

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

BMJ Open

Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Study

mjopen-2018-024719 esearch 8-Jun-2018 aghizadeh, Niloofar; University of Calgary, Medicine remblay, Alain; University of Calgary, Medicine ressman, Sonya; The British Columbia Cancer Agency , eacock, Stuart; Canadian Centre for Applied Research in Cancer Control, cWilliams, Annette; Fionna Stanley Hospital and University of Western ustralia acEachern, Paul; University of Calgary, Medicine ohnson, Michael; Beatrice Hunter Cancer Research Institute and Dalhousie niversity offin, John; The Juravinski Cancer Centre and McMaster University
8-Jun-2018 aghizadeh, Niloofar; University of Calgary, Medicine remblay, Alain; University of Calgary, Medicine ressman, Sonya; The British Columbia Cancer Agency , eacock, Stuart; Canadian Centre for Applied Research in Cancer Control, cWilliams, Annette; Fionna Stanley Hospital and University of Western ustralia acEachern, Paul; University of Calgary, Medicine ohnson, Michael; Beatrice Hunter Cancer Research Institute and Dalhousie niversity
aghizadeh, Niloofar; University of Calgary, Medicine remblay, Alain; University of Calgary, Medicine ressman, Sonya; The British Columbia Cancer Agency , eacock, Stuart; Canadian Centre for Applied Research in Cancer Control, cWilliams, Annette; Fionna Stanley Hospital and University of Western ustralia acEachern, Paul; University of Calgary, Medicine ohnson, Michael; Beatrice Hunter Cancer Research Institute and Dalhousie niversity
remblay, Alain; University of Calgary, Medicine ressman, Sonya; The British Columbia Cancer Agency , eacock, Stuart; Canadian Centre for Applied Research in Cancer Control, cWilliams, Annette; Fionna Stanley Hospital and University of Western ustralia acEachern, Paul; University of Calgary, Medicine ohnson, Michael; Beatrice Hunter Cancer Research Institute and Dalhousie niversity
oss, Glen ; The Ottawa Hospital Cancer Center icholas, Garth ; The Ottawa Hospital Cancer Center artel, Simon; Centre de recherche, Institut universitaire de cardiologie et e pneumologie de Québec, aberge, Francis; Centre de recherche, Institut universitaire de cardiologie t de pneumologie de Québec hatia, Rick; Memorial University u, Geoffrey; University Health Network and Princess Margaret Cancer entre chmidt, Heidi; University Health Network and Princess Margaret Cancer entre hattra, Sukhinder; University of British Columbia, Faculty of Medicine- espiratory Division sao, Ming-Sound; University of Toronto Department of Laboratory edicine and Pathobiology, ammemagi, Martin; Brock University, Community Health Sciences am, Dr. Stephen; University of British Columbia, Faculty of Medicine- espiratory Division
ung cancer, Health-related quality of life, low-dose chest CT, screening, arly detection
a at a a

SCHOLARONE[™] Manuscripts

BMJ Open

Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Study

Niloofar Taghizadeh¹, Alain Tremblay¹, Sonya Cressman², Stuart Peacock², Annette M. McWilliams³, Paul MacEachern¹, Michael R. Johnston⁴, John Goffin⁵, Glen Goss⁶, Garth Nicholas⁶, Simon Martel⁷, Francis Laberge⁷, Rick Bhatia⁸, Geoffrey Liu⁹, Heidi Schmidt⁹, Sukhinder Atkar-Khattra², Ming-Sound Tsao⁹, Martin C. Tammemagi¹⁰, Stephen C. Lam², for the Pan-Canadian Early Lung Cancer Study Group.

Corresponding Author: Alain Tremblay MDCM, 3300 Hospital Drive NW, Calgary, AB, Canada T2N4N1. Phone 403-210-3866, fax 403-944-1577. ORCID 0000-0002-0025-7426 Email: atrembla@ucalgary.ca

Institutions:

- University of Calgary, Calgary, AB, Canada. 1.
- The British Columbia Cancer Agency, Vancouver, BC, Canada. 2.
- Fionna Stanley Hospital and University of Western Australia, Perth, WA, Australia. 3.
- Beatrice Hunter Cancer Research Institute and Dalhousie University, Halifax, NS, Canada. 4.
- The Juravinski Cancer Centre and McMaster University, Hamilton, ON, Canada. 5.
- 6. The Ottawa Hospital Cancer Center, Ottawa, ON, Canada.
- 7. Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, QC, Canada.
- Memorial University, St-John's NF, Canada 8.
- University Health Network and Princess Margaret Cancer Centre, Toronto, Ontario, Canada. 9.
 - 10. Brock University, St. Catharines, ON, Canada.
- Word Count: 3404

Strengths and Limitation of this Study:

- This study is the first to describe the psychological and quality of life impacts of lung cancer screening on *discrete* individuals undergoing low-dose CT examinations.
- This allows the calculation of number-needed-to-harm estimates based on the minimal clinically significant difference of each instrument rather than mean group changes, important in the informed decision-making process with individuals considering this intervention.
- Our cohort was drawn from a multi-center study with high follow-up rates using a participant's baseline status to detect any changes post-screening.
- Limitations include the lack of an unscreened control group and the relative homogeneity of our participants (Canadian, Caucasian).

1 2	
3	Abbreviation list
4	
5 6	
7	
8	
9	
10 11	AFB: Autofluorescence bronchoscopy
12	
13	CCO: Ground glass operative
14	GGO: Ground-glass opacity
15 16	
17	HRQoL: Health-related quality of life
18	
19 20	
20	LDCT: Low-dose computed tomography
22	
23	
24 25	MCID: Minimal Clinically Important Difference
26	
27	NLST: The National Lung Screening Trial
28	NEST. The National Eulig Screening That
29 30	NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales
31	NNH: Number-needed-to-harm
32	
33 34	
35	SF-12: Physical and Mental Component Scales
36	
37	
38 39	SIFs: Incidental findings
40	STAI: State Trait Anxiety Inventory
41	STAI: State Trait Anxiety Inventory
42 43	
44	
45	
46	
47 48	
49	
50	
51 52	
52 53	
54	
55	
56 57	
58	3
59	
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Objectives: The impact of lung cancer screening with low-dose chest CT (LDCT) on participants' anxiety levels and health-related quality of life (HRQoL) is an important consideration in the implementation of such programs. We aimed to describe changes in anxiety and HRQoL in a high-risk Canadian cohort undergoing LDCT lung cancer screening.

Methods: 2,537 subjects who had 2% or greater lung cancer risk over 6 years using a risk prediction tool were recruited from 8 centers across Canada in the Pan-Canadian Early Detection of Lung Cancer Study (2008-2010). We compared HRQoL and anxiety levels before and after screening of 1,237 participants with LDCT, (excluding a subset of 1,300 participants who also underwent autofluorescence bronchoscopy screening), as well as after investigations performed because of a positive screening examination. The 12-item short-form Physical and Mental Component Scales (SF-12), EQ-5D-3L scores, and State Trait Anxiety Inventory (STAI) - State anxiety were used at each assessment.

Results: Overall, there were no clinically significant differences in HRQoL outcomes between baseline and each of the survey time points following initial screening. No mean change in anxiety in the overall cohort was noted following baseline LDCT, but more participants had clinically significant increase in anxiety vs. decrease after baseline screening [increase > Minimal Clinically Important Difference (MCID) (n=180) vs. decrease >MCID (n=50), p<0.001]. This finding persisted but to a lesser degree at the 12month time point [increase >MCID (n=146) vs. decrease >MCID (n=87), p<0.001] and was present in both the cohort with negative and positive examinations.

1	
2 3	
4	Conclusions: CT Screening for Lung Cancer has no major overall impact on HRQoL among participants,
5	although a minarity of nonticinants (number needed to home 7 often baseling concerning and 19 of one
6	although a minority of participants (number-needed-to-harm = 7 after baseline screening and 18 at one
7	year) demonstrated alinically significant increased anyiety layels
8 9	year) demonstrated clinically significant increased anxiety levels.
9 10	
11	
12	
13	
14	
15	Clinical Trial Registration: ClinicalTrials.gov; No.: NCT00751660; URL: www.clinicaltrials.gov.
16 17	
17	
19	
20	
21	
22	Keywords: Health-related quality of life, lung cancer, low-dose chest CT, screening, early detection
23 24	
24 25	
26	
27	
28	
29	
30	Keywords: Health-related quality of life, lung cancer, low-dose chest CT, screening, early detection
31 32	
32 33	
34	
35	
36	
37	
38 39	
40	
41	
42	
43	
44	
45 46	
40 47	
48	
49	
50	
51 52	
52 53	
55 54	
55	
56	
57	_
58 50	5
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
00	

INTRODUCTION

 Lung cancer is the leading cause of cancer death in North America and around the world,[1]. Early detection and treatment of lung cancer through screening is a promising strategy to reduce lung cancer mortality,[2]. The largest trial performed to date, the National Lung Screening Trial (NLST), demonstrated that low-dose computed tomography (LDCT) screening in high risk individuals (i.e., ever smokers aged 55 to 74 years, \geq 30 pack-years of smoking and <15 years since quitting) significantly reduced lung cancer mortality,[3]. American and Canadian preventative health care agencies have since published recommendations in favor of LDCT lung cancer screening, [3,4]. However, no screening intervention is without potential harm, including adverse psychological impact of the screening intervention, screening results, or subsequent investigations in most participants who will not be found to have cancer. Potential detriments of lung cancer screening include anxiety, and distress from the evaluation of both CT detected false positive and over-diagnosed cancers. A small proportion of the screen-detected tumors would never lead to clinical symptoms, but these over-diagnosed lung cancers are frequently treated, with associated risks of adverse effects, [5,6]. Moreover, studies have shown that CT lung screening has a high rate of significant lung cancer-unrelated incidental findings (SIFs),[7]. These SIFs may require additional investigations and therefore can be associated with adverse psychological impact on participants in a screening program,[6].

A recent systematic review on the psychological burden of LDCT revealed that LDCT screening may be associated with a short-term psychological burden in participants,[8]. Studies to date have explored mean changes in groups of individuals rather than rates of clinically significant changes in individuals screened. Effective policy decisions regarding the implementation of lung cancer screening and informed decision making by individuals requires reliable evidence on its potential impacts on Health Related Quality of

1	
2 3	_
5 4	L
5	
6	e
7	
8	С
9	
10	
11	
12 13	
14	
15	
16	
16 17	
18	
19	
20	
21	
22 23	
25 24	
25	
26	
27	
28	
29	
30	
31	
32 33	
33 34	
35	
36	
37	
38	
39	
40	
41	
42	
43 44	
44 45	
46	
47	
48	
49	
50	
51	
52	
53	
54	

59

60

Life (HRQoL) and psychological wellbeing of individual participants,[9]. Therefore, this study aimed to evaluate the impact of screening modalities on the quality of life and anxiety of participants in the Pan-Canadian Early Detection of Lung Cancer Study.

for peer teries only

METHODS

Study design and population

The Pan-Canadian Early Detection of Lung Cancer Study, which has been described in detail previously,[10,11], enrolled current or former smokers aged between 50-75 years and with a 2% or greater lung cancer risk over 6 years using a risk-prediction model developed using Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data,[12]. Participants were recruited in 8 centers across Canada (Calgary, Halifax, Hamilton, Laval, Ottawa, St-John's, Toronto and Vancouver) from September 2008 to December 2010 with each centers' institutional review board approving the study. Signed informed consent was obtained from each participant.

All participants were offered baseline LDCT with repeat screening at year 1 and 4 in addition to LDCT scans as appropriate for nodule follow-up, with the first half of the recruited subjects to receive autofluorescence bronchoscopy (AFB) as an additional screening modality,[13]. However, since AFB does not appear effective in the screening environment,[13], and to avoid the potential confounding impact of AFB on HRQL, participants in the AFB arm of the study are excluded from the current analysis.

LDCT scan follow-up protocol were determined by the maximum long axis diameter of the largest nodule identified. Participants with any semi-solid or solid nodule 5 to 10 mm, or ground-glass opacity (GGO) 8-10 mm were to receive an additional LDCT at 3 months, with larger lesion being referred for clinical consultation. Any participant requiring repeat LDCT or investigation for a lung lesion other than a planned 12-month follow-up examination were considered to have a positive screening exam for the purpose of this analysis (figure 1). Participants were informed of the various possible findings which may be found on CT examinations and general protocols for investigations at the time of study consent.

Individualized results letters with description of findings appropriate for a non-medical reader were developed by each study site.

Health-Related Quality of life (HRQoL), and anxiety

The 12-item short-form (SF-12) Physical and Mental Component Scales (PCS, and MCS, respectively),[14] and the EuroQoL questionnaire [EQ-5D-3L (Three-level version of EQ-5D)] were used to determine the participants' HRQoL at each assessment. The test–retest reliability coefficient is reported to be 0.89 for the PCS and 0.76 for the MCS. The EQ-5D-3L consists of a preference-based index score and a visual analogue scale (VAS); the index scores were derived from the current Canadian tariff,[15], (a maximum (best) value of 1 (for health state 11111) and a minimum value of -0.34 (for 33333)). The VAS is a likert scale asking participants to draw a line to their current health status on a visual scale ranging between 0 and 100. Scores on the SF-12 are standardized (i.e., mean = 50 and SD = 10), with a higher score indicating better HRQoL.

To evaluate potential anxiety induced by the results of the screening tests, we used the Spielberger State Trait Anxiety Inventory (STAI),[16]. Additional methodology details are provided in the online supplement.

The questionnaires were administered in person at the time of study enrolment (baseline), then by phone within 1 month after the CT results were received by the participants, 1 month after any additional followup CT scan or other testing following a positive screen (post investigations) and prior to the 1st annual repeat LDCT (12 months post baseline) (figure 1).

3 Statistical analyses

Descriptive analyses of the participants' characteristics and screening outcome were performed. We calculated summary scores of outcome measures for participants in each category at each of the study time points (at baseline, 1 month post baseline CT scan, 12 months after baseline, and post investigations). In addition, the above scores were compared separately in the subset of participants with a positive screening intervention.

To compare overall differences in HRQoL and State-anxiety scores between baseline and each of the survey time points, Generalized Linear Mixed Models were used to take into account the clustering of data within the 8 study sites and the repeated measurement of each individuals as well as non-normally distributed/skewed outcomes. The estimated margin of means with adjustment for multiple comparisons (Bonferroni correction) was calculated to contrast baseline versus each of the study time points. In these estimations, margins involving empty cells were treated as not estimable. When significant long-term differences were noted in our mixed model, we further explored the factor association with the observed changes using a multivariate regression model with adjustment for scan results, age, gender, self-reported race, smoking status, pack-years, alcohol consumption, education, family history of any cancer, participants' concern about getting lung cancer at baseline, and for the clustering of data within 8 study sites.

We further calculated the proportion of individuals with improvement vs. deterioration greater than the MCID for each instrument. MCIDs for outcome measures were selected based on previously published results as follows: EQ visual analog scale (VAS)=8,[17], EQ-5D-3L index values=0.05,[18], PCS=8.1,[19], MCS=4.7,[14], STAI-State Anxiety=10,[20]. The comparisons between these two proportions were performed using Z-test and if significant, the excess number of cases with improvement vs. worsening scores were calculated as a percentage of cases with available data. When significant

BMJ Open

differences were noted, a number-needed-to-harm (NNH) calculation was applied (total number of case/excess cases with worsened score).

Two-sided p-values < 0.05 were considered as statistically significant. All analyses were performed using SPSS, version 24 (IBM Corp., Armonk, N.Y., USA) or STATA version 14 (StataCorp, College Station, Texas). Sample size was determined by other primary study factors relating to the screening intervention and not the current analysis.

Patient and Public Involvement

Patient and public involvement in the design of the research was included through the main funding agencies collaborating on the project. This includes the Terry Fox Research Institute, the research arm of The Terry Fox Foundation. In addition, public input was obtained through involvement of the Canadian Partnership Against Cancer, an independent organization funded by the federal government to accelerate action on cancer control for all Canadians. Patients were not specifically involved in the recruitment and conduct of the study and no specific plan to disseminate research findings to participants has been made.

RESULTS

Participant characteristics

Two thousand five hundred and thirty-seven participants were enrolled in the Pan-Can study, and 1,237 underwent LDCT alone (without AFB). The mean (SD) age of these participants was 62.9 (6.1) at baseline. Males 558 (45.1 %), Caucasian 1201 (97.1 %), current smokers 768 (62.1 %), and regular alcohol drinkers 961 (77.7 %) comprised the largest groups of participants. The median (IQR) pack-years of smokers was 51.3 (21.6) and mean (SD) duration of smoking was 43.9 (6.1) years. A family history of lung cancer was present in 392 participants (26.6 %), (table 1). Median (IQR) lung cancer risk score was 3.5% (2.9) over 6 years. Positive baseline LDCT examinations were noted in 279 (22.6 %) participants of which 110 (15.1 %) led to a diagnosis of lung cancer.

Table 1-Baseline characteristics of Pan-Canadian Early Detection of Lung Cancer Study participants.

Characteristics	All Enrolled (n=1237)	
Age, mean (SD)	62.9 (6.1)	
Gender (males), n (%)	558 (45.1)	
Race *		
Caucasian	1201 (97.1)	
Asian	15 (1.2)	
Black or African Canadian	7 (0.6)	
Aboriginal	4 (0.3)	
Pacific Islander	0 (0.0)	
Other	10 (0.8)	
Education		
8 th grade or less	32 (2.3)	
9 th to 12 th grade	153 (12.4)	

1	
2	
3	
4	
5	
5	
6	
7	
8	
9	
1	0
1	
1	2
1	3
	4
	5
1	6
1	7
	8
1	9
	0
	1
2	2
2	3
	4
2	5
2	6
	7
	8
2	9
3	0
3	
3	
3	3
3	4
З	5
3	6
3	7
3	8
	9
4	
4	-
4	2
4	3
4	Δ
	· ·
	5
4	
4	7
4	8
	9
J	-
5	1
5	2
5	
5	
J	4
5	5
5	6
5	7
	, 8
J	-
5	9
6	0

High school graduate	337 (27.2)
Bachelor's degree	107 (8.7)
Technical/Vocational/School certificate	260 (21.0)
Associate degree/some college	205 (16.6)
Advanced Degree	144 (11.6)
Smoking habits	
Current smokers, n (%)	768 (62.1)
Pack- years, median (IQR, range)	51.3 (21.6, 2.2-230)
Smoking duration, mean (SD)	43.9 (6.1)
Alcohol consumption	
Current regular drinkers**	961 (77.7)
Family history of lung cancer, n (%)	392 (31.7)
Being worried about getting lung cancer	
Rarely or never	267 (21.6)
Sometimes	656 (53.0)
Often	235 (19.0)
All of the time	75 (6.1)
Scan results at baseline	
Positive	279 (22.6)
Negative	958 (77.4)
Lung cancer risk score, median (IQR, range)	3.5 (2.9, 2.0-33.5)

* Missing, n (%)=5 (0·2).

**Regular alcohol consumption: having more than one drink per week for a period of 6 months or more. Missing, n=11.

Health-related quality of life and anxiety measures

Baseline

- 60

At baseline, participants reported being concerned about getting lung cancer always (6.1 %), often (19.0%) and sometimes (53.0%). General health problems were reported by 65.0% of respondents on at least one item on the EQ-5D-3L. Average baseline EQ visual analogue scale (VAS), EQ-5D-3L index values, PCS, MCS, and STAI-State Anxiety scores were 76.3, 0.84, 46.1, 51.1, and 30.9, respectively (Table 2).

Initial screening

No statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or MCS levels were noted following baseline CT screening. In addition, the proportion of individuals experiencing a deterioration vs. improvement greater than the MCID for EQ VAS(figure 2), EQ-5D-3L(figure 3), PCS(figure 4) and MCS(figure 5) were not significantly different. However, the STAI-State Anxiety levels increased in participants following baseline LDCT [change (95% CI): 2.27 (0.57 to 3.96), p-value <0.001] (Table 2). A greater proportion of individuals experienced a deterioration vs. improvement greater than the MCID of 10 for the STAI - State Anxiety levels was also noted [increase >MCID (n=180) vs. decrease >MCID (n=50), p-value <0.001](figure 6). The excess number of participants with increased vs. decreased anxiety represents 13.8% [(180-50)/937, NNH = 7] of participants with available data. This change remained significant even if only participant with a negative screen were considered [increase >MCID (n=129) vs. decrease >MCID (n=40), p-value < 0.0001]. Multivariate regression analysis demonstrated female gender and increased baseline concern about getting lung cancer to be associated with increased anxiety following screening (Table 3).

Table 2- HRQoL, and anxiety measures at baseline and at different time-points within the study. Generalized linear mixed model.

	Baseline (n=1,237)	1-month post baseline CT scan Mean, change (95% CI) (n=953)	12-months after baseline CT Mean, change (95% CI) (n=1066)
EQ VAS ¹	76.3	76.8, 0.42 (-1.39 to 2.23)	76.8, 0.22 (-0.88 to 1.32)
EQ-5D-3L index values	0.84	0.84, -0.00 (-0.02 to 0.01)	0.84, -0.00 (-0.01 to 0.01)
SF-12: PCS ²	46.1	46.8, 0.61 (-0.15 to 1.37)	46.4, 0.31 (-0.55 to 1.17)
SF-12: MCS ³	51.1	50.9, -0.26 (-1.04 to 0.52)	51.2, -0.14 (-1.14 to 0.86)
STAI-State Anxiety ⁴	30.9	33.1, 2.27 (0.57 to 3.96) ⁵	31.7, 1.11 (-1.11 to 3.33)

¹⁸
¹ EQ Visual Analogue Scale "We would like to know how good or bad your health is today" (100 – best imaginable, 0 – worst imaginable).

²¹ ² Physical Health Composite Scores (US population mean = 50 + -10), with higher score corresponding to better state.

²³ Mental Health Composite Scores (US population mean = 50 + -10), with higher score corresponding to better state.

²⁴ ⁴ STAI-State score >39 considered clinically significant symptoms.

⁵ P-value < 0.05 compared with baseline. Post-estimated marginal means with adjustment for multiple comparison
 (Bonferroni).

Table 3-Factor associated with changes in anxiety levels from baseline to 1-month post baseline CT scan. Changes in anxiety levels (STAI-S) Beta coefficient (95 % CI) -0.70 (-1.91 to 0.51) **Positive scan results** -0.09 (-0.18 to 0.01) Age Females 1.01 (0.02 to 2.16)* **Current smokers** 0.57 (-0.50 to 1.64) **Pack-years** -0.01 (-0.03 to 0.01) **Current alcohol consumption** -0.63 (-1.86 to 0.60) Family history of any cancer -1.14 (-2.28 to 0.01) Participants' concern about getting lung cancer All the time 3.79 (0.24 to 7.32)* 1.73 (-0.00 to 3.47) Often Sometimes 0.99 (-0.12 to 2.10)

Multivariate regression model with adjustment for scan results, age, gender, race, smoking status, pack-years, alcohol consumption, education, family history of any cancer, participants' concern about getting lung cancer at baseline, and for the clustering of data within 8 study sites. *p<0.05 Twelve-month assessment No statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or STAI - State Anxiety levels were detected in participants at the 12 month interview. The proportion of individuals with deterioration vs. improvement greater than the MCID for the instrument remained significant for the State anxiety levels [increase >MCID (n=146) vs. decrease >MCID (n=87), p-value <0.0001], representing 5.5% [(146-87)/1066, NNH=18] of participants (figure 6). The proportion of individuals experiencing a deterioration vs. improvement greater than the MCID for EQ VAS(figure 2), EQ-5D-3L(figure 3), PCS(figure 4) and MCS(figure 5) were not significantly different. Positive screen and investigation Among participants receiving a positive scan results (n=279), no statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or MCS were detected following baseline LDCT (online Supplementary Table 1). However, more participants experienced a clinically significant increase vs. decrease in anxiety score [increase >MCID (n= 20) vs. decrease >MCID (n=41), p-value=0.002] representing 8.8% [(41-20)/238, NNH=11] of these participants (figure 7). This increase persisted at the 12 month interview [increase >MCID (n=14) vs. decrease >MCID (n=35), p-value=0.003] representing 8.5% [(35-14)/246, NNH=12] of participants (figure 8). For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2	
2 3 4	Following investigation examinations, no statistically significant mean changes in EQ VAS, EQ-5D-3L
5 6	index values, PCS, MCS, or anxiety were detected. Post-investigation changes revealed no statistically
7 8 9	significant changes in the proportion of individuals with deterioration vs. improvement greater than the
10 11	MCID (figure 7).
12 13 14	The proportion of different levels of each questionnaires' dimensions by study visits, as well as number of
15 16	
17 18	
19 20 21	
22 23	
24 25 26	
27 28	
29 30 31	
32 33	
34 35 36	missing values, are shown in the online Supplementary Table 2 to 4.
37 38	
39 40 41	
41 42 43	
44 45 46	
40 47 48	
49 50	
51 52 53	
54 55	
56 57 58	17
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

DISCUSSION

 This study offers detailed information on HRQoL and anxiety following LDCT for lung cancer screening in a Canadian high-risk selected population using validated assessment tools measuring overall HRQoL as well as specific physical, psychological and anxiety scores. Our study found no clinically significant differences in HRQoL outcomes between baseline and each of the survey time points following initial screening in the cohort as a whole. However, more participants experienced a clinically significant increased anxiety (vs. decreased) following baseline LDCT. This finding was more pronounced among females and participants who were concerned about getting lung cancer at baseline. Higher anxiety was also more frequent in the subgroup with positive baseline scan, although the impact of scan results did not reach statistical significance in the multivariate analysis. Over the long-term, no adverse effects on HRQoL were noted but some of the excess in increased anxiety levels persisted.

In line with our findings, analyses of other screening cohorts including NLST,[21] NELSON,[22] PLCO,[23] and UKLS,[24] as well as two recent meta-analyses have demonstrated that lung cancer screening is associated with little to no adverse physical or psychological long-term impact on participants[8,25]. While analysis of the Danish Lung Cancer Screening Trial did show negative consequences at 1 year, [26] and 2 year, [27] follow-up, the degree of change was actually greater in the control (no screening) arm of the trial.

Our finding of increased anxiety following a positive screen is in line with those reported in the UKLS,[24] and NLST trials,[21] which observed a short-term increase in distress levels two weeks or 2 months respectively after a positive result notification of baseline screening. Results from NELSON,[28] and from the Pittsburgh Lung Screening Study,[29] also reported a short-term lung cancer-specific

BMJ Open

distress, a poorer quality of life and a higher level of anxiety among participants with indeterminate scan results compared with those with negative results. However, in both studies these negative impacts disappeared over time.

Similar to our findings, NELSON study reported a worse HRQoL outcomes among females compared to males,[28]. Furthermore, our observation regarding females is also consistent with the results of a study of PLCO participants,[23] that found a poorer MCS outcomes in females compared to males.

In most cases reported to date, statistically significant mean changes in HRQoL-related scores detected in groups of screened individuals have been small and of questionable clinical significance limiting the impact of such findings in clinical decision-making. Conversely, lack of statistically significant changes in population means can mask clinically meaningful changes in individuals. The MCID has been suggested to be a useful benchmark to define the smallest difference in HRQoL that individuals perceive as beneficial or harmful and that mandates a change in management, [30]. Only two previous lung cancer screening trial have reported MCID levels to interpret the changes in HRQoL of participants, [22,24,28]. However, both applied this concept to mean population changes rather than to discrete individual changes. Our study is unique in providing discrete participant data on the proportion of individuals with improvement vs. deterioration greater than the MCID for each assessment tool. This has allowed us to attribute to the intervention excess cases of deterioration vs. improvement given normal expected variations in each individual over time. This is not only helpful in determining if a true clinically significant impact is present, but also in specifying how many individuals are impacted by such a change, in order to calculate a "number-needed-to-harm" value. With this approach, we found that the proportion of individuals with improvement vs. deterioration greater than the MCID for the STAI was significantly different among all participants with a number needed to harm of 7 in the short term following screening,

and 18 at one-year post screening. Our data adds to an evolving body of evidence which suggests that LDCT screening for lung cancer does not have overall significant negative impacts on the HRQoL of the population screened. However, a minority of individuals do experience small but clinically significant increases in anxiety levels following screening.

The major strengths of our study include the use of a large multicenter sample of eligible participants, and reporting of individual participant data using three different and well-established instruments for measuring HRQoL and anxiety as well as the risk prediction model used for the recruitment,[31]. Another strength of our study is the longitudinal design with a high follow-up and response rate, which enabled us to assess short- and long-term outcomes at different time points during screening process with each participant serving as his/her own control. While we enrolled a high risk cohort using a risk prediction model, our participants' baseline HRQoL metrics appeared comparable to those of similarly aged individuals in the general population [Adult aged 55-69; mean EQ VAS: 76,[32] State anxiety: 32.2-34.5,[15]. Adult aged 50-69; PCS: 50.9-51.3, MCS: 50.7-50.9,[13]] suggesting that our findings could be generalizable to a broader population of screen-eligible individuals but with lower risk of lung cancer than in our population.

The current study has potential limitations. Our population was made up almost entirely of Caucasians, so that a differential impact of screening on other ethnic communities cannot be determined. Owing to the study design for HRQoL assessments, we were unable to address the impacts of incidental findings on HRQoL and anxiety of participants. Another potential limitation is that we did not compare our results to an unscreened control group but instead used each participant's baseline scores. As such, other factors unrelated to the screening intervention, such as aging or changes in smoking status, could affect the longitudinal changes (or lack thereof) noted in our study,[34]. However, two previous studies with a Page 21 of 46

BMJ Open

randomized design and a control group reported the HRQoL results that were comparable to our findings,[14,20]. Another potential limitation is that the EQ-5D-3L is usually associated with a ceiling effect (i.e., scores recording perfect health),[35] and has limited ability to determine small changes in health status compared to the five-level EQ-5D-5L, which might offer improved measure of population-weighted health state utility,[36,37]. In our study, 35 % of participants reported perfect scores on EQ-5D-3L at baseline; suggesting a ceiling effect that was adjusted for with a generalized linear mixed modeling approach,[38]. Moreover, HRQoL in our study was also measured by SF-12, which has been known to demonstrate a smaller ceiling/floor effect compared to EQ-5D-3L,[35]. In our study, no ceiling/floor effect was observed for the SF-12 scores. Finally, the statistical power to detect changes in some participants subgroups such as those with positive screens may be limited because of low number of participants with a positive scan results. Therefore, caution should be used in drawing conclusions.

The complexity of longitudinal analysis of HRQoL and the lack of agreed upon standardized approach compromise the comparison of results between studies,[39]. Even the specific MCID level for each instrument can be debated. Ideally such levels are determined in the specific population of interest, but such information is rarely available. Levels chosen for our analysis were determined prior to any data analysis based on best evidence for each instrument. As a confirmatory step, MCIDs selected in this study were found to approximate estimates obtained as half a Standard Deviation (SD) (MID) of HRQol measures in our population (results not shown), an alternative distribution-based approach to MCID determination,[40].

The findings of our study corroborate and expand the current evidence-based information on lung cancer screening decision making by showing that there is a minimal overall psychological impact associated with lung cancer screening. However, certain populations (i.e., females, participants with higher baseline

concern about lung cancer) may be at a higher risk of negative psychological impact. This suggests that an improved communication is needed throughout the entire lung cancer screening process, especially for the potentially vulnerable subgroups. Since most positive screens do not result in a lung cancer diagnosis, approaches to better define screening exam findings and reduce false positive rates could be effective in reducing the anxiety burden in this subgroup. Despite the high rate of false positive CT results in lung cancer screening, there is no clear recommendation yet on psychological interventions to help individuals cope with abnormal CT screening results. However, literature on mammography screening has shown that immediate follow-up and consultation can significantly reduce anxieties after receiving abnormal mammograms,[41].

In conclusion, our study demonstrated that CT Screening for Lung Cancer has no major impact on HRQoL among participants overall, but some individuals experience clinically significant increase in anxiety with a number needed to harm of 18 at one year post initial screen. While these impacts may appear minor in view of the robust mortality reduction associated with LDCT screening, ongoing work to further define and minimize these negative aspects of screening is warranted given recommendations for broad screening of at risk populations in North America.

Author's contributions:

AT, SCL, MCT, NT, SC and SAK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects as well as the final version of the manuscript. AMC, PM, SP, MJ, JG, GG, GN, SM, FL, RB, GL, HR, MST, contributed substantially to the study design, data interpretation, and review of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

The study was funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer. Additional research support provided by the Arnie Charbonneau Cancer Institute and the Alberta Cancer Foundation. Primary results of the study have been published previously [11].

Data Sharing Statement

No additional unpublished data from the study is made available.

2	
3	References
4	
5	
6 7	[1] Brambilla E, Travis WD, Brennan P, et al. Lung cancer. In: Stewart BW, Wild CP, eds. World cancer
8 9 10	report 2014. International Agency for Research on Cancer (2014) 350-361.
11 12 13	[2] National Lung Screening Trial Research Team, Aberle DR, Berg CD, Black WC, et al. The National
14 15	Lung Screening Trial: overview and study design. Radiology (2011) 258:243-253.
16 17	
18 19	[3] Recommendations on screening for lung cancer. CMAJ (2016)188:425-432.
20	
21	[4] Mover VA Semaning for lung appear U.S. Proventive Services Tesk Force recommendation
22	[4] Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation
23 24	statement. Ann Intern Med (2014)160:330-338.
25	statement. Ann men Wed (2014)100.330-356.
26	
27 28	[5] Bach PB, Mirkin JN, Oliver TK. Benefits and harms of CT screening for lung cancer: a systematic
29 30	review. JAMA (2012) 307:2418-2429.
31 32	
32 33	[(] Det EF I. Dissing D. Cetanic C. et al. NI CT Occurring Managing Whiting Terms Occurring
34	[6] Patz EF Jr, Pinsky P, Gatsonis C, et al; NLST Overdiagnosis Manuscript Writing Team. Overdiagnosis
35	$\frac{1}{100}$
36	in low-dose computed tomography screening for lung cancer. JAMA Intern Med (2014)174:269-
37	
38	274.
39 40	
40 41	
42	[7] Marshall HM, Bowman RV, Yang IA, et al. Screening for lung cancer with low-dose computed
43	
44	tomography: a review of current status. J Thorac Dis (2013) 5 Suppl 5:S524-S539.
45	
46	
47 40	[8] Wu GX, Raz DJ, Brown L, et al. Psychological Burden Associated with Lung Cancer Screening: A
48 49	
50	Systematic Review. Clin Lung Cancer (2016) pii: S1525-7304 (16) 30053-30055.
51	
52	
53	
54	
55 56	
56 57	
58	24
59	
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2	
3 4	[9] Miller AB, Madalinska JB, Church T, et al. Health-related quality of life and cost-effectiveness studies
5 6	in the European randomised study of screening for prostate cancer and the US Prostate, Lung,
7 8 9	Colon and Ovary trial. Eur J Cancer (2001) 37: 2154-2160.
10 11 12	[10] McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules
13 14	detected on first screening CT. N Engl J Med (2013) 369:910-919.
15 16 17	[11] Tammemagi MC, Schmidt H, Martel S, et.al. Participant selection for lung cancer screening by risk
18 19 20	modelling (the Pan-Canadian Early Detection of Lung Cancer (PanCan) study): a single-arm,
21 22 23	prospective study. Lancet Oncol (2017) pii: S1470-2045(17)30597-1.
24 25 26	[12] Tammemagi MC, Freedman MT, Pinsky PF, et al. Prediction of true positive lung cancers in
27 28	individuals with abnormal suspicious chest radiographs: a prostate, lung, colorectal, and ovarian
29 30 31	cancer screening trial study. J Thorac Oncol (2009) 4:710-721.
32 33 34	[13] Tremblay A, Taghizadeh N, McWilliams AM, et al. Low Prevalence of High Grade Lesions Detected
35 36	with Autofluorescence Bronchoscopy in the Setting of Lung Cancer Screening in the Pan-
37 38 39	Canadian Lung Cancer Screening Study. Chest (2016) 150:1015-1022.
40 41 42	[14] Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate
43 44 45	results from the SF-36 in longitudinal studies? J Public Health Med (1997) 19:179-186.
46 47 48	[15] Bansback N Tsuchiya A BJAA. Canadian valuation of EQ-5D health states: preliminary value set and
49 50	considerations for future valuation studies. PLoS One (2012) 7:e31115. doi:
51 52 53	10.1371/journal.pone.0031115.
54 55 56	
57 58	25
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2	
3 4	[16] Spielberger CD, Gorsuch RL, Lushene RE. Test manual for the State-Trait Anxiety Inventory. Palo
5 6 7	Alto, CA: Consulting Psychologists Press, 1970.
8 9 10	[17] Zanini A, Aiello M, Adamo D, et al. Estimation of minimal clinically important difference in EQ-5D
11 12	visual analog scale score after pulmonary rehabilitation in subjects with COPD. Respir Care
13 14 15	(2015) 60:88-95.
16	
17 18	[18] Le QA, Doctor JN, Zoellner LA, Feeny NC. Minimal clinically important differences for the EQ-5D
19 20 21	and QWB-SA in Post-traumatic Stress Disorder (PTSD): results from a Doubly Randomized
22 23	Preference Trial (DRPT). Health Qual Life Outcomes (2013) 11:59.
24	
25 26 27	[19] Parker SL, Godil SS, Shau DN, Mendenhall SK, McGirt MJ. Assessment of the minimum clinically
27 28 29	important difference in pain, disability, and quality of life after anterior cervical discectomy and
30 31	fusion: clinical article. J Neurosurg Spine (2013)18:154-160.
32 33 34	[20] Corsaletti BF, Proença MGL, Bisca GKW, et al. Minimal important difference for anxiety and
35 36	depression surveys after intervention to increase daily physical activity in smokers. Fisioter Pesq
37 38 39	(2014) 21:359-364.
40	
41 42	[21] Gareen IF, Duan F, Greco EM, et al. Impact of lung cancer screening results on participant health-
43 44 45	related quality of life and state anxiety in the National Lung Screening Trial. Cancer (2014) 3401-
46 47	3409.
48	
49 50	[22] Van den Bergh KA, Essink-Bot ML, Borsboom GJ, Scholten ET, van Klaveren RJ, de Koning HJ.
51 52 53	Long-term effects of lung cancer computed tomography screening on health-related quality of life:
54 55	the NELSON trial. Eur Respir J (2011) 38:154-161.
56	
57 58	26
58 59	
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

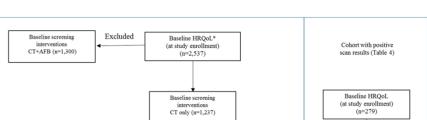
1	
2 3	[23] Taylor KL, Shelby R, Gelmann E, et al. Quality of life and trial adherence among participants in the
4	[25] Taylor KE, Sherby K, Germann E, et al. Quanty of the and that adherence among participants in the
5 6	prostate, lung, colorectal, and ovarian cancer screening trial. J Natl Cancer Inst (2004) 96: 1083-
7 8	1094.
9 10	
11 12	[24] Brain K, Lifford KJ, Carter B, et al. Long-term psychosocial outcomes of low-dose CT screening:
13 14	results of the UK Lung Cancer Screening randomised controlled trial. Thorax (2016) 71:996-1005.
15 16	
17 18	[25] Slatore CG, Sullivan DR, Pappas M, et al. Patient-centered outcomes among lung cancer screening
19 20	recipients with computed tomography: a systematic review. J Thorac Oncol (2014) 9:927-934.
21	
22 23 24	[26] Aggestrup LM, Hestbech MS, Siersma V, et al. Psychosocial consequences of allocation to lung
25 26	cancer screening: a randomised controlled trial. BMJ Open (2012) 1;2:e000663.
27	
28 29	[27] Rasmussen JF, Siersma V, Pedersen JH, et al. Psychosocial consequences in the Danish randomised
30 31	controlled lung cancer screening trial (DLCST). Lung Cancer (2015) 87:65-72.
32 33	
33 34 35	[28] Van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Short-term health-related quality of life
36 37	consequences in a lung cancer CT screening trial (NELSON). British Journal of Cancer (2010)
38 39	102, 27 - 34.
40 41	
41	
43	[29] Byrne MM, Weissfeld J, Roberts MS. Anxiety, fear of cancer, and perceived risk of cancer following
44 45	lung cancer screening. Med Decis Making (2008) 28:917-925.
46	
47 49	
48 49	[30] Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically
50 51	important difference. Control Clin Trials (1989)10:407-415.
52	
53	
54 55	
56	
57 59	77
58 59	27
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2 3 4 5 6	I
7 8 9 10 11 12	[
11 12 13 14 15 16 17 18	[
19 20 21 22 23 24	[
25 26 27 28 29 30	[
31 32 33 34 35 36 37 38	1
39 40 41 42 43 44	[
45 46 47 48 49	I
50 51 52 53 54 55 56	I
57 58 59 60	

[31] Tammemagi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. N Engl
J Med 2013;368:728-736.
[32] Johnson JA, Pickard AS. Comparison of the EQ-5D and SF-12 health surveys in a general population
survey in Alberta, Canada. Med Care (2000) 38:115-121.
[33] Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using
postmyocardial infarction patients in the Dutch population. Qual Life Res (2009) 18:403-414.
[34] Hestbech MS, Siersma V, Dirksen A, et al. Participation bias in a randomised trial of screening for
lung cancer. Lung Cancer (2011) 73:325-331.
[35] Tramontano AC, Schrag DL, Malin JK, et al. Catalog and comparison of societal preferences
(utilities) for lung cancer health states: results from the Cancer Care Outcomes Research and
Surveillance (CanCORS) study. Med Decis Making (2015) 35:371-387.
[36] Pickard AS, De Leon MC, Kohlmann T, et al. Psychometric comparison of the standard EQ-5D to a 5
level version in cancer patients. Med Care (2007) 45:259-263.
[37] Wang P, Luo N, Tai ES, et al. The EQ-5D-5L is More Discriminative Than the EQ-5D-3L in Patients
with Diabetes in Singapore. Value Health Reg Issues (2016) 9:57-62.
[38] Lo S, Andrews S. To transform or not to transform: using generalized linear mixed models to analyse
reaction time data. Front Psychol (2015) 6:1171.
[39] Bonnetain F, Fiteni F, Efficace F, et al. Statistical Challenges in the Analysis of Health-Related
Quality of Life in Cancer Clinical Trials. J Clin Oncol (2016) 34:1953-1956.
28

1 2 3	[40] Names CD. Share IA. Warrich V.W. Internetation of charges in hardet and its of life, the
4	[40] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the
5 6	remarkable universality of half a standard deviation. Med Care (2003) 41:582-592.
7	
8 9	[41] Barton MB, Morley DS, Moore S, et al. Decreasing women's anxieties after abnormal mammograms:
10 11	a controlled trial. J Natl Cancer Inst (2004) 96:529-538.
12	a controlled that. J Nati Cancer first (2004) 90:529-558.
13 14	
15	
16 17	
18	
19 20	
21	
22 23	
23 24	
25	
26 27	
28	
29 30	
31	
32 33	
34	
35 36	
37	
38 39	
40	
41 42	
43	
44 45	
46	
47 48	
49	
50 51	
52	
53 54	
55	
56 57	
58	29
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
00	

2 3	Figure legends
4	i igui e legentus
5 6	
7	Figure 1- Assessments of the health-related quality of life (HRQoL) and anxiety in the Pan-Canadian Early Detection of Lung
8	Cancer Study.
9 10	
11	Figure 2: Changes in EuroQoL Visual Analog Scale (VAS) from baseline to post baseline CT(A), and 12 months after
12	Tigure 2. Changes in Eurogol. Visual Analog Scale (VAS) from baseline to post baseline CT(A), and 12 months arter
13 14	baseline(B).
15	
16	Figure 3: Changes in EuroQoL(EQ)-5D-3L from baseline to post baseline CT(A), and 12 months after baseline(B).
17 18	
19	Figure 4: Changes in 12-item short-form Physical Component Scale(PCS) from baseline to post baseline CT(A), and 12 months
20	Figure 4. Changes in 12-nem short-form i hysical component scale(1 C3) from baseline to post baseline C1(A), and 12 months
21 22	after baseline(B).
23	
24	Figure 5: Changes in 12-item short-form Mental Component Scale (MCS) from baseline to post baseline CT(A), and 12 months
25 26	
27	after baseline(B).
28	
29 30	Figure 6: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT(A), and 12 months
31	after baseline(B).
32	
33 34	Figure 7: Changes in Spielhanser State Trait Anviety Inventory (STAI) from baseline to past baseline CT (A) and next
35	Figure 7: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT (A) and post
36 37	investigation (B) among participants with a positive scan results.
38	
39	Figure 8: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to 12 months among participants with a
40 41	
42	positive scan results.
43	
44 45	
46	
47	
48 49	
50	
51 52	
52 53	
54	
55 56	
56 57	
58	30
	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
	30 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



CT & Notifications of scan results

1 month post baseline CT HRQoL (n=953)

12 months after baseline HRQoL / prior to annual repeat CT (n=1066)

207x146mm (300 x 300 DPI)

Baseline screening interventions CT only (n=238)

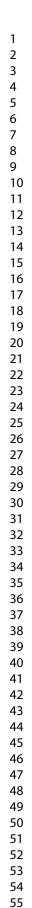
Post Investigation of a positive screen HRQoL (n=168)

12 months after baseline HRQoL / prior to annual repeat CT (n=246)

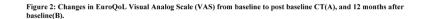
Figure 1- Assessments of the health-related quality of life (HRQoL) and anxiety in the Pan-Canadian Early Detection of Lung Cancer Study.

+MCID=8

BMJ Open



60



-MCID=-8

↑> MCID (n=203) vs. ↓<MCID (n=203)</p>

value = NA

500

Frequency

(A)

56-48-

change in VAS from baseline to post baseline

72-64-56-48-40-32-24-

change in VAS from baseline to 12 months after baseline

-24 -32 -40

64 -72

-80+

↑> MCID (n=267) vs. ↓<MCID (n=249) P-value =0.594

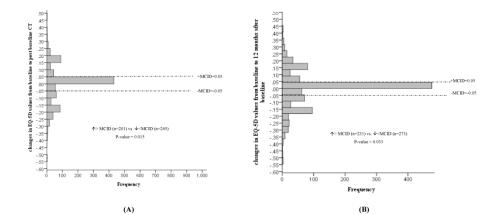
200

Frequency

(B)

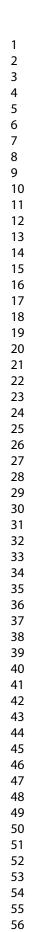
279x361mm (300 x 300 DPI)

 Figure 3: Changes in EuroQoL(EQ)-5D-3L from baseline to post baseline CT(A), and 12 months after baseline(B).



279x361mm (300 x 300 DPI)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



57 58 59

60



+MCID=8.1

MCID=-8.1

800 900 1,000

from baseline to 12 months after baseline

changes in PCS values

72.90 64.80

56.70 48.60

40.50 32.40 24.30

16.2

8.10

-8.10

16.2

-81.00

100 200 300 400 500 600 700

↑> MCID (n=158) vs. ↓>MCID (n=149) P-value = 0.513

Frequency

(B)

+MCID=8.1

-MCID=-8.1

800 900 1,000

89.10

81.00 72.90 64.80 56.70 48.60 40.50 32.40 24.30 16.20

8.10

.00 -8.10

-16.20 -24.30 -32.40 -40.50

48.60

56.70

-64.80 -72.90 -81.00

100 200

↑> MCID (n=106) vs. ↓>MCID (n=87)

P-value = 0.151

500 600 700

Frequency

(A)

changes in PCS values from baseline to post baseline CT

279x361mm (300 x 300 DPI)

3 4

1 2

- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12 13
- 14 15
- 16 17 18
- 19 20
- 21 22
- 23 24
- 25 26
- 27 28
- 29
- 30
- 31 32
- 33 34
- 35
- 36 37
- 38
- 39 40
- 41 42
- 43 44
- 45 46
- 47 48 49
- 50 51
- 52 53
- 54 55
- 56 57 58
- 59 60

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 5: Changes in 12-item short-form Mental Component Scale (MCS) from baseline to post baseline CT(A), and 12 months after baseline(B).

changes in MCS levels from baseline to 12 months after baseline

42.3

37.6

32.9

28.20 23.50 18.80 14.10

9.40 4.70

.00

-4.70 -9.40 -14.10

-18.8

-23.5

-28.20

32.9

-47.0

-51.70

↑> MCID (n=152) vs. ↓>MCID (n=164)

P-value = 0.512

150

Frequency (B)

42.3

32.9 28.2 23.5 18.8 14.1

9.40 4.70

.0

-4.7

-14.11 -18.80 -23.50 -28.20

-32.9

42.3

-51.7

96) vs. ↓>MCID (r

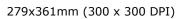
P-value = 0.185

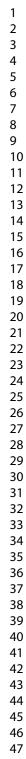
150

(A)

Ð

changes in MCS levels from baseline to post baseline





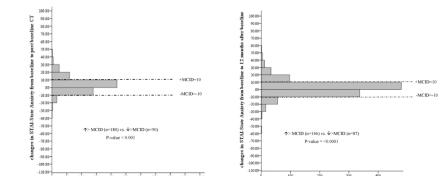
48 49

- 50 51
- 52 53

56

- 54 55
- 57 58
- 59 60

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



Frequency

(B)

1,000

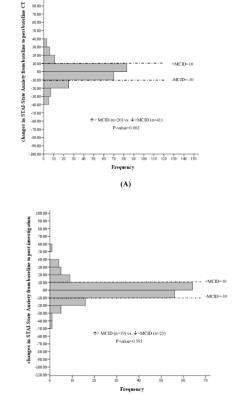
600 800 Frequency

(A)

Figure 6: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT(A), and 12 months after baseline(B).

279x361mm (300 x 300 DPI)

Figure 7: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT (A) and post



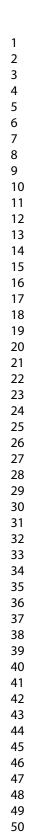
(B)

investigation (B) among participants with a positive scan results.

90.0

279x361mm (300 x 300 DPI)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



60



changes in STAI-State Auxiety from baseline to 12 months after baseline 90.00-90.00-50.00-50.00-50.00-40.00-30.00 20.00 10.0 -----+MCID=10 .00 -10.00 -MCID=-10 -20.00 -30.00 -40.00--50.00--60.00--70.00--30.00--90.00-↑> MCID (n=35) vs. ↓>MCID (n=14) P-value=0.003 110.0 70 80 90 100 110 120 130 140 150 10 20 30 40 50 60

Frequency

279x361mm (300 x 300 DPI)

Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Study

Niloofar Taghizadeh¹, Alain Tremblay¹, Sonya Cressman², Stuart Peacock², Annette M. McWilliams³, Paul MacEachern¹, Michael Johnston⁴, John Goffin⁵, Glen Goss⁶, Garth Nicholas⁶, Simon Martel⁷, Francis Laberge⁷, Rick Bhatia⁸, Geoffrey Liu⁹, Heidi Roberts⁹, Martin C. Tammemagi¹⁰, Sukhinder Atkar-Khattra², Ming-Sound Tsao⁹, Stephen C. Lam², for the Pan-Canadian Early Lung Cancer Study Group.

to beet eview only

e-Appendix 1:

Study design and population

Institutional Review Board (IRB) Approvals: Vancouver: UBC BCCA Research Ethics Board (UBC BCCA REB) H08-01132 Calgary: Conjoint Health Research Ethics Board (CHREB) ethics ID: 21852 Hamilton: McMaster University Research Ethics Board; ID: 08-367 Toronto: University Health Network Research Ethics Board; ID: 08-0576-C Ottawa: The Ottawa Hospital Research Ethics Board; ID 2008581-01H Quebec: Institute Universitaire de Cardiologie et de Pneumologie; ID: CER: 20319 Halifax: Capital Health Research Ethics Board; ID: CDHA-RS/2009-097 h Department St.John's: Eastern Health Department of Reseasrch/Knowledge transfer; ID; HIC#10.070

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Supplementary Table 1 – HRQoL, and anxiety levels in participants with positive baseline LDCT.

	Baseline (n=279)	1-month post baseline CT scan Mean, change (95% CI) (n=238)	Post investigation Mean, change (95% CI) (n=168)	12-months after baseline Mean, change (95% CI) (n= 246)
EQ VAS ¹	76.2	76.1, -0.21 (-2.54 to 2.13)	76.9, 0.89 (-3.28 to 5.07)	76.4, 0.19 (-1.73 to 2.11)
EQ-5D-3L index values	0.84	0.84, -0.00 (-0.03 to 0.03)	0.85, 0.00 (-0.03 to 0.04)	0.83, -0.01 (-0.05 to 0.02)
SF-12: PCS ²	46.2	46.5, 0.22 (-0.83 to 1.28)	46.6, 0.45 (-0.93 to 1.83)	45.3, -0.86 (-1.90 to 1.67)
SF-12: MCS ³	51.3	51.2, 0.01 (-1.66 to 1.67)	51.4, 0.54 (-2.06 to 3.15)	51.3, 0.01 (-2.30 to 2.33)
STAI-State Anxiety ⁴	29.9	33.2, 3.28 (-0.42 to 6.97)	32.9, 2.42 (-1.14 to 5.99)	31.7, 1.79 (-0.62 to 4.19)

¹ EQ Visual Analogue Scale "We would like to know how good or bad your health is today" (100 – best imaginable,

0 -worst imaginable).

² Physical Health Composite Scores (US population mean = 50 ± -10), with higher score corresponding to better state.

state

³ Mental Health Composite Scores (US population mean = 50 + -10), with higher score corresponding to better state.

⁴ STAI-State score >39 considered clinically significant symptoms.

Supplementary Table 2 - Proportion of different levels of EQ-5D-3L dimensions by study visits (Total n=1237).

Mobility I have no problems in walking ab I have some problems in walking I am confined to bed Missing Self-care I have no problems with self-care I have some problems washing or I am unable to wash or dress mys Missing Usual activities I have no problems with perform activities	about	918 (74.2) 311 (25.2) 4 (0.3) 4 (0.3) 1191 (96.2) 36 (2.9)	705 (74.0) 240 (25.2) 3 (0.3) 5 (0.5) 914 (95.9)	782 (73.4) 278 (26.1) 0 (0.0) 6 (0.6)
I have some problems in walking I am confined to bed Missing Self-care I have no problems with self-care I have some problems washing or I am unable to wash or dress mys Missing Usual activities I have no problems with perform	about	311 (25.2) 4 (0.3) 4 (0.3) 1191 (96.2)	240 (25.2) 3 (0.3) 5 (0.5)	278 (26.1) 0 (0.0) 6 (0.6)
I am confined to bed Missing Self-care I have no problems with self-care I have some problems washing or I am unable to wash or dress mys Missing Usual activities I have no problems with perform	dressing myself	4 (0.3) 4 (0.3) 1191 (96.2)	3 (0.3) 5 (0.5)	0 (0.0) 6 (0.6)
Missing Self-care I have no problems with self-care I have some problems washing or I am unable to wash or dress mys Missing Usual activities I have no problems with perform	dressing myself	4 (0.3) 1191 (96.2)	5 (0.5)	6 (0.6)
Self-care I have no problems with self-care I have some problems washing or I am unable to wash or dress mys Missing Usual activities I have no problems with perform	dressing myself	1191 (96.2)		
I have no problems with self-care I have some problems washing or I am unable to wash or dress mys Missing Usual activities I have no problems with perform	dressing myself		914 (95.9)	
I have some problems washing or I am unable to wash or dress mys Missing Usual activities I have no problems with perform	dressing myself		914 (95.9)	
I am unable to wash or dress mys Missing Usual activities I have no problems with perform	•••	36 (2.9)		1018 (95.5)
Missing Usual activities I have no problems with perform	elf		31 (3.3)	39 (3.7)
Usual activities I have no problems with perform		7 (0.6)	2 (0.2)	3 (0.3)
I have no problems with perform		3 (0.3)	6 (0.6)	6 (0.6)
activities	ing my usual	930 (75.1)	710 (74.5)	785 (73.6)
I have some problems with perfo	rming my usual	284 (22.9)	228 (23.9)	261 (24.5)
activities				
I am unable to perform my usual	activities	18 (1.5)	8 (0.8)	15 (1.4)
Missing Pain/discomfort		5 (0.5)	7 (0.7)	5 (0.5)
I have no pain or discomfort		575 (46.4)	471 (49.4)	498 (46.7)
I have moderate pain or discomfor	rt	622 (50.2)	443 (46.5)	520 (48.8)
I have extreme pain or discomfor		36 (2.9)	33 (3.5)	40 (3.8)
Missing		4 (0.4)	6 (0.6)	8 (0.8)
Anxiety/depression		. (0.1)		0 (0.0)
I am not anxious or depressed		835 (64.4)	610 (64.0)	708 (66.4)
I am moderately anxious or depre	ssed	375 (30.3)	307 (32.2)	332 (31.1)
I am extremely anxious or depres	sed	23 (1.9)	28 (2.9)	19 (1.8)
Missing		4 (0.4)	8 (0.8)	7 (0.7)
Missing		4 (0.4)		



1 2

3 4 5 6	
7 8 9	
10 11 12 13	
14 15 16	
17 18 19	
20 21 22 23	
24 25 26	
27 28 29 30	
30 31 32 33	
34 35 36	
37 38 39 40	
41 42 43	
44 45 46	
47 48 49 50	
51 52 53	
54 55 56 57	
57 58 59 60	

Supplementary Table 3- Proportion of different levels of SF_12 dimensions by study visits (Total n=2537).

SF_12 Dimensions	Baseline (n=1237)	1 month post baseline CT scan (n=953)	12 months after baseline (n=1066)
Consult health $\pi(\theta/)$			
General health, n (%) Excellent	93 (7.5)	85 (8.9)	89 (8.3)
Very good	453 (36.6)	367 (38.5)	392 (36.8)
Good	532 (43.0)	381 (40.0)	450 (42.2)
Fair	138 (11.1)	105 (11.0)	108 (10.1)
Poor	18 (1.5)	12 (1.3)	20 (1.9)
Missing Moderate activities	3 (0.3)	3 (0.3)	7 (0.7)
Yes, limited a lot	97 (7.8)	77 (8.1)	75 (7.0)
Yes, limited a little	310 (25.0)	256 (26.9)	267 (25.0)
No, not limited at all	827 (66.8)	617 (64.7)	714 (67.0)
Missing Climbing several flights of stairs	3 (0.3)	3 (0.3)	10 (0.9)
Yes, limited a lot	191 (15.4)	140 (14.7)	161 (15.1)
Yes, limited a little	551 (44.5)	432 (45.3)	462 (43.3)
No, not limited at all	491 (39.7)	376 (39.5)	436 (40.9)
Missing	4 (0.3)	5 (0.5)	7 (0.7)
Accomplished less than you would like (physically) Yes	335 (27.1)	221 (23.2)	265 (24.9)
No	899 (72.6)	727 (76.3)	795 (74.6)
Missing	3 (0.3)	5 (0.5)	6 (0.6)
Limited in kind of activities			
Yes	299 (24.2)	221 (23.2)	265 (24.9)
No Missing	934 (75.4)	729 (76.5)	795 (74.6) 6 (0.6)
Accomplished less than you would like (emotionally)	4 (0.4)	3 (0.5)	0 (0.0)
Yes	251 (20.3)	212 (22.2)	222 (20.8)
No	982 (79.3)	735 (77.1)	833 (78.1)
Missing Did not do activities as carefully as usual	4 (0.4)	6 (0.6)	11 (1.0)
Yes	215 (17.4)	181 (19.0)	181 (17.0)
No	1018 (82.2)	764 (80.2)	875 (82.1)
Missing	4 (0.4)	8 (0.8)	10 (0.9)
Pain interferes with normal work			
Not at all	596 (48.1)	479 (50.3)	515 (48.3)
A little bit Moderately	312 (25.2) 194 (15.7)	243 (25.5) 138 (14.5)	288 (27.0) 142 (13.3)
Quite a bit	109 (8.8)	77 (8.1)	98 (9.2)
Extremely	20 (1.6)	13 (1.4)	18 (1.7)
Missing	6 (0.5)	3 (0.3)	5 (0.5)
Felt calm and peaceful	97 (7.0)	72 (7.7)	94 (7.0)
All of the time Most of the time	87 (7.0) 630 (50.9)	73 (7.7) 460 (48.3)	84 (7.9) 527 (49.4)
A good bit of the time	184 (14.9)	163 (17.1)	176 (16.5)
Some of the time	214 (17.3)	171 (17.9)	164 (15.4)
A little of the time	96 (7.8)	70 (7.3)	88 (8.3)
None of the time Missing	23 (1.9)	11 (1.2)	18 (1.7)
Missing Have a lot of energy	3 (0.3)	5 (0.5)	9 (0.8)
All of the time	36 (2.9)	36 (3.8)	41 (3.8)
Most of the time	416 (33.6)	317 (33.3)	375 (35.2)
A good bit of the time	263 (21.2)	206 (21.6)	213 (20.0)
Some of the time	322 (26.0)	240 (25.2)	249 (23.4)
A little of the time None of the time	156 (12.6) 41 (3.3)	116 (12.2) 34 (3.6)	145 (13.6) 34 (3.2)
Missing	3 (0.3)	4 (0.4)	9 (0.8)
Felt downhearted and blue			
All of the time	4(0.3)	5 (0.5)	4 (0.4)
Most of the time A good bit of the time	37 (3.0) 79 (6.4)	37 (3.9) 51 (5.4)	34 (3.2) 76 (7.1)
Some of the time	273 (22.1)	196 (20.6)	216 (20.3)
A little of the time	480 (38.8)	399 (41.9)	414 (38.8)
None of the time	361 (29.2)	261 (27.4)	312 (29.3)
Missing	3 (0.3)	4 (0.4)	10 (0.9)
Health interferes/social activities All of the time	8 (0.6)	10 (1.0)	16 (1.5)
Most of the time	63 (5.1)	42 (4.4)	54 (5.1)
Some of the time	203 (16.4)	150 (15.7)	169 (15.9)
Some of the time		100 (10 1)	
A little of the time None of the time	238 (19.2) 722 (58.3)	182 (19.1) 565 (59.3)	200 (18.8) 617 (57.9)

Supplementary Table 4- Proportion of different levels of State anxiety dimensions by study visits (Total n=2537).

6 State			Baseline (n=1237)				1 mont	h post baseline (n=953)	CT scan			12 month	s after baseliı	ne (n=1066)	
89 9 Dimensions	Not at all	Somewhat	Moderately so	Very much so	Missing	Not at all	Somewhat	Moderately so	Very much so	Missing	Not at all	Somewhat	Moderately so	Very much so	Missin
1 If feel calm	17 (1.4)	167 (13.5)	407 (32.9)	643 (51.9)	3 (0.3)	31 (3.3)	136 (14.3)	338 (35.5)	442 (46.4)	6 (0.6)	18 (1.7)	131 (12.3)	393 (36.9)	516 (48.4)	8 (0.8)
1 / feel secure	16 (1.3)	106 (8.6)	304 (24.6)	808 (65.3)	3 (0.3)	21 (2.2)	115 (12.1)	283 (29.7)	528 (55.4)	6 (0.6)	24 (2.3)	83 (7.8)	330 (31.0)	621 (58.3)	8 (0.8)
J feel tense	685 (55.3)	319 (25.8)	192 (15.5)	36 (2.9)	3 (0.3)	465 (48.8)	300 (31.5)	144 (15.1)	39 (4.1)	5 (0.5)	562 (52.7)	282 (26.5)	177 (16.6)	35 (3.3)	10 (1.0)
4 feel strained	834 (67.4)	231 (18.7)	131 (10.6)	38 (3.1)	3 (0.3)	543 (57.0)	261 (27.4)	109 (11.4)	35 (3.7)	5 (0.5)	652 (61.2)	240 (22.5)	134 (12.6)	33 (3.1)	7 (0.7)
1 🤄 feel at ease	41 (3.3)	154 (12.4)	361 (29.2)	678 (54.8)	3 (0.3)	45 (4.7)	154 (16.2)	289 (30.3)	460 (48.3)	5 (0.5)	27 (2.5)	170 (15.9)	323 (30.3)	538 (50.5)	8 (0.8)
🗗 feel upset	1003 (81.0)	137 (11.1)	75 (6.1)	19 (1.5)	3 (0.3)	660 (69.3)	182 (19.1)	78 (8.2)	28 (2.9)	5 (0.5)	792 (74.3)	175 (16.4)	75 (7.0)	16 (1.5)	8 (0.8)
7 am presently worrying over possible misfortunes	694 (56.1)	332 (26.8)	156 (12.6)	52 (4.2)	3 (0.3)	480 (50.4)	295 (31.0)	121 (12.7)	52 (5.5)	5 (0.5)	555 (52.1)	339 (31.8)	115 (10.8)	49 (4.6)	8 (0.8)
d feel satisfied	36 (2.9)	193 (15.6)	469 (37.9)	536 (43.3)	3 (0.3)	47 (4.9)	167 (17.5)	324 (34.0)	410 (43.0)	5 (0.5)	33 (3.1)	192 (18.0)	378 (35.5)	456 (42.8)	7 (0.7)
d feel frightened	1008 (81.4)	149 (12.0)	56 (4.5)	21 (1.7)	3 (0.3)	718 (75.3)	150 (15.7)	59 (6.2)	21 (2.2)	5 (0.5)	846 (79.4)	148 (13.9)	53 (5.0)	11 (1.0)	8 (0.8)
I feel comfortable	30 (2.4)	133 (10.7)	352 (28.4)	719 (58.1)	3 (0.3)	31 (3.3)	135 (14.2)	291 (30.5)	490 (51.4)	6 (0.6)	23 (2.2)	142 (13.3)	333 (31.2)	561 (52.6)	7 (0.7)
J feel self-confident	36 (2.9)	127 (10.3)	439 (35.5)	632 (51.1)	3 (0.3)	38 (4.0)	106 (11.1)	359 (37.7)	445 (46.7)	5 (0.5)	24 (2.3)	127 (11.9)	394 (37.0)	514 (48.2)	7 (0.7)
J feel nervous	780 (63.0)	308 (24.9)	117 (9.5)	29 (2.3)	3 (0.3)	559 (58.7)	255 (26.8)	99 (10.4)	35 (3.7)	5 (0.5)	662 (62.1)	261 (24.5)	114 (10.7)	22 (2.1)22	2 7 (0.7)
↓ am jittery	968 (78.2)	174 (14.1)	73 (5.9)	18 (1.5)	4 (0.4)	692 (72.6)	152 (15.9)	77 (8.1)	27 (2.8)	5 (0.5)	811 (76.1)	155 (14.5)	77 (7.2)	15 (1.4)	8 (0.8)
d feel indecisive	846 (68.3)	269 (21.7)	97 (7.8)	22 (1.8)	3 (0.3)	557 (58.4)	246 (25.8)	113 (11.9)	32 (3.4)	5 (0.5)	662 (62.1)	256 (24.0)	100 (9.4)	39 (3.7)	9 (0.9)
am relaxed	48 (3.9)	181 (14.6)	394 (31.8)	611 (49.4)	3 (0.3)	52 (5.5)	173 (18.2)	313 (32.8)	409 (42.9)	6 (0.6)	30 (2.8)	172 (16.1)	377 (35.4)	480 (45.0)	7 (0.7)
J feel content	48 (3.9)	161 (13.0)	436 (35.2)	589 (47.6)	3 (0.3)	52 (5.5)	147 (15.4)	339 (35.6)	410 (43.0)	5 (0.5)	37 (3.5)	151 (14.2)	408 (38.3)	463 (43.4)	7 (0.7)
d am worried	651 (52.6)	390 (31.5)	146 (11.8)	47 (3.8)	3 (0.3)	423 (44.4)	333 (34.9)	134 (14.1)	58 (6.1)	5 (0.5)	518 (48.6)	361 (33.9)	129 (12.1)	51 (4.8)	7 (0.7)
d feel confused	1075 (86.8)	112 (9.0)	32 (2.6)	12 (1.0)	6 (0.5)	755 (79.2)	135 (14.2)	40 (4.2)	18 (1.9)	5 (0.5)	887 (83.2)	99 (9.3)	50 (4.7)	20 (1.9)	10 (1.0)
3d feel steady	43 (3.5)	141 (11.4)	327 (26.4)	720 (58.2)	6 (0.5)	43 (4.5)	126 (13.2)	272 (28.5)	507 (53.2)	5 (0.5)	41 (3.8)	120 (11.3)	316 (29.6)	581 (54.5)	8 (0.8)
a 1 feel pleasant	25 (2.0)	118 (9.5)	416 (33.6)	672 (54.3)	6 (0.5)	30 (3.1)	117 (12.3)	319 (33.5)	482 (50.6)	5 (0.5)	25 (2.3)	115 (10.8)	365 (34.2)	552 (51.8)	9 (0.9)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 45 of 46

PAGE		Item No	Recommendation
4	Title and abstract	1	(<i>a</i>) Indicate the study's design with a commonly used term in the title or th abstract
4	-		(b) Provide in the abstract an informative and balanced summary of what
			was done and what was found
	Introduction		
6	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
7	Objectives	3	State specific objectives, including any prespecified hypotheses
	Methods		
8	Study design	4	Present key elements of study design early in the paper
8	Setting	5	Describe the setting, locations, and relevant dates, including periods of
-	6		recruitment, exposure, follow-up, and data collection
8	Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of
	<u>I</u> I I I I		participants. Describe methods of follow-up
n/a	-		(b) For matched studies, give matching criteria and number of exposed and
			unexposed
8-9	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders,
			and effect modifiers. Give diagnostic criteria, if applicable
9	Data sources/	8*	For each variable of interest, give sources of data and details of methods of
	measurement		assessment (measurement). Describe comparability of assessment methods
			if there is more than one group
n.a.	Bias	9	Describe any efforts to address potential sources of bias
11	Study size	10	Explain how the study size was arrived at
10	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If
			applicable, describe which groupings were chosen and why
10	Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for confounding
10	-		(b) Describe any methods used to examine subgroups and interactions
10	-		(c) Explain how missing data were addressed
10	-		(d) If applicable, explain how loss to follow-up was addressed
n/a			(e) Describe any sensitivity analyses
	Results		
12	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers
			potentially eligible, examined for eligibility, confirmed eligible, included i
			the study, completing follow-up, and analysed
n.a.	-		(b) Give reasons for non-participation at each stage
FIG 1	-		(c) Consider use of a flow diagram
12	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical,
	-		social) and information on exposures and potential confounders
14	-		(b) Indicate number of participants with missing data for each variable of
	_		interest
n.a.			(c) Summarise follow-up time (eg, average and total amount)
14-17	Outcome data	15*	Report numbers of outcome events or summary measures over time
14-17	Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted
			estimates and their precision (eg, 95% confidence interval). Make clear

			which confounders were adjusted for and why they were included
n.a.			(b) Report category boundaries when continuous variables were categorized
14, 16			(<i>c</i>) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Suppl	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
	Discussion		
18	Key results	18	Summarise key results with reference to study objectives
20	Limitations	19	Discuss limitations of the study, taking into account sources of potential
			bias or imprecision. Discuss both direction and magnitude of any potential
			bias
21-22	Interpretation	20	Give a cautious overall interpretation of results considering objectives,
			limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
22	Generalisability	21	Discuss the generalisability (external validity) of the study results
	Other information	~	
23	Funding	22	Give the source of funding and the role of the funders for the present study
			and, if applicable, for the original study on which the present article is
			based
		~	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Cohort

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-024719.R1
Article Type:	Research
Date Submitted by the Author:	19-Oct-2018
Complete List of Authors:	Taghizadeh, Niloofar; University of Calgary, Medicine Tremblay, Alain; University of Calgary, Medicine Cressman, Sonya; The British Columbia Cancer Agency, Peacock, Stuart; Canadian Centre for Applied Research in Cancer Control, McWilliams, Annette; Fionna Stanley Hospital and University of Western Australia MacEachern, Paul; University of Calgary, Medicine Johnston, Michael; 4. Beatrice Hunter Cancer Research Institute and Dalhousie University Goffin, John; The Juravinski Cancer Centre and McMaster University Goss, Glen ; The Ottawa Hospital Cancer Center Nicholas, Garth ; The Ottawa Hospital Cancer Center Martel, Simon; Centre de recherche, Institut universitaire de cardiologie et de pneumologie de Québec, Laberge, Francis; Centre de recherche, Institut universitaire de cardiologie et de pneumologie de Québec Bhatia, Rick; Memorial University Liu, Geoffrey; University Health Network and Princess Margaret Cancer Centre Schmidt, Heidi; University of British Columbia, Faculty of Medicine- Respiratory Division Tsao, Ming-Sound; University of Toronto Department of Laboratory Medicine and Pathobiology, Tammemagi, Martin; Brock University, Community Health Sciences Lam, Stephen; University of British Columbia, Faculty of Medicine- Respiratory Division
Primary Subject Heading :	Oncology
Secondary Subject Heading:	Public health, Radiology and imaging, Respiratory medicine, Smoking and tobacco
Keywords:	Lung cancer, Health-related quality of life, low-dose chest CT, screening early detection

Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Cohort

Niloofar Taghizadeh¹, Alain Tremblay¹, Sonya Cressman², Stuart Peacock², Annette M. McWilliams³, Paul MacEachern¹, Michael R. Johnston⁴, John Goffin⁵, Glen Goss⁶, Garth Nicholas⁶, Simon Martel⁷, Francis Laberge⁷, Rick Bhatia⁸, Geoffrey Liu⁹, Heidi Schmidt⁹, Sukhinder Atkar-Khattra², Ming-Sound Tsao⁹, Martin C. Tammemagi¹⁰, Stephen C. Lam², for the Pan-Canadian Early Lung Cancer Study Group.

Corresponding Author: Alain Tremblay MDCM, 3300 Hospital Drive NW, Calgary, AB, Canada T2N4N1. Phone 403-210-3866, fax 403-944-1577. ORCID 0000-0002-0025-7426 Email: atrembla@ucalgary.ca

Institutions:

- 1. University of Calgary, Calgary, AB, Canada.
- 2. The British Columbia Cancer Agency, Vancouver, BC, Canada.
- 3. Fionna Stanley Hospital and University of Western Australia, Perth, WA, Australia.
- 4. Beatrice Hunter Cancer Research Institute and Dalhousie University, Halifax, NS, Canada.
- 5. The Juravinski Cancer Centre and McMaster University, Hamilton, ON, Canada.
- 6. The Ottawa Hospital Cancer Center, Ottawa, ON, Canada.
- 7. Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, QC, Canada.
- 8. Memorial University, St-John's NF, Canada
- 9. University Health Network and Princess Margaret Cancer Centre, Toronto, Ontario, Canada.
 - 10. Brock University, St. Catharines, ON, Canada.

22 Word Count: 3509

 Abbreviation list AFB: Autofluorescence bronchoscopy GGO: Ground-glass opacity HRQoL: Health-related quality of life LDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SF: Incidental findings STAI: State Trait Anxiety Inventory 	1	
24 25 AFB: Autofluorescence bronchoscopy 26 GGO: Ground-glass opacity 27 HRQoL: Health-related quality of life 278 LDCT: Low-dose computed tomography 289 MCID: Minimal Clinically Important Difference 280 NLST: The National Lung Screening Trial 281 NNH: Number-needed-to-harm 283 SF-12: Physical and Mental Component Scales 284 STAI: State Trait Anxiety Inventory	2	
24 25 AFB: Autofluorescence bronchoscopy 26 GGO: Ground-glass opacity 27 HRQoL: Health-related quality of life 278 LDCT: Low-dose computed tomography 289 MCID: Minimal Clinically Important Difference 280 NLST: The National Lung Screening Trial 281 NNH: Number-needed-to-harm 283 SF-12: Physical and Mental Component Scales 284 STAI: State Trait Anxiety Inventory	³ 23	Abbreviation list
6 AFB: Autofluorescence bronchoscopy 726 GGO: Ground-glass opacity 727 HRQoL: Health-related quality of life 728 LDCT: Low-dose computed tomography 729 MCID: Minimal Clinically Important Difference 730 NLST: The National Lung Screening Trial 731 NNH: Number-needed-to-harm 732 SF-12: Physical and Mental Component Scales 733 SIFs: Incidental findings 734 STAI: State Trait Anxiety Inventory	4	
724 125 AFB: Autofluorescence bronchoscopy 136 GGO: Ground-glass opacity 137 HRQoL: Health-related quality of life 138 LDCT: Low-dose computed tomography 139 MCID: Minimal Clinically Important Difference 139 NLST: The National Lung Screening Trial 139 NNH: Number-needed-to-harm 131 NNH: Number-needed-to-harm 133 SIFs: Incidental findings 139 STAI: State Trait Anxiety Inventory 131 STAI: State Trait Anxiety Inventory		
 AFB: Autofluorescence bronchoscopy GGO: Ground-glass opacity HRQoL: Health-related quality of life LDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory 	7 24	
9925 AFB: Autofluorescence bronchoscopy 111 GGO: Ground-glass opacity 112 HRQoL: Health-related quality of life 112 LDCT: Low-dose computed tomography 112 MCID: Minimal Clinically Important Difference 113 NNH: Number-needed-to-harm 114 SF-12: Physical and Mental Component Scales 115 SIFs: Incidental findings 114 STAI: State Trait Anxiety Inventory		
 GGO: Ground-glass opacity HRQoL: Health-related quality of life LDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings SIFs: Incidental findings STAI: State Trait Anxiety Inventory 		
 GGO: Ground-glass opacity HRQoL: Health-related quality of life LDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings SIFs: Incidental findings STAI: State Trait Anxiety Inventory 	10 ₉₅	AFB. Autofluorescence bronchoscopy
 GGO: Ground-glass opacity HRQoL: Health-related quality of life LDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings SIFs: Incidental findings STAI: State Trait Anxiety Inventory 	11	
 HRQoL: Health-related quality of life LDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory STAI: State Trait Anxiety Inventory 		
 HRQoL: Health-related quality of life LDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory STAI: State Trait Anxiety Inventory 	13	GGO: Ground-glass onacity
 HRQoL: Health-related quality of life LDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory STAI: State Trait Anxiety Inventory 		000. Oround glass opacity
127 HRQoL: Health-related quality of life 129 LDCT: Low-dose computed tomography 233 MCID: Minimal Clinically Important Difference 256 NLST: The National Lung Screening Trial 278 NNH: Number-needed-to-harm 233 SF-12: Physical and Mental Component Scales 373 SIFs: Incidental findings 383 SIFs: Incidental findings 384 STAI: State Trait Anxiety Inventory 384 STAI: State Trait Anxiety Inventory		
LDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings SIFs: Incidental findings STAI: State Trait Anxiety Inventory		UPOol : Health related quality of life
 IDCT: Low-dose computed tomography MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory STAI: State Trait Anxiety Inventory 		TIRQUE. Treattil-related quality of the
MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings SIFs: Incidental findings STAI: State Trait Anxiety Inventory	19	
MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings SIFs: Incidental findings STAI: State Trait Anxiety Inventory	20	I DCT. I any dage commuted tome granter
 MCID: Minimal Clinically Important Difference NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory STAI: State Trait Anxiety Inventory 		LDC1: Low-dose computed tomography
249 MCID: Minimal Clinically Important Difference 26 NLST: The National Lung Screening Trial 29 NNH: Number-needed-to-harm 33 SF-12: Physical and Mental Component Scales 36 Silfs: Incidental findings 39 STAI: State Trait Anxiety Inventory 41 State Trait Anxiety Inventory 43 Silfs: State Trait Anxiety Inventory 33 Silfs: State Trait Anxiety Inventory 33 Silfs: State Trait Anxiety Inventory 34 Silfs: State Trait Anxiety Inventory 35 Silfs: State Trait Anxiety Inventory 36 Silfs:		
 NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory STAI: State Trait Anxiety Inventory 		MCID: Minimal Clinically Investors Difference
 NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory STAI: State Trait Anxiety Inventory Attack <l< th=""><th></th><th>MCID: Minimal Clinically Important Difference</th></l<>		MCID: Minimal Clinically Important Difference
 NLST: The National Lung Screening Trial NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory STAI: State Trait Anxiety Inventory Attack <l< th=""><th></th><th></th></l<>		
 NNH: Number-needed-to-harm SF-12: Physical and Mental Component Scales SIFs: Incidental findings STAI: State Trait Anxiety Inventory STAI: State Trait Anxiety Inventory 	27	
3/ SIFs: Incidental findings 39 40 40 41,4 41,4 STAI: State Trait Anxiety Inventory 43 44 4335 46 46 47 48 49 50 51 52 53 54 55 56 2 57 2 58 2		
3/ SIFs: Incidental findings 39 40 40 41,4 41,4 STAI: State Trait Anxiety Inventory 43 44 4335 46 46 47 48 49 50 51 52 53 54 55 56 2 57 2 58 2		
3/ SIFs: Incidental findings 39 40 40 41,4 41,4 STAI: State Trait Anxiety Inventory 43 44 4335 46 46 47 48 49 50 51 52 53 54 55 56 2 57 2 58 2		
3/ SIFs: Incidental findings 39 40 40 41,4 41,4 STAI: State Trait Anxiety Inventory 43 44 4335 46 46 47 48 49 50 51 52 53 54 55 56 2 57 2 58 2		NNH: Number-needed-to-harm
3/ SIFs: Incidental findings 39 40 40 41,4 41,4 STAI: State Trait Anxiety Inventory 43 44 4335 46 46 47 48 49 50 51 52 53 54 55 56 2 57 2 58 2		
3/ SIFs: Incidental findings 39 40 40 41,4 41,4 STAI: State Trait Anxiety Inventory 43 44 4335 46 46 47 48 49 50 51 52 53 54 55 56 2 57 2 58 2		
3/ SIFs: Incidental findings 39 40 40 41,4 41,4 STAI: State Trait Anxiety Inventory 43 44 4335 46 46 47 48 49 50 51 52 53 54 55 56 2 57 2 58 2	3532	SF-12: Physical and Mental Component Scales
3/ SIFs: Incidental findings 39 40 40 41,4 41,4 STAI: State Trait Anxiety Inventory 43 44 4335 46 46 47 48 49 50 51 52 53 54 55 56 2 57 2 58 2		
 39 40 4134 STAI: State Trait Anxiety Inventory 43 44 4355 46 47 48 49 50 51 52 53 54 55 56 57 58 2 59 		
40 41 42 43 44 4335 46 47 48 49 50 51 52 53 54 55 56 57 58 59 2		
43 44 4335 46 47 48 49 50 51 52 53 53 54 55 56 57 58 59		
43 44 4335 46 47 48 49 50 51 52 53 53 54 55 56 57 58 59		
43 44 4335 46 47 48 49 50 51 52 53 54 55 56 57 58 59	42 ³⁴	STAI: State Trait Anxiety Inventory
435 46 47 48 49 50 51 52 53 54 55 56 57 58 2 59	43	
46 47 48 49 50 51 52 53 54 55 56 57 58 58 2 59		
47 48 49 50 51 52 53 54 55 56 57 58 58 2 59		
48 49 50 51 52 53 54 55 56 57 58 58 59		
49 50 51 52 53 54 55 56 57 58 58 2 59		
50 51 52 53 54 55 56 57 58 58 2 59		
51 52 53 54 55 56 57 58 58 2 59		
53 54 55 56 57 58 2 59		
54 55 56 57 58 2 59		
55 56 57 58 2 59		
56 57 58 2 59		
57 58 2 59		
58 2 59 2		
59		2
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Objectives: The impact of lung cancer screening with low-dose chest CT (LDCT) on participants' anxiety levels and health-related quality of life (HRQoL) is an important consideration in the implementation of such programs. We aimed to describe changes in anxiety and HRQoL in a high-risk Canadian cohort undergoing LDCT lung cancer screening.

Methods: 2,537 subjects who had 2% or greater lung cancer risk over 6 years using a risk prediction tool were recruited from 8 centers across Canada in the Pan-Canadian Early Detection of Lung Cancer Study (2008-2010). We compared HRQoL and anxiety levels before and after screening of 1,237 participants with LDCT, (excluding a subset of 1,300 participants who also underwent autofluorescence bronchoscopy screening), as well as after investigations performed because of a positive screening examination. The 12-item short-form Physical and Mental Component Scales (SF-12), EQ-5D-3L scores, and State Trait Anxiety Inventory (STAI) - State anxiety were used at each assessment.

Results: Overall, there were no clinically significant differences in HRQoL outcomes between baseline and each of the survey time points following initial screening. No mean change in anxiety in the overall cohort was noted following baseline LDCT, but more participants had clinically significant increase in anxiety vs. decrease after baseline screening [Increase > Minimal Clinically Important Difference (MCID) (n=180) vs. decrease >MCID (n=50), p<0.001]. This finding persisted but to a lesser degree at the 12-month time point [increase >MCID (n=146) vs. decrease >MCID (n=87), p<0.001].

 Conclusions: CT Screening for Lung Cancer has no major overall impact on HRQoL among participants, although a minority of participants (number-needed-to-harm = 7 after baseline screening and 18 at one year) demonstrated clinically significant increased anxiety levels. Clinical Trial Desistantiant Clinical Trials new New NCT007516(0); UBL summe clinical trials new clinical trials are clinical trials and the second state of th
participants, although a minority of participants (number-needed-to-harm = 7 after baseline screening and 18 at one year) demonstrated clinically significant increased anxiety levels. and 18 at one year) demonstrated clinically significant increased anxiety levels.
 and 18 at one year) demonstrated clinically significant increased anxiety levels. and 18 at one year) demonstrated clinically significant increased anxiety levels. 10 1158 12 13 14
 and 18 at one year) demonstrated clinically significant increased anxiety levels. and 18 at one year) demonstrated clinically significant increased anxiety levels. and 18 at one year) demonstrated clinically significant increased anxiety levels. and 18 at one year) demonstrated clinically significant increased anxiety levels. and 18 at one year) demonstrated clinically significant increased anxiety levels. and 18 at one year) demonstrated clinically significant increased anxiety levels. and 18 at one year) demonstrated clinically significant increased anxiety levels. and 18 at one year) demonstrated clinically significant increased anxiety levels. b at a strategies of the strate
11 ₅₈ 12 13 14
13 14
14
Clinical Trial Desistantians Clinical Trials and No. NOT00751((0, UDL)
159 Clinical Trial Registration: ClinicalTrials.gov; No.: NCT00751660; URL: www.clinicaltrials.gov.
16 17
¹⁸ 60 19
20 21
2261 Keywords: Health-related quality of life, lung cancer, low-dose chest CT, screening, early detection
2462 cohort study 25 26 27 38 28 29 30 31 31 32 33 34 35 36 37 38
26
²⁷ ₂₈ 63
28 29
30
31
32 33
34
35 36
37
38
38 39 40 41 42 43
41
42
43 44
45
46
47 48
49
50
51 52
53
54
55 56
57
58 4
59 60 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

³ 64	Strengths and Limitation of this Study:
4	

⁶ 65

⁸ 66

*2*73

- This study is the first to describe the psychological and quality of life impacts of lung cancer screening on *discrete* individuals undergoing low-dose CT examinations.
- This allows the calculation of number-needed-to-harm estimates based on the minimal clinically significant • difference of each instrument rather than mean group changes, important in the informed decision-making process with individuals considering this intervention.
 - Our cohort was drawn from a multi-center study with high follow-up rates using a participant's baseline status to detect any changes post-screening.
 - Limitations include the lack of an unscreened control group and the relative homogeneity of our participants (Canadian, Caucasian).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

4 5 6

8

INTRODUCTION

7 76 Lung cancer is the leading cause of cancer death in North America and around the world,[1]. Early 9 77 detection and treatment of lung cancer through screening is a promising strategy to reduce lung cancer 10 11 78 12 mortality,[2]. The largest trial performed to date, the National Lung Screening Trial (NLST), 13 1479 demonstrated that low-dose computed tomography (LDCT) screening in high risk individuals (i.e., ever 15 smokers aged 55 to 74 years, \geq 30 pack-years (number of cigarettes per day / 20 x number of years of 1680 17 ¹⁸81 smoking) and <15 years since quitting) of smoking significantly reduced lung cancer and overall 19 20 21⁸² mortality,[3]. American and Canadian preventative health care agencies have since published 22 recommendations in favor of LDCT lung cancer screening, [3,4]. However, no screening intervention is 2383 24 2584 without potential harm, including adverse psychological impact of the screening intervention, screening 26 27 28 28 results, or subsequent investigations in most participants who will not be found to have cancer. Potential 29 detriments of lung cancer screening include anxiety, and distress from the evaluation of both CT detected 3086 31 3287 false positive and over-diagnosed cancers. A small proportion of the screen-detected tumors would never 33 34 35 lead to clinical symptoms, but these over-diagnosed lung cancers are frequently treated, with associated 36 37⁸⁹ risks of adverse effects, [5,6]. Moreover, studies have shown that CT lung screening has a high rate of 38 significant lung cancer-unrelated incidental findings (SIFs),[7]. These SIFs may require additional 3990 40 4¹91 42 investigations and therefore can be associated with adverse psychological impact on participants in a 43 44</sub>92 screening program,[6]. 45

4793 A recent systematic review on the psychological burden of LDCT revealed that LDCT screening may ⁴⁹94 be associated with a short-term psychological burden in participants, [8]. Studies to date have explored 52⁹⁵ mean changes in groups of individuals rather than rates of clinically significant changes in individuals 5496 screened. Effective policy decisions regarding the implementation of lung cancer screening and

46

48

50 51

53

informed decision making by individuals requires reliable evidence on its potential impacts on Health
Related Quality of Life (HRQoL) and psychological wellbeing of individual participants,[9]. Therefore,
this study aimed to evaluate the impact of screening modalities on the quality of life and anxiety of
participants in the Pan-Canadian Early Detection of Lung Cancer Study.

to beer terrier only

³102 **METHODS**

Study design and population

The Pan-Canadian Early Detection of Lung Cancer Study, which has been described in detail previously,[10,11], enrolled current or former smokers aged between 50-75 years and with a 2% or greater lung cancer risk over 6 years using a risk-prediction model developed using Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data,[12]. Participants were recruited in 8 centers across Canada (Calgary, Halifax, Hamilton, Laval, Ottawa, St-John's, Toronto and Vancouver) from September 2008 to December 2010 with each centers' institutional review board approving the study (e-Appendix 1). Signed informed consent was obtained from each participant.

All participants were offered baseline LDCT with repeat screening at year 1 and 4 in addition to LDCT scans as appropriate for nodule follow-up, with the first half of the recruited subjects to receive autofluorescence bronchoscopy (AFB) as an additional screening modality,[13]. However, since AFB does not appear effective in the screening environment,[13], and to avoid the potential confounding impact of AFB on HRQL, participants in the AFB arm of the study are excluded from the current analysis.

LDCT scan follow-up protocol were determined by the maximum long axis diameter of the largest nodule identified. Participants with any semi-solid or solid nodule 5 to 10 mm, or ground-glass opacity (GGO) 8-10 mm were to receive an additional LDCT at 3 months, with larger lesion being referred for clinical consultation. Any participant requiring repeat LDCT or investigation for a lung lesion other than a planned 12-month follow-up examination were considered to have a positive screening exam for the purpose of this analysis (figure 1). Participants were informed of the various possible findings which

may be found on CT examinations and general protocols for investigations at the time of study consent.
Individualized results letters with description of findings appropriate for a non-medical reader were developed by each study site.

Health-Related Quality of life (HRQoL), and anxiety

The 12-item short-form (SF-12) Physical and Mental Component Scales (PCS, and MCS, respectively),[14] and the EuroQoL questionnaire [EQ-5D-3L (Three-level version of EQ-5D)] were used to determine the participants' HRQoL at each assessment. The test–retest reliability coefficient is reported to be 0.89 for the PCS and 0.76 for the MCS. The EQ-5D-3L consists of a preference-based index score and a visual analogue scale (VAS); the index scores were derived from the current Canadian tariff,[15], (a maximum (best) value of 1 (for health state 11111) and a minimum value of -0.34 (for 33333)). The VAS is a Likert scale asking participants to draw a line to their current health status on a visual scale ranging between 0 and 100. Scores on the SF-12 are standardized (i.e., mean = 50 and SD = 10), with a higher score indicating better HROoL.

To evaluate potential anxiety induced by the results of the screening tests, we used the Spielberger State
Trait Anxiety Inventory Form Y (STAI),[16]. Additional methodology details are provided in the online
supplement.

The questionnaires were administered in person at the time of study enrolment (baseline), then by phone within 1 month after the CT results were received by the participants, 1 month after any additional follow-up CT scan or other testing following a positive screen (post investigations) and prior to the 1st annual repeat LDCT (12 months post baseline) (figure 1).

7144

1447

³143 **Statistical analyses**

Descriptive analyses of the participants' characteristics and screening outcome were performed. We calculated summary scores of outcome measures for participants in each category at each of the study time points (at baseline, 1 month post baseline CT scan, 12 months after baseline, and post investigations). In addition, the above scores were compared separately in the subset of participants with a positive screening intervention.

149 70 To compare overall differences in HRQoL and State-anxiety scores between baseline and each of the survey time points, Generalized Linear Mixed Models were used to take into account the clustering of <u>2</u>450 24/51 data within the 8 study sites, the repeated measurement of each individual, the non-normally ²⁶ 152 distributed/skewed outcomes, and any missing data. The estimated margin of means with adjustment for 2153 multiple comparisons (Bonferroni correction) was calculated to contrast baseline versus each of the study time points. In these estimations, margins involving empty cells were treated as not estimable. 34 When significant long-term differences were noted in our mixed model, we further explored the factor 156 36 association with the observed changes using a multivariate regression model with adjustment for scan results, age, gender, self-reported race, smoking status, pack-years, alcohol consumption, education, family history of any cancer, participants' concern about getting lung cancer at baseline, and for the 459 43 clustering of data within 8 study sites.

We further compared the proportion of individuals with improvement vs. deterioration greater than the Minimal Clinically Important Difference (MCID) for each instrument. MCIDs for outcome measures 162 51 were selected based on previously published results as follows: EQ visual analog scale (VAS)=8,[17], EQ-5D-3L index values=0.05,[18], PCS=8.1,[19], MCS=4.7,[14], STAI-State Anxiety=10,[20]. The

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

comparisons between these two proportions were performed using Z-test and if significant, the excess number of cases with improvement vs. worsening scores were calculated as a percentage of cases with available data. When significant differences were noted, a number-needed-to-harm (NNH) or numberneeded-to-treat (NNT) calculation was applied as appropriate (total number of case/excess cases with worsened or improved score).

Two-sided p-values < 0.05 were considered as statistically significant. All analyses were performed using SPSS, version 24 (IBM Corp., Armonk, N.Y., USA) or STATA version 14 (StataCorp, College Station, Texas). Sample size was determined by other primary study factors relating to the screening intervention and not the current analysis.

Patient and Public Involvement

Patient and public involvement in the design of the research was included through the main funding agencies collaborating on the project. This includes the Terry Fox Research Institute, the research arm of The Terry Fox Foundation. In addition, public input was obtained through involvement of the Canadian Partnership Against Cancer, an independent organization funded by the federal government to accelerate action on cancer control for all Canadians. Patients were not specifically involved in the recruitment and conduct of the study and no specific plan to disseminate research findings to participants has been made.

³182 **RESULTS**

A83 Participant characteristics

Two thousand five hundred and thirty-seven participants were enrolled in the Pan-Can study, and 1,237 underwent LDCT alone (without AFB). The mean (SD) age of these participants was 62.9 (6.1) at baseline. Males 558 (45.1 %), Caucasian 1201 (97.1 %), current smokers 768 (62.1 %), and regular alcohol drinkers 961 (77.7 %) comprised the largest groups of participants. The median (IQR) pack-years of smokers was 51.3 (21.6) and mean (SD) duration of smoking was 43.9 (6.1) years. A family history of lung cancer was present in 392 participants (31.7%), (table 1). Median (IQR) lung cancer risk score was 3.5% (2.9) over 6 years. Positive baseline LDCT examinations were noted in 279 (22.6%) participants of which 35 (2.8%) led to a diagnosis of lung cancer.

Table 1-Baseline characteristics of Pan-Canadian Early Detection of Lung Cancer Study participants.

Characteristics	All Enrolled (n=1237)
Age, mean (SD)	62.9 (6.1)
Gender (males), n (%)	558 (45.1)
Race *, n (%)	
Caucasian	1201 (97.1)
Asian	15 (1.2)
Black or African Canadian	7 (0.6)
Aboriginal	4 (0.3)
Pacific Islander	0 (0.0)
Other	10 (0.8)
Education, n (%)	
8 th grade or less	32 (2.3)
9 th to 12 th grade	153 (12.4)

1
2
3
4
5
6
-
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
31694
37
3495
31996
A00 -
4097 41 42 42
41 198
4200
43
4499 45
45
46
46 47
4/
4300
49
50
⁵²¹ 01
52 52
53
54
55
56
57
58
59

	1
High school graduate	337 (27.2)
Bachelor's degree	107 (8.7)
Technical/Vocational/School certificate	260 (21.0)
Associate degree/some college	205 (16.6)
Advanced Degree	144 (11.6)
Smoking habits	
Current smokers, n (%)	768 (62.1)
Pack- years, median (IQR, range)	51.3 (21.6, 2.2-230)
Smoking duration (years), mean (SD)	43.9 (6.1)
Alcohol consumption	
Current regular drinkers**, n (%)	961 (77.7)
Family history of lung cancer, n (%)	392 (31.7)
Being worried about getting lung cancer, n (%)	
Rarely or never	267 (21.6)
Sometimes	656 (53.0)
Often	235 (19.0)
All of the time	75 (6.1)
Scan results at baseline, n (%)	
Positive	279 (22.6)
Negative	958 (77.4)
Lung cancer risk score, median (IQR, range)	3.5 (2.9, 2.0-33.5)

* Missing, n (%)=5 (0·2).

**Regular alcohol consumption: having more than one drink per week for a period of 6 months or more. Missing, n=11.

0 Health-related quality of life and anxiety measures

Baseline

Page 15 of 48

BMJ Open

At baseline, participants reported being concerned about getting lung cancer always (6.1 %), often (19.0%) and sometimes (53.0 %). General health problems were reported by 65.0% of respondents on at least one item on the EQ-5D-3L. Average baseline EQ visual analogue scale (VAS), EQ-5D-3L index values, PCS, MCS, and STAI-State Anxiety scores were 76.3, 0.84, 46.1, 51.1, and 30.9, respectively (Table 2).

Baseline screening

No statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or MCS levels were noted following baseline CT screening. In addition, the proportion of individuals experiencing a deterioration vs. improvement greater than the MCID for EQ VAS(figure 2), EQ-5D-3L(figure 3), PCS(figure 4) and MCS(figure 5) were not significantly different. However, the STAI-State Anxiety levels increased in participants following baseline LDCT [change (95% CI): 2.27 (0.57 to 3.96), p-value <0.001] (Table 2). A greater proportion of individuals experiencing a deterioration vs. improvement greater than the MCID of 10 for the STAI - State Anxiety levels was also noted [increase >MCID (n=180) vs. decrease >MCID (n=50), p-value <0.001](figure 6). The excess number of participants with increased vs. decreased anxiety represents 13.8% [(180-50)/937, NNH = 7] of participants with available data. This change remained significant even if only participant with a negative screen were considered [mean baseline STAI 31.2; increase >MCID (n=129) vs. decrease >MCID (n=40), p-value < 0.0001]. Multivariate regression analysis demonstrated female gender and increased baseline concern about getting lung cancer to be associated with increased anxiety following screening (Table 3).

Table 2- HRQoL, and anxiety measures at baseline and at different time-points within the study. Generalized linear mixed model.

	Baseline (n=1,237)	1-month post baseline CT scan Mean, change (95% CI) (n=953)	12-months after baseline CT Mean, change (95% CI) (n=1066)
EQ VAS ¹	76.3	76.8, 0.42 (-1.39 to 2.23)	76.8, 0.22 (-0.88 to 1.32)
EQ-5D-3L index values	0.84	0.84, -0.00 (-0.02 to 0.01)	0.84, -0.00 (-0.01 to 0.01)
SF-12: PCS ²	46.1	46.8, 0.61 (-0.15 to 1.37)	46.4, 0.31 (-0.55 to 1.17)
SF-12: MCS ³	51.1	50.9, -0.26 (-1.04 to 0.52)	51.2, -0.14 (-1.14 to 0.86)
STAI-State Anxiety ⁴	30.9	33.1, 2.27 (0.57 to 3.96) ⁵	31.7, 1.11 (-1.11 to 3.33)

¹EQ Visual Analogue Scale "We would like to know how good or bad your health is today" (100 – best imaginable, 0 – worst imaginable).

21 2229 ² Physical Health Composite Scores (US population mean = 50 ± 10), with higher score corresponding to better state.

³ Mental Health Composite Scores (US population mean = 50 ± -10), with higher score corresponding to better state.

⁴ STAI-State score >39 considered clinically significant symptoms.

231 25

<u>2</u>632

⁵ P-value < 0.05 compared with baseline. Post-estimated marginal means with adjustment for multiple comparison (Bonferroni).

Table 3-Factor associated with changes in anxiety levels from baseline to 1-month post baseline CT scan.

	Changes in anxiety levels (STAI- Beta coefficient (95 % CI)
Positive scan results	-0.70 (-1.91 to 0.51)
Age	-0.09 (-0.18 to 0.01)
Females	1.01 (0.02 to 2.16)*
Current smokers	0.57 (-0.50 to 1.64)
Pack-years	-0.01 (-0.03 to 0.01)
Current alcohol consumption	-0.63 (-1.86 to 0.60)
Family history of any cancer	-1.14 (-2.28 to 0.01)
Participants' concern about getting lung cancer	
All the time	3.79 (0.24 to 7.32)*
Often	1.73 (-0.00 to 3.47)
Sometimes	0.99 (-0.12 to 2.10)

Multivariate regression model with adjustment for scan results, age, gender, race, smoking status, pack-years, alcohol consumption, education, family history of any cancer, participants' concern about getting lung cancer at baseline, and for the clustering of data within 8 study sites. *p<0.05

No statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or STAI - State Anxiety levels were detected in participants at the 12 month interview. The proportion of individuals with deterioration vs. improvement greater than the MCID for the instrument remained significant for the STAI - State anxiety levels [increase >MCID (n=146) vs. decrease >MCID (n=87), p-value <0.0001], representing 5.5% [(146-87)/1066, NNH=18] of participants (figure 6). The proportion of individuals experiencing a deterioration vs. improvement greater than the MCID for EQ VAS(figure 2), EQ-5D-3L(figure 3), PCS(figure 4) and MCS(figure 5) were not significantly different.

Positive screen and investigation

Among participants receiving a positive scan results (n=279), no statistically significant mean changes 54 in EQ VAS, EQ-5D-3L index values, PCS, or MCS were detected following baseline LDCT (Online 255 supplementary Table 1). However, more participants experienced a clinically significant decrease vs. increase in anxiety score [increase >MCID (n= 20) vs. decrease >MCID (n=41), p-value=0.002] representing 8.8% [(41-20)/238, NNT=11] of these participants (figure 7). This decreased anxiety persisted at the 12-month interview [increase >MCID (n=14) vs. decrease >MCID (n=35), pvalue=0.003] representing 8.5% [(35-14)/246, NNT=12] of participants (figure 8). -259

³260 4 Following investigation examinations, no statistically significant mean changes in EQ VAS, EQ-5D-3L 6261 index values, PCS, MCS, or anxiety were detected. Post-investigation changes revealed no statistically 62 significant changes in the proportion of individuals with deterioration vs. improvement greater than the 11 MCID (figure 7). // els of each qu.. 1264 The proportion of different levels of each questionnaires' dimensions by study visits, as well as number of missing values, are shown in the online supplementary Tables 2 to 4. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

DISCUSSION

This study offers detailed information on HRQoL and anxiety following LDCT for lung cancer screening in a Canadian high-risk selected population using validated assessment tools measuring overall HRQoL as well as specific physical, psychological and anxiety scores. Our study found no clinically significant differences in HRQoL outcomes between baseline and each of the survey time points following initial screening in the cohort as a whole. However, more participants experienced a clinically significant increased anxiety (vs. decreased) following baseline LDCT. This finding was more pronounced among females and participants who were concerned about getting lung cancer at baseline. Paradoxically, decreased anxiety was more frequent in the subgroup with positive baseline scan, although the impact of scan results did not reach statistical significance in the multivariate analysis. Over the long-term, no adverse effects on HRQoL were noted but some of the excess in increased anxiety levels persisted.

In line with our findings, analyses of other screening cohorts including NLST,[21] NELSON,[22] PLCO,[23] and UKLS,[24] as well as two recent meta-analyses have demonstrated that lung cancer screening is associated with little to no adverse physical or psychological long-term impact on participants[8,25]. While analysis of the Danish Lung Cancer Screening Trial did show negative consequences at 1 year,[26] and 2 year,[27] follow-up, the degree of change was actually greater in the control (no screening) arm of the trial.

Our finding of decreased anxiety following a positive screen is in contrast with those reported in the UKLS,[24] and NLST trials,[21] which observed a short-term increase in distress levels two weeks or 2 months respectively after a positive result notification of baseline screening. Results from

NELSON,[28] and from the Pittsburgh Lung Screening Study,[29] also reported a short-term lung cancer-specific distress, a poorer quality of life and a higher level of anxiety among participants with indeterminate scan results compared with those with negative results. However, in both studies these negative impacts disappeared over time. The explanation for this finding may relate to the small size of our program and personalized communication process for results in the study. The absolute number of participants with significant changes in this metric was also relatively small, so that this finding should not be over-interpreted.

Similar to our findings, NELSON study reported a worse HRQoL outcomes among females compared to males,[28]. Furthermore, our observation regarding females is also consistent with the results of a study of PLCO participants,[23] that found a poorer MCS outcomes in females compared to males.

In most studies reported to date, statistically significant mean changes in HRQoL-related scores detected in groups of screened individuals have been small and of questionable clinical significance limiting the impact of such findings in clinical decision-making. Conversely, lack of statistically significant changes in population means can mask clinically meaningful changes in individuals. The MCID has been suggested to be a useful benchmark to define the smallest difference in HRQoL that individuals perceive as beneficial or harmful and that mandates a change in management,[30]. Only two previous lung cancer screening trial have reported MCID levels to interpret the changes in HRQoL of participants,[22,24,28]. However, both applied this concept to mean population changes rather than to discrete individual changes. Our study is unique in providing discrete participant data on the proportion of individuals with improvement vs. deterioration greater than the MCID for each assessment tool. This has allowed us to attribute to the intervention excess cases of deterioration vs. improvement given normal expected variations in each individual over time. This can suggest if a true clinically significant impact is present, Page 21 of 48

BMJ Open

and specifying how many individuals are impacted by such a change, in order to calculate a "numberneeded-to-harm" value. With this approach, we found that the proportion of individuals with improvement vs. deterioration greater than the MCID for the STAI was significantly different among all participants with a number needed to harm of 7 in the short term following screening, and 18 at oneyear post screening. Our data adds to an evolving body of evidence which suggests that LDCT screening for lung cancer does not have overall significant negative impacts on the HRQoL of the population screened. However, a minority of individuals do experience small but clinically significant increases in anxiety levels following screening.

The major strengths of our study include the use of a large multicenter sample of eligible participants, and reporting of individual participant data in relation to their MCID using three different and wellestablished instruments for measuring HRQoL and anxiety as well as the risk prediction model used for the recruitment,[31]. Another strength of our study is the longitudinal design with a high follow-up and response rate (see online supplementary tables 2-4), which enabled us to assess short- and long-term outcomes at different time points during screening process with each participant serving as his/her own control. While we enrolled a high risk cohort using a risk prediction model, our participants' baseline HRQoL metrics appeared comparable to those of similarly aged individuals in the general population [Adults aged 55-69, mean EQ VAS: 76,[32]; age 50-59, mean STAI: 32.2(female)/34.5(male),[16]; age 50-69, PCS: 50.9-51.3, MCS: 50.7-50.9,[33]] suggesting that our findings could be generalizable to a broader population of screen-eligible individuals but with lower risk of lung cancer than in our population. Our study is also the first to use the full EQ-5D score in this population, which can be used to calculate quality-adjusted-life-years.

The current study has potential limitations. Our population was made up almost entirely of Caucasians, so that a differential impact of screening on other ethnic communities cannot be determined. Owing to the study design for HROoL assessments, we were unable to address the impacts of incidental findings on HROoL and anxiety of participants. Another potential limitation is that we did not compare our results to an unscreened control group but instead used each participant's baseline scores. As such, other factors unrelated to the screening intervention, such as aging or changes in smoking status, could affect the longitudinal changes (or lack thereof) noted in our study [34]. However, two previous studies with a randomized design and a control group reported the HRQoL results that were comparable to our findings, [14,20]. Another potential limitation is that the EQ-5D-3L is usually associated with a ceiling effect (i.e., scores recording perfect health) [35] and has limited ability to determine small changes in health status compared to the five-level EQ-5D-5L, which might offer improved measure of populationweighted health state utility, [36,37]. In our study, 35 % of participants reported perfect scores on EQ-5D-3L at baseline; suggesting a ceiling effect that was adjusted for with a generalized linear mixed modeling approach,[38]. Moreover, HRQoL in our study was also measured by SF-12, which has been known to demonstrate a smaller ceiling/floor effect compared to EQ-5D-3L,[35]. In our study, no ceiling/floor effect was observed for the SF-12 scores. Finally, the statistical power to detect changes in some participant subgroups such as those with positive screens may be limited because of low number of participants with a positive scan results. Therefore, caution should be used in drawing conclusions.

The complexity of longitudinal analysis of HRQoL and the lack of agreed upon standardized approach compromise the comparison of results between studies,[39]. Even the specific MCID level for each instrument can be debated. Ideally such levels are determined in the specific population of interest, but such information is rarely available. Levels chosen for our analysis were determined prior to any data

BMJ Open

analysis based on best evidence for each instrument. As a confirmatory step, MCIDs selected in this study were found to approximate estimates obtained as half a Standard Deviation (SD) (MID) of HRQol measures in our population (results not shown), an alternative distribution-based approach to MCID determination,[40].

The findings of our study corroborate and expand the current evidence-based information on lung cancer screening decision making by showing that there is a minimal overall psychological impact associated with lung cancer screening. However, certain populations (i.e., females, participants with higher baseline concern about lung cancer) may be at a higher risk of negative psychological impact. This suggests that an improved communication is needed throughout the entire lung cancer screening process, especially for the potentially vulnerable subgroups. Since most positive screens do not result in a lung cancer diagnosis, approaches to better define screening exam findings and reduce false positive rates could be effective in reducing the anxiety burden in this subgroup. Despite the high rate of false positive CT results in lung cancer screening, there is no clear recommendation yet on psychological interventions to help individuals cope with abnormal CT screening results. However, literature on mammography screening has shown that immediate follow-up and consultation can significantly reduce anxieties after receiving abnormal mammograms,[41].

In conclusion, our study demonstrated that CT Screening for Lung Cancer has no major impact on HRQoL among participants overall, but some individuals experience clinically significant increase in anxiety with a number needed to harm of 18 at one year post initial screen. While these impacts may appear minor in view of the robust mortality reduction associated with LDCT screening, ongoing work to further define and minimize these negative aspects of screening is warranted given recommendations for broad screening of at risk populations.

$ 1 2 3 3 74 5 6 7 3 7 5 8 9 \frac{1}{9}76 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 5 $	
56 57 58 59 60	23 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
	. , , , , , , , , , , , , , , , , , , ,

BMJ Open

³₄77 **Author's contributions:**

5	
6 7378 °	NT: led data analysis & data interpretation; prepared the draft manuscript; approved final manuscript;
8 % 79 10	agrees to be accountable for all aspects of the work.
11 380 12	AT: contributed to study conception and design, data acquisition, analysis and interpretation; prepared
13 13 13 15	the draft manuscript; approved final manuscript; agrees to be accountable for all aspects of the work.
15 1 3682 17	SCL: contributed to study conception and design, data acquisition and interpretation; critically
18 383 19	reviewed and approved final manuscript; agrees to be accountable for all aspects of the work.
20 384 21	MCT: contributed to study conception and design, data analysis and interpretation; critically reviewed
22 23885 24	and approved final manuscript; agrees to be accountable for all aspects of the work.
24 2586 26	MST: contributed to study conception and design, data analysis and interpretation; critically reviewed
27 387 28	and approved final manuscript; agrees to be accountable for all aspects of the work.
29 3088	SC: contributed to study conception and design, data analysis and interpretation; critically reviewed
31 33289 33	and approved final manuscript; agrees to be accountable for all aspects of the work.
34 390 35	SAK: contributed to study conception, design and data acquisition; critically reviewed and approved
36 39 1	final manuscript; agrees to be accountable for all aspects of the work.
38 33992 40	AMC: contributed to study conception and design, data acquisition and interpretation; critically
40 4393 42	reviewed and approved final manuscript; agrees to be accountable for all aspects of the work.
43 394 44	PM, SP, MJ, JG, GG, GN, SM, FL, RB, GL, HS: contributed to study conception and design, data
45 4695	acquisition and interpretation; critically reviewed and approved final manuscript; agrees to be
47 4 39 96 49	accountable for all aspects of the work.
50 397 51	Conflict of interest
52 53	
53498	The authors declare that there is no conflict of interest.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page Funding Point The study was funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer. Additional research support provided by the Arnic Charbonneau Cancer Institute and the Alberta Cancer Foundation. Primary results of the study have been published previously [11]. Pata Sharing Statement No additional unpublished data from the study is made available. Pate Sharing Statement No additional unpublished data from the study is made available. Pate Sharing Statement No additional unpublished data from the study is made available. Pate Sharing Statement No additional unpublished data from the study is made available. Pate Sharing Statement Pate Sharing Statement No additional unpublished data from the study is made available.	1	
 Funding Funding The study was funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer. Additional research support provided by the Arnie Charbonneau Cancer Institute and the Alberta Cancer Foundation. Primary results of the study have been published previously [11]. Data Sharing Statement No additional unpublished data from the study is made available. 	2 3000	
Funding Instruction Instruction Additional research support provided by the Arnic Charbonneau Cancer Institute and the Alberta Cancer Foundation. Primary results of the study have been published previously [11]. Instruction Instruction </td <td>399 4</td> <td></td>	399 4	
Funding Point Funding Point The study was funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer. Additional research support provided by the Arnie Charbonneau Cancer Institute and the Alberta Cancer Foundation. Primary results of the study have been published previously [11]. Point Data Sharing Statement No additional unpublished data from the study is made available. Point State Statement Point State Statement Point State Statement Point		
Point The study was funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer. Additional research support provided by the Arnie Charbonneau Cancer Institute and the Alberta Cancer Foundation. Primary results of the study have been published previously [11]. Pata Sharing Statement No additional unpublished data from the study is made available.		Funding
Photo The study was funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer. Additional research support provided by the Arnie Charbonneau Cancer Institute and the Alberta Cancer Foundation. Primary results of the study have been published previously [11]. Data Sharing Statement No additional unpublished data from the study is made available.		runding
Intel study was funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer. Additional research support provided by the Arnie Charbonneau Cancer Institute and the Alberta Cancer Foundation. Primary results of the study have been published previously [11]. Partnership Against Cancer. No additional unpublished data from the study is made available. No additional unpublished data from the study is made available. Partnership Against Cancer. Partn		
Additional research support provided by the Arnie Charbonneau Cancer Institute and the Alberta Cancer Foundation. Primary results of the study have been published previously [11]. Data Sharing Statement No additional unpublished data from the study is made available. No 308 3108 <		The study was funded by the Terry Fox Research Institute and the Canadian Partnership Against Cancer
Foundation. Primary results of the study have been published previously [11]. Data Sharing Statement No additional unpublished data from the study is made available. No additional unpublished data from the study is made available. 25		
Foundation. Primary results of the study have been published previously [11]. Data Sharing Statement No additional unpublished data from the study is made available. No additional unpublished data from the study is made available. 25	12 402	Additional research support provided by the Arnie Charbonneau Cancer Institute and the Alberta Cancer
Foundation. Primary results of the study have been published previously [11]. Data Sharing Statement No additional unpublished data from the study is made available. No additional unpublished data from the study is made available. No additional unpublished data from the study is made available. Primary results of the study is made a		
7894 7905 9706 No additional unpublished data from the study is made available. 7907 7908 7909<		Foundation. Primary results of the study have been published previously [11].
bit		
Pata Sharing Statement No additional unpublished data from the study is made available. Pata Sharing Statement Pata Sharing Statement <td></td> <td></td>		
Pata Sharing Statement No additional unpublished data from the study is made available. Pata Sharing Statement Pata Sharing Statement <td>404 19</td> <td></td>	404 19	
405 Data Sharing Statement 406 No additional unpublished data from the study is made available. 407 4 408 4 4097 4 408 4 4097 4 4097 4 4097 4 4097 4 41 4 42 4 43 4 44 4 44 4 45 4 46 4 47 4 48 4 49 4 41 4 42 4 43 4 44 4 45 4 46 4 47 4 48 4 49 4 41 4 42 4 43 4 44 4 45 4 46 4 47 4		
24 26 27 287 287 297 297 297 298 299 299 291 292	21	Dete Charing Statement
24 26 No additional unpublished data from the study is made available. 80 81 82 82 82 82 82 82		Data Sharing Statement
260 No additional unpublished data from the study is made available. 260 260 260 250		
27 28 497 30 31 3408 33 34 35 36 37 38 99 40 41 42 43 44 45 46 47 48 99 50 51 53 54 55 56 57 58 59 50 50 50 50 50 50 50 50 50 50		No additional unpublished data from the study is made available
2497 30 31 34 35 36 37 38 39 40 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 50 51 52 53 54 55 56 57 58 59 59 50 50 50 50 50 50 50 50 50 50 50 50 50		The additional anguenished data from the study is made available.
37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 25		
37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 25	28 γ4007	
37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 25		
37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 25	31	
37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 25	3408	
37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 25		
37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 25		
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 25		
44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 25 59		
45 46 47 48 49 50 51 52 53 54 55 56 57 58 25 59		
47 48 49 50 51 52 53 54 55 56 57 58 58 25 59		
48 49 50 51 52 53 54 55 56 57 58 58 25 59		
49 50 51 52 53 54 55 56 57 58 25 59		
50 51 52 53 54 55 56 57 58 58 25 59		
52 53 54 55 56 57 58 25 59		
53 54 55 56 57 58 25 59		
54 55 56 57 58 25 59		
55 56 57 58 25 59		
57 58 25 59		
58 25 59		
59		25
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2	
3409 4 5	References
6 7410 8	[1] Brambilla E, Travis WD, Brennan P, et al. Lung cancer. In: Stewart BW, Wild CP, eds. World cancer
9411 10 11	report 2014. International Agency for Research on Cancer (2014) 350-361.
12 412 14	[2] National Lung Screening Trial Research Team, Aberle DR, Berg CD, Black WC, et al. The National
14 14513 16 17	Lung Screening Trial: overview and study design. Radiology (2011) 258:243-253.
¹ 814 19 20	[3] Recommendations on screening for lung cancer. CMAJ (2016)188:425-432.
21 24015 23	[4] Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation
24416 25 26	statement. Ann Intern Med (2014)160:330-338.
27 417 28	[5] Bach PB, Mirkin JN, Oliver TK. Benefits and harms of CT screening for lung cancer: a systematic
29 3401.8 31 32	review. JAMA (2012) 307:2418-2429.
3319 3419 34	[6] Patz EF Jr, Pinsky P, Gatsonis C, et al; NLST Overdiagnosis Manuscript Writing Team.
$\frac{35}{420}$	Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med
37 34821 39 40	(2014)174:269-274.
41 422 42	[7] Marshall HM, Bowman RV, Yang IA, et al. Screening for lung cancer with low-dose computed
43 423 45 46	tomography: a review of current status. J Thorac Dis (2013) 5 Suppl 5:S524-S539.
4 7 24 48	[8] Wu GX, Raz DJ, Brown L, et al. Psychological Burden Associated with Lung Cancer Screening: A
49 50 51 52 53	Systematic Review. Clin Lung Cancer (2016) pii: S1525-7304 (16) 30053-30055.
54 55 56 57	
57 58 59	26
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2					
³ 426 4	[9] Miller AB, Madalinska JB, Church T, et al. Health-related quality of life and cost-effectiveness				
5 6427	studies in the European randomised study of screening for prostate cancer and the US Prostate,				
7 8428 9	Lung, Colon and Ovary trial. Eur J Cancer (2001) 37: 2154-2160.				
10 11 429 12	[10] McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules				
13 1430 15	detected on first screening CT. N Engl J Med (2013) 369:910-919.				
16 1431 18	[11] Tammemagi MC, Schmidt H, Martel S, et.al. Participant selection for lung cancer screening by risk				
19 432 20	modelling (the Pan-Canadian Early Detection of Lung Cancer (PanCan) study): a single-arm,				
21 24233 23 24	prospective study. Lancet Oncol (2017) pii: S1470-2045(17)30597-1.				
24 24 34 26	[12] Tammemagi MC, Freedman MT, Pinsky PF, et al. Prediction of true positive lung cancers in				
27 435 28	individuals with abnormal suspicious chest radiographs: a prostate, lung, colorectal, and ovarian				
29 3 1 36 31	cancer screening trial study. J Thorac Oncol (2009) 4:710-721.				
32 3237 3437 34	[13] Tremblay A, Taghizadeh N, McWilliams AM, et al. Low Prevalence of High Grade Lesions				
35 438 36	Detected with Autofluorescence Bronchoscopy in the Setting of Lung Cancer Screening in the				
37 34839 39 40	Pan-Canadian Lung Cancer Screening Study. Chest (2016) 150:1015-1022.				
41 440 42	[14] Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate				
43 441 45 46	results from the SF-36 in longitudinal studies? J Public Health Med (1997) 19:179-186.				
40 44742 48	[15] Bansback N Tsuchiya A BJAA. Canadian valuation of EQ-5D health states: preliminary value set				
49 443 50	and considerations for future valuation studies. PLoS One (2012) 7:e31115. doi:				
51 54244 53 54 55 56	10.1371/journal.pone.0031115.				
57 58	27				

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 29 of 48

1

BMJ Open

2	
³ 445 4	[16] Spielberger CD, Gorsuch RL, Lushene RE. Test manual for the State-Trait Anxiety Inventory. Palo
5 6446 7	Alto, CA: Consulting Psychologists Press, 1970.
8 9447 10	[17] Zanini A, Aiello M, Adamo D, et al. Estimation of minimal clinically important difference in EQ-
11 448 12	5D visual analog scale score after pulmonary rehabilitation in subjects with COPD. Respir Care
13 14 19 15	(2015) 60:88-95.
16 14750 18	[18] Le QA, Doctor JN, Zoellner LA, Feeny NC. Minimal clinically important differences for the EQ-
19 451 20	5D and QWB-SA in Post-traumatic Stress Disorder (PTSD): results from a Doubly Randomized
21 2452 23	Preference Trial (DRPT). Health Qual Life Outcomes (2013) 11:59.
24 2453 26	[19] Parker SL, Godil SS, Shau DN, Mendenhall SK, McGirt MJ. Assessment of the minimum clinically
27 454 28	important difference in pain, disability, and quality of life after anterior cervical discectomy and
29 34555 31	fusion: clinical article. J Neurosurg Spine (2013)18:154-160.
32 3456 34	[20] Corsaletti BF, Proença MGL, Bisca GKW, et al. Minimal important difference for anxiety and
35 457 36	depression surveys after intervention to increase daily physical activity in smokers. Fisioter Pesq
37 34858 39 40	(2014) 21:359-364.
41 459 42	[21] Gareen IF, Duan F, Greco EM, et al. Impact of lung cancer screening results on participant health-
43 4460	related quality of life and state anxiety in the National Lung Screening Trial. Cancer (2014)
45 4 16 51 47 48	3401-3409.
49 462 50	[22] Van den Bergh KA, Essink-Bot ML, Borsboom GJ, Scholten ET, van Klaveren RJ, de Koning HJ.
51 ₅4263	Long-term effects of lung cancer computed tomography screening on health-related quality of
53 54464 55 56	life: the NELSON trial. Eur Respir J (2011) 38:154-161.
57 58	28
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2
3465 4
405
5
5 6466
7
8467
9
10
1,100
11 468 12
13
4 69
15
14570
17
18
19 471 20
20′ L
21
21 24572
22
23
24
2473
20
27 474 28
4/4 28
29
30
34175
341/5
32
3376 34
34
35
36
3 4 77
38
34978
40
40 479 42
42
43
44
4 4 580
46
44781
48
49
50
50 482
52
5483
54
54 55
56
57
58
59
60

[23] Taylor KL, Shelby R, Gelmann E, et al. Quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. J Natl Cancer Inst (2004) 96: 1083-1094.
[24] Brain K, Lifford KJ, Carter B, et al. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. Thorax (2016) 71:996-1005.
[25] Slatore CG, Sullivan DR, Pappas M, et al. Patient-centered outcomes among lung cancer screening recipients with computed tomography: a systematic review. J Thorac Oncol (2014) 9:927-934.

[26] Aggestrup LM, Hestbech MS, Siersma V, et al. Psychosocial consequences of allocation to lung cancer screening: a randomised controlled trial. BMJ Open (2012) 1;2:e000663.

[27] Rasmussen JF, Siersma V, Pedersen JH, et al. Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST). *Lung Cancer* (2015) 87:65-72.

[28] Van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). British Journal of Cancer (2010) 102, 27 - 34.

[29] Byrne MM, Weissfeld J, Roberts MS. Anxiety, fear of cancer, and perceived risk of cancer
 following lung cancer screening. Med Decis Making (2008) 28:917-925.

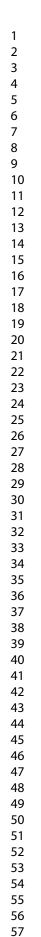
[30] Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically
 important difference. Control Clin Trials (1989)10:407-415.

BMJ Open

2	
³ 484 4	[31] Tammemagi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. N
5 6485 7	Engl J Med 2013;368:728-736.
8 9486 10	[32] Johnson JA, Pickard AS. Comparison of the EQ-5D and SF-12 health surveys in a general
11 487 12 13	population survey in Alberta, Canada. Med Care (2000) 38:115-121.
14 14588 16	[33] Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using
10 14789 18 19	postmyocardial infarction patients in the Dutch population. Qual Life Res (2009) 18:403-414.
20 490 22	[34] Hestbech MS, Siersma V, Dirksen A, et al. Participation bias in a randomised trial of screening for
22 2491 24 25	lung cancer. Lung Cancer (2011) 73:325-331.
2692 27	[35] Tramontano AC, Schrag DL, Malin JK, et al. Catalog and comparison of societal preferences
28 249-3 30	(utilities) for lung cancer health states: results from the Cancer Care Outcomes Research and
30 34194 32 33	Surveillance (CanCORS) study. Med Decis Making (2015) 35:371-387.
34 495 35	[36] Pickard AS, De Leon MC, Kohlmann T, et al. Psychometric comparison of the standard EQ-5D to
36 3496 38 39	a 5 level version in cancer patients. Med Care (2007) 45:259-263.
4497 41	[37] Wang P, Luo N, Tai ES, et al. The EQ-5D-5L is More Discriminative Than the EQ-5D-3L in
42 498 43 44 45	Patients with Diabetes in Singapore. Value Health Reg Issues (2016) 9:57-62.
45 44699 47	[38] Lo S, Andrews S. To transform or not to transform: using generalized linear mixed models to
4800 49 50	analyse reaction time data. Front Psychol (2015) 6:1171.
51 5501	[39] Bonnetain F, Fiteni F, Efficace F, et al. Statistical Challenges in the Analysis of Health-Related
53 5502 55 56	Quality of Life in Cancer Clinical Trials. J Clin Oncol (2016) 34:1953-1956.
57 58	30
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

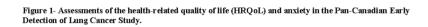
2					
3503 4	[40] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life:				
5 6 ⁵ 04	the remarkable universality of half a standard deviation. Med Care (2003) 41:582, 592				
6 ⁷⁰⁴ 7	the remarkable universality of half a standard deviation. Med Care (2003) 41:582-592.				
8					
% 05	[41] Barton MB, Morley DS, Moore S, et al. Decreasing women's anxieties after abnormal				
10 11					
11 506 12	mammograms: a controlled trial. J Natl Cancer Inst (2004) 96:529-538.				
13					
14 1 5 507					
16					
17					
18 508 19					
20					
21					
22 23					
23 24					
25					
26					
27 28					
29					
30					
31 32					
33					
34					
35 36					
37					
38					
39 40					
41					
42					
43 44					
45					
46					
47 48					
49					
50					
51 52					
52 53					
54					
55 56					
56 57					
58	31				
59					
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml				

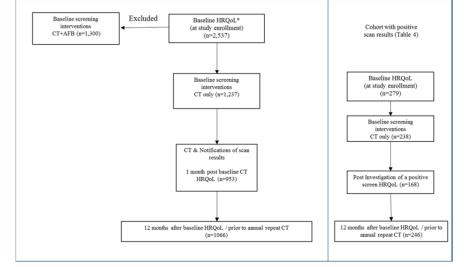
1 2	
3509 4	Figure legends
5 6-10	
6510 7	Figure 1- Assessments of the health-related quality of life (HRQoL) and anxiety in the Pan-Canadian Early Detection of
8511 9	Lung Cancer Study.
10 512 12	Figure 2: Changes in EuroQoL Visual Analog Scale (VAS) from baseline to post baseline CT(A), and 12 months after
1 5 13 14 15	baseline(B).
15/14 17 18	Figure 3: Changes in EuroQoL(EQ)-5D-3L from baseline to post baseline CT(A), and 12 months after baseline(B).
19 515 20	Figure 4: Changes in 12-item short-form Physical Component Scale(PCS) from baseline to post baseline CT(A), and 12
25116 22 23	months after baseline(B).
24 517 25	Figure 5: Changes in 12-item short-form Mental Component Scale (MCS) from baseline to post baseline CT(A), and 12
2618 27 28	months after baseline(B).
29 519 30	Figure 6: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT(A), and 12
3520 32 33	months after baseline(B).
34 521 35	Figure 7: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT (A) and post
3522 37 38	investigation (B) among participants with a positive scan results.
39 323 40	Figure 8: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to 12 months among participants
45 42 43	with a positive scan results.
44	
45 46	
47 48	
49 50	
50 51	
52 53	
54	
55 56	
57 58	32
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
00	



58 59

60





207x146mm (300 x 300 DPI)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

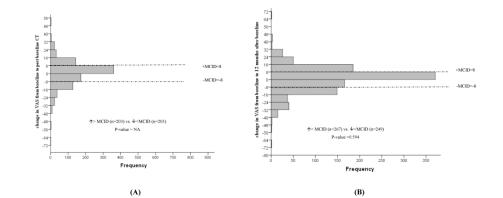
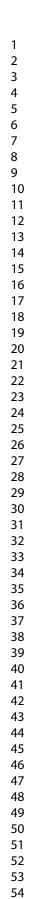


Figure 2: Changes in EuroQoL Visual Analog Scale (VAS) from baseline to post baseline CT(A), and 12 months after

baseline(B).

279x361mm (300 x 300 DPI)



60



.45 .40 .35 .30 .25

↑> MCID (n=201) vs. ↓<MCID (n=245)

-value = 0.015

500 600

Frequency

(A)

700

800 900 1.00

clanges in EQ-5D values from baseline to post baseline CT

-.55 -.60

200 300

.50 .45 .40 .35 .30

-.10

-.20 -.25

-.30

-.35 -.40 -.45 -.50 -.55 -.60

100

↑> MCID (n=231) vs. ↓<MCID (n=273)</p>

P-value = 0.033

Frequency

(B)

300

400

200

-MCID=-0.03

changes in EQ-5D values from baseline to 12 months after baseline

279x361mm (300 x 300 DPI)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

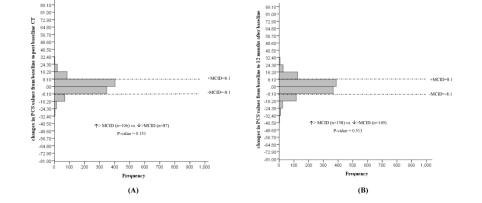
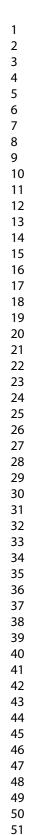


Figure 4: Changes in 12-item short-form Physical Component Scale(PCS) from baseline to post baseline CT(A), and 12

months after baseline(B).

279x361mm (300 x 300 DPI)



60



changes in MCS levels from baseline to 12 months after baseline

42.3

37.6

32.9

28.2 23.5 18.8 14.1

9.40 4.70

.00

-9.40 -14.10

-18.8

-23.5

-28.20

32.9

-47.0

-51.70

↑> MCID (n=152) vs. ↓>MCID (n=164)

P-value = 0.512

150

Frequency (B)

42.3

32.9 28.2 23.5 18.8 14.1

9.40 4.70

.0

-4.7

-14.1 -18.8 -23.5 -28.2

32.9

42.3

-51.7

an we want to a

P-value = 0.185

150

(A)

Ð

changes in MCS levels from baseline to post baseline

279x361mm (300 x 300 DPI)



279x361mm (300 x 300 DPI)

Figure 6: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT(A), and 12 months after baseline(B).

+MCID=10

-MCID=-10

1,000

\$60

100.00-50.00-70.00-60.00-50.00-50.00-30.00-10.00-10.00-00-

-10.00--20.00--30.00--40.00--50.00--70.00--50.00--50.00--100.00-

110.00-

CID (n=146) vs. ↓>MCID (n=87)

Frequency

(B)

P-value = <0.0001

+MCID=10

-MCID=-10

aseline

hanges in STAI-State Auxiety from baseline to 12 months after

100 00-50 00-50 00-70 00-60 00-50 00-40 00-

30.00 20.00

10.0

-10.00--20.00--30.00--40.00--50.00--70.00--50.00-

100.00 -110.00

A> MCID (n=180) vs ↓>MCID (n

P-value < 0.001

Frequency

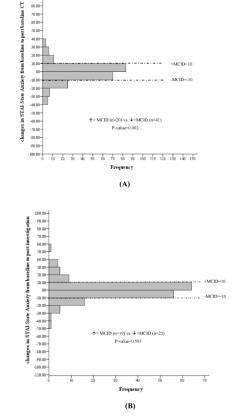
(A)

changes in STAI-State Auxiety

t

iom baseline to post baseline

Figure 7: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT (A) and post investigation (B) among participants with a positive scan results.



90.0

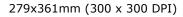


 Figure 8: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to 12 months among participants with a positive scan results.

changes in STAI-State Auxiety from baseline to 12 months after baseline 90.00-90.00-80.00-70.00-60.00-50.00-40.00-30.00-20.00 10.0 ----+MCID=10 .00 ------MCID=-10 -20.00 -30.00 -40.00--50.00--60.00--70.00--30.00--90.00-↑> MCID (n=35) vs. ↓>MCID (n=14) P-value=0.003 110.0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 Frequency

279x361mm (300 x 300 DPI)

Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Study

Niloofar Taghizadeh¹, Alain Tremblay¹, Sonya Cressman², Stuart Peacock², Annette M. McWilliams³, Paul MacEachern¹, Michael R. Johnston⁴, John Goffin⁵, Glen Goss⁶, Garth Nicholas⁶, Simon Martel⁷, Francis Laberge⁷, Rick Bhatia⁸, Geoffrey Liu⁹, Heidi Schmidt⁹, Sukhinder Atkar-Khattra², Ming-Sound Tsao⁹, Martin C. Tammemagi¹⁰, Stephen C. Lam², for the Pan-Canadian Early Lung Cancer Study Group.

to beet terien only

e-Appendix 1:

Study design and population

Institutional Review Board (IRB) Approvals: Vancouver: UBC BCCA Research Ethics Board (UBC BCCA REB) H08-01132 Calgary: Conjoint Health Research Ethics Board (CHREB) ethics ID: 21852 Hamilton: McMaster University Research Ethics Board; ID: 08-367 Toronto: University Health Network Research Ethics Board; ID: 08-0576-C Ottawa: The Ottawa Hospital Research Ethics Board; ID 2008581-01H Quebec: Institute Universitaire de Cardiologie et de Pneumologie; ID: CER: 20319 Halifax: Capital Health Research Ethics Board; ID: CDHA-RS/2009-097 h Department St.John's: Eastern Health Department of Reseasrch/Knowledge transfer; ID; HIC#10.070

1	
2	
3	
4	
5	
6	
7	
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	
29	
30	
31	
31 32 33 34 35 36 37 38	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
40 49	
49 50	
50 51	
52	
52 53	
53 54	
54 55	
55 56	
57 58	
59	

1

Supplementary Table 1 – HRQoL, and anxiety levels in participants with positive baseline LDCT.

	Baseline (n=279)	1-month post baseline CT scan Mean, change (95% CI) (n=238)	Post investigation Mean, change (95% CI) (n=168)	12-months after baseline Mean, change (95% CI) (n= 246)
EQ VAS ¹	76.2	76.1, -0.21 (-2.54 to 2.13)	76.9, 0.89 (-3.28 to 5.07)	76.4, 0.19 (-1.73 to 2.11)
EQ-5D-3L index values	0.84	0.84, -0.00 (-0.03 to 0.03)	0.85, 0.00 (-0.03 to 0.04)	0.83, -0.01 (-0.05 to 0.02)
SF-12: PCS ²	46.2	46.5, 0.22 (-0.83 to 1.28)	46.6, 0.45 (-0.93 to 1.83)	45.3, -0.86 (-1.90 to 1.67)
SF-12: MCS ³	51.3	51.2, 0.01 (-1.66 to 1.67)	51.4, 0.54 (-2.06 to 3.15)	51.3, 0.01 (-2.30 to 2.33)
STAI-State Anxiety ⁴	29.9	33.2, 3.28 (-0.42 to 6.97)	32.9, 2.42 (-1.14 to 5.99)	31.7, 1.79 (-0.62 to 4.19)

¹EQ Visual Analogue Scale "We would like to know how good or bad your health is today" (100 – best imaginable,

0 – worst imaginable).

² Physical Health Composite Scores (US population mean = 50 + - 10), with higher score corresponding to better state.

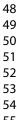
³ Mental Health Composite Scores (US population mean = 50 ± -10), with higher score corresponding to better state.

STAI-State score >39 considered clinically significant symptoms.

Supplementary Table 2 - Proportion of different levels of EQ-5D-3L dimensions by study visits (Total n=1237).

EQ-5D-3L Dimensions, n (%)	Baseline (n=1237)	1 month post baseline CT scan (n=953)	12 months after baseline (n=1066)
Overall score missing	9 (0.7)	12 (1.3)	16 (1.5)
Mobility			
I have no problems in walking about	918 (74.2)	705 (74.0)	782 (73.4)
I have some problems in walking about	311 (25.2)	240 (25.2)	278 (26.1)
I am confined to bed	4 (0.3)	3 (0.3)	0 (0.0)
Missing	4 (0.3)	5 (0.5)	6 (0.6)
Self-care			
I have no problems with self-care	1191 (96.2)	914 (95.9)	1018 (95.5)
I have some problems washing or dressing myself	36 (2.9)	31 (3.3)	39 (3.7)
I am unable to wash or dress myself	7 (0.6)	2 (0.2)	3 (0.3)
Missing	3 (0.3)	6 (0.6)	6 (0.6)
Usual activities			
I have no problems with performing my usual activities	930 (75.1)	710 (74.5)	785 (73.6)
I have some problems with performing my usual activities	284 (22.9)	228 (23.9)	261 (24.5)
I am unable to perform my usual activities	18 (1.5)	8 (0.8)	15 (1.4)
Missing	5 (0.5)	7 (0.7)	5 (0.5)
Pain/discomfort			
I have no pain or discomfort	575 (46.4)	471 (49.4)	498 (46.7)
I have moderate pain or discomfort	622 (50.2)	443 (46.5)	520 (48.8)
I have extreme pain or discomfort	36 (2.9)	33 (3.5)	40 (3.8)
Missing	4 (0.4)	6 (0.6)	8 (0.8)
Anxiety/depression			
I am not anxious or depressed	835 (64.4)	610 (64.0)	708 (66.4)
I am moderately anxious or depressed	375 (30.3)	307 (32.2)	332 (31.1)
I am extremely anxious or depressed	23 (1.9)	28 (2.9)	19 (1.8)
Missing	4 (0.4)	8 (0.8)	7 (0.7)





1	
2	
3	
4	
5	
6	
7	
8	
8 9	
10	
11	
12	
13	
14	
15	
16 17	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
50	
51 52	
53	
54	
55	
56	
57	
58	
59	

1

Supplementary Table 3- Proportion of different levels of SF_12 dimensions by study visits (Total n=2537).

SF_12 Dimensions	Baseline (n=1237)	1 month post baseline CT scan (n=953)	12 months after baseline (n=1066)
General health, n (%)	02 (7.5)	05 (0.0)	00 (0.2)
Excellent Very good	93 (7.5) 453 (36.6)	85 (8.9) 367 (38.5)	89 (8.3) 392 (36.8)
Good	532 (43.0)	381 (40.0)	450 (42.2)
Fair	138 (11.1)	105 (11.0)	108 (10.1)
Poor	18 (1.5)	12 (1.3)	20 (1.9)
Missing	3 (0.3)	3 (0.3)	7 (0.7)
Moderate activities Yes, limited a lot	97 (7.8)	77 (8.1)	75 (7.0)
Yes, limited a little	310 (25.0)	256 (26.9)	267 (25.0)
No, not limited at all	827 (66.8)	617 (64.7)	714 (67.0)
Missing	3 (0.3)	3 (0.3)	10 (0.9)
Climbing several flights of stairs	101 (15.4)	140 (14.7)	
Yes, limited a lot Yes, limited a little	<u>191 (15.4)</u> 551 (44.5)	140 (14.7) 432 (45.3)	161 (15.1) 462 (43.3)
No, not limited at all	491 (39.7)	376 (39.5)	436 (40.9)
Missing	4 (0.3)	5 (0.5)	7 (0.7)
Accomplished less than you would like (physically)			
Yes	335 (27.1)	221 (23.2)	265 (24.9)
No Missing	899 (72.6) 3 (0.3)	727 (76.3) 5 (0.5)	795 (74.6) 6 (0.6)
Limited in kind of activities	5 (0.5)	3 (0.3)	0 (0.0)
Yes	299 (24.2)	221 (23.2)	265 (24.9)
No	934 (75.4)	729 (76.5)	795 (74.6)
Missing	4 (0.4)	3 (0.3)	6 (0.6)
Accomplished less than you would like (emotionally)	251 (20.3)	212 (22.2)	222 (20.8)
Yes No	982 (79.3)	735 (77.1)	833 (78.1)
Missing	4 (0.4)	6 (0.6)	11 (1.0)
Did not do activities as carefully as usual			
Yes	215 (17.4)	181 (19.0)	181 (17.0)
No Missing	1018 (82.2) 4 (0.4)	764 (80.2) 8 (0.8)	875 (82.1) 10 (0.9)
Pain interferes with normal work	4 (0.4)	8 (0.8)	10 (0.9)
Not at all	596 (48.1)	479 (50.3)	515 (48.3)
A little bit	312 (25.2)	243 (25.5)	288 (27.0)
Moderately	194 (15.7)	138 (14.5)	142 (13.3)
Ouite a bit Extremely	109 (8.8) 20 (1.6)	77 (8.1) 13 (1.4)	<u>98 (9.2)</u> 18 (1.7)
Missing	6 (0.5)	3 (0.3)	5 (0.5)
Felt calm and peaceful	0 (0.0)	5 (015)	5 (0.5)
All of the time	87 (7.0)	73 (7.7)	84 (7.9)
Most of the time	630 (50.9)	460 (48.3)	527 (49.4)
A good bit of the time Some of the time	184 (14.9) 214 (17.3)	<u>163 (17.1)</u> 171 (17.9)	176 (16.5) 164 (15.4)
A little of the time	<u>214 (17.3)</u> 96 (7.8)	70 (7.3)	88 (8.3)
None of the time	23 (1.9)	11 (1.2)	18 (1.7)
Missing	3 (0.3)	5 (0.5)	9 (0.8)
Have a lot of energy	26.000	26 (2.0)	41.00.00
All of the time	36 (2.9)	36 (3.8)	41(3.8) 375(352)
A good bit of the time	416 (33.6) 263 (21.2)	<u>317 (33.3)</u> 206 (21.6)	375 (35.2) 213 (20.0)
Some of the time	322 (26.0)	240 (25.2)	249 (23.4)
A little of the time	156 (12.6)	116 (12.2)	145 (13.6)
None of the time	41 (3.3)	34 (3.6)	34 (3.2)
Missing Felt downhearted and blue	3 (0.3)	4 (0.4)	9 (0.8)
All of the time	4 (0.3)	5 (0.5)	4 (0.4)
Most of the time	37 (3.0)	37 (3.9)	34 (3.2)
A good bit of the time	79 (6.4)	51 (5.4)	76 (7.1)
Some of the time	273 (22.1) 480 (38.8)	196 (20.6) 399 (41.9)	216 (20.3) 414 (38.8)
A little of the time None of the time	361 (29.2)	261 (27.4)	312 (29.3)
Missing	3 (0.3)	4 (0.4)	10 (0.9)
Health interferes/social activities			
All of the time	8 (0.6)	10 (1.0)	16 (1.5)
Most of the time	63 (5.1) 203 (16.4)	42 (4.4) 150 (15.7)	54 (5.1) 169 (15.9)
Some of the time A little of the time	238 (19.2)	130 (13.7)	200 (18.8)
None of the time	722 (58.3)	565 (59.3)	617 (57.9)
Missing	3 (0.3)	4 (0.4)	10 (0.9)

3 4 5

BMJ Open

Supplementary Table 4- Proportion of different levels of State anxiety dimensions by study visits (Total n=2537).

Baseline 1 month post baseline CT scan 12 months after baseline (n=1066) (n=1237)(n=953) State Not at all Somewhat Moderately so Very much so Missing Not at all Somewhat Moderately so Very much so Missing Not at all Somewhat Moderately so Very much so Missing Dimensions 1 feel calm 17(1.4)167 (13.5) 407 (32.9) 643 (51.9) 3 (0.3) 31 (3.3) 136 (14.3) 338 (35.5) 442 (46.4) 6 (0.6) 18(1.7)131 (12.3) 393 (36.9) 516 (48.4) 8 (0.8) 7 feel secure 16(1.3)106 (8.6) 304 (24.6) 808 (65.3) 3 (0.3) 21(2.2)115 (12.1) 283 (29.7) 528 (55.4) 6(0.6)24 (2.3) 83 (7.8) 330 (31.0) 621 (58.3) 8 (0.8) **Figure 1** feel tense 177 (16.6) 685 (55.3) 319 (25.8) 192 (15.5) 36 (2.9) 3 (0.3) 465 (48.8) 300 (31.5) 144 (15.1) 39 (4.1) 5 (0.5) 562 (52.7 282 (26.5) 35 (3.3) 10 (1.0) 4 feel strained 834 (67.4) 231 (18.7) 131 (10.6) 3 (0.3) 543 (57.0) 261 (27.4) 35 (3.7) 5 (0.5) 652 (61.2) 240 (22.5) 134 (12.6) 38 (3.1) 109(11.4)33 (3.1) 7 (0.7) **5** feel at ease 41 (3.3) 154 (12.4) 3 (0.3) 154 (16.2) 5 (0.5) 27 (2.5) 323 (30.3) 361 (29.2) 678 (54.8) 45 (4.7) 289 (30.3) 460 (48.3) 170 (15.9) 538 (50.5) 8 (0.8) **d** feel upset 1003 (81.0) 137 (11.1) 75 (6.1) 19 (1.5) 3 (0.3) 660 (69.3) 182 (19.1) 78 (8.2) 28 (2.9) 5(0.5)792 (74.3) 175 (16.4) 75 (7.0) 16 (1.5) 8 (0.8) 7 am presently worrying 694 (56.1) 332 (26.8) 156 (12.6) 52 (4.2) 3(0.3)480 (50.4) 295 (31.0) 121 (12.7) 52 (5.5) 5 (0.5) 555 (52.1) 339 (31.8) 115 (10.8) 49 (4.6) 8 (0.8) over possible misfortunes d feel satisfied 36 (2.9) 193 (15.6) 469 (37.9) 536 (43.3) 3(0.3)47 (4.9) 167 (17.5) 324 (34.0) 410 (43.0) 5(0.5)33 (3.1) 192 (18.0) 378 (35.5) 456 (42.8) 7 (0.7) A feel frightened 1008 (81.4) 149 (12.0) 56 (4.5) 21 (1.7) 3 (0.3) 718 (75.3) 150 (15.7) 59 (6.2) 21 (2.2) 5 (0.5) 846 (79.4) 148 (13.9) 53 (5.0) 11 (1.0) 8 (0.8) I feel comfortable 30 (2.4) 133 (10.7) 352 (28.4) 719 (58.1) 3 (0.3) 31 (3.3) 135 (14.2) 291 (30.5) 490 (51.4) 6(0.6)23 (2.2) 142 (13.3) 333 (31.2) 561 (52.6) 7 (0.7) J feel self-confident 439 (35.5) 632 (51.1) 3 (0.3) 38 (4.0) 359 (37.7) 445 (46.7) 5 (0.5) 36 (2.9) 127 (10.3) 106 (11.1) 24(2.3)127 (11.9) 394 (37.0) 514 (48.2) 7 (0.7) **J** feel nervous 780 (63.0) 308 (24.9) 117 (9.5) 29 (2.3) 3 (0.3) 559 (58.7) 255 (26.8) 99 (10.4) 35 (3.7) 5 (0.5) 662 (62.1) 261 (24.5) 114 (10.7) 22 (2.1)2 7 (0.7) 4(0.4)I am jittery 968 (78.2) 174 (14.1) 73 (5.9) 18(1.5)692 (72.6) 152 (15.9) 77 (8.1) 27 (2.8) 5(0.5)811 (76.1) 155 (14.5) 77 (7.2) 15(1.4)8 (0.8) **d** feel indecisive 846 (68.3) 269 (21.7) 97 (7.8) 22 (1.8) 3 (0.3) 557 (58.4) 246 (25.8) 113 (11.9) 32 (3.4) 5 (0.5) 662 (62.1) 256 (24.0) 100 (9.4) 39 (3.7) 9 (0.9) 394 (31.8) 409 (42.9) 30 (2.8) 172 (16.1) 48 (3.9) 181 (14.6) 611 (49.4) 3 (0.3) 52 (5.5) 173 (18.2) 313 (32.8) 6(0.6)377 (35.4) A am relaxed 480 (45.0) 7 (0.7) 147 (15.4) -I feel content 48 (3.9) 161 (13.0) 436 (35.2) 589 (47.6) 3 (0.3) 52 (5.5) 339 (35.6) 410 (43.0) 5(0.5)37 (3.5) 151 (14.2) 408 (38.3) 463 (43.4) 7 (0.7) 423 (44.4) 333 (34.9) 5 (0.5) 518 (48.6) 651 (52.6) 390 (31.5) 146 (11.8) 47 (3.8) 3 (0.3) 134 (14.1) 58 (6.1) 361 (33.9) 129 (12.1) 51 (4.8) 7 (0.7) d am worried 1075 (86.8) 112 (9.0) 32 (2.6) 12 (1.0) 755 (79.2) 135 (14.2) 40 (4.2) 5 (0.5) 887 (83.2) 99 (9.3) 50 (4.7) 20 (1.9) 10 (1.0) d feel confused 6 (0.5) 18 (1.9) A feel steady 43 (3.5) 141 (11.4) 327 (26.4) 720 (58.2) 6(0.5)43 (4.5) 126 (13.2) 272 (28.5) 507 (53.2) 5(0.5)41 (3.8) 120 (11.3) 316 (29.6) 581 (54.5) 8 (0.8) 25 (2.0) 118 (9.5) 416 (33.6) 672 (54.3) 30 (3.1) 117 (12.3) 319 (33.5) 482 (50.6) 5 (0.5) 25 (2.3) 115 (10.8) 365 (34.2) ₁ feel pleasant 6 (0.5) 552 (51.8) 9 (0.9)

- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45 46
- 47

6

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2 3
5 4
4 5
5 6
7
7 8
8 9
10 11
12 13
14 15
15 16
17
17
10
19 20
21 22
22
25 24
24 25
25
26
27
28
29
30
31
32 33
34 35
35 36
37 38
38 39
40 41
42 43
43 44
44 45
46 47
48 49
49 50
51
55
74
55
50
57
50
59 60
60

STROBE Statement—Checklist of items that should be included in reports of cohort studies

PAGE		Item No	Recommendation
4	Title and abstract	1	(<i>a</i>) Indicate the study's design with a commonly used term in the title or the abstract
4			(b) Provide in the abstract an informative and balanced summary of what
			was done and what was found
	Introduction		
6	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
7	Objectives	3	State specific objectives, including any prespecified hypotheses
	Methods		
8	Study design	4	Present key elements of study design early in the paper
8	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
8	Participants	6	(<i>a</i>) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
n/a			(b) For matched studies, give matching criteria and number of exposed and unexposed
8-9	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
9	Data sources/	8*	For each variable of interest, give sources of data and details of methods o
	measurement		assessment (measurement). Describe comparability of assessment methods if there is more than one group
n.a.	Bias	9	Describe any efforts to address potential sources of bias
11	Study size	10	Explain how the study size was arrived at
10	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
10	Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for confounding
10			(b) Describe any methods used to examine subgroups and interactions
10			(c) Explain how missing data were addressed
10			(d) If applicable, explain how loss to follow-up was addressed
n/a			(<u>e</u>) Describe any sensitivity analyses
	Results		
12	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
n.a.			(b) Give reasons for non-participation at each stage
FIG 1			(c) Consider use of a flow diagram
12	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
14	-		(b) Indicate number of participants with missing data for each variable of interest
n.a.	- 		(c) Summarise follow-up time (eg, average and total amount)
14-17	Outcome data	15*	Report numbers of outcome events or summary measures over time
14-17	Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear

	_		which confounders were adjusted for and why they were included
n.a.			(b) Report category boundaries when continuous variables were categorized
14, 16			(c) If relevant, consider translating estimates of relative risk into absolute
			risk for a meaningful time period
Suppl	Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and
			sensitivity analyses
	Discussion		
18	Key results	18	Summarise key results with reference to study objectives
20	Limitations	19	Discuss limitations of the study, taking into account sources of potential
			bias or imprecision. Discuss both direction and magnitude of any potential
			bias
21-22	Interpretation	20	Give a cautious overall interpretation of results considering objectives,
			limitations, multiplicity of analyses, results from similar studies, and other
			relevant evidence
22	Generalisability	21	Discuss the generalisability (external validity) of the study results
	Other information		
23	Funding	22	Give the source of funding and the role of the funders for the present study
			and, if applicable, for the original study on which the present article is
			based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.