0.59)	2.02 (0.94)
Lower vocational or lower secondary general education ¶	**-2.40 (0.77)‖**	0.56 (0.92)	-0.47 (1.22)	0.27 (0.81)	0.28 (0.3)	0.09 (0.39)	0.38 (0.62)
Intermediate vocational or higher secondary general education ¶	-0.58 (0.85)	1.71 (1.01)	1.40 (1.34)	-1.33 (0.89)	0.02 (0.30)	-0.01 (0.43)	-0.00 (0.68)
Pack-years	**-0.08 (0.2)‖**	-0.01 (0.02)	**-0.07 (0.03)‖**	0.02 (0.02)	0.00 (0.01)	0.00 (0.01)	0.01 (0.01)
Smoking status (current)	**-1.66 (0.62)‖**	-0.25 (0.74)	**-2.44 (0.98)§**	0.17 (0.65)	**1.24 (0.22)‖**	**2.02 (0.32)‖**	**3.25 (0.50)‖**

Appendix 4.1, continued

3. Long-term HRQoL follow-up (i.e. 1.5 years after baseline screening) in the negative and indeterminate *baseline* result group**							
Intercept	55.77(3,02)	48.57 (3,91)	78.85 (5,00)	37.43 (3.41)	-0.20 (1.11)	-1.15 (1.60)	-1.36 (2.52)
Time (T0) †	-0.53 (0,37)	-0.57 (0,42)	-0.19 (0,52)	0.53 (0.32)	-0.27 (0.15)	0.26 (0.22)	0.56 (0.33)
Time (T1) †	0.02 (0,37)	**-0.85 (0,42)§**	**-1.28 (0,52)§**	0.54 (0.32)	**-0.49 (0.15)‖**	-0.39(0.22)	**-0.90 (0.33)‖**
Baseline result (indeterminate) #	**-1.40 (0,69)§**	0.78 (0,89)	-1.92 (1,14)	0.87 (0.77)	N.a.	N.a.	N.a.
Time*result (T0,indet) ††	N.a.	N.a.	N.a.	N.a.	0.17 (0.31)	-0.17 (0.45)	-0.06 (0.70)
Time*result (T1, indet) ††	N.a.	N.a.	N.a.	N.a.	**2.40 (0.32)‖**	**2.72 (0.46)‖**	**5.12 (0.72‖**
Time*result (T2, indet) ††	N.a.	N.a.	N.a.	N.a.	0.30 (0.32)	0.72 (0.46)	1.01 (0.71)
Sex (male)	**1.67 (0.56)‖**	**2.00 (0.73)‖**	**2.16 (0.93)§**	**-1.46(0.63)§**	**-0.79 (0.21)‖**	**-0.95 (0.30)‖**	**-1.73 (0.47)‖**
Age	-0.02 (0.05)	0.06 (0.07)	0.09(0.08)	-0.10 (0.06)	0.02 (0.02)	0.04 (0.03)	0.06 (0.04)
Primary education ¶	-1.82 (1.04)	-0.53 (1.34)	-0.72 (1.72)	1.77 (1.17)	**0.98 (0.38)§**	0.69 (0.55)	**1.74 (0.86)§**
Lower vocational or lower secondary general education ¶	**-2.51 (0.70)‖**	0.59 (0.90)	-0.48 (1.15)	0.35 (0.78)	0.24 (0.25)	0.11 (0.37)	0.36 (0.58)
Intermediate vocational or higher secondary general education ¶	-0.61 (0.77)	1.73 (0,99)	0.87 (1.27)	-1.16(0.87)	-0.06 (0.28)	0.12 (0.41)	0.06 (0.64)
Pack-years	**-0.07 (0.02)‖**	-0.02 (0.02)	**-0.09 (0.03)‖**	0.03 (0.02)	0.00(0.01)	0.00 (0.01)	0.01 (0.01)
Smoking status (current)	**-1.68 (0.56)‖**	-0.68 (0.72)	**-2.94 (0.92)‖**	0.76 (0.63)	**1.10 (0.20)‖**	**2.04 (0.29)‖**	**3.14 (0.46)‖**
3.a. Long-term HRQoL follow-up (i.e. 1.5 years after baseline screening) in the indeterminate *baseline* result subgroup: a group with at least one indeterminate/ positive and a group with only negative follow-up results*							
Intercept	51.62 (7.05)	47.90 (8.94)	74.56 (11.50)	39.62 (8.02)	-2.96 (2.68)	-2.26 (3.86)	-5.27 (6.16)
Time (T0) †	-0.08 (0.84)	**-1.79 (0.76)§**	-0.08 (1.19)	0.01 (0.67)	0.16 (0.42)	-0.61 (0.53)	-0.46 (0.85)
Time (T1) †	0.63 (0.87)	**-1.88 (0.79)§**	**-2.78 (1.22)§**	1.28 (0.69)	1.62 (0.42)	**1.61 (0.55)‖**	**3.22 (0.87)‖**
Follow-up results after the indeterminate baseline result (at least one indeterminate/ positive) ‡‡	-0.71 (1.47)	1.98 (1.87)	2.09 (2.42)	-1.37 (1.69)	-0.63 (0.56)	-0.91 (0.81)	-1.54 (1.29)
Sex (male)	0.60 (1.40)	1.49 (1.78)	1.86 (2.29)	-1.99 (1.60)	**-1.58 (0.53)‖**	**-2.04 (0.77)‖**	**-3.62 (1.22)‖**
Age	0.09 (0.12)	0.07 (0.15)	0.18 (0.19)	-0.11 (0.14)	0.09 (0.05)	0.10 (0.06)	0.19 (0.10)

Primary education ¶	**-5.40 (2.47)§**	0.65 (3.12)	-6.03 (4.01)	1.24 (2.79)	0.00 (0.93)	-1.92 (1.34)	-1.92 (2.13)
Lower vocational or lower secondary general education ¶	**-4.45 (1.77)§**	0.40 (2.26)	-2.11 (2.88)	0.14 (2.01)	0.30 (0.67)	-0.56 (0.96)	-0.23 (1.54)
Intermediate vocational or higher secondary general education ¶	-0.85 (1.84)	2.72 (2.34)	1.40 (3.00)	-3.64 (2.10)	-0.33 (0.70)	-1.28 (1.00)	-1.59 (1.60)
Pack-years	**-0.14 (0.04)‖**	0.00 (0.05)	**-0.14 (0.06)§**	0.06 (0.04)	0.00 (0.01)	0.01 (0.02)	0.01 (0.03)
Smoking status (current)	-0.89 (1.30)	-1.27 (1.66)	-2.39 (2.14)	0.12 (1.50)	0.55 (0.49)	**2.07 (0.71)‖**	**2.63 (1.14)§**

HRQoL = health-related quality of life; PCS = Physical Component Summary of SF-12, MCS = Mental Component Summary of SF-12, EQ-5D VAS = EuroQol questionnaire Visual Analog Scale, STAI-6 = State-Trait Anxiety Inventory, IES = Impact of Event Scale, T0 = before trial randomisation; T1 = 2 months after baseline screening, T2 = 1.5 years after baseline screening, N.a. not applicable.

*For research question 1, 2, and 3 subgroups, the interaction term was not significant.

† Reference category for time is T2.

‡ Reference category for the trial arm is the control arm .

§ $p<0.05$.

‖ $p<0.01$.

¶ Reference category for education is higher vocational education or university.

Reference category for screening result is a negative result.

**For research question 3, outcome measure IES, the interaction term was significant and therefore the parameters are presented in this table.

†† Reference category for the interaction term is the same assessment point for the negative result group.

‡‡Reference category for the results after an indeterminate baseline result is all negative follow-up results.

EQ-5D, PCS, MCS: higher scores indicate better scores.

STAI-6 and IES: lower scores indicate better scores.

Appendix 4.2. Average health-related quality of life scale scores (95% confidence interval) over time during lung cancer screening*.

Research question and groups	PCS		MCS		EQ-5D		STAI-6		IES-intrusive		IES-avoidance		IES-total	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
1. screen group (1) control group (2)														
T0	49.50 (48.76-50.25)	49.67 (48.81-50.54)	51.66 (50.77-52.55)	51.72 (50.69-52.75)	79.19 (78.02-80.36)	78.50 (77.15-79.85)	33.27 (32.51-34.03)	33.75 (32.87-34.62)	1.74 (1.46-2.01)	1.76 (1.45-2.08)	2.26 (1.89-2.65)	2.25 (1.82-2.69)	4.05 (3.45-4.65)	4.02 (3.33-4.71)
T2	49.95 (49.20-50.71)	49.07 (48.10-50.04)	52.50 (51.60-53.40)	51.69 (50.54-52.84)	79.53 (78.35-80.71)	77.45 (75.95-78.95)	32.67 (31.91-33.43)	33.42 (32.44-34.39)	1.49 (1.21-1.76)	1.63 (1.28-1.99)	2.21 (1.83-2.59)	2.37 (1.88-2.87)	3.72 (3.12-4.32)	4.03 (3.24-4.81)
2. Second-round screening result: negative (1) indeterminate (2)														
T0	49.58 (48.76-50.40)	50.94 (48.37-53.50)	52.01 (51.06-52.96)	50.31 (47.34-53.29)	79.50 (78.25-80.75)	79.59 (75.65-83.52)	33.22 (32.40-34.04)	32.33 (29.78-34.88)	1.74 (1.45-2.03)	2.07 (1.16-2.98)	2.28 (1.85-2.70)	2.70 (1.37-4.02)	4.07 (3.41-4.73)	4.77 (2.72-6.82)
T2	50.20 (49.38-51.03)	49.24 (46.70-51.79)	52.70 (51.74-53.66)	51.82 (48.87-54.77)	80.12 (78.86-81.37)	78.22 (74.35-82.10)	32.49 (31.66-33.31)	33.14 (30.60-35.68)	1.45 (1.16-1.74)	2.30 (1.39-3.21)	2.13 (1.70-2.55)	3.65 (2.32-4.97)	3.61 (2.95-4.26)	50.20 (49.38-51.03)
3. Baseline result: negative (1) indeterminate (2)														
T0	49.90 (49.08-50.72)	48.67 (47.14-50.20)	51.86 (50.84-52.88)	51.97 (50.07-53.87)	79.84 (78.55-81.13)	78.59 (76.19-80.99)	33.11 (32.25-33.98)	33.28 (31.69-34.87)	1.71 (1.41-2.01)	1.88 (1.33-2.44)	2.33 (1.90-2.76)	2.16 (1.36-2.96)	4.10 (3.42-4.77)	49.90 (49.08-50.72)
T1	50.44 (49.61-51.26)	49.31 (47.71-50.92)	51.50 (50.48-52.53)	51.99 (50.01-53.97)	79.14 (77.83-80.45)	75.89 (73.43-78.35)	32.81 (31.94-33.68)	34.55 (32.92-36.17)	0.95 (0.65-1.26)	3.35 (2.78-3.92)	1.68 (1.24-2.11)	4.40 (3.57-5.23)	2.64 (1.97-3.32)	50.44 (49.61-51.26)
T2	50.55 (49.73-51.38)	48.72 (47.17-50.28)	52.09 (51.07-53.12)	53.87 (51.95-55.80)	80.05 (78.75-81.35)	78.69 (76.27-81.12)	32.45 (31.59-33.32)	33.24 (31.63-34.85)	1.45 (1.14-1.75)	1.75 (1.18-2.31)	2.07 (1.64-2.51)	2.79 (1.98-3.61)	3.54 (2.86-4.22)	4.55 (3.29-5.81)

PCS = Physical Component Summary of SF-12, MCS = Mental Component Summary of SF-12, EQ-5D VAS = EuroQol questionnaire Visual Analog Scale, STAI-6 = State-Trait Anxiety Inventory, IES = Impact of Event Scale, T0 = before trial randomisation; T1 = 2 months after baseline screening, T2 = 1.5 years after baseline screening.

* The mean scores (least squares means) are based on models with time, time*group and adjusted for the covariates age, gender, education, smoking status, and smoking pack-years.

EQ-5D, PCS, MCS: higher scores indicate better scores.

STAI-6 and IES: lower scores indicate better scores.

Chapter 5

High affective risk perception is associated with more lung cancer-specific distress in CT screening for lung cancer

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Abstract

Screening for cancer can cause distress. People who perceive their risk of cancer as high may be more vulnerable to distress. This study evaluated whether participants of a lung cancer Computed Tomography (CT) screening trial with a high affective risk perception of developing lung cancer had a higher level of lung cancer-specific distress during CT screening. Furthermore, we evaluated whether participants perceived their risk of developing lung cancer differently 6 months after screening compared with 1 day before screening. A total of 351 subsequent participants of the NELSON-trial (Dutch-Belgian randomized controlled trial for lung cancer screening in high-risk subjects), who were randomized to the screen arm, were asked to fill in questionnaires 1 day before and 6 months after screening. Lung cancer-specific distress (Impact of Event Scale (IES)), generic health-related quality of life (SF-12) and affective risk perception were assessed. One day before screening, the participants with a high affective risk perception (n= 47/321, 14.6%) had significantly higher (i.e., worse) median IES scores than participants with a low affective risk perception (11.5 vs. 2.0, $p<0.01$). Although median IES scores were significantly lower 6 months after screening than 1 day before screening, participants with a high affective risk perception still showed significantly higher IES scores than participants with a low affective risk perception (6.5 vs. 1.0, $p<0.01$). Six months after screening, significantly less participants (10.5%) felt that their risk of developing lung cancer was high than 1 day before screening (14.5%) ($p<0.01$). Levels of distress were not severe, but were elevated compared to participants with a low affective risk perception, and therefore, attention for this group is recommended.

Introduction

For men, lung cancer is the most common cause of cancer-related deaths, and for women it is the second one (1). In the Netherlands and Belgium, a randomized controlled trial for lung cancer screening in high-risk subjects (NELSON-trial) is being conducted to examine whether Computed Tomography (CT) screening and early intervention reduces lung cancer mortality (2).

Negative side effects of screening may include that participants experience psychological distress due to screening. Some anxiety may be an appropriate response to screening as a stressor and may hence aid coping (3). However, the number of people who benefit from screening due to early detection of lung cancer with a higher chance of cure is (much) lower than the number of people being screened. Thus, high levels of distress in a large proportion of the screen population could be a barrier towards implementation of the screening program (4).

Various other cancer screening studies have demonstrated that the impact of screening in terms of psychological distress is generally acceptable (5-7). Nevertheless, a specific subgroup may experience more psychological distress than the average participant. Subjects who perceived their risk of developing a certain disease or specific disease consequences as high have a poorer psychological well-being (8, 9). Since the participants of the NELSON-trial were selected because they are at high risk of developing lung cancer, we hypothesized that they may perceive their risk of developing lung cancer as high, and that the participants with a high perceived risk consequently could experience more psychological distress during lung cancer screening.

Therefore, we evaluated how many participants of a lung cancer CT screening trial had a low or high affective risk perception of developing lung cancer, and whether participants with a high affective risk perception showed a higher level of lung cancer-specific distress during lung cancer CT screening. Furthermore, we evaluated whether participants perceived their risk of developing lung cancer differently 6 months after screening compared with 1 day before screening.

Methods

NELSON-trial

A general questionnaire on smoking history and health was sent to a selection of subjects living in the Netherlands or Belgium, aged between 50 and 75 years old, who were registered in population registries. Subjects at high risk of developing lung cancer were invited to participate in the NELSON-trial. High-risk subjects were defined as those who had smoked more than 15 cigarettes a day for more than 25 years, or who had smoked

more than 10 cigarettes a day for more than 30 years, and were still smoking or quitted less than 10 years ago at the time of inclusion. Almost 16,000 high-risk subjects from the general population gave informed consent for randomization. Participants were randomized (1:1) to the CT screening group, or to the control group in which no screening was offered. For a more distinct description of the NELSON-trial, see Van Iersel et al. (2).

Three CT screening test results at baseline were possible: a negative test result in which case the participant was invited for a repeat scan one year later, an indeterminate test result which required a repeat scan 3-4 months later, or a positive test result which required referral to a pulmonologist for further work-up and diagnosis (10).

The NELSON-trial was approved by the Dutch Ministry of Health and by each Regional Medical Ethical Review Board of the participating centres.

Study population

The 351 subsequent participants of the NELSON-trial who were randomized to the screen arm in May and June 2005, and who had an appointment for the baseline CT screening, were eligible for this part of the study. They were asked to fill in two questionnaires, the first 1 day before screening and the second 6 months after screening. The participants with a negative test result at baseline, and the participants with a negative repeat scan (i.e., after an indeterminate baseline test result) were included in the six-months questionnaire. The six-months questionnaire was not sent to trial participants who had a positive test result at baseline screening or after the 3-4 months repeat scan (n=20) or who did not undergo baseline screening (n=10). One participant did not wish to receive any further questionnaires.

Measures

Different components of risk perception include cognitive risk perception and affective risk perception. Measuring cognitive risk perception requires a respondent to provide a numerical estimate of his or her risk of developing a certain disease. In measuring affective risk perception a subject is asked to evaluate how he or she *feels* about this risk. There is ongoing discussion as to which component is the most relevant to measure (11). Feeling at risk (i.e., affective risk perception) has been shown to be a better predictor of self-protective behaviour (12) and psychological distress (9) than cognitive risk perception. Therefore, we measured affective risk perception with a single item ("Besides the estimated chance, you possibly have a certain feeling about your chance of developing lung cancer. What do you feel your chance of developing lung cancer is? Very low, low, not low/not high, high, very high).

Lung cancer-specific distress was measured by the Impact of Event Scale (IES) (13). The IES can be tailored to a specific event, in our study 'lung cancer'. The IES contains two sub-scales that measure intrusion (7 items) and avoidance (8 items) of stressful events.

All items have four response options: not at all (score = 0), seldom (score = 1), sometimes (score = 3) and often (score = 5). Scores were calculated if participants had filled in 5 or more items on the intrusion subscale, and 6 or more items on the avoidance scale. Higher scores indicate higher levels of psychological distress. Total IES score ranges between 0 and 75.

The SF-12 was used to measure generic health-related quality of life (HRQoL)(14). The SF-12 is a shorter version of the SF-36 and consists of a physical component summary and a psychological component summary. A higher score indicates a better HRQoL. Missing items for subjects with one missing item on the SF-12 were imputed by the median. If more items were missing, SF-12 scores were not calculated.

All measures were part of a larger questionnaire, which was completed 1 day before screening and 6 months after screening.

Variables

Participants were divided into two groups based on their responses to the affective risk perception item. Since one of the aims was to evaluate whether participants with a high affective risk perception showed a higher level of lung cancer-specific distress, we made a distinction in risk perception that allowed us to compare participants with a high risk perception to the other participants. The first group consisted of participants who felt their risk of developing lung cancer was very low, low, or not low/not high (n=274, =low affective risk group, 85.4%). The second group (n=47, 14.6%) consisted of participants who felt their risk was high or very high (high affective risk group). Three participants did not fill in this question.

If participants reported to smoke daily or occasionally at the time of completion of the first questionnaire, they were defined as current smokers. All other participants were defined as former smokers, since all NELSON-trial participants were ever smokers. We calculated pack-years by multiplying the number of packs of cigarettes a day by the number of years of smoking.

Statistical analyses

Non-parametric tests were used because of non-normally distributed data. Chi-square tests were used to determine the association between gender and affective risk perception, and between smoking and affective risk perception. Spearman rank correlation was used to calculate the correlation between age and affective risk perception and pack-years, respectively; all as continuous variables. The Mann-Whitney U test was used to evaluate differences in IES scores and SF-12 scores between risk perception groups. The Wilcoxon Signed Rank test was used to determine significant differences within risk perception groups over time.

To determine whether significant differences between or within risk perception groups were relevant, we used the minimally important difference (MID) of half a standard deviation (S.D.). The MID can serve as a default value for important patient-perceived change on HRQoL(15). The McNemar test was used to test whether there was a greater transition from high to low affective risk perception than from low to high affective risk perception, 6 months after screening.

Results

Response rates were 92.3% (n=324) 1 day before screening and 90.0% (n=288) 6 months after screening. Mean age of the participants was 60.3±6.4 years; 50.9% of the participants of this study were men and 25.3% was a former smoker. Of the 288 participants who completed the questionnaire 6 months after screening, 239 (83.0%) had a negative baseline screening test result and 49 (17.0%) had an indeterminate screening test result. These 49 participants underwent a repeat scan which was negative for all of them; they received the screening test results before they completed the six-months questionnaire.

14.6% (n= 47) of the participants felt that their risk of developing lung cancer was high, as measured 1 day before screening. There were neither significant associations between gender and affective risk perception, nor between smoking status (defined as current vs. former smokers, or as pack-years) and affective risk perception. There was a low but significant correlation (ρ =-0.13, $p < 0.05$) between age and affective risk perception; younger subjects tended to perceive their risk of developing lung cancer as higher than older subjects.

At 1 day before screening, participants with a high affective risk perception had significantly higher (i.e., worse) median IES total scores and IES sub-scale scores than participants with a low affective risk perception (Table 5.1). Participants in the high affective risk group had significantly lower (i.e., worse) median scores on the mental component scale (MCS) of the SF-12. These differences in median IES and MCS scores between the groups with high and low affective risk perception were larger than a half S.D. and hence can be considered as representing clinically relevantly differences.

Median IES scores were significantly lower 6 months after screening than 1 day before screening within the low affective risk group as well as within the high affective risk group. Six months after screening, median IES scores were still significantly higher in the high affective risk group than in the low affective risk group (Table 5.1). The low affective risk group was divided into two subgroups for additional analyses. The first subgroup consisted of participants who felt their risk was very low or low (n=92) and the second subgroup consisted of participants who felt their risk was not low/not high (n=182). The participants with a very low or low affective risk perception did not show a lower median

Table 5.1 Scores for IES and SF-12 1 day before screening and 6 months after screening divided by affective risk perception 1 day before screening.

	One day before screening[a]					Six months after screening				
	Low affective risk group[b] (n=274)		High affective risk group[c] (n=47)		P-value (low vs. high risk group)	Low affective risk group (n=236)		High affective risk group (n=40)		P-value (low vs. high risk group)
	Mean (S.D.)	Median	Mean (S.D.)	Median		Mean (S.D.)	Median	Mean (S.D.)	Median	
IES intrusive	2.2 (3.2)	1.0[1]	6.6 (7.0)	5.0[4]	< 0.01	1.8 (3.3)	0.0[1]	4.8 (5.3)	3.5[4]	< 0.01
IES avoidance	3.4 (5.4)	1.0[2]	8.1 (8.5)	5.0[5]	< 0.01	2.6 (4.4)	0.5[2]	5.6 (6.2)	3.0[5]	< 0.01
IES total	5.6 (7.9)	2.0[3]	14.7 (14.4)	11.5[6]	< 0.01	4.3 (7.2)	1.0[3]	10.3 (11.0)	6.5[6]	< 0.01
SF-12 physical	48.3 (8.6)	51.2	47.7 (12.0)	51.9	NS	48.5 (9.4)	52.0	50.4 (9.7)	52.0	NS
SF-12 mental	52.0 (10.1)	54.5	46.8 (12.0)	50.4	< 0.01	51.2 (11.1)	55.5	46.0 (15.4)	52.2	NS

NS = not significant.

[1,2,4,5] $P < 0.05$ (differences within groups).

[3,6] $p \leq 0.01$ (differences within groups).

[a] data of 3 participants on estimating own risk were missing.

[b] participants who felt their risk of developing lung cancer was very low, low or not low/not high.

[c] participants who felt their risk of developing lung cancer was high or very high.

total IES score 6 months after screening (1.0 vs. 1.0), while the participants who felt their risk was not low/not high showed a significantly lower median total IES score 6 months after screening compared to 1 day before screening (3.0 vs. 2.0, $p < 0.01$).

The MSC no longer showed significant differences between participants with a low or high affective risk perception.

In total, 35 participants (12.7%) perceived their risk of developing lung cancer differently 6 months after screening than 1 day before screening (Table 5.2). Six months after screening, significantly less participants (29/276=10.5%) felt that their risk of developing lung cancer was 'high', or 'very high' than 1 day before screening (40/276=14.5%) ($p<0.01$). The difference between transition from high to low affective risk perception versus low to high affective risk perception was borderline significant ($p=0.09$). There was no association between baseline CT test results (negative or indeterminate) and affective risk perception 6 months after screening.

Of the 23 participants who were in the high affective risk group before screening and in the low affective risk group after 6 months, 22 had a negative and one had an indeterminate baseline test result. Of the 12 participants who were in the low affective risk group before screening and in the high affective risk group after screening all had a negative baseline test result. Of the participants who were in the low affective risk group before and 6 months after screening, 81,7% (183/224) had a negative test result. Of the participants who were in the high affective risk group before and 6 months after screening, 82.4% (14/17) had a negative test result.

Table 5.2 Risk perception 1 day before screening and 6 months after screening (only data of participants who completed both questionnaires).

	Low affective risk group 6 months post scana **n**	**High affective risk group 6 months post scanb** **n**
Low affective risk group at baselinea	224	12
High affective risk group at baselineb	23	17

[a] participants who felt their risk of developing lung cancer was very low, low or not low/not high.
[b] participants who felt their risk of developing lung cancer was high or very high.

Discussion

This is the first study to explore affective risk perception and lung cancer-specific distress in a lung cancer CT screening trial. About 15% of the participants of a lung cancer screening CT program felt that their risk of developing lung cancer was high. These participants had higher levels of lung cancer-specific distress 1 day before screening,

and although median IES scores were significantly lower 6 months after screening than 1 day before screening, they still reported more lung cancer-specific distress 6 months after screening. Perhaps subjects with a high affective risk perception also have more lung cancer worries in a situation without screening. Furthermore, CT screening may have led to some kind of reassurance, because more participants considered their risk to be low 6 months after screening and IES scores were significantly lower (all participants had a negative test result at baseline, or had a negative test result at the repeat scan after an indeterminate result at baseline).

The majority of participants felt that their risk of developing lung cancer was 'low' or 'not low/not high', and 6 months after screening this proportion was even higher. This is in line with previous research that showed that smokers were unrealistically optimistic about their risk of developing lung cancer. Smokers underestimated their relative risk compared to non-smokers and judged their own risk of lung cancer lower than they judged the risk of lung cancer of the average smoker (16). Another explanation could be that the participants in the screen arm of the trial feel safe because they are being screened and hence expect to be diagnosed in time in case they have lung cancer. To gain more insight into this, it would be interesting to evaluate affective risk perception in the control arm and to compare the results with the screen arm, and also to measure cognitive risk perception.

Limitations

Our study was limited to measurements after randomization, and the first measurement occurred just before screening. Therefore, we cannot be entirely sure that the IES scores 1 day before screening were only (or mainly) raised because of the upcoming CT scan (17). Distress levels may have already been raised by the whole process of screening (e.g., by reading the information leaflet of the trial which describes the relationship between smoking and lung cancer). However, this does not apply for the low affective risk group, because the median IES score was 2.0 1 day before screening. This score could have hardly been relevantly lower before the whole process of screening.

Because we only had data from the screen arm, we could not evaluate whether there were differences in affective risk perception between the screen arm and the control arm of the NELSON-trial. The participants of the control arm could also suffer from lung cancer-specific distress related to the trial itself and to the information leaflet. Finally, we had no data on the non-participants. Because people with a higher perceived risk of lung cancer are reported to be more interested in screening (18, 19), it is possible that our participants already had higher affective risk perceptions before they received information on the NELSON-trial than the non-participants.

Regression to the mean at the measurement 6 months after screening due to the exclusion of the participants with a positive CT screening test result is not very likely.

At 1 day before screening, the participants with a positive, negative or indeterminate CT screening test result were equally divided over the risk perception groups; there was also no correlation between test results and total IES scores 1 day before screening.

Previous studies

Our results are in accordance with results from studies on screening for breast cancer in high-risk women. Women who had a higher affective risk perception showed higher general distress and breast cancer-specific distress (9). Other studies also showed a correlation between high risk perception and higher levels of disease-specific distress in a screening or surveillance situation (20, 21). However, there are also some differences. We found that about 15% of the participants felt their risk was (very) high. In a breast cancer screening study in high-risk women, 58% felt that their risk was (very) high (22), while in a surveillance study in patients with Barrett's oesophagus, 1.2% of the participants felt their risk was high (21). Some of these differences may be explained by the fact that the actual risk of breast cancer in these high-risk women is higher and the risk for oesophagus cancer in Barrett's oesophagus is lower than the risk of lung cancer in our study population. Furthermore, in these studies, 7-point Likert scales were used, while we used a 5-point scale.

Conclusion

Levels of distress in the participants of a lung cancer CT screening trial with a high affective risk perception of developing lung cancer were not severe, but were elevated compared to participants with a low affective risk perception, especially just before screening. Therefore, attention for this group is recommended.

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Part 3
Informed decision-making

Chapter 6

Informed participation in a randomised controlled trial of computed tomography screening for lung cancer

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Abstract

Background: The actual lung cancer (screening) knowledge, attitudes, risk perceptions, reasons to participate in or decline participation, and informed decisions of subjects who decided to or decided not to participate in the Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects (the NELSON trial) were evaluated.
Methods: A total of 2,500 high-risk subjects were asked to complete a questionnaire 3 weeks after they had received a brochure with information about the trial. Differences in knowledge, attitude and risk perception between participants and nonparticipants were analysed with logistic regression analyses adjusted for sex and smoking status.
Results: The questionnaire response of trial participants was 80% (n=889) whereas the response of nonparticipants was low (7%, n=97) and selective. Participants' responses to knowledge items on lung cancer as a disease were on average more often correct (mean±SD 68±17%) than items on lung cancer screening (49±29%). Participants had adequate knowledge on lung cancer screening (51%) more often than the nonparticipants (38%)(p=0.009). Of the decisions regarding participation, 49% were uninformed mainly due to insufficient knowledge. Most of the participants (99%) and 64% of the nonparticipants had a positive attitude towards lung cancer screening.
Conclusion: Additional efforts are required to improve the knowledge and understanding of subjects who are in the process of decision-making regarding participation in a lung cancer screening trial.

Introduction

Lung cancer is the leading cause of cancer deaths in males and the second-greatest cause of cancer deaths in females (1, 2). Currently, lung cancer can be detected in an earlier stage by computed tomography (CT) screening (3). Although the public demand and enthusiasm for screening are high (4), a reduction in mortality due to lung cancer screening has not yet been proven and the results of randomised controlled trials are still awaited (5-7).

An informed decision (or informed choice) is defined as a decision based on relevant information, whereas screening behaviour is consistent with the decision-maker's values (8, 9). Ideally, subjects make an informed decision to participate or not in a lung cancer CT screening programme (10) because this can have a positive effect on quality of life and reduce decisional conflicts (8, 11). Although knowledge is a prerequisite for making an informed decision (8, 12, 13), previous cancer screening studies have shown that this knowledge is often limited (14, 15).

In the current study, we examined subjects at high risk of developing lung cancer who were in the decision-making process regarding participation in the Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects (the NELSON trial).

The following questions were addressed:

1. What is the knowledge about lung cancer (screening), what are the attitudes, lung cancer risk perceptions, and the reasons to participate or decline participation in lung cancer screening among (non-) participants in the NELSON trial?
2. Can differences in knowledge among participants be explained by differences in sex and education?
3. To what extent is decision-making regarding participation in the NELSON trial based on an informed decision?

Materials and Methods

NELSON trial

Dutch and Belgian subjects registered in population registries and aged 50-75 yrs were sent a letter with an information leaflet and a first questionnaire (Figure 6.1) (7). The two-sided paper leaflet contained brief information about the aim, background, and design of the trial. Current and former smokers were asked to complete the first NELSON questionnaire on smoking history and health. It was explained that those eligible for the NELSON trial would receive an invitation to participate together with detailed information about the trial. Respondents to the first questionnaire who reported to have smoked

>15 cigarettes/day for >25 yrs or >10 cigarettes/day for >30 yrs, who still smoked or who had quit ≤10 yrs previously were invited to participate in the trial. Exclusion criteria were a self-reported moderate or bad health status in combination with inability to climb two stairs; a history of renal cancer, melanoma or breast cancer; a history of lung cancer diagnosed <5 years ago, or >5 years ago but still under treatment; a chest CT examination <1 year before recruitment; or a bodyweight ≥140 kg (7).

Subjects eligible for trial participation received a second letter with an information brochure and a second NELSON questionnaire, including the informed consent form (7). The letter was explained that the subject was eligible for the trial and they were asked to read the information brochure carefully. Furthermore, it was explained that they had to complete the informed consent form and the second questionnaire if they decided to participate in the trial. The 14-page brochure contained extensive information about the aim, background and design of the trial, the procedures for diagnostic follow-up, potential unfavourable effects of lung cancer screening, randomisation procedure, etc. Subjects who completed and signed the informed consent form were subsequently randomised (1:1) to a screening group with 3 subsequent CT screening rounds, or to a control group without screening.

The trial was approved by the Dutch Ministry of Health (The Hague, The Netherlands) and by the ethics committees of the participating centres. The Ministry of Health gave permission to start the trial after a positive test of the 'comprehensibility' of the trial information.

Informed Decision-Making study

For the Informed Decision-Making (IDM) study, the present authors were interested in the responses of the subjects at the moment they were actually deciding, or had just made a decision about participation in the NELSON trial. It was decided that this would be the case at 2-3 weeks after sending the second NELSON trial questionnaire with the informed consent form for the NELSON trial (July 2005). A higher response to the IDM questionnaires was expected from subjects who had already decided to participate in the NELSON trial (i.e., who had returned the informed consent for trial participation) than from subjects who had not yet decided about participation in the NELSON trial 2 weeks after the questionnaire had been sent, or who had decided not to participate in the NELSON trial (i.e. did not return the trial informed consent form). Therefore, the subjects who had not returned the informed consent form within 2 weeks we oversampled: 2,100 questionnaires were sent to this group, and a sample of 400 subjects was drawn from the group had already returned the informed consent form to participate in the NELSON trial (Figure 6.1).

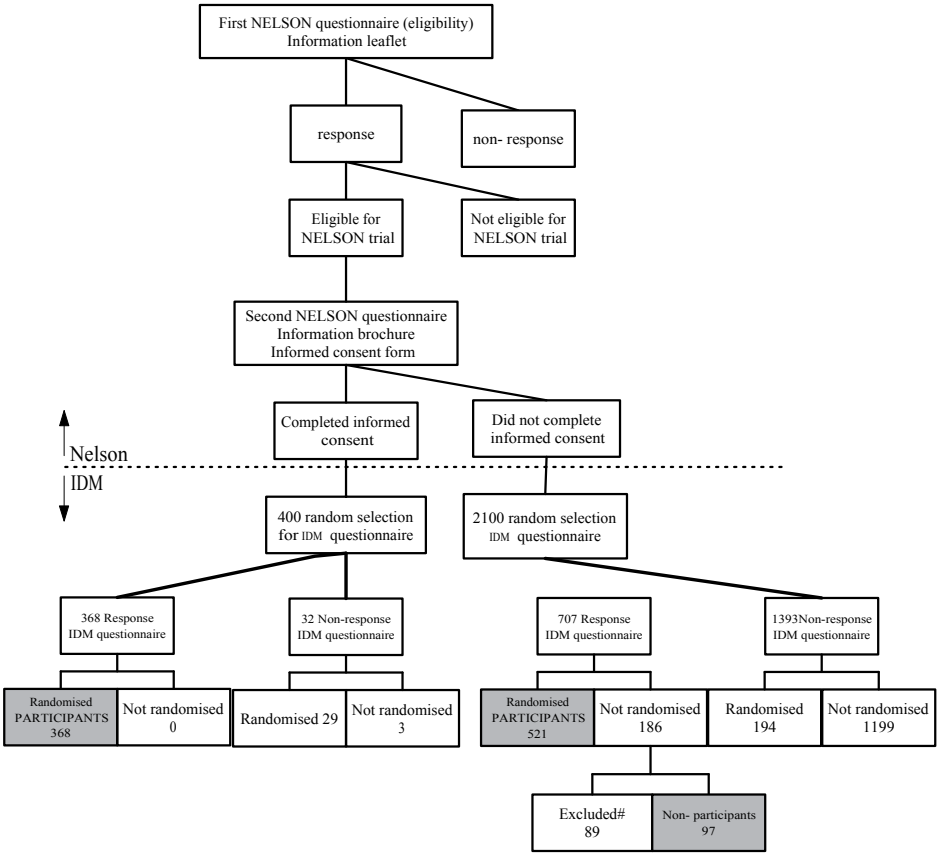

Figure 6.1. Flow chart of data collection for the Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects (NELSON) and the Informed Decision-making (IDM) study, with a definition of participants and nonparticipants.
[#] these subjects filled in that they "certainly would" participate in the NELSON trail but were not randomised because of an administrative failure (i.e. we never received the informed consent form).

Questionnaires

Knowledge

A measure of lung cancer (screening) knowledge was developed for this study, based on the items deemed important in guidelines for informed decision-making for screening (12, 16). There were 7 multiple-choice items and 14 statements ("true/false/do not know") related to three domains of knowledge: 1) characteristics of lung cancer screening (7 items), 2) the trial and the test (6 items), and 3) lung cancer (8 items) (Table 6.1). Based on Marteau et al. (8, 12) and Wald (8, 12) the items on lung cancer *screening* we reconsidered to be the most relevant for the decision regarding participation. A summary score was calculated by summing the correct responses (2), nearly correct responses (1),

Table 6.1 Percentages of correct answers on knowledge items of the participants (n=889) and nonparticipants (n=97) and significant differences between participants and nonparticipants.

Information given in the brochure	Knowledge item (correct answer)	Correct answers %#		p-value (participants versus non-participants)¶
Characteristics of lung cancer				
Not mentioned in brochure	In the past, before the CT scan was introduced, the chance of dying due to lung cancer after diagnosis was … (very high)	Participants Nonparticipants	38.8 27.8	0.024
Not mentioned in brochure	Lung cancer is one of the most common cancers (yes)	Participants Nonparticipants	66.0 58.8	0.137
Not mentioned in brochure	Changing of cough pattern is a frequent sign of lung cancer (yes)	Participants Nonparticipants	69.7 67.0	0.448
Not mentioned in brochure	Coughing up some blood is a frequent sign of lung cancer (yes)	Participants Nonparticipants	58.0 55.7	0.496
Not mentioned in brochure	Lung cancer is hereditary (no)	Participants Nonparticipants	64.2 54.6	0.112
Not mentioned in brochure	Lung cancer is infectious (no)	Participants Nonparticipants	96.9 87.6	<0.0005
Not mentioned in brochure	A subject can have lung cancer without complaints (yes)	Participants Nonparticipants	83.2 71.1	0.003
Not mentioned in brochure	Someone who has quit smoking has a higher risk of developing lung cancer than someone who has never smoked (yes)	Participants Nonparticipants	64.8 52.6	0.008
Characteristics of lung cancer screening				
The radiologist reads the CT scans for the existence of lung cancer. No screening for abnormalities in organs other than the lungs will be performed.	For which disorder are subjects being screened by a CT scan in the NELSON trial? (more than one item could be ticked) (lung cancer/all visible disorders on the CT scan)	Participants Nonparticipants	69.2 59.8	0.056
A normal CT scan means that no abnormalities suspicious for lung cancer were found. A normal CT scan does not guarantee that lung cancer will never appear.	Meaning of a "normal" CT result (Probably/certainly no lung cancer) (false-negative result)	Participants Nonparticipants	94.4 86.6	0.004
An abnormality suspicious for lung cancer is found in 2% of the CT scans.	Percentage of subjects with a screen positive CT scan result (2)	Participants Nonparticipants	33.1 25.8	0.094

An indeterminate result will be found in 18% of the CT scans. (i.e. an abnormality for which it is unclear whether it is benign or malignant)	Percentage of subjects with an indeterminate screening CT scan result (18)	Participants Nonparticipants	22.4 14.4	0.050
The pulmonologist or radiologist will contact you with the result and make appointments for follow-up. You will undergo diagnostic follow-up. You will be referred by your GP to a pulmonologist who will do diagnostic follow-up.	Follow-up after positive CT scan result (message by phone and referral to pulmonologist for diagnostic follow-up)	Participants Nonparticipants	68.3 58.8	0.023
The only way to distinguish between a benign or malignant abnormality is to repeat the CT scan after 3-4 months. You will receive this message by mail.	Follow-up after indeterminate CT scan result (message by mail and repeat scan after 3-4 months)	Participants Nonparticipants	36.2 27.8	0.092
It is possible that, although the CT scan result was "an abnormality suspicious for lung cancer", after extensive diagnostic research or even surgery, no lung cancer is diagnosed.	When a lung lesion is removed surgically, it is possible that it was not lung cancer (yes)	Participants Nonparticipants	16.9 15.5	0.777
Characteristics of the trial and the test				
The CT photos are made with X-rays.	A CT scan is made with X-rays (yes)	Participants Nonparticipants	58.8 47.4	0.020
The research table moves through the arch of the CT scanner. The brochure shows a picture of the CT scanner.	Subjects lie in an enclosed tunnel (no)	Participants Nonparticipants	38.4 28.9	0.059
To undergo the CT scan, you do not have to undress (but it is necessary to remove all metal objects).	For the CT scan you have to undress your upper body (no)	Participants Nonparticipants	53.0 38.1	0.002
	Lung cancer screening is standard for all subjects with a high risk (no)	Participants Nonparticipants	67.9 55.7	0.011
If you are in the screen group, you will be invited for a CT scan 3 times in the next 4 years	Subjects in the screen group receive 3 CT scans (yes)	Participants Nonparticipants	57.4 45.4	0.007
One group will not be scanned (control group)	Subjects in the control group receive 1 CT scan (no)	Participants Nonparticipants	50.7 27.8	<0.0005

CT = computed tomography; NELSON = Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects.
Original wording was in Dutch, the translations are conceptual, not literal.
[#]: missing answers for the lung cancer screening items, lung cancer items, and for the trial and test items for the participants were: 0.6-1.5%, 0.3-2.0% and 0.7-1.6%, respectively; and for the nonparticipants 5.2-7.6%, 4.1-8.2%, and 7.2-11.3%, respectively. A missing answer was counted as an incorrect answer.
[¶]: differences in percentage correct answers were adjusted for sex and smoking status.

and incorrect and missing responses (0), resulting in a score ranging from 0-14. Similarly, a scale score summarising all knowledge items was calculated (score range 0-42).

Attitude

Attitudes towards lung cancer screening were measured using six 5-point Likert scales (bad-good, not reassuring-reassuring, beneficial-harmful, important-unimportant, unwise-wise and desirable-undesirable). The choice of items was based on Marteau et al. and Van den Berg et al. (8, 11). The scale score ranged 6-30 with higher scores indicating a more positive attitude.

Risk perception

Cognitive risk perception was measured with two population risk estimations. Affective risk perception was measured with one item to evaluate how a person felt about his or her risk (Table 6.2).

Reasons to participate or decline

Reasons to participate in or decline lung cancer screening were assessed using 11 response options for participation and 12 for non-participation, based on previous research in prostate cancer screening (17), and the reasons given by subjects in the test of "comprehensibility" of the NELSON trial information. Subjects could also respond "other reasons". Furthermore, they were asked to give their decisive reason. We also asked subjects whether they had already decided to participate in the trial.

Informed decision

Following Marteau et al. (8), an informed choice (decision) is based on adequate decision-relevant knowledge and a behaviour that is consistent with attitude. Hence, an informed decision to participate is characterised by adequate knowledge, a positive attitude towards lung cancer screening, and actual participation (randomisation in the NELSON trial). An informed decision to decline participation was characterised by adequate knowledge, a negative attitude towards lung cancer screening, and actual non-participation. All other combinations were defined as uninformed.

Demographic and other data

The IDM questionnaire contained items on sex, date of birth, marital status and whether the subject had children. Educational level, smoking status (current and former), and smoking history in pack-yrs were derived from the first NELSON questionnaire.

Table 6.2 Cognitive and affective risk perception about lung cancer of the participants and nonparticipants.

	Participants	Non-participants
Total subjects n	889	97
Cognitive risk perception		
How do you estimate the chance of an average man getting lung cancer during his lifetime in the Netherlands?		
Answers n	871	92
Approximately 1 out of 5 (20%)	5.9	3.3
Approximately 1 out of 15 (6.6%)#	30.0	22.8
Approximately 1 out of 25 (4%)	13.8	15.2
Approximately 1 out of 50 (2%)	19.2	16.3
Approximately 1 out of 100 (1%)	16.8	21.7
Approximately 1 out of 250 (0.4%)	14.5	20.7
How do you estimate the chance of an average woman getting lung cancer during her lifetime in the Netherlands?		
Answers n	873	93
Approximately 1 out of 5 (20%)	3.8	5.4
Approximately 1 out of 15 (6.6%)	10.1	6.5
Approximately 1 out of 25 (4%)	14.0	15.1
Approximately 1 out of 50 (2%)#	32.1	29.0
Approximately 1 out of 100 (1%)	20.4	25.8
Approximately 1 out of 250 (0.4%)	19.7	18.3
Affective risk perception		
What do you feel your chance is of developing lung cancer?		
Answers n	884	93
Very low	3.6	3.2
Low	21.5	24.7
Not low/not high	60.5	65.6
High	13.5	5.4
Very high	0.9	1.1

Data are presented as %, unless otherwise stated.
Original wording was in Dutch, the translations are conceptual, not literal.
correct answer

Statistical analyses

Subjects with scores above the midpoint of the lung cancer screening knowledge scale (>7), complete knowledge scale (>21) and attitude scale (>18), were classified as having adequate knowledge (first two scores), and a positive attitude (third score), respectively; others were classified as not having adequate knowledge (first two scores), and a negative attitude (third score), respectively (9). Cronbach's alphas for the three scales were

0.54, 0.75 and 0.83, respectively. The affective risk perception item was divided into a low affective risk group (response options very low, low, and not low/not high) and a high affective risk group (response options high and very high).

The present study describes two groups. The first (n=889) is the "participant group" of the NELSON trial (Figure 6.1); they were randomised for the NELSON trial and completed the IDM questionnaire. The second group (n=97) is the "nonparticipant group" of the NELSON trial who completed the IDM questionnaire but were not randomised. Excluded from analysis were 89 subjects who completed the IDM questionnaire and intended to participate in the NELSON trial but were not randomised due to administrative reasons (e.g. the informed consent form was never received). Chi-square tests (sex, smoking status) or Mann-Whitney U-tests (age, smoking history in pack-yrs) were applied to determine the selectivity of questionnaire response among participants and nonparticipants.

Analysis of the differences between participants and nonparticipants was adjusted for sex and smoking status (former/current smoker). Logistic regression analysis was used to evaluate differences in response to each knowledge item (correct/incorrect), in knowledge sum scores (adequate/inadequate), attitudes (positive/negative), lung cancer risk estimations (correct/incorrect), and in affective risk perceptions (high/low).

Multiple logistic regression analysis was used to analyse the association of sex and education with knowledge in the group of participants. The following covariates were included: age, smoking history in pack-yrs, smoking status, sex and education.

Data are presented as mean±SD, unless otherwise stated.

Results

Response and characteristics of the respondents

For participants in the NELSON trial the response to the IDM questionnaire was 79.9% (889/1,112); for the nonparticipants it was 7.5%: i.e. 97/(1,388-89) (Figure 6.1).

Table 6.3 shows the characteristics of the NELSON subjects selected for the IDM study (participants and nonparticipants), and the characteristics of the IDM respondents from among the NELSON participants and NELSON nonparticipants. The nonparticipants showed a low response rate. Females from the group of nonparticipants responded more often than males (p=0.003) and former smokers from the nonparticipants group responded more often than current smokers (p=0.035). At the time of completion of the IDM questionnaire, 0.5% of the participants and 4.2% of the nonparticipants were undecided about their participation in the trial.

Table 6.3 Background characteristics of respondents to the Informed Decision-Making (IDM) questionnaire.

	Subjects eligible for the NELSON trial[#]		**Respondents to the IDM questionnaire**	
	Participants in trial	**Nonparticipants in trial[#]**	**Participants in trial**	**Nonparticipants in trial**
Subjecsts n	1112	1299	889	97
Sex: male %	49.6	47.7	48.5	33.0
Age yrs	57.7±5.6 (56.5)	58.8±6.3 (57.8)	57.7±5.6 (56.6)	59.3±6.2 (58.6)
Education				
1 Primary education %	9.3	15.5	8.6	15.5
2 Lower vocational or lower secondary general education %	40.0	43.2	41.3	38.1
3 Intermediate vocational or higher secondary general education %	24.4	22.7	24.5	22.7
4 Higher vocational education or university %	26.3	18.6	25.6	23.7
Married/ living with partner (%)			76.1	63.5
Children: yes %			80.5	72.2
Smoking[¶]				
Current smokers %	43.6	46.4	43.0	36.1
Smoking history pack-yrs	40.6±17.9 (38.0)	40.2±17.3 (38.0)	40.4±17.9 (35.8)	39.4±16.5 (34.2)
Have you decided yet whether or not to participate in the NELSON trial? n			864	95
Yes, certainly %			93.6	NA
Yes, certainly not %			0.0	65.3
I am still in doubt, but probably yes %			5.8	15.8
I am still in doubt, but probably no %			0.3	14.7
I do not know yet %			0.2	4.2

NELSON = Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects; NA = not applicable.
Data are presented as mean±SD (median), unless otherwise stated.
Original wording was in Dutch, the translations are conceptual, not literal.
[#]: excluded were 89 subjects who intended to participate in the NELSON trial and completed the IDM questionnaire, but were not randomised due to administrative reasons (i.e. informed consent form was never received).
[¶]: all participants are ever-smokers.

Knowledge

Responses to the lung cancer items were more often correct than responses to lung cancer screening items and responses to the trial and the test items (Table 6.1). On average, 67.7±17.1 %of the participants' responses to the knowledge items relating to lung cancer as a disease were correct, and 54.4±9.8% of their responses to knowledge items relating to the trial and the test were correct. Responses to items relating to lung cancer screening were the least often correct (48.6±28.9%).

About one-third of the participants responded 'Do not know' to the item about how often a positive or indeterminate result would be obtained. About 40% underestimated the number of indeterminate results of the CT scan; more than 50% thought that they would be referred to a pulmonologist after such a result. Only 16.9% knew that it might be possible that a surgically removed lung lesion could be benign (false-positive result).

Participants significantly more often exhibited a correct item response to 12 of the 21 items (Table 6.1).

The participants' responses more often reflected adequate knowledge regarding lung cancer screening (51.4%: 432/889) than the responses from nonparticipants (38.1%: 37/97)(p=0.009). When knowledge about lung cancer and about the trial was included in the knowledge sum score, then 72.7% (646/889) of the participants and 53.6% (52/97) of the nonparticipants had adequate knowledge (p<0.0005).

The percentage of correct responses was significantly higher in females and higher-educated participants compared to males and lower-educated participants in 7 and 8 of the 21 knowledge items, respectively (Table 6.4).

Attitude

Participants more often showed a positive attitude (98.7%) than the nonparticipants (63.8%) (p<0.0005).

Risk perception

About one-third of the participants made the correct estimation of the risk for an average male/female in the Netherlands to develop lung cancer during their lifetime (Table 6.2). No differences were found between participants and nonparticipants. Participants (14.4%) more often reported their opinion of their risk of developing lung cancer as high or very high than the nonparticipants (6.5%) (p=0.049).

Reasons to participate or decline

About 80% of the participants mentioned "I may have an advantage if lung cancer is detected in an early stage", and "Smoke(d) much" as a reason for participation (Table 6.5).

Table 6.4 Differences in correct answers on knowledge items between males and females and high/low education among participants (n=889).

Knowledge items (correct answer)	Females versus males[#]	High versus low education[¶]
Characteristics of lung cancer		
In the past, before the CT scan was introduced, the chance of dying due to lung cancer after diagnosis was … (very high)	1.25 (0.94-1.65)	0.85 (0.65-1.15)
Lung cancer is one of the most common cancers (yes)	0.96 (0.72-1.28)	1.22 (0.92-1.62)
Changing of cough pattern is a frequent sign of lung cancer (yes)	1.40 (1.04-1.88)*	1.27 (0.95-1.70)
Coughing up some blood is a frequent sign of lung cancer (yes)	1.35 (1.03-1.78)*	1.03 (0.79-1.36)
Lung cancer is hereditary (no)	0.76 (0.57-1.01)	1.29 (0.97-1.71)
Lung cancer is infectious (no)	1.10 (0.50-2.41)	2.95 (1.22-7.14)*
A subject can have lung cancer without complaints (yes)	1.22 (0.85-1.75)	1.67 (1.16-2.41)*
Someone who has quit smoking has a higher risk of developing lung cancer than someone who has never smoked (yes)	1.15 (0.87-1.54)	1.66 (1.24-2.21)*
Characteristics of lung cancer screening		
For which disorder are subjects being screened by a CT scan in the NELSON trial? (more than one item could be ticked) (lung cancer/all visible disorders on the CT scan)	1.02 (0.76-1.37)	0.91 (0.68-1.22)
Meaning of a "normal" CT result (Probably/certainly no lung cancer) (false-negative result)	1.15 (0.64-2.09)	0.99 (0.55-1.79)
Percentage of subjects with a screen positive CT scan result (2)	1.44 (1.08-1.92)*	1.30 (0.97-1.73)
Percentage of subjects with an indeterminate screening CT scan result (18)	1.33 (0.96-1.84)	1.41 (1.01-1.95)*
Follow-up after positive CT scan result (message by phone and referral to pulmonologist for diagnostic follow-up)	1.66 (1.24-2.23)*	1.30 (0.97-1.74)
Follow-up after indeterminate CT scan result (message by mail and repeat scan after 3-4 months)	1.15 (0.87-1.52)	1.22 (0.92-1.62)
When a lung lesion is removed surgically, it is possible that it was not lung cancer (yes)	1.07 (0.74-1.54)	1.55 (1.07-2.23)*
Characteristics of the trial and the test		
A CT scan is made with X-rays (yes)	1.30 (0.99-1.71)	1.06 (0.80-1.39)
Subjects lie in an enclosed tunnel (no)	1.11 (0.84-1.47)	1.12 (0.85-1.48)
For the CT scan you have to undress your upper body (no)	1.91 (1.46-2.50)*	1.19 (0.90-1.56)
Lung cancer screening is standard for all subjects with a high risk (no)	1.32 (0.98-1.77)	1.82 (1.36-2.45)*
Subjects in the screen group receive 3 CT scans (yes)	1.74 (1.32-2.30)*	1.45 (1.11-1.92)*
Subjects in the control group receive 1 CT scan (no)	1.59 (1.21-2.09)*	1.50 (1.14-1.97)*

CT = computed tomography; NELSON = Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects.

Data are presented as OR (95% CI).

Original wording was in Dutch, the translations are conceptual, not literal.

[#]: ORs reflect the odds of a female having a correct answer divided by the odds of a male having a correct answer, adjusted for age category (<57, >57 years), education (low and high education), smoking history in pack-yrs and smoking status (current/former) in a logistic regression model.

[¶] ORs reflect the odds of someone with a high education having a correct answer divided by the odds of someone with a low education having a correct answer, adjusted for age category (<57, >57 years), education (low and high education), smoking history in pack-yrs and smoking status (current/former) in a logistic regression model.

* $p<0.05$

Table 6.5. Reasons to participate in lung cancer screening in the Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects (NELSON) by participants (n=889).

	One of the reasons[#]	Decisive reason
Subjects n (%)	889 (100)	830 (93.4)
I smoke(d) a lot	79.2	25.2
If I'm in the screen group I may have an advantage if lung cancer is detected in an early stage	79.0	34.2
For science	60.0	11.1
It will guarantee me good health when the CT scan result is normal	42.9	11.0
For public interest	40.0	6.9
I think it is interesting	32.2	2.9
Lung cancer occurs in my family	19.0	2.8
I have complaints of my respiratory tract	12.5	1.9
Lung cancer occurs in my circle of acquaintances	10.6	0.5
My partner/family/friends/acquaintances thought I should participate	9.6	1.4
I'm afraid that I have lung cancer	3.1	1.1
Other reasons	3.6	1.1

CT = computed tomography.
Data are presented as %, unless otherwise stated. Original wording was in Dutch, the translations are conceptual, not literal.
[#]: more than one item could be ticked; mean±SD number of ticked reasons was 3.9±1.4.

Table 6.6. Reasons to decline participation in lung cancer screening in the Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects (NELSON) by nonparticipants (n=97).

	One of the reasons[#]	Decisive reason
Subjects n (%)	93 (95.9)	83 (89.2)
Participation is too much effort	45.2	30.1
I don't have enough insight into the personal consequences of the test	30.1	19.3
I don't have complaints of my respiratory tract	20.4	7.2
I'd rather not undergo a CT scan	18.3	10.8
I have no reason not to undergo screening	11.8	6.0
I think the information in the brochure is frightening	10.8	4.8
Because of reasons 'on principle'	4.3	1.2
I'm afraid that I have lung cancer	3.2	2.4
I have complaints of my respiratory tract	4.3	1.2
I think it is not interesting	2.2	2.4
Lung cancer occurs in my family	2.2	0
Information in the brochure is not clear enough	1.1	0
Other reasons	21.5	14.5

CT = computed tomography.
Data are presented as %, unless otherwise stated.
Original wording was in Dutch, the translations are conceptual, not literal.
[#]: more than one item could be ticked; mean±SD number of ticked reasons was 1.8±0.9.

Almost half of the nonparticipants mentioned "Participation too much effort" as one of the reasons to decline participation (Table 6.6); 14.5% (n=12) gave other reasons, e.g. that they already had regular examination for something else, or were anxious.

Informed decision

Using only knowledge on lung cancer *screening*, 51.3% of the participants (n=427/832) made an informed decision to participate. When using all knowledge items, 72.7% (605/832) made an informed decision to participate.

Discussion

The results of this study show that, when deciding to participate in a lung cancer screening trial, the knowledge of subjects was fairly good with regard to lung cancer but only moderate with regard to lung cancer screening itself. In general, nonparticipants had less knowledge than participants. Nonparticipants' attitudes towards lung cancer screening were less positive than those of participants, but they were still positive for two-thirds of the nonparticipants. Participants had a higher perceived risk of developing lung cancer than did nonparticipants. Due to their low knowledge level regarding lung cancer screening, only half of the participants made an informed decision to participate.

Knowledge

The present results again illustrate the difficulties in getting information on cancer screening across to screening invitees (17, 18). In Sweden, one-third of the cervical cancer screening attendees were unaware of the type of cancer for which they were being screened (19). Participants in a prostate cancer screening study also had limited knowledge about the meaning of the test results (20). The results of the present study also confirm the findings of previous cancer screening studies that showed a better knowledge among participants (14, 21). For example, participants in a prostate cancer trial were more aware than nonparticipants that someone can have cancer without having symptoms (17).

In the present study, responses to knowledge items relating to lung cancer as a disease were more often correct than responses to items relating to lung cancer screening, the trial and the test. The brochure did not contain detailed information on lung cancer as a disease, whereas information relating to screening, the trial and the test, was present. Apparently, these subjects eligible for lung cancer CT screening already had a relatively good general knowledge of lung cancer.

Attitude

The result that almost all participants and about two-thirds of the nonparticipants had a positive attitude towards lung cancer screening is not surprising, since people are generally enthusiastic about cancer screening (4, 22).

Risk perception

It has been shown that a higher perceived risk for lung cancer is associated with more interest and willingness to be screened for lung cancer (23, 24). The results of our study showed that participants had a higher affective risk perception than nonparticipants but not a higher cognitive risk perception. Nevertheless, most subjects underestimated the risk of lung cancer in men and women, and only 14% of the participants and 6.5% of the nonparticipants experienced their risk of developing lung cancer as being high.

Reasons to participate or decline

Reasons for participation were comparable with those for prostate cancer screening, especially regarding the most important reason, i.e. the possibility of personal benefit (17, 19). For 20% of the nonparticipants 'Having no complaints of the respiratory tract' was one of the reasons to decline participation in the trial. Although this is lower than in a prostate cancer screening trial (41%), subjects should be aware that someone can have lung cancer without complaints (17). For cervical cancer screening, an important reason to decline was a lack of confidence in the benefits of screening (19, 25).

Informed Decision-Making

The percentage of informed decisions depended on which knowledge scale we used. Based on responses to items relating to lung cancer, screening, and the trial and the test, approximately 70% made an informed decision. Restricting the knowledge scores to items relating to lung cancer *screening* (that are deemed to reflect the most relevant knowledge concerning decision-making), only 50% made an informed decision to participate (12, 16). The levels of informed decision-making were almost completely determined by knowledge, since almost all participants had a positive attitude towards lung cancer screening.

Limitations

Nonparticipants showed a low response rate to the IDM questionnaire and the response came from a selected group. However, comparisons could be made between participants and nonparticipants because we could adjust for sex and smoking status. Although these results have to be interpreted with caution, we consider the results of the analyses to be potentially useful.

Sending reminders and posting the questionnaire at a different time of the year (e.g. avoiding the summer vacation period) might have improved the response. However, studies that did this still showed low response rates among nonparticipants, and selective response remains hard to avoid among nonparticipants (17, 26).

Because a decision about participating in a screening programme is different from deciding to participate in a trial, the results of the present study might not be generalisable to the general population at risk for lung cancer, or to the situation when lung cancer screening may be implemented as a population-based screening programme. However, it is expected that trial subjects will read and try to understand the trial information better than the information of an established screening programme (11). Moreover, some subjects may not want to participate in a trial, but may do so in case of an established programme. Effects of IDM are speculative, because a prenatal screening study showed evidence for a decrease of IDM when the screening is part of standard practice (27).

Although the present study aimed to measure attitudes and knowledge at a time when the subjects were in the decision-making process, almost all subjects had already made their decision to participate or decline participation. Apparently, decision-making takes place soon after receipt of the invitation. Knowledge may have been better at the moment they made their decision about participation, because many people cannot recall information given shortly beforehand, and knowledge generally decreases over time (13, 28). Nevertheless, we consider it important that people remember the essential facts about lung cancer screening after their decision has been made.

Implications

Improving knowledge about lung cancer screening of subjects eligible for CT screening is necessary, because an inappropriate understanding of the screening test results may increase the negative psychosocial effects (18). Although most topics were mentioned in the brochure, 51% of the subjects showed inadequate knowledge. Some participants were over-optimistic about the CT scan (e.g. it represents a guarantee for good health). Improving the content of the brochure is a possibility. However, although a brochure may not be the best way to convey information (14, 29), how to improve the transfer of information still needs to be determined (10, 14). It remains unclear whether written, verbal, videotape, decision aids or the internet may be the method for this.

However, there is a growing belief that not all subjects that are offered screening should be forced to informed decision-making (10, 30). As Irwig et al. recently stated: "*…all those eligible for screening should be aware of the screening program and have received and understood an agreed minimum of information about benefits and harms of the procedure so that they can decide whether to follow the advice of an authoritative health body or make an individual choice*" (10). This means that, on the one hand, we have to acknowledge that not all subjects are able/want to make an informed decision

by rational deliberation and, on the other, that everyone who makes a decision should have at least a minimum level of knowledge (10, 13, 28, 30). Then, the critical question is: what precisely constitutes "adequate (decision relevant) knowledge", and who decides what that is (31).

Conclusions

Only about half of the participants in the NELSON trial made an informed decision. If population-based lung cancer screening is to be implemented, then additional effort is needed to convey essential knowledge to subjects who are in the process of decision-making about participation in lung cancer screening.

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Chapter 7

Informed decision making does not affect health-related quality of life in lung cancer screening (NELSON trial)

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Abstract

Background: It is believed that making an informed decision about (screening) participation is associated with better health-related quality of life (HRQoL) outcomes. This is the first study in cancer screening to explore this association in subjects participating in a lung cancer computed tomography (CT) screening trial.

Methods: Participants that made either an informed decision to participate (n=155) or not (n=133), were selected for this study. Differences in HRQoL, measured as generic HRQoL (Short Form 12 [SF-12] and EuroQol questionnaire [EQ-5D]), anxiety/distress (State-Trait Anxiety Inventory [STAI-6], Impact of Event Scale [IES], and Consequences of Screening - Lung Cancer [COS-LC]) were tested with Mann-Whitney U tests and ANOVA at three assessment points (when deciding about participation, before trial randomization and 2 months after receiving the CT result).

Results: Subjects who made an informed decision to participate had no better scores than those who did not make an informed decision for 23 out of 24 HRQoL comparisons, except for a better mean score for mental health (Mental Component Summary (MCS) = 53.9±9.2 versus 51.0±10.1, p=0.003) before randomisation. For subjects with an indeterminate CT result (n=64), no significant differences were found between subjects with (n=35) or without (n=29) an informed decision.

Conclusion: Subjects who did not make an informed decision to participate in lung cancer CT screening trial did not experience worse HRQoL during screening than subjects who did make an informed decision, either in general or after receiving an indeterminate result.

Introduction

The number of screening offers is increasing. Even if the benefits of a screening program at population level outweigh the disadvantageous side-effects, not all subjects will experience health gains from screening. Subjects eligible for screening should therefore be informed about the benefits and harms of the screening and should be supported to decide about participation in a screening program on the basis of an informed decision (1-3).

An informed decision (or informed choice) is a decision based on relevant knowledge, and the screening behaviour is consistent with the decision-makers values (4, 5). It is believed that making an informed decision is associated with better psychological and health outcomes, especially when receiving an unfavourable screening result (5, 6). However, the relationship with making an informed decision or not and health-related quality of life (HRQoL) in screening is a relatively unexplored area of investigation and evidence is limited to prenatal screening (5, 7). Recently, Kleinveld and colleagues reported that subjects whose participation in prenatal screening was based on an informed decision, seemed to have less adverse emotional reaction when confronted with a positive screening test outcome (7).

Studies on HRQoL in lung cancer computed tomography (CT) screening showed that receiving an unfavourable result caused a decrease in HRQoL (8-10). The purpose of the current study is to evaluate whether subjects who made an informed decision had a better HRQoL than subjects who did not make an informed decision, especially those receiving an indeterminate test result which required a follow-up CT scan.

Materials and Methods

The current study was performed within the Dutch-Belgian randomised controlled trial for lung cancer screening in high-risk subjects (NELSON trial).

Characteristics of the study group

Details of the NELSON trial and the informed decision making (IDM) study have been described before (9, 11-13). In brief, subjects aged between 50 and 75 years who smoke or have smoked heavily were selected for participation in the NELSON trial. The aim of the trial is to establish whether screening by low-dose CT can reduce lung cancer mortality with 25%. Subjects who gave informed consent were randomised (1:1) to a screen group with 3 subsequent CT screening rounds, or to a control group without screening. The outcome of the screening test at baseline could either be negative, indeterminate (requires follow-up CT after 3 months) or positive (work-up by pulmonologist) (14). The trial was approved by the Dutch Ministry of Health and by the ethics committees of the participating centres. The

Ministry of Health gave permission to start the trial after a positive test of the 'comprehensibility' of the trial information. Informed consent was obtained from all participants. The NELSON trial was registered at www.trialregister.nl with number ISRCTN63545820.

About 288 participants of the NELSON trial were eligible for the current study: they completed the IDM questionnaire in our previous study (T0) (11), and made or made not an informed decision to participate in the NELSON trial; they were included in the HRQoL study (9); and they were randomised to the screening arm. These 288 subjects further received questionnaires on HRQoL before trial randomisation (T1) and after the baseline result (T2). The T2 questionnaire was not sent to subjects with a positive test result (n= 5) or without baseline scan (n= 4).

Measures

Informed decision

In the definition regarding the informed choice (decision), we followed Marteau and colleagues (4). Accordingly, in our study an informed decision to participate was characterised by adequate knowledge, a positive attitude towards lung cancer screening, and actual participation (randomisation in the NELSON trial) (11). A decision to participate, but without adequate knowledge, and/or a negative attitude was regarded as uninformed. The knowledge and attitude scales were described elsewhere (11). In brief, these scales were based on the Multidimensional Measure of Informed Choice, developed and validated by Marteau and Michie to quantify informed decisions in prenatal screening (4, 5). Seven items on lung cancer screening were considered relevant for the decision regarding lung cancer screening participation (4, 15): disorder being screened for, meaning of a normal CT result, percentage of positive and indeterminate CT results, follow-up after positive and indeterminate CT results and false-positive results (see Van den Bergh and colleagues for the exact content of de knowledge items (11)). A summary score was calculated by summing the correct responses (2), nearly correct responses (1), and incorrect and missing responses (0), resulting in a score ranging 0–14. Attitudes towards lung cancer screening were measured using six five-point Likert scales (bad–good, not reassuring–reassuring, beneficial–harmful, important–unimportant, unwise–wise and desirable–undesirable). The choice of items was based on Marteau et al. and Van den Berg et al. (4, 16). The scale score ranged 6–30 with higher scores indicating a more positive attitude. Subjects with scores above the midpoint of the knowledge scale (>7), and attitude scale (>18), were classified as having adequate knowledge, and a positive attitude, respectively; others were classified as not having adequate knowledge, and a negative attitude, respectively (5).

Based on the definition of Marteau and colleagues 155 subjects (54%) made an informed decision to participate and 133 did not made an informed decision to participate (46%).

This distinction was almost completely determined by knowledge, since almost all participants (98%) had a positive attitude towards lung cancer screening (11).

Health-related quality of life (HRQoL)

Generic HRQoL

The participant's generic HRQoL was measured with the 12-item Short Form (SF-12) and the EuroQol questionnaire (EQ-5D) (17-20). The SF-12 is a shorter version of the SF-36 and consists of a Physical Component Summary (PCS) and a Mental Component Summary (MCS) (20). We used the acute (1-week recall) form of Version 1. A higher score indicates a better HRQoL. Respondents were also asked to rate their own health on the visual analogue scale (VAS) of the EQ-5D, ranging from 0 (worst imaginable health status) to 100 (best imaginable health status) (17, 18).

Generic anxiety

Generic anxiety was measured using the short form of the Spielberger State-Trait Anxiety Inventory (STAI-6) (21). Six items related to anxiety (calm, tense, upset, relaxed, content, and worried) were rated on a four-point scale. The total summary score was calculated in subjects with a maximum of three missing values and could range from 20-80, with higher scores indicating more anxiety (22). The STAI-6 is reported to have good reliability and validity, and was found useful to evaluate the effectiveness of screening programs on subjective anxiety levels (21).

Lung cancer-specific distress

Lung cancer-specific distress was measured using the Impact of Event Scale (IES) (23, 24). The 15 IES items were tailored to lung cancer as the specific stressor. Each item was scored on a four-point scale: not at all (score of 0), rarely (score of 1), sometimes (score of 3), and often (score of 5). The total score and subscales (avoidance and intrusion) were calculated for those who completed 75% of the questions on each subscale, and were corrected for the total number of questions on the subscale. The total summary score could range from 0-75 (intrusive scale 0-35, avoidance scale 0-40), with a higher score indicating more lung cancer-specific distress.

Psychological consequences of lung cancer screening

The psychological consequences of lung cancer screening test results were measured using part 1 of the Consequences of Screening – Lung Cancer questionnaire (COS-LC). This questionnaire was based on the COS-Breast Cancer questionnaire (25), but adapted for lung cancer screening into the COS-LC (26). With a formal procedure the COS-LC was

adapted from Danish into Dutch with two panels: a bilingual panel and a lay people panel (27). After that it was field-tested in the NELSON population.

Respondents rated experiences of the last week on a four-point scale (score 0-3): not at all, a bit, quite a bit and a lot). These 29 items were organised into eight dimensions: anxiety (6 items, e.g. I have felt scared/nervous/terrified), behavioural (6 items, e.g. have been quiet / have had difficulty meeting work or other commitments), worry (3 items, e.g. I have been worried about my future), depression (3 items, e.g. I have felt sad / unable to cope), sleep (2 items, e.g. I have slept badly), self-blame (4 items, e.g. I have felt guilty / disappointed, because I smoked for so many years), introvert (3 items, e.g. I have felt not confident / change of moods) and tobacco (2 items, e.g. I have felt regret, because I smoked for so many years). A higher score indicates more unfavourable psychological consequences of lung cancer screening. The COS-LC was only used at T2.

Demographic and other data

Educational level, smoking status and smoking pack-years were derived from the NELSON questionnaire used to determine eligibility for the NELSON trial (12). The number of self-reported conditions such as asthma and hypertension (0-9) and risk perceptions were measured at T0. Cognitive risk perception was measured with two population risk estimations for men and for women on a six-point scale: "How do you estimate the chance of an average man/woman getting lung cancer during his lifetime in the Netherlands?" (approximately 1 in 5, 1 in 15, 1 in 25, 1 in 50, 1 in 100, 1 in 250). For a man the correct answer was "approximately 1 in 15" and for a woman "approximately 1 in 50". Affective risk perception was measured with one item on a five-point scale to evaluate how a person feels about his or her risk: "What do you feel your chance of developing lung cancer is?" (very low - very high) (28).

Statistical analysis

Differences in respondent characteristics between subjects who made an informed decision or made not an informed decision were analysed with chi-square tests for nominal and ordinal variables, and with Mann-Whitney U test for continues variables. Differences in HRQoL between subjects with and without an informed decision were tested with Mann-Whitney U tests for T0, T1 and T2, because the data were not normally distributed. Since the non-parametric analyses (Mann-Whitney U tests) did not differ from the parametric analyses (T-tests), analyses of variance (ANOVA) analyses were used to test differences in HRQoL at T2 for subjects with and without an informed decision, corrected for the T1 HRQoL assessment. As a result possible type-1 errors due to multiple testing in the HRQoL comparisons, a p-value <0.01 was considered statistically significant.

Results

Response and Respondent characteristics

The questionnaire response was 93% (267/288)(95% confidence interval (CI) = 89-95%) for the assessment before randomisation (T1) and 89% (248/279) (95% CI = 85-92%) for the assessment after the baseline result (T2). About 215 subjects (75%) had a negative

Table 7.1. Respondent characteristics at T0

	Total group	Total group		Indeterminate result[a]	
	All	Informed decision	No informed decision	Informed decision	No informed decision
N	**288**	**155**	**133**	**35**	**29**
Sex: male: n (%)	142 (49)	74 (48)	68 (51)	20 (57)	16 (55)
Age (years): mean (SD), median (range)	57.3 (5.3), 56.1 (51-75)	57.2 (5.1), 55.8 (51-74)	57.6 (5.5), 56.5 (51-75)	57.9 (5.3), 56.7 (51-71)	58.0 (6.2), 56.3 (51-75)
Education					
1 primary education: n (%)	22 (8)	10 (7)	12 (9)	2 (6)	4 (14)
2 lower vocational or lower secondary general education: n (%)	114 (40)	62 (41)	52 (39)	12 (35)	11 (38)
3 intermediate vocational or higher secondary general education: n (%)	74 (26)	42 (27)	32 (24)	11 (32)	9 (31)
4 Higher vocational education or university: n (%)	75 (26)	39 (25)	36 (27)	9 (27)	5 (17)
Smoking					
Current smokers: n (%)	140 (49)	76 (49)	64 (48)	18 (51)	14 (48)
Pack-years: mean (SD), median (range)	39.4 (16.0), 35.0 (21-96)	38.7 (15.1), 34.2 (21-92)	40.2 (17.1), 35.8 (21-96)	38.1 (13.5), 35.8 (21-72)	44.2 (18.9), 38.0 (21-92)
Amount of illnesses and chronic diseases: mean (SD), median (range)	0.8 (0.9), 1.0 (0-4)	0.8 (0.9), 1.0 (0-4)	0.7 (0.9), 0.0 (0-3)	0.6 (0.8), 0.0 (0-3)	1.0 (1.1), 1.0 (0-3)
Risk perception					
Cognitive:					
For men (n (%) correct answer)	80 (28)	52 (34)[b]	28 (21)[b]	13 (37)	6 (21)
For women (n (%) correct answer)	91 (32)	58 (37)[c]	33 (25)[c]	15 (43)	8 (28)
Affective (n (%) high or very high)	47 (16)	27 (18)	20 (15)	5 (14)	7 (24)

SD = standard deviation

[a] No significant differences in indeterminate result group between subjects with and without an informed decision (Chi-square and Mann-Whitney-U test)(α=0.05).

[b] p= 0.020 (Chi-square).

[c] p= 0.024 (Chi-square).

Table 7.2 Unadjusted HRQoL scores (mean (SD), median (range)) at each assessment for subjects with and without making an informed decision.

	T0, when deciding about trial participation		**T1,** before randomisation		**T2,** after receipt of baseline result[a]			
	Total group		**Total group**		**Total group**		**Indeterminate result**	
	Informed decision	**No informed decision**	**Informed decision**	**No informed decision**	**Informed decision**	**No informed decision**	**Informed decision**	**No informed decision**
N	**(155)**	**(133)**	**(143)**	**(124)**	**(135)**	**(113)**	**(30)**	**(25)**
SF-12								
PCS	-	-	49.4 (7.8), 52.3 (23-67)	49.3 (9.2), 52.9 (11-63)	50.6 (7.9), 53.2 (22-69)	50.1 (8.1), 52.5 (23-66)	48.5 (8.8), 52.4 (29-60)	48.0 (7.4), 51.0 (26-55)
MCS	-	-	53.9 (9.2), 56.2 (22-66)[b]	51.0 (10.1), 54.1 (21-65)[b]	51.2 (12.6), 55.9 (9-67)	51.4 (11.0), 55.9 (16-65)	54.4 (9.3), 56.3 (25-66)	53.5 (8.2), 56.0 (31-63)
EQ-5D - VAS	78.5 (12.1), 80.0 (40-100)	76.4 (14.6), 80.0 (20-100)	80.5 (12.6), 80.0 (50-100)	78.7 (13.6), 80.0 (40-100)	79.3 (11.9), 80.0 (35-100)	78.0 (12.1), 80.0 (33-99)	75.8 (12.9), 75.0 (50-95)	76.1 (9.2), 80.0 (60-95)
STAI-6	33.8 (9.0), 33.3 (20-63)	35.0 (8.4), 33.3 (20-67)	31.5 (7.8), 30.0 (20-60)	33.4 (8.4), 33.3 (20-70)	32.6 (10.1), 30.0 (20-77)	33.4 (9.3), 30.0 (20-67)	33.0 (7.0), 33.3 (20-47)	34.8 (10.5), 33.3 (20-67)
IES								
IES intrusive	-	-	1.5 (3.2), 0.0 (0-25)	1.6 (2.8), 0.0 (0-14)	1.3 (3.2), 0.0 (0-19)	1.4 (3.7), 0.0 (0-30)	3.2 (4.9), 1.0 (0-19)	4.1 (6.8), 1.0 (0-30)
IES avoidance	-	-	2.0 (4.1), 0.0 (0-22)	2.3 (4.5), 0.0 (0-22)	2.3 (4.9), 0.0 (0-29)	2.0 (4.6), 0.0 (0-29)	4.6 (6.3), 2.0 (0-26)	5.1 (7.8), 1.0 (0-29)
IES total	-	-	3.6 (6.5), 0.0 (0-35)	3.9 (6.9), 0.0 (0-36)	3.6 (7.2), 0.0 (0-42)	3.4 (7.8), 0.0 (0-59)	7.8 (10.1), 4.0 (0-42)	9.3 (13.9), 5.0 (0-59)

COS-LC								
Anxiety	-	-	-	-	1.9 (2.8), 1.0 (0-15)	1.8 (2.1), 1.0 (0-12)	2.0 (2.1), 1.5 (0-7)	2.3 (2.8), 2.0 (0-12)
Behavioural	-	-	-	-	2.4 (3.0), 1.5 (0-16)	2.3 (2.5), 2.0 (0-10)	2.5 (2.3), 2.0 (0-8)	2.0 (2.3), 2.0 (0-10)
Worry	-	-	-	-	1.5 (1.6), 1.0 (0-8)	1.7 (1.6), 1.5 (0-6)	1.8 (1.3), 2.0 (0-4)	2.2 (1.9), 2.0 (0-6)
Depression	-	-	-	-	1.2 (2.0), 1.0 (0-9)	1.0 (1.4), 1.0 (0-6)	0.9 (1.2), 0.5 (0-4)	1.0 (1.6), 0.0 (0-6)
Sleep	-	-	-	-	1.2 (1.3), 1.0 (0-6)	1.6 (1.5), 1.5 (0-6)	1.0 (1.2), 1.0 (0-5)	1.4 (1.6), 1.0 (0-6)
Self-blame	-	-	-	-	1.2 (2.0), 0.0 (0-11)	1.1 (1.9), 0.0 (0-8)	1.5 (1.7), 1.0 (0-4)	2.2 (2.5), 1.0 (0-8)
Introvert	-	-	-	-	0.9 (1.5), 0.0 (0-9)	0.9 (1.2), 0.0 (0-7)	1.0 (1.0), 1.0 (0-3)	1.2 (1.5), 1.0 (0-7)
Tobacco	-	-	-	-	1.0 (1.2), 1.0 (0-6)	1.0 (1.3), 0.5 (0-6)	1.6 (1.2), 2.0 (0-4)	1.6 (1.7), 1.0 (0-6)

SD = standard deviation, SF-12 = Short Form 12 (generic HRQoL), PCS = physical component summary, MCS = mental component summary, EQ-5D VAS = self-reported health status, STAI-6 = anxiety, IES = lung cancer-specific distress, COS-LC = Consequences of Screening – Lung cancer.

[a] No significant differences in SF-12, EQ-5D, STAI-6 and IES scores between subjects with and without an informed decision at T2 when corrected for the SF-12, EQ-5D, STAI-6 or IES scores respectively at T1 (ANOVA).

[b] MCS score was significantly higher (i.e. better) in the group with an informed decision than in the group without an informed decision (p=0.003) (Mann-Whitney-U test).

baseline test result, 64 subjects (22%) had an indeterminate result, 5 (2%) a positive result, and 4 subjects did not undergo baseline screening. Of the total group, 49% was male and the respondents were on average 57.3 (SD = 5.3) years old (Table 7.1). No significant differences in respondent characteristics were found between subjects with and without an informed decision either in the total group or in the group that received an indeterminate baseline result. Subjects who made an informed decision provided the correct response to the cognitive risk perception items more often correct than subjects without an informed decision (risk perception for men: p=0.020 and risk perception for women 0.024, Table 7.1).

HRQoL differences between subjects with and without an informed decision

Subjects of the total group who made an informed decision had better scores for MCS than subjects who did not make an informed decision (53.9 (9.2) and 51.0 (10.1)) before randomisation (p=0.003) (Table 7.2). For subjects with an indeterminate baseline result, no differences were found between the subjects with and without an informed decision at each assessment (table 7.2). At T2, the ANOVA analyses in which was adjusted for the T1 measure, no differences were found in SF-12, EQ-5D, and IES scores between subjects

Table 7.3 Parameter estimates of parameter estimates (Beta (SE)) health-related quality of life

	Intercept	HRQoL score at T2[a]	Informed decision (yes)
Total group			
PCS	26.5 (2.8)	0.5 (0.1)[b]	0.4 (0.9)
MCS	11.5 (3.5)	0.8 (0.1)[b]	-1.8 (1.2)
EQ-5D VAS	31.4 (3.9)	0.6 (0.0)[b]	0.4 (1.2)
STAI-6	8.0 (2.2)	0.8 (0.1)[b]	0.2 (1.0)
IES intrusion	0.8 (0.3)	0.4 (0.1)[b]	-0.1 (0.4)
IES avoidance	0.8 (0.4)	0.6 (0.1)[b]	0.3 (0.5)
IES total	1.5 (0.7)	0.5 (0.1)[b]	0.3 (0.9)
Indeterminate result group			
PCS	31.7 (5.6)	0.4 (0.1)[b]	-0.7 (2.4)
MCS	21.4 (9.0)	0.6 (0.1)[b]	1.2 (2.5)
EQ-5D VAS	46.1 (8.4)	0.4 (0.1)[b]	-0.3 (2.8)
STAI-6	13.3 (3.8)	0.7 (0.1)[b]	-1.2 (1.9)
IES intrusion	3.3 (1.3)	0.4 (0.3)	-1.0 (1.6)
IES avoidance	3.3 (1.4)	0.7 (0.2)[b]	-0.0 (1.8)
IES Total	6.2 (2.6)	0.7 (0.2)[b]	-0.8 (3.1)

HRQoL = Health-related quality of life, PCS = physical component summary, MCS = mental component summary, EQ-5D VAS = self-reported health status, STAI-6 = anxiety, IES = lung cancer-specific distress
[a]HRQoL at T2 depends on the outcome measure, e.g. if the outcome measure is PCS, HRQoL at T0 is PCS.
[b] p<0.01

with and without an informed decision in the total group and in the indeterminate result group (Table 7.3). For the ANOVA analyses in the total group and in the indeterminate result group, the T1 HRQoL measure was significantly associated with the outcome measure except from IES intrusion (Table 7.3).

Discussion

This first study on the effect of informed decision making on HRQoL in cancer screening showed that subjects who made an informed decision to participate in a lung cancer CT screening trial in general did not experience better HRQoL compared with subjects who had not made an informed decision. We did not find differences in HRQoL between subjects who made an informed decision to participate or who made not an informed decision to participate after receiving an indeterminate baseline test result that required follow-up screening.

Only one out of 24 HRQoL comparisons between subjects who made an informed decision and subjects who did not make an informed decision was significantly different. Because the absolute differences was small and this is possibly a result of multiple testing we did not consider this difference relevant.

Michie and colleagues evaluated the effect of informed decision making on post-test anxiety (STAI-6) in subjects in prenatal screening (5). They did not find differences between subjects with and without an informed decision in the group with a low-risk (i.e. favourable) outcome following serum screening for Down syndrome. This is in accordance with our findings in the total group with mainly negative (i.e. favourable) outcomes. In another prenatal screening study, Kleinveld and colleagues found that subjects who made an informed decision seemed to have a less adverse emotional reaction when confronted with an unfavourable screening outcome (i.e. an increased risk of having a child with Down syndrome) than subjects who did not make an informed decision (7). This result was not confirmed in our study, because we did not find HRQoL differences in the subjects with and without an informed participation decision who received an unfavourable (i.e. indeterminate) CT result. The differential result may be partly attributable to the choice of anxiety measures: Kleinveld and colleagues used items on the emotional reaction specifically relating to the screening outcome whereas we used more generic scales.

Some hypothesise that former smokers may not be aware of their continuing risk of developing lung cancer. If they are made aware of this risk by the screening invitation, they may not be interested at all in potential disadvantageous effects of screening. However, in our previous paper, we found that former smokers were more often aware

that their risk of developing lung cancer is still higher than of someone who has never smoked (data not shown) (11).

Limitations

In the indeterminate screening result group, the groups with and without an informed participation decision seemed to differ in some demographic characteristics (e.g. education level and smoking history) in an absolute sense, although these differences did not reach statistical significance, probably due to the small groups. However, larger groups would probably show differences in demographic characteristics, but not in finding differences in HRQoL since the absolute differences in HRQoL scores were very small.

Psychometric analyses for the COS-LC found differential item functioning (DIF) for screening result or gender for three subscales. We have not corrected for DIF because it would not have changed the conclusions.

A decision about participating in a screening program is different from deciding to participate in a screening trial. Therefore, the results of the present study may not be generalised to the situation when lung cancer screening may be implemented in a population-based screening programme.

Implications

Although we did not find differences in HRQoL, this does not imply that we should stop informing potential screenees. Those who want to be informed should have easy access to honest, complete, and balanced information about the favourable and unfavourable aspects of participation in (lung) cancer screening. In a previous study (11) we showed that uninformed participation decision-making in lung cancer screening was almost completely determined by lacks in knowledge: If adequately informed, subjects can decide whether undergoing the screening is best for themselves (1, 3, 29). Previous research in other health care contexts showed unfavourable effects of uninformed participation decisions in domains that may be related to HRQoL, for example, more decisional conflict (5). Research in other cancer screening groups on the effects of informed decision making on HRQoL is recommended, especially in groups with unfavourable screening results.

In conclusion, subjects who made an informed decision to participate in lung cancer CT screening trial, in general, and after receiving an indeterminate CT result do not differ in health-related quality of life during screening from the subjects who did not make an informed decision.

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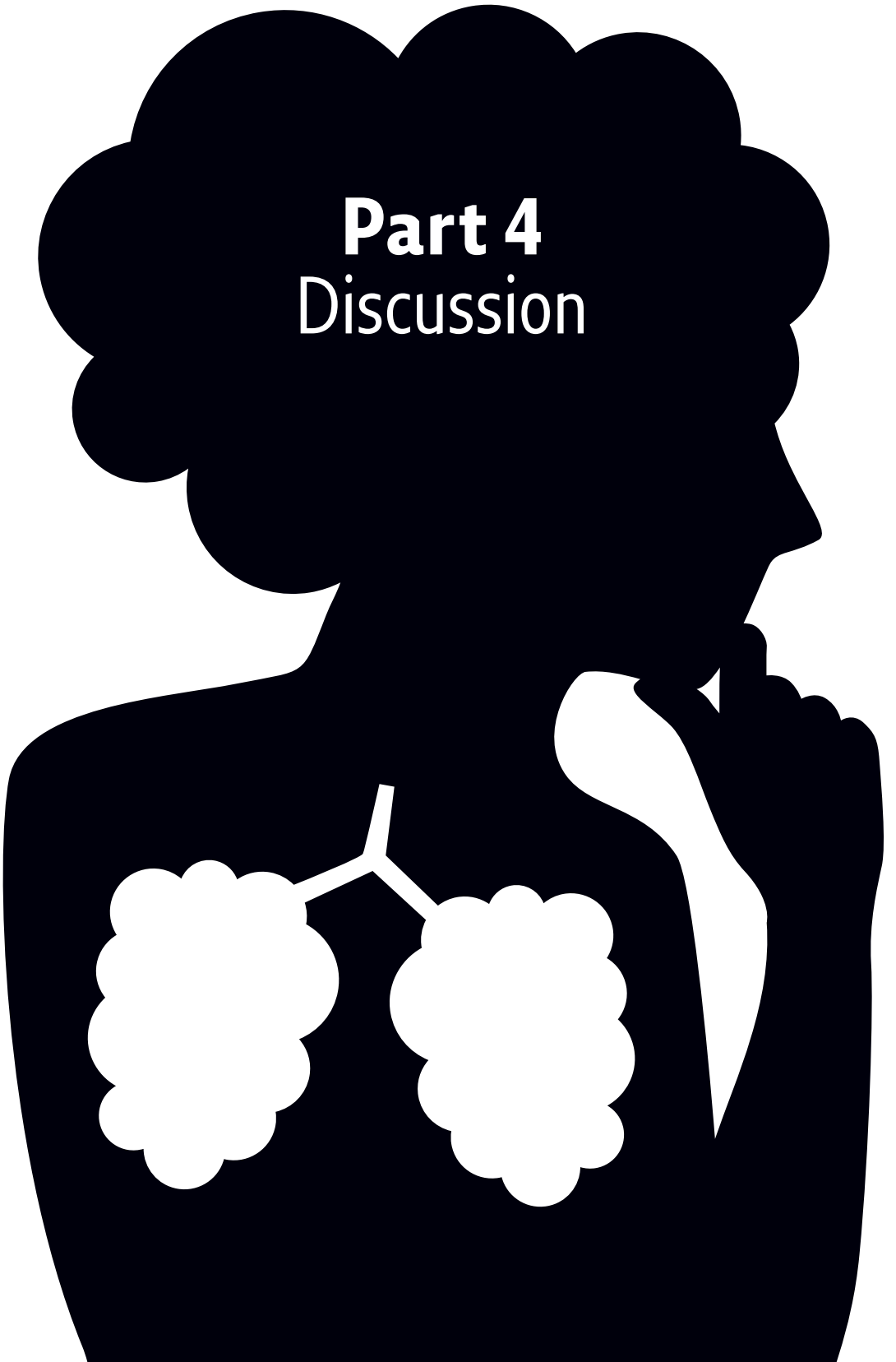
Part 4
Discussion



Chapter 8

General discussion

This chapter begins by addressing each of the research questions. This is followed by a general discussion focusing on methodological considerations, interpretation of the findings, main conclusions, and recommendations for future research.

Answers to the research questions

Research question 1:

What are the effects, both in size and extent, of lung cancer CT screening in high risk subjects on health-related quality of life?

a) To what extent do screened subjects experience discomfort before and during CT scanning and while waiting for the baseline scan results?

It appears that undergoing lung cancer screening with a CT scan causes almost no discomfort to participants (Chapter 2). Nevertheless, about 50% of the respondents experienced at least some discomfort whilst waiting for the CT scan results. Most participants rated 'waiting for the result' as the most distressing part of screening, and only a few mentioned the 'prospect of undergoing CT scanning' or 'undergoing the CT scan'.

b) To what extent does the course of HRQoL change in the short- and in the long-term? Does the course of HRQoL differ between participants with an indeterminate result and a negative result, received both after the baseline scan or second-round scan?

In the short term, 2 months after receiving the baseline screening result, participants with an indeterminate result experienced increased lung cancer-specific distress when compared with participants with a negative result (Chapter 3). However, generic HRQoL (general physical and mental health and generic anxiety) was not affected: no relevant differences over time were found within or between negative and indeterminate test result groups. In the long term, at 2-years follow-up we found that the increased distress after an indeterminate baseline result was only temporary (Chapter 4). Even in participants receiving one or more abnormal CT results after the indeterminate baseline result, the distress did not persist. No unfavourable impact on HRQoL was found 6 months after receiving an indeterminate screening result at incidence screening (i.e. the second round) that required a 1-year follow-up: no differences in HRQoL were found between subjects with an indeterminate or a negative second-round screening result.

c) To what extent does the course of HRQoL change over time and differ in the long-term between the screen and control group?

Chapter 4 shows that HRQoL of the screened participants who do not have (screen-detected) lung cancer was comparable with control group participants, before trial randomization and at 2-years follow-up.

d) Is a high perceived risk of lung cancer associated with more lung cancer-specific distress prior to screening and does perceived risk of lung cancer decrease after CT screening?

About 30% of subjects eligible for the NELSON trial provided correct estimates of the risk of getting lung cancer, whereas most of the remaining respondents underestimated the risk of lung cancer. In contrast with cognitive risk estimation, participants more often than non-participants felt that their risk of developing lung cancer was high (i.e. high perceived risk or affective risk perception) (Chapter 6). Regarding the participants, those who made an informed decision more often had a correct risk estimation than participants who did not make an informed decision, whereas informed decision-making was not associated with higher perceived risk (Chapter 7). Although participants in the NELSON trial more often perceived their risk of lung cancer as high compared to non-participants, only 15% of the participants felt that their risk of developing lung cancer was high at 1 day before screening (Chapter 5). These participants had elevated, but not severely elevated levels, of lung cancer-specific distress compared with participants with a low perceived risk. Six months after screening, when all participants had received a negative screening result for their latest CT (17% had an indeterminate baseline result that was negative at 3-months follow-up screening), all participants were less distressed compared with before screening. Nevertheless, subjects with a high perceived risk of lung cancer still expressed more distress than subjects with a low perceived risk of lung cancer. The proportion of participants who considered their risk of lung cancer to be high decreased from 14.5% to 10.5% after 6 months.

In summary, lung cancer screening with CT has only a transient negative effect on HRQoL. Only after receiving an indeterminate result did participants have more feelings of lung cancer-specific distress; however, these feelings were only temporary and did not persist in the long term. Furthermore, almost 50% of the participants reported some discomfort while waiting for the results, although an unfavourable effect on HRQoL was not found. Subgroups of subjects with a high perceived risk of lung cancer, or subgroups of subjects reporting discomfort whilst waiting for the results, reported slightly reduced HRQoL that remained stable over time.

Research question 2:

How do high-risk subjects decide about lung cancer screening and does informed decision-making affect their HRQoL?

a) Among (non-) participants in the NELSON trial, what is their level of knowledge about lung cancer (screening), their attitudes, lung cancer perceived risk, and their reasons to participate or not in lung cancer screening, when making their decision about participation?

Chapter 6 showed that, when deciding to participate in a lung cancer screening trial, knowledge on topics considered most relevant for decision-making about participation in screening, was only moderate. In particular, participants did not know about the chance of getting an indeterminate or positive result, or what the follow-up procedures of these results were. On the other hand, their knowledge was fairly good with regard to lung cancer, although these topics were not mentioned in the brochure. Non-participants in general had less knowledge than participants. Almost all participants expressed a positive attitude towards lung cancer screening. Moreover, about two-thirds of the non-participants were also positive about lung cancer screening. Participants more often perceived their risk of developing lung cancer as high compared with non-participants (14% and 7%, respectively). The two main reasons to participate (reported by 80% of the participants) were "I may have an advantage if lung cancer is detected in an early stage" and "I smoke(d) a lot". Non-participants mentioned "Participation is too much effort" as the main reason to decline participation (reported by almost 50% of the non-participants).

c) To what extent is decision-making regarding participation in the NELSON trial based on an informed decision?

About 50% of the participants in the NELSON trial made an uninformed decision regarding their participation (Chapter 6). This was mainly due to the participants' low level of knowledge about lung cancer screening, because almost all participants had a positive attitude towards lung cancer screening.

d) Do participants who make an informed decision about lung cancer screening have a better HRQoL than participants who do not make an informed decision, especially those who received an indeterminate test result requiring a follow-up CT scan?

Participants who made an informed decision about participation generally did not report better HRQoL compared with participants who did not make an informed decision

(Chapter 6). Also, no differences were found in HRQoL between participants who made an informed decision or not after receiving an indeterminate baseline test result that required follow-up screening.

In summary, participants' knowledge was fairly good with regard to lung cancer and almost all participants expressed a positive attitude towards lung cancer screening. Therefore, almost 50% of the participants made an informed decision to participate. Compared with the participants, non-participants' knowledge was worse and their attitude was less positive. Participants who made an informed decision to participate in a lung cancer CT screening trial generally did not experience better HRQoL compared with participants who had not made an informed decision.

Methodological considerations

Strengths and limitations

One of the strengths of this thesis is that it was performed within a population-based randomised controlled trial. All potential participants in the age group 50-74 years were approached by the use of population registries and were randomized in two groups. Another strength is that participants completed several questionnaires over time (longitudinal design). Moreover, we used both generic and lung cancer screening-specific instruments which enabled us to evaluate HRQoL from a generic perspective, as well as in more detail.

A limitation of the work is that, so far, only the effects of indeterminate and negative test results have been investigated, as well as the CT screening itself and HRQoL effects (in screen and control group) at 2-years follow-up (screening phase). For an overall evaluation of the effects on HRQoL, the effects of false-positive screening results, true-positive results and the effects of diagnostic work-up on HRQoL should also be evaluated. In addition, we did not evaluate the phase of early-stage lung cancer with the short and long-term effects of early treatment and early-stage lung cancer, and the favourable HRQoL effects of a possible reduction in the incidence of advanced lung cancer. Screening will also result in a decrease in the number of subjects experiencing advanced phases of the disease. This would prevent or avoid undergoing, for example, chemotherapy, radiotherapy and surgery; screening may therefore diminish or abolish the unfavourable effects on HRQoL of advanced cancer (treatment) (1-3).

The power in this thesis seems appropriate to answer the research questions, especially in the HRQoL part. We found several statistical significant differences between groups and/or over time that seemed rather small in absolute terms. Therefore we had to use a criterion for clinical relevance of statistically significant differences. We used the

internationally accepted scientific distribution-based standard for minimal important differences of more than half of a standard deviation (4, 5). Possibly, in the evaluation of the effect of IDM on HRQoL in the indeterminate result group in chapter 7, the power was limited because of the small groups.

Furthermore, several potential sources of bias may have threatened the internal validity (what we did measure vs. what we aimed to measure) and the external validity (generalizability) of the results.

In the previous chapters we discussed specific methodological limitations of the individual studies. The following sections address more general methodological issues.

Internal validity

Selection bias

In general, the response to our questionnaires was very high (80-94%) except for the control group at follow-up in the HRQoL study (65%; Chapter 4) and for the non-participants to the NELSON trial in the IDM study (7%; Chapter 6). The question remains, however, whether the low response rates have influenced the interpretation of the results.

The estimated response to the HRQoL follow-up questionnaire in the control group may be lower than it actually was. Compared with the screen group, in the control group we had less opportunity to correct the denominator for address changes and serious events associated with being 'off-screen'. The response may have been selective because some control group participants were probably disappointed about not being in the screen group and were perhaps less interested in completing the questionnaire. However, because comparison of respondents of the screen and control group revealed no significant differences in demographic characteristics, selective response in the control group was not demonstrated. To minimize the effects of selective response, we used repeated-measures ANOVA with which we could use all available data. When at least one HRQoL measure was completed, these data were included in the analyses.

Regarding the non-response in the IDM study of the non-participants in the NELSON trial, we were able to determine whether or not the response was selective because all invited subjects eligible for the NELSON trial completed the first NELSON questionnaire on smoking history and health. It appeared that the respondents to the IDM questionnaire were more often women and former smokers (Chapter 6). Although we were able to adjust for sex and smoking status, the results regarding non-participants in the NELSON trial have to be interpreted with caution. Questionnaire response of non-participants to a (screening) trial is often very low and selective, and is difficult to avoid (6, 7). The most often reported reason for non-participation in the NELSON trial was 'Too much effort' (Chapter 6). For most of the non-participants in the NELSON trial, completing the questionnaire was probably also 'Too much effort'. Nevertheless, it will probably always

be difficult to determine whether non-participants made an informed decision regarding their non-participation.

Information bias

Information bias refers to systematic measurement errors (i.e. the measurement measures what it purports to measure). Concerning the attitude scale, we found that almost all participants and about two-thirds of the non-participants expressed a positive attitude. This seemed very high, although the general population is enthusiastic about screening (8, 9). The six-item attitude scale was based on previous research in prenatal screening (10, 11). We asked the invitees about their attitude towards lung cancer screening participation *for themselves*. From the literature we expected these attitudes to be related to their screening behaviour (12). However, there is some evidence that respondents interpreted these attitude items as their opinion about the availability of the specific screening program, despite the instruction that the attitude should be about undergoing screening *for themselves* (Chapter 6) (13, 14). Apparently this message was not made clear enough and this instruction probably needs further clarification. In addition, a recent study revealed new insights in attitudes in prenatal screening (15). The authors found that it was not attitudes towards undergoing screening that were related to the actual testing behaviour, but attitudes towards the target condition. It seems that attitudes towards diagnostic testing and termination of pregnancy were not reflected in the women's attitudes towards undergoing the screening test (15). This 'problem' may also have played a role in our study. For example, participants expressing a positive attitude towards screening who did not undergo screening, may not have taken into account the unknown personal (unfavourable) consequences of screening when completing the attitude items on undergoing lung cancer screening. However, precisely which attitude plays a role in decision-making for (lung) cancer screening is still not clear.

Confounding

In all analyses, various confounding factors could have influenced the results. For example, smoking status could be a confounder in evaluating the effect of screening on HRQoL, because current smokers generally have a worse HRQoL than non-smokers, and may experience more anxiety and fear of cancer (16). To minimise bias by confounding we adjusted for gender, age, education, smoking status and smoking pack-years. However, this adjustment most likely had no effect on the conclusions, because there were no substantial differences between the analyses with and without adjustment for confounders.

External validity

The results of the studies in this thesis cannot easily be generalized to the general population. First of all, our study was performed within the NELSON trial in which the study population was a selection of subjects with a high-risk of developing lung cancer. All participants were heavy smokers or former heavy smokers. Therefore, the question is to what extent the results of our study are generalizable to the population of high-risk subjects eligible for lung cancer CT screening. In previous cancer screening trials, the trial participants showed to be a healthy selection of the population selected for the screening, i.e. the 'healthy screenee' effect (17). It is possible that participants in the NELSON trial were a healthy selection of the 'general' population of heavy smokers and former smokers. Due to the selection criteria of the NELSON trial of having a heavy smoking history, we expected our trial participants to be less healthy than the age and gender-adjusted reference population. However, they appeared in fact to be relatively healthy (Chapter 2). Therefore, the healthy screenee effect also occurred in our study. What this means for our study results remains unclear; nevertheless we compared HRQoL in the screen group with that in the control group and found no differences at baseline and at 2-years follow-up.

Both the screen and the control group are selected from subjects eligible for participation in screening by randomization across screening or no screening. In such a design both groups share the same characteristics, which makes an evaluation justifiable.

Secondly, regarding decision-making, a decision about participating in a trial is different from a decision about participating in an established screening program (Chapter 6). It is expected that subjects invited for trial participation will read and try to understand the (trial) information to a greater extent than subjects invited for an established screening program (11). Therefore, the observed knowledge scores in Chapter 6 may be better than they would have been if the NELSON trial had been an established screening program.

Finally, because the NELSON trial had a specific management protocol for small nodules (18), the results cannot be easily generalized to other lung cancer screening trials and studies. Participants in the NELSON trial with an indeterminate CT result at baseline (i.e. nodules 50-500 mm^3 /4.6-9.8 mm diameter) (19.2%) were advised to have a 3-month repeat screening, whereas in many other studies the subjects with nodules larger than 5 mm in diameter were referred to a pulmonologist for additional diagnostic evaluation (19). In the NELSON trial only a small proportion (1.6%) of participants undergoing baseline screening had nodules for which they were referred to a pulmonologist for work-up and diagnosis.

Interpretation of the findings

This thesis aimed at evaluating the effects of lung cancer CT screening on HRQoL. The study was limited to the screening phase itself. We also determined the extent of informed decision-making and the effect of informed decision-making on HRQoL during screening. In the following sections we discuss the research questions in the light of other study findings and give possible explanations for our findings.

Health-related quality of life

Comparisons with other lung cancer screening studies

Research in the lung cancer screening field on health-related quality of life is limited. Two other studies showed comparable results to ours (20, 21). Firstly, as discussed in Chapter 3, Byrne et al. also found a statistically significant increase in generic anxiety after an indeterminate baseline result. The anxiety scores diminished over time to baseline levels when the follow-up screening result was negative (20). They also analyzed changes in perceived risk of lung cancer and showed a slight decrease in perceived risk from baseline to 6 months (similar to our report in Chapter 5). The second study by Vierikko et al. showed no differences in health anxiety between baseline and 1-year follow-up (21). We also found no differences from baseline to 6-months follow-up when all results were negative (Chapter 2).

Comparisons with other cancer screening studies

To our knowledge, no other studies have evaluated the burden of CT screening in lung cancer screening. CT screening is also used in colon cancer screening (CT colonography) and caused mild or no discomfort. This is more than the frequency of reported discomfort in our study, but could have been expected since CT colonography also includes a subcutaneous injection of glucagon and rectal insufflation with CO_2 (22-24). Other screening tools, such as a MRI, colonoscopy and mammography, are more often related to discomfort at screening, or even pain (25-27).

As found in other cancer screening studies, some subgroups have a higher predisposition towards anxiety. Previous studies also showed that subjects who had a high cancer risk perception, had a worse HRQoL compared with subjects who had a low cancer risk perception (26, 28).

Earlier cancer screening studies showed that receiving a positive screening result induced unfavourable HRQoL effects (28, 29). These unfavourable effects were generally transient when they appeared to be false-positive, and differed in strength across screenings for various types of cancers (28). In breast cancer screening significant unfavourable psychological consequences were reported in the short term after receiving

an abnormal result. Women reported increased distress, fear, worry, anxiety, and mood changes. The unfavourable HRQoL effects decreased over time until the final result that identified the first abnormal results as false-positive, but sometimes persisted for 6 months or more (28, 30). The literature shows conflicting evidence about the persistence of unfavourable HRQoL effects in the long term after notification that the initial positive screening result appeared to be false-positive (30). Some studies reported long-term (i.e. until 18 months) unfavourable HRQoL effects of false-positive screening results and increased anxiety at subsequent screening rounds, whereas other studies showed no long-term effects (30, 31). Prostate cancer screening seemed to be less distressing than breast cancer screening. The receipt of an abnormal PSA result that needed further investigation (prostate biopsy) showed limited or no decrease of HRQoL (28, 32, 33). Some unfavourable HRQoL effects appeared to be transient after the result was false-positive (28, 33). The largest unfavourable effect of prostate cancer screening was found in men who underwent prostate biopsy and were not yet aware of the results (33). However, the anxiety scores were within the range of age and gender-adjusted reference scores. Taylor et al. found increased intrusive thoughts about cancer when receiving an abnormal result that did not persist after the follow-up results appeared to be normal (i.e. false-positive) (29).

The results of our HRQoL study mainly concur with the prostate cancer screening studies, i.e. a limited unfavourable HRQoL effect was found after receiving an abnormal result. However, the screening tests of prostate and breast cancer screening generate negative and positive results, whereas we evaluated indeterminate results. Follow-up procedures of positive and indeterminate screening results are different: positive screening results require further (invasive) follow-up procedures, whereas indeterminate screening results require follow-up screening. In the NELSON trial the number of subjects with positive results was limited (2.6% at baseline screening) and they were not a topic of research in this thesis, whereas an indeterminate screening result was relatively common (about 20%) (19). In cervical cancer screening such an 'indeterminate' type of result is also possible: a borderline or mildly dyskaryotic smear result that requires a repeat smear after 6 months. This initial 'indeterminate' result led to much worse scores on generic anxiety and mental health after 6-24 months compared with those in our study (34). Apparently, the HRQoL effects of cancer screening differ across different types of cancer screenings.

Possible explanation of the findings

Our study showed that lung cancer screening with CT had only a transient negative effect on HRQoL in the screening phase: increased feelings of lung cancer-specific distress after receiving an indeterminate test result at baseline requiring additional follow-up CT. If followed by a favourable result of the follow-up CT, these feelings did not persist on the long term. The unfavourable HRQoL effects were smaller than expected before-

hand – we anticipated that receiving an indeterminate screening result would cause substantial distress. It is possible that the carefully worded indeterminate result letter was effective in limiting unfavourable HRQoL effects of the indeterminate test result.

The letter explaining the indeterminate result at baseline to the participant stated: *"... we have observed a very small abnormality in your lung (5 to 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."* The letter also explained the possible results and related work-up after this follow-up CT scan: "*Participants with an abnormality showing no growth will receive a negative test result and will be invited for a CT scan 1 year after the baseline screening. Those with an abnormality showing some growth will be referred to a pulmonologist for further investigations.*"

Nevertheless, at the time of the HRQoL assessment, the unfavourable HRQoL effects of the indeterminate test result may have already diminished. The unfavourable HRQoL effects may have been larger immediately after receiving the indeterminate baseline result or after receiving an indeterminate second-round screening result. HRQoL effects often diminish over time and we measured HRQoL about 4-5 weeks after receiving the (indeterminate) baseline CT result and again about 6 months after the second-round screening. However, Byrne et al. also found no relevant change in anxiety 1-4 weeks after receiving the indeterminate baseline CT result (20).

Possible explanations for finding such small transient HRQoL effects include the insensitivity of generic HRQoL instruments and response shift/coping:

1) Insensitivity of generic HRQoL instruments

Finding no clinically relevant differences could be due to the insensitivity of generic HRQoL instruments (e.g., the SF-12, STAI and EQ-5D) (2, 35). The clinically relevant HRQoL differences we found (over time or between groups) were most often detected with a specific instrument: a measure for lung cancer-specific distress (IES) (Chapters 3-5). However, we also found statistically significant differences in generic anxiety (STAI-6) and self-reported health (EQ-5D-VAS) over time and even clinically-relevant differences in generic anxiety between groups of subjects reporting discomfort of waiting for the results or not (Chapter 2). Thus, as explained in the Introduction (Part 1), it is unlikely that insensitivity is an issue here. Generic instruments serve the purpose of providing the opportunity to equate and calibrate the results against other adverse health outcomes, whilst results of specific instruments can provide a detailed description of all psychological consequences and can be used for counselling and for developing effective information brochures.

2) Response shift / coping

In the evaluation of HRQoL over time, it is assumed that the meaning of the HRQoL concept remains stable over time and is similar between groups (36). However, in case of an event, e.g. receiving an indeterminate test result in lung cancer screening, the meaning of HRQoL scores may change. This phenomenon is called response shift and is said to be: the result of a change in a subject's internal standards of measurement (i.e. recalibration), a change in the importance attributed to the domains constituting HRQoL (changing values or reprioritization), or a change in the definition of the concept of HRQoL (reconceptualization) (37, 38). When receiving an indeterminate result, a HRQoL score may not have the same meaning both before and after the event. Receiving this unfavourable test result means that there is a realistic chance of having lung cancer, and this situation replaces the expectation of being reassured by an 'all clear' message. Everything that happens afterwards will be interpreted in this new context: a change of concepts and/or a change in internal standards or, in other words, a response shift. However, the subject receiving an indeterminate test result may also realize that the risk of having lung cancer is still not high and that if lung cancer is diagnosed, there is still a good chance that it will be in a curable stage. This could explain why only lung cancer-specific distress increased to a limited extent after receiving the indeterminate result. Folkman's theory of the coping processes associated with positive psychological states in the context of intense distress may also be helpful to explain the limited HRQoL effects after the receipt of an indeterminate screening result. In this theory, a subject's frame of reference changes in a stressful situation, such as receiving an unfavourable test result and, subsequently, the adverse mental and physical health effects of distress are minimized or avoided (2, 39). For example, the subject receiving an indeterminate test result may avoid the distress of a potential lung cancer diagnosis by telling himself that if lung cancer is found, it will probably be curable and thus the situation is better than it would have been without screening. However, to what extent such theories explain what was found in the NELSON study is a question for future research.

These, and similar explanatory mechanisms, led Ransohoff et al. to describe prostate cancer screening as *'… a process without negative feedback'* (40). Participants in cancer screening tend to be positive about having been screened, irrespective of what happened to them during the screening process. In case of a negative test result, or in case of an initially (false-) positive test result followed by a negative result of diagnostic work-up, the participant is grateful for being reassured that 'all is well'. In case of a positive result followed by a cancer diagnosis, screening makes a patient grateful because the cancer was detected early. Cancer screening may lead to distress due to positive test results, to diagnostic work-up, and to primary treatment with inevitable side-effects, but participants may tend to perceive the side-effects of cancer screening as acceptable or "worth it". In the perception of participants, the side-effects of cancer screening

constitute inevitable consequences of the process that either leads to reassurance or to being saved from cancer death by early detection (2, 40, 41).

Based on the results of our studies we may conclude that:

- unfavourable HRQoL effects of screening itself appear to be minor; screening is not associated with large-scale distress
- participants seem to be able to cope well (temporarily) with indeterminate results
- the letter following an indeterminate result should clearly explain that, although the individual has only a small chance of actually having lung cancer, a follow-up CT is recommended to be certain.

Although receiving an indeterminate result has a minor effect on HRQoL, the proportion of indeterminate results should preferably be minimized. In the NELSON trial as much as about 20% received this result at baseline (19). Therefore, further research should aim at reducing these numbers, for example by identifying subgroups of participants with increased lung cancer risk, or by combining proteomic or genomic biomarkers. Nevertheless, it seems that the lung cancer screening policy is not unfavourable in terms of HRQoL effects of screening. Although this should be further investigated, the HRQoL effects of a positive screening result that require a referral to a pulmonologist are expected to be worse.

Informed decision-making

When this study started, limited data were available concerning informed decision-making for lung cancer screening. To our knowledge, Marteau's concept that someone makes an informed decision if they have sufficient decision-relevant knowledge and their attitude is consistent with his/her behaviour has not previously been applied to the field of lung cancer screening (10). In our study, participants' informed choices were determined by the knowledge scores, because almost all participants expressed a positive attitude towards lung cancer screening (Chapter 6).

Knowledge

The knowledge of lung cancer screening invitees was only moderate about lung cancer screening, but fairly good about lung cancer in general. Other cancer screening studies, however, showed that it is difficult to get adequate information on cancer screening across to the screening invitees (7, 42, 43). For example, prostate and cervical cancer screening studies found limited awareness of the cancer being screened for, or the meaning of the test results (44, 45). Although most topics were mentioned in the NELSON brochure, apparently this information was either not read or not well understood

by everyone. Invited subjects had most difficulty with understanding false-negative results and remembering the chance of getting an indeterminate or positive result.

To determine knowledge for IDM, we adapted the multidimensional measure of informed choice (MMIC) for lung cancer CT screening (10, 46). The MMIC was originally developed and validated for prenatal screening. For cancer screening no validated questionnaires were available (47). The adapted knowledge measure was based on topics considered necessary in information leaflets for cancer screening by Wald et al. (10, 48). However, the precise content and level of decision-relevant knowledge still needs to be established for (lung) cancer screening, and this may lead to improved measurements (49-51). For example, it is not realistic and/or necessary to expect screening invitees to know everything about the screened cancer and the test. However, the question as to who decides on what exactly constitutes 'adequate decision-relevant' knowledge needs to be addressed.

In the current study, we distinguished adequate from inadequate knowledge by using the midpoint of the scale (46). All items were deemed equally important. To determine informed choice, we chose to include only cancer screening knowledge items, as was also done in the questionnaire developed by Marteau et al. (10). To illustrate that this was an arbitrary choice, we showed that knowledge was adequate in 51% of the participants when using lung cancer screening items according to previous studies, but that knowledge might be considered as adequate in almost 75% of the participants if all knowledge items were included (i.e. items about lung cancer and the CT screening test).

Besides the knowledge items of Marteau et al., we included additional knowledge items on lung cancer and the trial/test. In addition, items about lung cancer risk estimations, and the reasons for (non)participation, provided us with extra information. Some participants had unrealistic ideas and misunderstandings. For example, for almost 50% of the participants, undergoing the CT scan and receiving normal results was interpreted as a guarantee for good health; and only about 30% made a correct estimation of the risk for men and women to get lung cancer, whereas most of them underestimated the risks.

Attitude

Previous studies showed high interest in participating in lung cancer screening (52, 53). Our participants, and also most of the non-participants, were positive about lung cancer screening. Studies focusing on screening for other cancers also reported high percentages of positive attitudes among non-participants/non-attenders (14, 54). In prostate cancer screening, at least 70% of those who did not have the intention to have a PSA test nevertheless reported positive attitudes (55).

Thus the question remains why did these subjects with a positive attitude, not participate in screening? It is possible that the attitude towards undergoing lung cancer CT screening was not measured in a valid way (as discussed in the Methodological consider-

ations section). If however, non-participants had a positive attitude, there may have been barriers to their participation in lung cancer CT screening. Important reasons for non-participation in the NELSON trial were, for example, that it is "too much effort", or that invitees found that they did not have enough insight in the personal consequences of the test (Chapter 6). Indeed, these consequences are not known exactly, and lung cancer screening is currently only performed within a study setting. Nevertheless, because a low participation rate will limit the effectiveness of a screening program (health benefits at the population level), it is important to understand why subjects with a positive attitude do not participate. For one third of the non-participants a reason to decline was that they "do not have enough insight into the personal consequences of the test". We think that in case of lung cancer screening the net benefit of lung cancer screening is not yet known.

Informed decision-making and HRQoL in screening invitees

Participants who made an informed decision showed a HRQoL that was comparable to participants who did not make an informed decision. Michie et al. evaluated the effect of informed decision-making on post-test anxiety (STAI-6) in subjects in prenatal screening (46). They found no differences between subjects with and without an informed decision in the group with a low-risk (i.e. favourable) outcome following serum screening for Down's syndrome. We found no differences in the total group in which 80% had a negative (i.e. favourable) outcome. Since we found no differences between subjects with and without an informed decision in the indeterminate result group (20%), we would not have found differences in the negative result group only. In another prenatal screening study, Kleinveld et al. found that subjects who made an informed decision seemed to have a less adverse emotional reaction when confronted with an unfavourable screening outcome (i.e. an increased risk of having a child with Down's syndrome) than subjects who did not make an informed decision (56). In contrast to Kleinveld et al., we found no differences between subjects who made an informed decision and subjects who did not make an informed decision. The differential result may be partly attributable to the choice of anxiety measures: Kleinveld et al. used items on the emotional reaction specifically related to the screening outcome, whereas we used more generic scales.

Main conclusions

- The impact of lung cancer CT screening in high risk subjects on health-related quality of life was limited, just before, during and just after the CT scan.
- The unique policy of the NELSON trial to advise a follow-up screening of small, but relevant pulmonary nodules (indeterminate test result) caused a clinically

relevant, but transient increase of lung cancer-specific distress after receiving this test result.
- Two years after trial randomization, HRQoL did not differ between the screen group and the control group.
- Half of the participants in the NELSON lung cancer screening trial made an informed decision about participation.
- Health-related quality of life effects of CT screening did not differ between participants who made an informed decision to participate in the NELSON trial or not. This applied to the total group and to those who received an indeterminate baseline test result.

Implications for further research

- So far we have investigated the effects of CT screening itself, an indeterminate and negative test result on HRQOL, and long-term differences in HRQoL between the screen and control group. For an overall evaluation of the HRQoL effects of a lung cancer CT screening program the following effects of lung cancer screening should be investigated: the HRQoL effects of a (false-)positive screening result, the HRQoL effects of diagnostic work-up, and the short and long-term effects of early treatment in screen-detected early-stage lung cancer (because it can cause additional side-effects). In addition, the favourable HRQoL effects as a result of prevention of advanced disease should be taken into account.
- Qualitative research among experts, and in subjects eligible for/participants in a lung cancer CT screening program should investigate the content and level of minimally required decision-relevant knowledge to make an informed decision about participation in a lung cancer screening program. For example, background information about the specific disease being screened for should probably be included. Outcomes of this research could be used to develop valid instruments to assess decision-relevant knowledge of lung cancer screening.
- The validity of the current attitude measurement scale towards participation in lung cancer screening needs to be investigated. If the attitude scale proves to be valid, qualitative research should first explore attitude-uptake inconsistency. After this, further studies can quantify these value-uptake inconsistencies and the importance of the reasons causing them.

Implications for policy and practice

- Minimizing the waiting time between the CT scan and receiving the test results is recommended, because this was reported discomforting by 50% of the participants.
- Subjects invited for a lung cancer screening trial or program should be provided with an agreed minimum of essential decision-relevant information about lung cancer screening tailored to each individual's understanding, so that each individual is enabled to make an informed choice. Those who want to be informed should have easy access to honest, complete, and balanced information about the favourable and unfavourable aspects of participation in lung cancer screening.
- This thesis confirms previous studies that knowledge needs to be improved in screening invitees. Because screening has become increasingly important in many areas of health and disease, we suggest, as a long-term plan, to develop strategies to educate the general population about the general characteristics of (cancer) screening. These characteristics include the fact that (large) potential screening health benefits will only apply to a small group of participants, whereas the majority of the screening participants will be subjected to (small) potential unfavourable side-effects.
- Although the current study showed limited HRQoL effects during the process of screening, the results on (possible) mortality reduction from current randomized trials have to be awaited before considering the initiation of a population-based lung cancer screening program.

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Summary

Part 1 Introduction

Lung cancer is worldwide the most common form of cancer and the most common cause of death from cancer. Despites advances in treatment, most patients will die within 5 years after diagnosis. Primary prevention, quitting smoking or, more importantly, measures to reduce starting smoking may almost totally eliminate the disease. However, although several such measures have been successful, the number of lung cancer deaths is still unacceptably high. Secondary prevention by multidetector spiral computed tomography (CT) is a possibility, as it is able to detect lung cancer in an early stage. This may lead to a more effective treatment and, at the population level, a reduction in lung cancer mortality; however, hard evidence for this is still lacking.

Several observational studies have been conducted and reported that 55-85% of the CT-detected lung cancers at baseline were in a surgically removable stage I. To determine whether this leads to a reduction in lung cancer mortality, several randomised controlled trials with CT screening for lung cancer have been initiated. The Dutch-Belgian randomised controlled trial for lung cancer screening (NELSON trial) was started to determine whether follow-up mortality from lung cancer will be reduced by at least 25% after 10 years.

Rational healthcare policy decision-making on cancer screening programs requires empirically-based data on the effects of screening on mortality, health-related quality of life (HRQoL), and cost-effectiveness. In general, the potential screening health benefits will apply to only a small group of participants, whereas the majority of the screening participants will be subjected to potential unfavourable side-effects. Many subjects eligible for screening are not fully aware of this low chance of success, and of the high risk for small disadvantages. Therefore, it is important that potential screenees are well informed about the possible benefits *and* harms of screening participation, and are able and supported to make an autonomous informed decision to accept or decline the screening offer. It is considered that informed decision-making can have a positive effect on psychological and health outcomes.

In this thesis, the following research questions were addressed:

1. What are the effects, both in size and extent, of lung cancer CT screening in high risk subjects on health-related quality of life?
    a. To what extent do screened subjects experience discomfort before and during CT scanning and while waiting for the baseline scan results?

b. To what extent does the course of HRQoL change in the short- and in the long-term? Does the course of HRQoL differ between participants with an indeterminate result and a negative result, received both after the baseline scan or second-round scan?
c. To what extent does the course of HRQoL change over time and differ in the long-term between the screen and control group?
d. Is a high perceived risk of lung cancer associated with more lung cancer-specific distress prior to screening and does perceived risk of lung cancer decrease after CT screening?

2. How do high-risk subjects decide about lung cancer screening and does informed decision-making affect their HRQoL?
   a. Among (non-) participants in the NELSON trial, what is their level of knowledge about lung cancer (screening), their attitudes, lung cancer perceived risk, and their reasons to participate or not in lung cancer screening, when making their decision about participation?
   b. To what extent is decision-making regarding participation in the NELSON trial based on an informed decision?
   c. Do participants who make an informed decision about lung cancer screening have a better HRQoL than participants who do not make an informed decision, especially those who received an indeterminate test result requiring a follow-up CT scan?

Part 2 Health-related quality of life

In **Chapter 2** we evaluated the discomfort associated with CT scanning and the subsequent wait for results, and HRQoL over time. A total of 351 participants were asked to complete questionnaires before, within 1 week after, and again about 6 months after the CT scan. The vast majority of respondents did not report any discomfort related to the various aspects of the CT scan. Generic health and anxiety were in the same range as Dutch reference scores. None of the HRQoL scores of generic health, generic anxiety and lung cancer-specific distress showed a clinically relevant change over time. Six months after screening, no differences were found between respondents with a negative baseline CT scan and those with an indeterminate baseline CT scan but a negative follow-up CT scan result. However, about 50% of the respondents reported discomfort related to waiting for and dreading the results. These participants had relevantly worse generic anxiety and lung cancer-specific distress scores at all three assessment points.

In **Chapter 3** we further evaluated the short-term HRQoL effects of lung cancer CT screening over time. We included an extra HRQoL assessment at a more neutral point in time i.e. before randomisation and followed a larger cohort of 733 screen group participants. The participants were asked to complete four questionnaires: before randomisation, before and within 1 week after CT screening, and again 2 months after the screening result but before the 3-month follow-up CT. We evaluated the changes in HRQoL over time and differences between subjects receiving a negative CT result and an indeterminate CT result (requiring a follow-up CT after about 3 months). For analyses repeated-measures analysis of variance (ANOVA) were used, adjusted for covariates. There were no clinically-relevant change in generic health, self-reported health and generic anxiety over time. Two months after screening, lung cancer-specific distress showed a clinically relevant increase after an indeterminate result, whereas lung cancer-specific distress showed a significant decrease after a negative result.

In **Chapter 4** the follow-up time was extended by one additional assessment 2 years after the first HRQoL assessment. The control group (n=733) was also included and evaluated, as well as the HRQoL effects of receiving an indeterminate result at second-round screening. Repeated-measures ANOVA, adjusted for covariates, were used to analyze differences between the screen and control group, and between indeterminate (requiring a follow-up CT) and negative screening result groups. HRQoL scores did not differ over time between the screen and control group from baseline to 2-years follow-up. Also, no differences were found between subjects with an indeterminate or negative second-round screening result 6 months after screening. The increase in lung cancer-specific distress (reported in Chapter 3) was shown to be transient: 1.5 years after baseline screening no differences were found between subjects with a negative or indeterminate baseline screening result. In addition, subgroup analyses of the indeterminate baseline result group, i.e. subgroups with subjects with at least one indeterminate/positive result at follow-up (n=35), and subjects with only negative results at follow-up (n=100), showed no differences in HRQoL scores over time.

In general, the HRQoL scores were worse for women than for men. Subjects with more pack-years and/or current smokers had significantly worse self-reported health and had significantly worse physical health scores than subjects with less pack-years and former smokers. Current smokers reported more lung cancer-specific distress.

Chapter 5 concerns the same cohort as in Chapter 2 and focused on perceived risk (affective risk perception). Subjects who perceive their risk of lung cancer as high may be more vulnerable to distress, and subjects may perceive their risk of developing lung cancer differently 6 months after screening than at 1 day before screening. About 15% of the participants felt that their risk of developing lung cancer was high or very high at

1 day before screening. They had significantly worse lung cancer-specific distress scores than participants who perceive their risk as low (median scores 11.5 vs. 2.0). Six months after screening, the lung cancer specific-distress scores were significantly lower than 1 day before screening, but participants with a high perceived risk showed significantly more distress than participants with a low perceived risk (6.5 vs. 1.0). Six months after screening all participants had a final negative CT result. Significantly less participants (11%) felt that their risk of developing lung cancer was high compared with at 1 day before screening (15%).

Part 3 Informed decision-making

The actual lung cancer (screening) knowledge, attitudes, risk perceptions, reasons to participate in or decline participation, and informed decisions of subjects who decided to or decided not to participate in the NELSON trial were evaluated in **Chapter 6**. A total of 2,500 high-risk subjects were asked to complete a questionnaire 3 weeks after they had received a brochure with information about the trial. The questionnaire response of subjects who decided to participate in the NELSON trial was 80% (n=889) whereas the response of subjects who decided to decline participation in the NELSON trial was low (7%, n=97) and selective.

Participants' response to the knowledge items on lung cancer as a disease was on average more often correct (mean±SD 68±17%) than their response to items on lung cancer screening (49±29%). Of all participants, 51% had adequate knowledge on lung cancer screening. This was higher than for the non-participants (38%). The percentage of correct responses was significantly higher in females and higher-educated participants compared to males and lower-educated participants in 7 and 8 out of 21 knowledge items, respectively. About one-third of the participants made a correct estimation of the risk for an average male/female in the Netherlands to develop lung cancer during their lifetime. Non-participants less often made a correct estimation, but this was not significantly different from the participants. Nevertheless, participants perceived their risk of developing lung cancer more often as (very) high compared to the non-participants (14.4% vs 6.5%).

The reasons most often mentioned to participate in screening were "I may have an advantage if lung cancer is detected in an early stage" and "I smoke(d) a lot". For the non-participants the reason most often mentioned to decline participation was "too much effort".

Of the decisions regarding participation, 49% were uninformed, mainly due to insufficient knowledge. Most of the participants (99%) and 64% of the non-participants expressed a positive attitude towards lung cancer screening.

Chapter 7 continues by evaluating the hypothesized association between informed decision-making about (screening) participation and better HRQoL outcomes (during screening). Participants who made an informed decision to participate (n=155) or made an uninformed decision to participate (n=133), were selected for this study. Subjects who made an informed decision did not have better scores than those who did not, on 23 of the 24 HRQoL comparisons at three assessment points: i.e. when deciding about participation, before trial randomisation, and 2 months after receiving the CT result. For subjects with an indeterminate CT result (n=64), no significant differences were found between participants whose decision to participate was based on an informed decision (n=35), or not based on an informed decision (n=29).

Part 4 General discussion

Chapter 8 summarizes the main results of this thesis by discussing the individual research questions, followed by a discussion of methodological issues that should be considered when interpreting the results. Potential sources of bias that may have threatened internal validity (e.g. selection bias, information bias and confounding) and external validity are also addressed.

Our findings are then interpreted by comparing the present results with other (lung) cancer screening studies, and explanations for our findings are presented. Our results on HRQoL proved to be comparable to other studies on lung cancer screening. Comparison of our results with other cancer screening studies reveals that HRQoL effects differ across different types of cancer screenings. Possible explanations are given for the finding that our study indicates that lung cancer screening with CT has only a transient negative effect on HRQoL in the screening phase: the carefully prepared indeterminate result letter, the timing of the HRQoL assessment, the insensitivity of generic HRQoL instruments, and response shift / coping. With regard to informed decision making, our results are comparable with other studies that report the difficulty of conveying information of cancer screening to screening invitees, and that many invitees (participants and non-participants) express positive attitudes towards cancer screening. The effects of informed decision making on HRQoL are discussed and compared with the few studies available in the field of prenatal screening.

We conclude that the impact of lung cancer CT screening in high-risk subjects on health-related quality of life is limited. An indeterminate CT result caused a clinically-

relevant but transient increase of lung cancer-specific distress. Half of the participants in the NELSON lung cancer screening trial made an informed decision about participation, and there was no difference in HRQoL between participants who did or did not make an informed decision regarding participation in the NELSON trial. We recommended further research on all screening phases, including the HRQoL effects of a (false-)positive screening result, diagnostic work-up, and early treatment in screen-detected early-stage lung cancer. Finally, research on the content and level of minimally-required decision-relevant knowledge to make an informed decision is recommended, as is the validation of the knowledge and attitude measures. Further investigation into the causes of value-uptake inconsistencies is also advised.

We recommend to develop strategies to educate the general population about the general characteristics of (cancer) screening. Furthermore, subjects invited for a lung cancer screening trial or program should be provided with an agreed minimum of essential decision-relevant information about lung cancer screening tailored to each individual's understanding, so that each person can make a well-informed choice.

Finally, we need the results from randomised trials to confirm whether or not screening leads to a reduction in lung cancer mortality. When we have these data, as well as information on other effects of screening on cost-effectiveness and HRQoL, the initiation of a population-based lung cancer screening program can be considered.

Samenvatting

Deel 1 Introductie

Longkanker is wereldwijd de meest voorkomende vorm van kanker. Daarbij geldt dat van alle kankersterfte, de meeste mensen aan longkanker overlijden. Ondanks dat de behandeling van longkanker is verbeterd, sterven de meeste patiënten binnen 5 jaar na de diagnose. Primaire preventie, stoppen met roken of nog belangrijker, maatregelen om het gaan roken tegen te gaan, kunnen ervoor zorgen dat longkanker bijna niet meer voorkomt. Maar hoewel dergelijke maatregelen succesvol zijn geweest, is het aantal mensen dat aan longkanker sterft nog steeds te groot. Door middel van secundaire preventie (screening) met behulp de low-dose multidetector computer tomografie (CT) is het mogelijk gebleken longkanker in een vroeg stadium te ontdekken. Dit zou kunnen leiden tot een effectievere behandeling en daardoor tot een daling in de sterfte aan longkanker op populatieniveau. Echter, bewijs hiervoor ontbreekt nog.

Verschillende observationele studies zijn gedaan en vonden dat 55-85% van de longkankers die door CT-screening op baseline werden ontdekt in een vroeg stadium waren (stadium I) en chirurgisch te verwijderen waren. Om te bepalen of dit ook leidt tot een vermindering in de longkankersterfte zijn er verschillende gerandomiseerde trials gestart. Het doel van het Nederlands-Leuvens LongkankerScreeningsONderzoek (NELSON trial) is om vast te stellen of 10 jaar na de start van de studie de longkankersterfte is afgenomen met minstens 25%.

Om verstandige politieke gezondheidszorgbeslissingen te kunnen nemen op het gebied van kankerscreeningsprogramma's moet empirisch worden vastgesteld wat de effecten van screening zijn op kankersterfte en de gezondheidsgerelateerde kwaliteit van leven (KvL) en wat de kosten-effectiviteit van dergelijke programma's is. Meestal zijn de potentieel gunstige gezondheideffecten van screening slechts van toepassing op een kleine groep screeningsdeelnemers, terwijl het grootste deel van de screeningsdeelnemers wordt blootgesteld aan mogelijk ongunstige bijeffecten. Veel mensen die aan screening meedoen, zijn zich niet geheel bewust van deze kleine kans op een gunstig effect en de grote kans op kleine nadelen. Daarom is het belangrijk dat een potentiële screeningsdeelnemer goed geïnformeerd wordt over de mogelijke voor- en nadelen van deelname aan screening en dat hij of zij in staat is en gestimuleerd wordt om een autonoom geïnformeerd besluit te nemen om wel of niet in te gaan op een screeningsvoorstel.

In dit proefschrift worden de volgende onderzoeksvragen gesteld:

1. Wat zijn de effecten van longkankerscreening met behulp van CT op de gezondheidsgerelateerde kwaliteit van leven bij mensen met een hoog risico op longkanker?
    a. In welke mate ervaren deelnemers het vooruitzicht en het ondergaan van een CT-scan en het wachten op de uitslag als vervelend?
    b. Wat zijn de veranderingen in KvL op de korte en lange termijn? Verschilt het verloop in KvL tussen deelnemers die een twijfelachtig of negatief testresultaat ontvangen na de baselinescan of de tweede ronde scan?
    c. Wat zijn de veranderingen in KvL op de lange termijn tussen de screen- en controlegroep?
    d. Is een als hoog ervaren longkankerrisico geassocieerd met meer longkankerspecifieke distress vóór screening en vermindert het ervaren longkankerrisico na CT-screening?

2. Hoe beslissen mensen met een hoog risico op longkanker over deelname aan longkankerscreening en heeft een geïnformeerd besluit invloed op de KvL van deze groep?
    a. Hoeveel kennis over longkanker(screening) hebben potentiële deelnemers en welke attitudes, ervaren longkankerrisico en redenen om wel of niet deel te nemen aan longkankerscreening als ze een besluit nemen over deelname?
    b. In welke mate is de keuze om deel te nemen aan de NELSON trial gebaseerd op een geïnformeerd besluit?
    c. Hebben deelnemers die een geïnformeerd besluit hebben genomen over longkankerscreening, in het bijzonder deelnemers die een twijfelachtige testuitslag ontvingen en waarvoor een herhaalscan noodzakelijk was, een betere KvL dan deelnemers die geen geïnformeerd besluit hebben genomen?

Deel 2 Gezondheidsgerelateerde kwaliteit van leven

In **hoofdstuk 2** is geëvalueerd in hoeverre het vooruitzicht, het ondergaan van de CT-scan en het wachten op de resultaten hiervan als vervelend werden ervaren. Daarnaast hebben we de verandering in KvL over de tijd geëvalueerd. Aan 351 deelnemers werden gevraagd om vragenlijsten vóór, 1 week na en 6 maanden na de CT-scan in te vullen. De meeste respondenten vulden in dat ze de verschillende aspecten van de CT-scan niet als vervelend hadden ervaren. Generieke gezondheid en angst waren vergelijkbaar met Nederlandse referentiescores. De KvL-scores generieke gezondheid, generieke angst en longkankerspecifieke distress veranderden in de tijd niet klinisch relevant. Zes maanden na screening waren er geen verschillen in KvL tussen respondenten met een negatieve

en twijfelachtige testuitslag (alle deelnemers met een twijfelachtige testuitslag hadden een negatieve 3-maanden follow-up uitslag). Desalniettemin rapporteerde ongeveer 50% van de respondenten dat ze het wachten op het resultaat vervelend vonden of opzagen tegen het resultaat. Zij bleken klinisch relevant meer generieke angst en longkankerspecifieke distress te vertonen op alle drie de meetmomenten.

In **hoofdstuk 3** zijn de korte termijn effecten van longkankerscreening op KvL verder geëvalueerd in de tijd. Hierbij is een extra KvL-meting toegevoegd op een neutraal meetmoment, namelijk voor randomisatie. Ook werd een groter cohort van 733 deelnemers uit de screengroep gevolgd dan in hoofdstuk 2. Deelnemers werden gevraagd om vier vragenlijsten in te vullen: vóór randomisatie, vóór en één week na de CT-scan en 2 maanden nadat het resultaat van de CT-scan was ontvangen, maar vóór de follow-up scan na 3 maanden. We hebben de veranderingen in KvL in de tijd en de verschillen tussen deelnemers met een negatieve en een twijfelachtige testuitslag geëvalueerd. Dit werd gedaan met variantieanalyses voor herhaalde metingen, waarbij gecorrigeerd werd voor covariaten. Er werden geen klinisch relevante veranderingen in generieke en zelfgerapporteerde gezondheid en generieke angst gevonden. De longkankerspecifieke distress nam klinisch relevant toe na een twijfelachtige testuitslag, terwijl deze afnam na een negatieve testuitslag.

In **hoofdstuk 4** werd nog een ander meetmoment toegevoegd, namelijk 2 jaar na de eerste KvL-meting. Bij deze analyses werd tevens de controlegroep (n=733) meegenomen voor evaluatie. Daarnaast werden de KvL effecten van het ontvangen van een twijfelachtige testuitslag bij de 2e ronde screening geëvalueerd. Om de verschillen tussen de screen- en controlegroep en verschillen tussen een twijfelachtige en negatieve testuitslag te evalueren, werden variantieanalyses voor herhaalde metingen uitgevoerd waarbij gecorrigeerd werd voor covariaten. De KvL-scores verschilden niet op baseline en na 2 jaar follow-up tussen de screen- en controlegroep. Ook werden er 6 maanden na de 2e ronde screening geen verschillen gevonden tussen deelnemers met een negatieve of twijfelachtige testuitslag. De verhoogde longkankerspecifieke distress die gevonden werd in hoofdstuk 3 bleek van voorbijgaande aard: 1,5 jaar na de baseline screening werden er geen verschillen meer gevonden tussen deelnemers met een negatieve of twijfelachtige testuitslag. Daarnaast werden ook geen verschillen gevonden in de subgroepanalyses van deelnemers met een twijfelachtige testuitslag bij baseline screening: bij deelnemers met minimaal één twijfelachtige of positieve testuitslag gedurende de follow-up (n=35) was de KvL niet anders dan bij deelnemers met alleen negatieve testresultaten gedurende de follow-up periode (n=100).

De KvL-scores bij vrouwen waren slechter dan bij mannen. Deelnemers met een hoger aantal pakjaren en/of huidige rokers hadden een significant slechtere zelfgerapporteer-

de gezondheid en slechtere fysieke gezondheid dan deelnemers met minder pakjaren en/of ex-rokers. Huidige rokers rapporteerden meer longkankerspecifieke distress dan ex-rokers.

Hoofdstuk 5 gaat over hetzelfde cohort als beschreven in hoofdstuk 2 maar focust op het ervaren longkankerrisico (affectieve risicoperceptie). Deelnemers die hun risico als hoog ervaren zijn mogelijk gevoeliger voor distress. Het ervaren risico kan 1 dag voor screening verschillend zijn van 6 maanden na screening. Eén dag voor screening ervoer ongeveer 15% van de deelnemers het risico om longkanker te ontwikkelen als hoog of erg hoog. Zij hadden significant slechtere scores bij het meten van de longkankerspecifieke distress dan deelnemers die hun risico als laag ervoeren (mediaan scores: 11,5 vs. 2,0). Zes maanden na screening waren de longkankerspecifieke distress scores significant lager dan één dag voor screening, maar deelnemers met een hoog ervaren risico hadden nog steeds significant meer distress dan deelnemers met een laag ervaren risico (6,5 vs. 1,0). Alle deelnemers hadden 6 maanden na screening een negatieve testuitslag bij hun laatste CT-scan. Op dat moment ervoeren minder deelnemers hun risico om longkanker te ontwikkelen als hoog in vergelijking met 1 dag voor screening (11 vs. 15%).

Deel 3 Geïnformeerde besluitvorming

In **hoofdstuk 6** worden ten aanzien van longkanker(screening), de kennis, attitudes, risicopercepties, redenen om wel of niet deel te nemen en geïnformeerde besluitvorming geëvalueerd. Bij 2.500 potentiële deelnemers aan de NELSON trial met een hoog risico op longkanker, werden 3 weken nadat zij een informatiebrochure hadden ontvangen, gevraagd om een vragenlijst in te vullen. De respons van mensen die besloten hadden om deel te nemen aan de NELSON trial was 80% (889), terwijl de respons van mensen die besluiten niet deel te nemen laag en selectief was (7%, n=79).

De antwoorden op de kennisitems over longkanker zelf waren gemiddeld vaker goed dan de antwoorden op items over longkankerscreening (gemiddelde±SD 68±17 en 49±29%). Bij 51% van de deelnemers was de kennis over longkankerscreening adequaat, terwijl dit maar 38% was bij de niet-deelnemers. Vrouwelijke en hoger opgeleide deelnemers hadden een significant hoger percentage correcte antwoorden dan mannelijke en lager opgeleide deelnemers voor respectievelijk 7 en 8 van de 21 kennisitems. Een derde van de deelnemers gaf een correcte schatting van het risico dat een gemiddelde man of vrouw in Nederland heeft om longkanker te ontwikkelen gedurende zijn of haar leven. Mensen die niet deelnamen gaven minder vaak een correcte schatting dan

deelnemers (niet significant). Echter, deelnemers ervoeren hun risico om longkanker te ontwikkelen vaker (erg) hoog in vergelijking met niet-deelnemers (14,4% vs 6,5%).

De meest genoemde redenen om deel te nemen waren: "Ik heb er misschien voordeel van als longkanker nog in een vroeg stadium is" en "Ik heb veel gerookt / ik rook veel". De meest genoemde reden om niet deel te nemen was: "Deelname is teveel moeite (tijd, kosten, etc)".

49% van de beslissingen om deel te nemen was ongeïnformeerd, met name door onvoldoende kennis. De meeste deelnemers (99%) maar ook veel niet-deelnemers (64%) lieten een positieve attitude ten opzichte van longkankerscreening zien.

In **Hoofdstuk 7** wordt er onderzocht of er een associatie bestaat tussen geïnformeerde besluitvorming over deelname aan screening en KvL-uitkomsten gedurende screening. Bij 155 deelnemers die een geïnformeerd besluit hadden genomen over deelname aan de NELSON trial en 133 deelnemers die geen geïnformeerd besluit hadden genomen werd deze vraag onderzocht. 24 KvL-vergelijkingen werden gedaan op drie meetmomenten: het moment van het beslissen tot wel of geen deelname, vóór randomisatie en 2 maanden nadat het baseline screeningsresultaat werd ontvangen. Deelnemers die een geïnformeerd besluit hadden genomen verschilden in 23 van de 24 vergelijkingen niet van deelnemers die geen geïnformeerd besluit hadden genomen. Daarnaast werden er geen KvL-verschillen gevonden tussen deelnemers die wel (n=35) en geen (n=29) geïnformeerd besluit hadden genomen en die een twijfelachtige testuitslag bij de baselinescreening ontvingen.

Deel 4 Algemene discussie

Hoofdstuk 8 vat de belangrijkste resultaten van dit proefschrift samen door elke onderzoeksvraag te bespreken. Vervolgens worden methodologische kwesties besproken die in overweging genomen moeten worden als de resultaten worden geïnterpreteerd. Potentiële bronnen van bias worden besproken die de interne (bijv. selectiebias, informatiebias en confounding) en externe validiteit kunnen bedreigen.

Onze bevindingen worden vervolgens geïnterpreteerd door de resultaten te vergelijken met andere (long)kankerscreening studies. Onze resultaten bleken vergelijkbaar te zijn. Vergelijkingen met andere kankerscreeningstudies lieten zien dat KvL-effecten verschillen tussen de verschillende kankerscreeningsprogramma's. Er worden mogelijke verklaringen gegeven voor de bevinding dat longkanker CT-screening slechts een voorbijgaand ongewenst KvL-effect heeft in de screening fase, namelijk: dat de brief waarin gemeld wordt dat een deelnemer een twijfelachtige testuitslag heeft zorgvuldig geformuleerd was, de ongevoeligheid van generieke KvL-instrumenten en response

shift / coping. Wat betreft geïnformeerde besluitvorming laten onze resultaten net als andere studies zien dat het moeilijk is om informatie over te brengen op mensen die uitgenodigd worden voor screening en dat veel mensen een positieve attitude rapporteren ten aanzien van kankerscreening. De effecten van geïnformeerde besluitvorming op de KvL worden bediscussieerd en vergeleken met de twee andere studies die gedaan zijn in het kader van prenatale screening.

Wij concluderen dat de impact van longkankerscreening met behulp van een CT-scan op de KvL beperkt is bij mensen met een hoog risico op longkanker. Een twijfelachtige testuitslag veroorzaakt een klinisch relevante, maar slechts tijdelijke toename van de longkankerspecifieke distress. Ongeveer de helft van de deelnemers neemt een geïnformeerd besluit om deel te nemen en er was geen verschil in de KvL tussen deelnemers die wel of geen geïnformeerd besluit hadden genomen. Ons advies is om verder onderzoek te doen in alle screeningsfases inclusief de fase waarin deelnemers die een (fout-) positieve tesuitslag hebben ontvangen, een diagnostische work-up hebben gehad en een behandeling van de door screening gedecteerde longkanker hebben gehad (in een vroeg stadium). Tot slot willen we onderzoek aanbevelen naar de inhoud en het niveau van minimale screeningsrelevante kennis om een geïnformeerd besluit te kunnen nemen.

Het verdient verder aanbeveling methoden te ontwikkelen om algemene (kanker) screeningskenmerken over te brengen op de algemene populatie. Verder zouden mensen die uitgenodigd worden voor een longkankerscreeningsstudie of -programma, minimale beslissingsrelevante informatie moeten krijgen over longkankerscreening die is toegepast op het niveau van het individu. Hiermee zou iedereen een goed geïnformeerd besluit moeten kunnen nemen.

Tot slot zijn de resultaten van gerandomiseerde onderzoeken nodig om aan te tonen of CT-screening wel of niet leidt tot een afname van de longkankersterfte. Pas nadat de resultaten hiervan en de resultaten van KvL- en kosteneffectiviteitsonderzoek bekend zijn, kan een gefundeerd besluit over het al dan niet invoeren van een bevolkingsonderzoek op longkanker genomen worden.

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About the author

Karien van den Bergh was born on February 2, 1978 in Grave, the Netherlands. After completing her secondary education at the Merletcollege in Cuijk, she studied Physiotherapy at the HAN University of Applied Sciences in Nijmegen. She received her Bachelor degree in 1999 and started working as a physiotherapist in Germany. In 2000, she started a Master of Health Sciences at Maastricht University. In 2004 she graduated with her Master of Health Sciences (majoring in Epidemiology and Movement Sciences). In March 2005 she started as a scientific researcher at the Department of Public Health, Erasmus MC, University Medical Center Rotterdam, which resulted in this thesis.
Karien lives together with Steven Koole and they have a son, Siem (2009).

Over de auteur

Karien van den Bergh werd geboren op 2 februari 1978 te Grave. Na het afronden van de middelbare school aan het Merletcollege in Cuijk is ze begonnen met de opleiding fysiotherapie aan de Hogeschool van Arnhem en Nijmegen in Nijmegen. Ze behaalde haar Bachelor diploma in 1999 en ging werken als fysiotherapeut in Duitsland. In 2000 startte ze de master Gezondheidswetenschappen aan de Universiteit van Maastricht. In 2004 behaalde ze haar doctoraal diploma Gezondheidswetenschappen met als afstudeerrichtingen Epidemiologie en Bewegingswetenschappen. In 2005 startte ze als onderzoeker op de afdeling Maatschappelijke Gezondheidszorg van het Erasmus MC in Rotterdam en voerde haar promotieonderzoek uit, wat resulteerde in dit proefschrift. Karien woont samen met Steven Koole en samen hebben zij een zoon, Siem (2009).

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PhD Portfolio

Summary of PhD training

Name PhD student: Karien A.M. van den Bergh	Promotor:	Prof.dr. H.J. de Koning
Erasmus MC Department: Public Health	Supervisors:	Dr. R.J. van Klaveren
PhD period: 2005-2010		Dr. M.L. Essink-Bot

	Year	Workload (Hours)
General courses		
Language & Training Centre, Erasmus University Rotterdam:		
Academic English for Lecturers and Staff.	2006	20 hours
Academic writing in English for PhD students.	2009	36 hours
Specific courses		
Netherlands Institute for Health Sciences (Nihes), Erasmus MC, Rotterdam:		
Planning and evaluation of screening.	2005	40 hours
Health status measurement.	2006	24 hours
Regression analysis.	2006	40 hours
Clinical decision analysis.	2008	20 hours
Cohort studies.	2008	20 hours
Repeated measurements in clinical studies.	2009	40 hours
Presentations		
International Conference on Screening for Lung Cancer. New York, US. *Short-term impact of lung cancer CT screening on participants in a randomised controlled trial (NELSON)*. Oral presentation.	2007	40 hours
Conference of the International Society for Quality of Life Research. Toronto, Canada, *Short-term impact of lung cancer CT screening on HRQoL in a randomised controlled trial (NELSON)*. Poster presentation.	2007	20 hours

Nederlands congres Volksgezondheid. Groningen. *Geïnformeerde besluitvorming over deelname aan CT screening voor longkanker in een gerandomiseerde studie (NELSON).* Oral presentation.	2008	30 hours
First Dutch conference on the early detection of Lung Cancer. Bunnik, *Quality of Life in NELSON: first results.* Oral presentation.	2008	20 hours
Conference of the International Society for Quality of Life Research. Montevideo, Uruguay. *Informed decision making for participation in a randomised controlled trial (NELSON) on CT screening for lung cancer*. Poster presentation.	2008	20 hours
(Inter)national conferences		
Nederlands congres Volksgezondheid, Rotterdam.	2005	8 hours
International Conference on Screening for Lung Cancer. New York, US.	2007	16 hours
Conference of the International Society for Quality of Life Research (ISOQOL). Toronto, Canada.	2007	24 hours
Nederlands congres Volksgezondheid, Groningen.	2008	8 hours
First Dutch conference on the early detection of Lung Cancer, Bunnik.	2008	12 hours
Conference of the International Society for Quality of Life Research (ISOQOL), Montevideo, Uruguay.	2008	24 hours
Seminars and workshops		
Attending seminars of the Department of Public Health.	2005-2010	100 hours
Attending and organizing meetings of the 'Risk perception, Informed decision-making, Quality of life – club' at the Department of Public Health.	2005-2010	50 hours
Symposia of the Werkgroep Onderzoek Gezondheidstoestand in Utrecht (2005, 2006, 2007, 2008).	2005-2008	16 hours
Scientific meeting of the Netherlands forum for medical decision making, Erasmus MC, Rotterdam	2007	8 hours
Workshops "Analysis of Longitudinal Studies of HRQOL Studies" and "Advancements in the Theory and Practical Application of Response Shift" at the ISOQOL, Toronto, Canada.	2007	8 hours

Workshops "Applying Item Response Theory (IRT) to Enhance Health Outcomes Assessment" and "Evaluating Changes in Health-Related Quality of Life Measures and Other Patient-Reported Outcomes" at the ISOQOL, Montevideo, Uruguay.	2008	8 hours