



Universiteit
Leiden
The Netherlands

Surgical outcome of colorectal cancer screening

Vermeer, N.C.A.

Citation

Vermeer, N. C. A. (2021, January 14). *Surgical outcome of colorectal cancer screening*. Retrieved from <https://hdl.handle.net/1887/139046>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/139046>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/139046> holds various files of this Leiden University dissertation.

Author: Vermeer, N.C.A.

Title: Surgical outcome of colorectal cancer screening

Issue Date: 2021-01-14

CHAPTER 3

Psychological distress and quality of life following positive fecal occult blood testing in colorectal cancer screening

N.C.A. Vermeer, M.J.M. van der Valk, H.S. Snijders,
H.F.A. Vasen, A. Gerritsen van der Hoop, O.R. Guicherit,
G.J. Liefers, C.J.H. van de Velde,
A.M. Stiggelbout, K.C.M.J. Peeters

ABSTRACT

Objective: This study aimed to assess psychological functioning, quality of life, and regret about screening after a positive Fecal Immunochemical Test (FIT) and subsequent colonoscopy, and to evaluate changes over time.

Methods: This is a prospective cohort study. Individuals aged 55-75 with a positive FIT that were referred for colonoscopy between July 2017 and November 2018, were invited to complete questionnaires related to psychological distress and health-related quality of life at three pre-defined time points: before colonoscopy, after histopathology result notification, and after 6 months. Four questionnaires were used: the Psychological Consequences Questionnaire (PCQ), the six-item Cancer Worry Scale (CWS), the Decision Regret Scale (DRS), and the 36-item Short-Form (SF-36).

Results: A total of 1066 participants out of 2151 eligible individuals were included. Patients with cancer showed a significant increase in psychological dysfunction ($P=0.01$) and cancer worry ($P=0.008$) after colonoscopy result notification, and a decline to pre-colonoscopy measurements after 6 months. In the no-cancer groups, psychological dysfunction and cancer worry significantly decreased over time ($P<0.05$) but there was no ongoing decline. After 6 months, 17% of participants with no cancer experienced high level of cancer worry ($CWS \geq 10$). Yet, only 5% reported high level of regret about screening participation ($DRS > 25$). A good global quality of life was reported in participants with no cancer.

Conclusion: Some psychological distress remains up to 6 months after colonoscopy in participants who tested false-positive in the Dutch bowel cancer screening program.

BACKGROUND

Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity. Population-based screening for CRC is recommended by the European Union to lower the burden of cancer by discovering early stage disease.^{1,2} In the Netherlands, a national CRC screening program was implemented in 2014, offering all individuals aged 55-75 a Fecal Immunochemical Test (FIT) every 2 years. Individuals are invited to sample a FIT at home and to return the test. The FIT uses antibodies that form a complex in the presence of human globin.³ With a cut-off level of 47 µg Hb/g feces, as currently applied in the Netherlands for referral for colonoscopy, the sensitivity of FIT is 82.9%.⁴ Yet, of all FIT positives who underwent colonoscopy in the Netherlands between 2014 and 2017, many individuals had false-positive result as 90292 individuals (50.1%) had no abnormalities or non-advanced adenomas.⁵ Because screening targets a previously healthy population, harms should be considered carefully in the evaluation of a CRC screening program. In contrast to the prospective registration of some harmful effects of screening, including complications due to colonoscopy or surgical treatment,⁶ there is no obliged national audit for potential consequences on psychological functioning. Psychological distress covers a wide spectrum ranging from normal feelings of vulnerability to problems that can become disabling, such as depression, anxiety, or extensive worries.⁷ Results from previous studies in cancer patients showed that fear of cancer recurrence (FCR), defined as fear, worry, or concern about cancer returning or progressing, has been identified as one of the most common psychological challenges.^{8,9} Studies on cancer worry in screening populations are limited and primarily conducted in screening populations with increased cancer risk.^{10,11} Previous meta-analyses in breast cancer screening have shown that false positive screening examinations affect psychosocial functioning that can persist for up to 3 years after the screening.^{12,13} Available studies on screen-related psychological distress in CRC screening show that an adverse effect on psychological well-being exists.^{14,15} However, data on long-term psychological well-being show conflicting results, and studies with a prospective design are limited.

Aim

The primary aim of this prospective cohort study was to assess psychological functioning, quality of life and regret about screening after a positive screening result, and to evaluate changes over time. Further, we aimed to explore associations between higher levels of psychological dysfunction and cancer worry related to sociodemographic characteristics and colonoscopy results.

METHODS

Study design

This prospective cohort study included patients with a positive FIT who were referred for colonoscopy in the Keizer Clinic between July 2017 and November 2018.

These patients were invited to complete questionnaires related to psychological functioning, cancer worry, regret about screening, and health-related quality of life (HR-QoL) at three pre-defined time points. The Keizer Clinic is a treatment center that collaborates with regional hospitals and the Leiden University Medical Center, and has three locations in different regions of the Netherlands, i.e. in The Hague, Voorschoten and in Assen. Only hospitals fulfilling the criteria as described by the National Health Institute for Public Health and environment (RIVM) are allowed to perform screening colonoscopies. The Keizer Clinic is one of them, and meets all predefined quality criteria.

This study was approved by the Medical Ethics Review Committee of the LUMC (reference number P16.327).

Population

The Keizer Clinic treats patients with no medical history or patients with only mild systemic disease, i.e. ASA I or II, according to the American Society of Anesthesiologists Physical Status Classification System. Men and women in the age range of 55-75 were eligible. Participants had to be able to read the Dutch language, have Digital identity (DigiD) and valid email address. Patients who were willing to participate but had no access to the questionnaires due to lack of computer and/or digital identity were excluded. All participants underwent subsequently colonoscopy and were diagnosed with either cancer or no cancer. Participants with no cancer were additionally classified into three groups according to histopathology: no abnormality, non-advanced adenoma (NAAD), and advanced adenoma (AAD). Advanced adenomas were defined as follows: ≥ 10 mm in diameter, with a villous component of more than 25%, or high-grade dysplasia.^{16,17}

Procedure

Four questionnaires were used: the 12-item Psychological Consequences Questionnaire (PCQ) to measure screen-specific psychological dysfunction, the 6-item Cancer Worry Scale (CWS) to measure worry of developing cancer, the 5-item Decision Regret Scale (DRS) to measure regret about screening participation, and the 36-item Short-Form (SF-36) to measure health related quality of life.

The PCQ was originally developed to measure the psychological consequences of screening mammography¹⁸ and has previously been used in CRC screening research.¹⁹ Invitees were asked to indicate how often they had experienced each of a list of 12 symptoms over the past week. It evaluates answers on a four-point Likert scale from 0 (not at all) to 3 (quite a lot of the time). The sum of scores resulted in a total score between 0 and 36. Higher scores indicate more psychological dysfunction.

The CWS quantifies the worry of developing (recurrent) cancer and the frequency and impact of worry on mood and daily functioning.²⁰ It was originally developed to assess fear of developing cancer in women at risk of hereditary cancer.²¹

The 8-item CWS was adapted in 2010 to assess worry about cancer recurrence in curatively treated colorectal cancer patients. Despite the 8-item CWS version already being well utilized in research, previous studies have highlighted concerns about

validity of the final two items.²² The six-item scale has been tested and validated for the Dutch context.²² Therefore, the six-item CWS was used in this study. Items are rated from 1 ("never") to 4 ("almost always"). The sum of scores resulted in a total score between 6 and 24, with higher scores indicating more worry. Based on a previous Dutch validation study, we divided patients into 3 categories: no cancer worry (score 6), low level of cancer worry (score 7-9) and high level of cancer worry (score ≥ 10).²²

The DRS involves items that assess a patient's regret about health-care decisions.²³ It consists of five items with Likert-scale responses that were transformed into a total score of 0-100, with greater scores associated with higher regret.²⁴ Based on a validation study in prostate cancer patients, we considered a DRS score of >25 as high level of regret.²⁴⁻²⁶

The SF-36 consists of 36 questions, categorized into eight health dimensions, to measure health-related quality of life. These items are coded, summed, and transformed to a scale from 0 to 100, with higher scores indicating better functioning. There are no standards for determining clinically important differences (CIDs) in SF-36 scale scores for individual CRC patients. Based on a Delphi study the minimal amount of change for CID is at least 5 points, up to 12.5 points on the Social Functioning scale.²⁷ A Dutch cohort from the general population in 2012 (N=1,294) was used as reference population for this study.²⁸

All questionnaires were conducted before colonoscopy (T1), after histopathology result notification after colonoscopy (T2), and 6 months after colonoscopy (T3). Surveys were available online via a digital patient portal, and secured with DigiD. Patients were asked to participate the moment they were called for colonoscopy. Completion of the first questionnaire was required for further participation, and indicated informed consent.

Statistical Analyses

To assess non-response bias, continuous variables of participants and non-participants were compared using an independent samples t test. Chi-square tests were used to compare categorical variables. A two-tailed *P*-value was used for all analyses, and *P*-values ≤ 0.05 were considered statistically significant. No adjustment for multiple testing was applied because only a few planned comparisons were made and therefore the probability of making a type I error was limited. Only complete questionnaires were analyzed. Sensitivity analysis was performed by repeating the analyses in both the cohort of patients that completed the PCQ on all time points, and the complete cohort of participants. This analysis showed similar results, allowing to do further analyses on the complete cohort.

Outcomes of the first questionnaires, i.e. before the colonoscopy result notification (T1), were seen as baseline measurement, because participants were unaware of their final diagnosis at this time point. Because the outcome of the questionnaires was not normally distributed, differences in medians were compared. To compare results with other literature mean scores were reported as well. Differences in absolute psychological dysfunction and cancer worry scores at different time points

were assessed using a Wilcoxon signed-rank test, for each subgroup according to histopathology result. The results before colonoscopy (baseline) were compared to those after colonoscopy (T1 vs T2), and the results before colonoscopy to those after six months (T1 vs T3). We hypothesized that a false positive FIT result would lead to decrease in psychological dysfunction (PCQ) and cancer worry (CWS) over time. Also, decision regret towards screening participation and quality of life were assessed. Second, to explore associations between demographic and clinical characteristics with higher levels of psychological dysfunction and cancer worry, logistic regression analyses were performed. Independent variables with P -value ≤ 0.05 in univariable analyses were entered into the multivariable logistic regression model. Median outcome after colonoscopy was chosen as the cut-off value for PCQ. Based on previous literature, the cut-off value of 10 was applied for CWS, indicating high cancer worry. SPSS 23.0 (SPSS Inc., Chicago, IL, USA) was used to manage and analyze the data.

RESULTS

A total of 4842 men and women with positive FIT were referred to the Keizer Clinic for a colonoscopy. Of these 2691 did not meet the inclusion criteria. The inability to validate a personal e-mail address was the main reason for exclusion. In total, 1066 (49.6%) of the remaining 2151 individuals responded and were included for analyses. Table 1 shows the characteristics of participants and non-participants.

Psychological Consequences

In participants with false positive FIT results (i.e. no cancer), the level of psychological dysfunction decreased after colonoscopy result notification ($P < 0.01$) (Figure 1, Supplementary Table 1). After 6 months, no additional decline was observed. This was different for the participants with cancer, as their psychological dysfunction increased significantly from pre-colonoscopy to post-colonoscopy ($Z = -2.59$, $P = 0.01$). Six months after the cancer diagnosis, it decreased to the baseline level ($Z = -0.18$, $P = 0.86$) (Supplementary Table 1). Factors associated with higher levels of psychological dysfunction (PCQ ≥ 3) after colonoscopy are shown in Table 2. The odds of reporting higher levels of psychological dysfunction significantly increased by female gender (adjusted OR 2.50, 1.85-3.37) and histopathology outcome, i.e. NAAD (adjusted OR 2.47, 1.68-3.64), AAD (adjusted OR 3.13, 2.13-4.62), and cancer (adjusted OR 12.28, 5.58-27.03). Age, education, marital status and employment status were non-significant variables.

Cancer Worry

Compared to baseline, all participants with no cancer showed a significant decline of cancer worry over time ($P < 0.05$). In participants with cancer, worry significantly increased from pre-colonoscopy to post-colonoscopy ($Z = -2.63$, $P = 0.008$). Six months after the cancer diagnosis, the scores returned to the baseline levels

Table 1. Background characteristics of FIT-positive participants and FIT-positive nonparticipants (nonresponders and persons that did not fulfil inclusion criteria)

	Participants	Nonparticipants	P-value
	N=1066	N=3776	
Age (years)			
Mean (SD)	64 (5.79)	65 (6.37)	< 0.001*
Male gender (%)	659 (61.82)	2226 (58.95)	0.097**
Pathology (%) [†]			
No abnormalities	218 (20.45)	855 (22.64)	0.127**
Non-advanced Adenoma [‡]	384 (36.02)	1342 (35.54)	
Advanced Adenoma	387 (36.30)	1239 (32.81)	
Cancer	69 (6.47)	205 (5.43)	
Missing	8 (0.75)	135 (3.58)	
Education (%)			
Low	215 (20.17)	NA	
Medium	630 (59.09)	NA	
High	135 (12.66)	NA	
Other	86 (8.07)	NA	
Marital status (%)			
Married/cohabiting	900 (84.43)	NA	
Living alone	166 (15.57)	NA	
Employment status (%)			
Employed	536 (50.28)	NA	
Unemployed/retired	529 (49.62)	NA	
Unknown	1 (0.09)	NA	

Note: Significant level set at $P \leq 0.05$.

Abbreviations: FIT, fecal immunochemical test; NA, not available.

* Independent samples t test for continuous variables.

** Chi-square test for categorical variables.

† P-value without missing values.

‡ Including serrated polyps.

($Z = -0.24$, $P = 0.81$) (Supplementary Table 1). A total of 17% ($n = 26$) of individuals with no abnormality and 17% ($n = 44$) of individuals with NAAD scored above cut-off level for high level of cancer worry ($CWS \geq 10$), six months after receiving positive FIT result (Figure 2).

As shown in Table 2, factors associated with higher levels of worry about developing cancer ($CWS \geq 10$) after colonoscopy are female gender (adjusted OR 1.48, 1.09-2.01) and histopathology outcome, i.e. NAAD (adjusted OR 2.00, 1.28-3.12), AAD (adjusted OR 2.34, 1.53-3.68), and cancer (adjusted OR 8.35, 4.37-15.97). The odds decreased with higher age (adjusted OR 0.97 per year, 0.95-1.00). Education, marital status and employment status were not significantly related to higher levels of cancer worry.

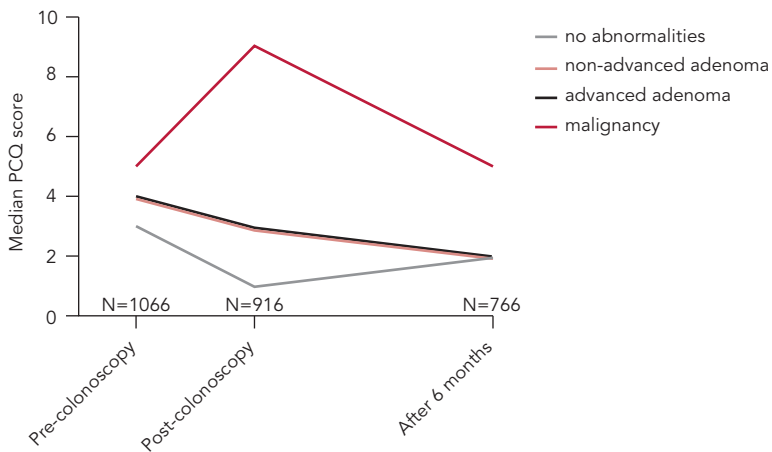


Figure 1. Changes in median PCQ score in function over time, according to colonoscopy result.

PCQ, Psychological Consequence Questionnaire, range 0 to 36 with higher scores indicating more psychological dysfunction. Error bars represent the standard error of the mean

48 Decision Regret

Regret about screening participation, as assessed by the DRS, was generally low. The distribution of regret scores was extremely left-skewed, as the median was zero both direct after colonoscopy (range 0-100) as well as after six months (range 0-60). Of all participants with no cancer, 5% reported a high level of regret (DRS > 25), both after colonoscopy as well as after six months. Of all individuals with cancer, 10% reported high level of regret.

Health-related quality of life

The mean scores for the eight subscales of the SF-36 over time in the cancer and no-cancer groups are presented in Table S2. No relevant changes over time were seen in the no-cancer group. In the cancer group, the mean scores of five of eight subscales decreased (indicating worse functioning) with >5 points directly after the colonoscopy (role limitations due to physical functioning, social functioning, mental health, role limitations due to emotional functioning, and general health). The largest decrease from baseline to six months was observed in the cancer group on the subscales role limitations due to physical functioning (90 to 64) and role limitations due to emotional functioning (91 to 76).

Table 2. Unadjusted and adjusted association between demographic and clinical characteristics of FIT-positive participants with higher levels of screen-related psychological dysfunction (PCQ ≥ 3) and fear of cancer (CWS ≥ 10) after colonoscopy result notification (T2)

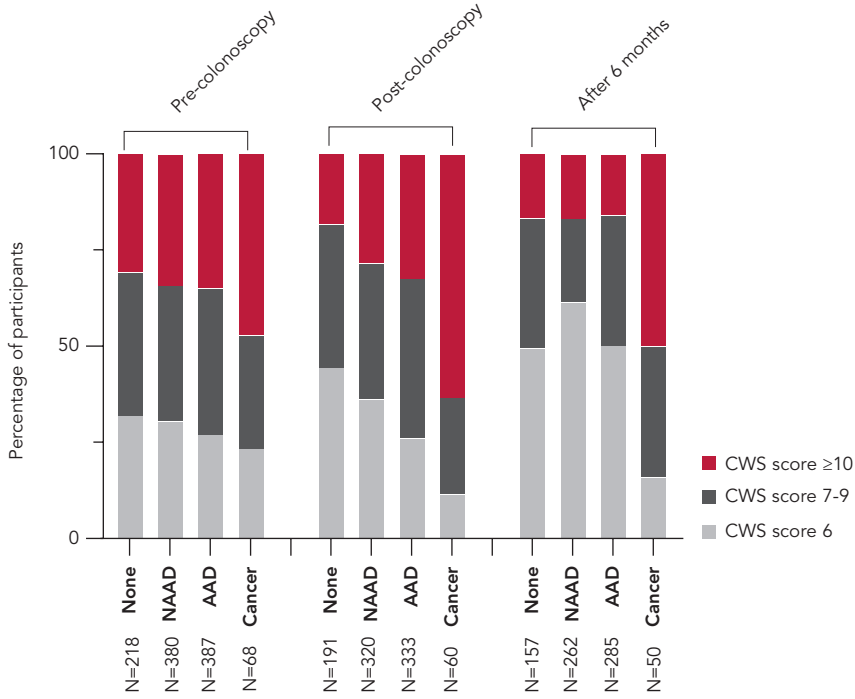
	PCQ ≥ 3			CWS ≥ 10		
	Unadjusted	Adjusted		Unadjusted	Adjusted	
	Odds ratio [†]	Odds ratio [†]	P-value [‡]	Odds ratio [†]	Odds ratio [†]	P-value [‡]
Age (years)	0.97 (0.95-0.99)	0.97 (0.94-1.00)	0.075	0.97 (0.95-0.99)	0.97 (0.95-1.00)	0.037
Gender						
Male	1 (ref.)	1 (ref.)		1 (ref.)	1 (ref.)	
Female	2.17 (1.64-2.86)	2.50 (1.85-3.37)	<0.001	1.41 (1.05-1.88)	1.48 (1.09-2.01)	0.012
Pathology						
No abnormalities	1 (ref.)			1 (ref.)		
Non-advanced Adenoma	1.89 (1.31-2.71)	2.47 (1.68-3.64)	<0.001	1.77 (1.14-2.75)	2.00 (1.28-3.12)	0.003
Advanced Adenoma	2.44 (1.70-3.52)	3.13 (2.13-4.62)	<0.001	2.14 (1.39-3.30)	2.34 (1.53-3.68)	<0.001
Cancer	9.63 (4.48-20.71)	12.28 (5.58-27.03)	<0.001	7.70 (4.06-14.61)	8.35 (4.37-15.97)	<0.001
Education						
Low	1 (ref.)			1 (ref.)		
Medium	1.02 (0.73-1.43)	NA	NA	1.08 (0.74-1.57)	NA	NA
High	0.98 (0.61-1.55)	NA	NA	1.07 (0.64-1.77)	NA	NA
Marital status						
Living alone	1 (ref.)	1 (ref.)		1 (ref.)		
Married/ cohabiting	0.70 (0.48-1.00)	0.69 (0.46-1.02)	0.059	1.10 (0.74-1.65)	NA	NA
Employment status						
Unemployed/retired	1 (ref.)	1 (ref.)		1 (ref.)		
Employed	1.30 (1.00-1.69)	1.13 (0.79-1.62)	0.503	1.15 (0.87-1.53)	NA	NA

Note: Significant level set at $P \leq 0.05$ and printed in bold.

Abbreviations: CWS, Cancer Worry Scale, range 6 to 24 with higher scores indicating more cancer worry; NA, not applicable; PCQ, Psychological Consequence Questionnaire, range 0 to 36 with higher scores indicating more psychological dysfunction.

[†] Values in parentheses are 95 per cent confidence intervals.

[‡] P-value for multi variable logistic regression analyses.



50 **Figure 2.** Frequency of scores on the CWS, before colonoscopy, after colonoscopy result notification and 6 months after colonoscopy, according to colonoscopy result.

CWS, Cancer Worry Scale (range 6-24), with a cutoff score of 10 indicating high level of cancer worry. Colonoscopy result: AAD, advanced adenoma, NAAD, non-advanced adenoma; None, no abnormality

DISCUSSION

Most important findings

Results of this large study on psychological impact of CRC screening suggest that individuals with positive FIT have elevated levels of psychological dysfunction and worry about developing cancer.

It is not surprising that psychological dysfunction in patients with no cancer was lower compared to patients with cancer. One would expect an ongoing decrease in psychological dysfunction after the reassuring outcome of colonoscopy. Yet, this was not seen in our study population. Hypothetically, after a false-positive FIT, patients are more aware of the possibility to develop cancer than they were prior to screening.

Interestingly, about one fourth of the participants with no cancer experienced a cancer worry score ≥ 10 after colonoscopy, indicating high levels of cancer-specific worries. After 6 months, still 1 in six participants experienced high levels of cancer-specific worries. Identifying these individuals seems worthwhile because they may benefit from psychosocial support in order to reduce levels of distress.

We found that FIT-positives in general do not regret their decision to screen for CRC. This is interesting since over half of FIT positive participants who undergo an invasive colonoscopy have no (advanced) neoplasia detected.

Last, as expected, the FIT participants in this study reported a good global quality of life. In participants with no cancer, HR-QoL fortunately was not affected by the colonoscopy. In the participants with cancer, as expected, the effect of colonoscopy result notification on HR-QoL was large. Directly after receiving the cancer diagnosis, patients rated their physical health as significantly worse compared to 2 weeks earlier, even ahead of treatment.

Clinical implications

Ideally, we would have had information from FIT-negatives and individuals that did not participate in screening in order to measure a true and clinically relevant effect on psychological dysfunction level. Two studies provided information on FIT negatives and found a mean PCQ of resp. 2.1 and 2.2.^{19,29} However, this low level was not reached in our cohort with FIT positive patients. Even in FIT positive patients with a negative colonoscopy, a mean PCQ score of 3.9 was observed after 6 months. The higher 6-months dysfunction level in patients in our study might be associated with an increased perception of the risk of developing CRC after a false-positive FIT result. This increased perception of risk is also seen in breast cancer patients where Rijnsburger et al. showed that a mean PCQ score of 6 corresponded to a "quite to very high" perceived risk of developing breast cancer.³⁰

In the current literature on CRC screening, results are often analyzed by comparing true-positives with false-positives. Denters et al. observed no significant differences between true-positives and false-positives in post-colonoscopy PCQ scores, which is an unexpected outcome. In our study, levels of psychological dysfunction of patients with AAD (defined as true-positives) were more comparable to those of individuals

with no abnormalities, than those of patients with cancer. The observation of Denters et al. might have been different if they had analyzed cancer patients and patients with AAD separately but since their group of participants was relatively small, it may have been underpowered.¹⁹ So in terms of psychological distress, patients with AAD should be reported separately from the patients with cancer.

A systematic review on FCR showed this to vary widely,³¹ possibly because there is no consensus about what are clinically relevant levels of FCR. Previous studies in CRC²⁰ and prostate cancer survivors³² both showed that one in four had high levels of worry of cancer recurrence (CWS ≥ 14 in eight-item CWS), with a median of 5.1 and 7.5 years after surgery, respectively.²⁰ Although the CWS has been validated for cancer survivors, it has also been used to measure worry about the risk of developing cancer among participants in a cancer surveillance program.³³ The cut-off point ≥ 10 , based on a Dutch validation study in cancer patients and survivors, has led to our conclusion that there was a high level (17%) of cancer specific worry up to 6 months in patients with no malignant lesions. However, since there is no data from the general population available, there is a possibility that some of these findings reflect general patterns of psychological distress.

In line with previous research, women were more likely to report cancer worry.^{34,35} Logistic regression analyses showed that this difference had not confounded the association between histology and cancer-specific distress. As shown in previous studies, women generally yield higher scores than men on anxiety measures.³⁵

The absence of regret in screening participation as observed in our cohort might be explained by the concept of misleading feedback as stated by Hofmann et al.: subjects who have a false positive test might experience a sense of relief. This is ironic because these participants have experienced harm of testing without a benefit. Still, they view themselves to be in the benefiting group and are enthusiastic about testing.³⁶

Strengths and limitations

This cohort study is one of the largest prospective studies on quality of life and psychological distress after screening with FIT and one of the first to assess the perception and satisfaction longitudinally of screening participants. Notable strengths are the large group of participants, permitting subgroup analyses and the prospective design of the study. The use of electronic online questionnaires allowed us to minimize the risks of data entry errors, hence no manual data entry was required. This might also contribute to the response rate.

Several limitations have to be mentioned. Most important are selection and participation bias. There was no information on individuals that decline FIT screening, FIT negatives or subjects unexposed to screening. Therefore outcome of this study should be interpreted with a degree of caution. Screening attendees are known to have higher socioeconomic status and better mental health, compared with nonattendees.^{37,38} In addition, previous research has shown that volunteers in medical trials are in general more psychologically robust and resourceful than those who choose not to participate.³⁹ Bearing this in mind, our results can be

underestimated as people who declined participation in the present study might have experienced more negative psychological consequences. This is endorsed by the study of Wangmar et al., in which individuals participating in a CRC screening trial with inadequate health literacy were more likely to experience higher anxiety levels.³⁵ In addition, individuals with high ASA-score as well as individuals with no computer and/or digital identity were excluded. This might limit the generalizability in the way that a relatively healthy, privileged population was included. There were no ethical considerations regarding this exclusion after our METC application. Another limitation is that we had no information on previous colonoscopy, family or personal history, nor on complications of colonoscopy or surgical treatment. One could assume that an adverse outcome could influence psychological distress and health-related quality of life. Also, we were unable to control for any confounders, such as psychological comorbidities or other life events. Future studies could consider including information on baseline mental health and previous severe illnesses as they likely influence psychosocial experiences during and after the screening process. Finally, the main question remains whether this adverse impact of screening on psychological dysfunction is clinically relevant since no clear cut-off values are available. In addition, as the data were skewed to such an extent, one might question if some of these questionnaires, for example the DRS, were sufficiently sensitive to detect effects of the decision to participate in screening. Despite these limitations, the results of this study are valuable and increase the knowledge on psychological wellbeing of CRC screening participants.

CONCLUSION

In conclusion, there is a certain level of psychological distress up to 6 months among participants who tested false positive in the Dutch bowel cancer screening program. Although differences were small and clinically relevant cut-off values are debatable, an initial positive test result has a negative impact on participants' emotional well-being. Therefore, participants should be informed not only on the assumed benefits of CRC screening such as decreased bowel cancer mortality, but also on the possibility of psychological distress related to screening participation. Yet, despite psychological distress, participants reported no regret about participating to the CRC screening program. Future research should focus on identifying subjects that are likely to develop substantial psychological distress. These patients may benefit from additional counseling or even be advised to decline screening participation.

Acknowledgements

The authors thank H. Putter, professor of Medical Statistics, E. Bastiaannet, assistant professor in Clinical Epidemiology, and M. van Egmond, manager IT and software analyst at the Keizer Clinic, for their contribution to this manuscript.

REFERENCES

1. Lansdorp-Vogelaar I, von Karsa L. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Introduction. *Endoscopy* 2012;44 Suppl 3: Se15-30.
2. von Karsa L, Patnick J, Segnan N, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. *Endoscopy* 2013;45(1): 51-59.
3. Halloran SP, Launoy G, Zappa M. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Faecal occult blood testing. *Endoscopy* 2012;44 Suppl 3: Se65-87.
4. Toes-Zoutendijk E, Kooyker AI, Dekker E, et al. Incidence of Interval Colorectal Cancer After Negative Results From First-round Fecal Immunochemical Screening Tests, by Cutoff Value and Participant Sex and Age. *Clin Gastroenterol Hepatol* 2019.
5. Monitor 2017 Bevolkingsonderzoek Darmkanker.
6. van Leersum N, Snijders H, Henneman D. The Dutch Surgical Colorectal Audit. 2013;39: 1063-1070.
7. Holland JC, Andersen B, Breitbart WS, et al. Distress management. *J Natl Compr Canc Netw* 2010;8(4): 448-485.
8. Simard S, Savard J. Screening and comorbidity of clinical levels of fear of cancer recurrence. *J Cancer Surviv* 2015;9(3): 481-491.
9. Lebel S, Maheu C, Tomei C, et al. Towards the validation of a new, blended theoretical model of fear of cancer recurrence. *Psychooncology* 2018;27(11): 2594-2601.
10. Bancroft EK, Saya S, Page EC, et al. Psychosocial impact of undergoing prostate cancer screening for men with BRCA1 or BRCA2 mutations. *BJU Int* 2019;123(2): 284-292.
11. Douma KF, Aaronson NK, Vasen HF, et al. Psychological distress and use of psychosocial support in familial adenomatous polyposis. *Psychooncology* 2010;19(3): 289-298.
12. Bond M, Pavey T, Welch K, et al. Systematic review of the psychological consequences of false-positive screening mammograms. *Health Technol Assess* 2013;17(13): 1-170, v-vi.
13. Salz T, Richman AR, Brewer NT. Meta-analyses of the effect of false-positive mammograms on generic and specific psychosocial outcomes. *Psychooncology* 2010;19(10): 1026-1034.
14. Vermeer NC, Snijders HS, Holman FA, et al. Colorectal cancer screening: Systematic review of screen-related morbidity and mortality. *Cancer Treat Rev* 2017;54: 87-98.
15. van der Velde JL, Blanker MH, Stegmann ME, de Bock GH, Berger MY, Berendsen AJ. A systematic review of the psychological impact of false-positive colorectal cancer screening: What is the role of the general practitioner? *Eur J Cancer Care (Engl)* 2017;26(3).
16. Bond JH. Polyp guideline: diagnosis, treatment, and surveillance for patients with colorectal polyps. Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 2000;95(11): 3053-3063.
17. Toelichting bij registratie van coloscopieverslagen in het kader van het Bevolkingsonderzoek Darmkanker.
18. Cockburn J, De Luise T, Hurley S, Clover K. Development and validation of the PCQ: a questionnaire to measure the psychological consequences of screening mammography. *Soc Sci Med* 1992;34(10): 1129-1134.
19. Denters MJ, Deutekom M, Essink-Bot ML, Bossuyt PM, Fockens P, Dekker E. FIT false-positives in colorectal cancer screening experience psychological distress up to 6 weeks after colonoscopy. *Support Care Cancer* 2013;21(10): 2809-2815.
20. Custers JAE, Gielissen MFM, Janssen SHV, de Wilt JHW, Prins JB. Fear of cancer recurrence in colorectal cancer survivors. *Support Care Cancer* 2016;24(2): 555-562.
21. Lerman C, Daly M, Masny A, Balshem A. Attitudes about genetic testing for breast-ovarian cancer susceptibility. *J Clin Oncol* 1994;12(4): 843-850.
22. Custers JAE, Kwakkenbos L, van de Wal M, Prins JB, Thewes B. Re-validation and screening capacity of the 6-item version of the Cancer Worry Scale. *Psychooncology* 2018;27(11): 2609-2615.
23. Wilson A, Winner M, Yahanda A, Andreatos N, Ronnekleiv-Kelly S, Pawlik TM. Factors associated with decisional regret among patients undergoing major thoracic and abdominal operations. *Surgery* 2017;161(4): 1058-1066.
24. Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. *Med Decis Making* 2003;23(4): 281-292.
25. Hurwitz LM, Cullen J, Kim DJ, et al. Longitudinal regret after treatment for low- and intermediate-risk prostate cancer. *Cancer* 2017;123(21): 4252-4258.
26. Becerra-Perez MM, Menear M, Turcotte S, Labrecque M, Legare F. More primary care patients regret health decisions if they experienced decisional conflict in the consultation: a secondary analysis of a multicenter descriptive study. *BMC Fam Pract* 2016;17(1): 156.
27. Wyrwich KW, Tierney WM, Babu AN, Kroenke K, Wolinsky FD. A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. *Health Serv Res* 2005;40(2): 577-591.
28. Schulte-van Maaren YW, Carlier IV, Zitman FG, et al. Reference values for generic instruments used in routine outcome monitoring: the Leiden Routine Outcome Monitoring Study. *BMC Psychiatry* 2012;12: 203.
29. Kapidzic A, Korfage IJ, van Dam L, et al. Quality of life in participants of a CRC screening program. *Br J Cancer* 2012;107(8): 1295-1301.
30. Rijnsburger AJ, Essink-Bot ML, van As E, Cockburn J, de Koning HJ. Measuring psychological consequences of screening: adaptation of the psychological consequences questionnaire into Dutch. *Qual Life Res* 2006;15(5): 933-940.

31. Simard S, Thewes B, Humphris G, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. *J Cancer Surviv* 2013;7(3): 300-322.
32. van de Wal M, Langenberg S, Gielissen M, Thewes B, van Oort I, Prins J. Fear of cancer recurrence: a significant concern among partners of prostate cancer survivors. *Psychooncology* 2017;26(12): 2079-2085.
33. Konings IC, Harinck F, Kuenen MA, et al. Factors associated with cancer worries in individuals participating in annual pancreatic cancer surveillance. *Fam Cancer* 2017;16(1): 143-151.
34. Ritvo P, Myers RE, Paszat L, Serenity M, Perez DF, Rabeneck L. Gender differences in attitudes impeding colorectal cancer screening. *BMC Public Health* 2013;13: 500.
35. Wangmar J, von Vogelsang AC, Hultcrantz R, Fritzell K, Wengstrom Y, Jervaeus A. Are anxiety levels associated with the decision to participate in a Swedish colorectal cancer screening programme? A nationwide cross-sectional study. *BMJ Open* 2018;8(12): e025109.
36. Hofmann B, Welch HG. New diagnostic tests: more harm than good. *Bmj* 2017;358: j3314.
37. Kirkoen B, Berstad P, Botteri E, et al. Do no harm: no psychological harm from colorectal cancer screening. *Br J Cancer* 2016;114(5): 497-504.
38. Hestbech MS, Siersma V, Dirksen A, Pedersen JH, Brodersen J. Participation bias in a randomised trial of screening for lung cancer. *Lung Cancer* 2011;73(3): 325-331.
39. Toft EL, Kaae SE, Malmqvist J, Brodersen J. Psychosocial consequences of receiving false-positive colorectal cancer screening results: a qualitative study. *Scand J Prim Health Care* 2019;37(2): 145-154.

APPENDICES

Supplementary Table 1. Median scores of the Psychological Consequence Questionnaire (PCQ) and Cancer Worry Scale (CWS) in function over time, by result of colonoscopy

	Pre-colonoscopy (T1)	Post-colonoscopy (T2)	T1 vs T2 P-value [†]	After six months (T3)	T1 vs T3 P-value [†]
PCQ (0-36)	Median	Median		Median	
No abnormalities	3.0 N=192	1.0	<0.001	2.0 N=159	<0.001
Non-advanced adenoma	4.0 N=326	3.0	<0.001	2.0 N=268	<0.001
Advanced adenoma	4.0 N=333	3.0	0.003	2.0 N=287	<0.001
Cancer	5.0 N=61	9.0	0.01	5.0 N=51	0.86
CWS (6-24)					
No abnormalities	9.0 N=191	7.0	<0.001	7.0 N=157	<0.001
Non-advanced adenoma	9.0 N=319	7.0	<0.001	6.0 N=262	<0.001
Advanced adenoma	9.0 N=333	8.0	0.02	7.0 N=263	<0.001
Cancer	9.5 N=60	10.5	0.008	9.5 N=50	0.81

Note: Significant level set at $P < 0.05$.

Abbreviations: CWS, Cancer Worry Scale, range 6 to 24 with higher scores indicating more cancer worry; NA, not applicable; PCQ, Psychological Consequence Questionnaire, range 0 to 36 with higher scores indicating more psychological dysfunction.

[†] The P-value indicates the significance level of differences in observed scores pre-colonoscopy vs post-colonoscopy and pre-colonoscopy vs after six months using a Wilcoxon signed-rank test.

Supplementary Table 2. Mean scores on the Short Form Health Survey (SF-36) before colonoscopy, after colonoscopy result notification and 6 months after colonoscopy, according to colonoscopy result (no cancer vs cancer)

	No cancer [†]			Cancer			Reference group
	Pre-colonoscopy	Post-colonoscopy	After six months	Pre-colonoscopy	Post-colonoscopy	After six months	
SF-36	N=983	N=840	N=703	N=68	N=60	N=49	N=1294
Physical functioning	90	89	89	91	90	83	93
Role - Physical	91	89	89	90	83	64	87
Bodily Pain	87	87	86	90	91	86	86
Social functioning	91	89	91	92	84	85	90
Mental health	83	81	84	81	75	82	80
Role - Emotional	91	88	90	91	78	76	90
Vitality	78	77	77	79	78	70	69
General health	73	74	74	76	69	69	76

Abbreviations: SF-36 = Short Form Health Survey, score ranges 0-100 with higher score indicating better health-related quality of life.

[†] No cancer includes no abnormalities, non-advanced adenoma, and advanced adenoma.

