Active surveillance as a management option for cervical intraepithelial neoplasia 2: an online experimental study

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ABSTRACT

Objective To investigate framing of active surveillance as a management option for cervical intraepithelial neoplasia (CIN)2 in women of childbearing age.

Methods We conducted a between-subjects factorial (2 × 2) randomised experiment. Women aged 25-40 living in Australia were presented with the same hypothetical pathway of testing human papillomavirus (HPV)-positive, high-grade cytology and a diagnosis of CIN2, through an online survey. They were randomised to one of four groups to evaluate the effects of (i) framing (method of explaining resolution of abnormal cells) and (ii) inclusion of an overtreatment statement (included versus not). Primary outcome was management choice following the scenario: active surveillance or surgery.

Results 1638 women were randomised. Overall, preference for active surveillance was high (78.9%; n=1293/1638). There was no effect of framing or providing overtreatment information, or their interaction, on management choice. After adjusting for intervention received, age, education, and other model covariates, participants were more likely to choose active surveillance over surgery if they had not already had children, had plans for children in the future, had no family history of cancer, had no history of endometriosis, had adequate health literacy, and more trust in their GP. Participants were less likely to choose active surveillance over surgery if they were more predisposed to seek health care for minor problems.

Conclusions Although we found no framing effect across the four conditions, we found a high level of preference for active surveillance with associations of increased preference that accord with the desire to minimise potential risks of CIN2 treatment on obstetric outcomes. These are valuable data for future clinical trials of active surveillance for management of CIN2 in younger women of childbearing age.

Trial registration Australian New Zealand Clinical Trials Registry (ACTRN12618002043213, 20/12/2018, prior to participant enrolment)

INTRODUCTION

The Australian National Cervical Screening Program (NCSP) now utilises primary human papillomavirus (HPV) screening [1]. Australian women who have either HPV16/18, or another high-risk HPV (non 16/18) detected and cervical cytology predictive of atypical squamous cells cannot exclude high-grade squamous intraepithelial lesions (ASC-H) and HSIL (ASC-H+) or any glandular abnormality, are referred for colposcopy. Those with histologically-confirmed low-grade squamous intraepithelial lesions (LSIL) are generally monitored with repeat testing 12 months later, but women with HSIL, including cervical intraepithelial neoplasia (CIN) 2 and 3, are generally recommended to receive immediate treatment [2]. These lesions are potentially premalignant, but are not cancers. Guidelines note that a period of observation (6-12 months) is seen as acceptable for CIN2 in some circumstances, including in women who have not completed childbearing [3]. In Australia, around 70% of histological high-grade cervical abnormalities occur in women aged 25-40 years [4].

The most common treatment for women diagnosed with high-grade cervical abnormalities is large loop excision of the transformation zone (LLETZ). Two systematic reviews have demonstrated the increased risk of obstetric complications following invasive treatment of the cervix such as LLETZ, compared with women not treated [5–7]. For example, there was a pooled relative risk of 1.58 (95%CI 1.37-1.81) for preterm birth <37 weeks and 2.13 (95%CI 1.66-2.75) for preterm birth <32 to 34 weeks [7]. Opportunities to reduce unnecessary treatment in women aged 25 to 40 are desirable as this is when high-grade cervical abnormalities are most commonly found, and where the impact from invasive treatment complications are greatest.

An alternative is active surveillance, which aims to avoid unnecessary treatment and associated treatment-related adverse effects that might lead to significant harms and decrease quality of life, but retain benefits of early detection and treatment of progressive lesions. A proposed protocol for this, supported by the 2012 American Society for Colposcopy and Cervical Pathology consensus guidelines [8], is to monitor women every six months with HPV, cytology and histology biopsies (from colposcopy), and to only treat women if CIN2 persists after two years from when it was first detected, or if it progresses to CIN3 (or worse) at a repeat screening visit. This is an extension to the existing option in Australia to observe (not actively monitor) CIN2 for 6-12 months in some cases [3]. Accumulating evidence suggests that 50% of these high-grade abnormalities (HPV status unknown) may regress to normal within two years [9], with higher rates of regression in younger women (under 30 years of age), but lower rates

(~40%) in those who have high-risk HPV (now the case for virtually all cases in Australia) [9]. The NCSP has taken steps to reduce unnecessary treatment in younger women by no longer recommending screening for women under the age of 25. A recent prospective trial in Australia and New Zealand (PRINCess) demonstrated 64% regression over two years in women under 25 years of age newly diagnosed with biopsy-confirmed CIN2 [10], although this was not confined to HPV-positive lesions. A limitation of these existing studies, however, is that they occurred prior to the introduction of Lower Anogenital Squamous Terminology (LAST) and the requirement (now adopted in Australian guidelines) that histological CIN2 must be positive for the biomarker p16, to improve diagnostic accuracy and reproducibility [11]. As with low-risk cancers such as prostate cancer, ductal carcinoma in situ, and papillary thyroid cancer, there is the potential that some women with CIN2, a potentially premalignant condition but not cancer, could be willing to choose active surveillance.

It is particularly important that women diagnosed with high grade cervical lesions understand that this is not a diagnosis of cancer, as women often confuse the two [12,13]. Framing can be used to contextualise information communicated to women about the potential for regression of cervical lesions and harms of unnecessary treatment, and this may affect the acceptability of active surveillance compared to immediate surgery following the presentation of this information. Both the harms and benefits of all management options need to be presented to women in a way that enables them to make an informed choice about their management. Changes to any cancer screening program can be contentious, and acceptability to women who may be potential patients is essential in the implementation of a new management option [14] to ensure informed choice, engagement and adherence to active surveillance. Using gain-framing (representing the positive outcomes of undertaking a particular behaviour) in addition to clear terminology to explain the natural regression process, this study aimed to investigate framing of communication about active surveillance as a management option for CIN2 in screen-eligible women of childbearing age.

METHODS

Participants

Australian women aged 25-40 years were invited to participate in the study between 25th October and 3rd November 2019 using a third party (*Dynata*) who have extensive online panels of participants (~600,000) taking part in research for credits towards small rewards. *Dynata* can approach panel members who meet the study eligibility criteria. Participants on their database have already indicated that they are willing to participate in online research. To avoid including

multiple responses from the same participant, we confirmed that that there were no duplicate IP addresses or Personal Identification numbers. Women were eligible if they lived in Australia, had not previously been diagnosed with cervical cancer, CIN2 or worse, and had not had a previous hysterectomy. Women over 40 years of age were not invited as fewer than 5% of births are in mothers aged 40 or over [15].

Design

In this online study, the participants were all presented with the same hypothetical scenario typical of a real-life pathway of screen-detected HPV, and diagnosis of CIN2 following further investigation. Women were randomly assigned to one of four groups using a between-subjects factorial (2 × 2) design to evaluate the effects of (i) framing of how regression was explained (natural clearance versus normal regression), (ii) inclusion of an overtreatment statement (overtreatment statement versus no information) and (iii) interaction between framing and overtreatment statement (Figure 1; S1).

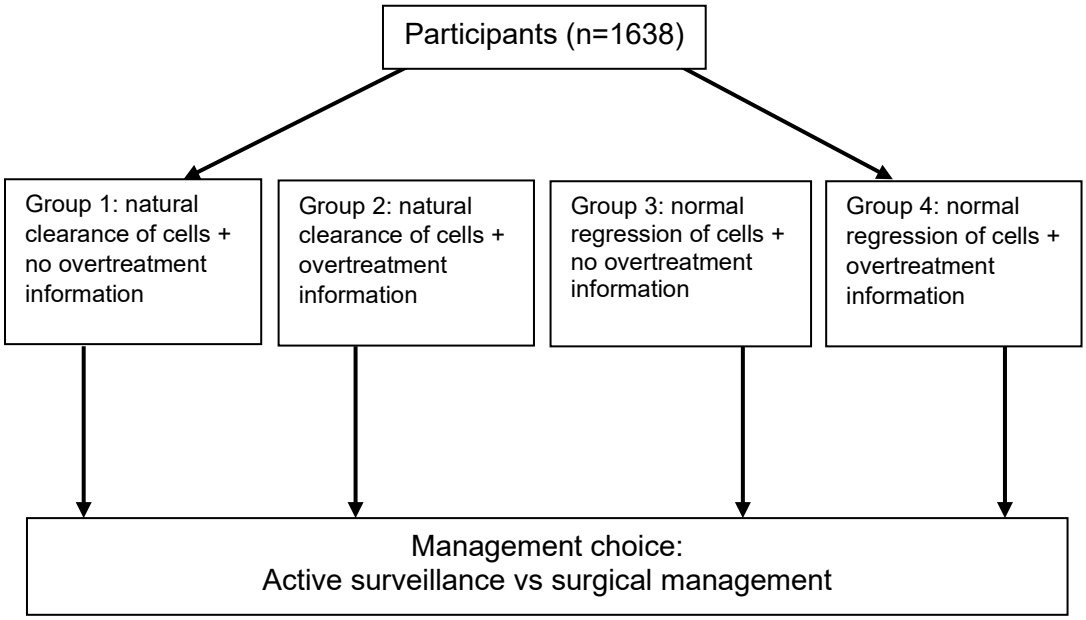

Figure 1: Study design

Scenarios

Prior to the intervention, women were given information about the changes to the NCSP, HPV, and what their results from the renewed NCSP would look like. The hypothetical scenario and framing are presented in Box 1.

Box 1: Scenarios and framing statements

Hypothetical scenario of doctor's visit

Women were asked to imagine they had returned to their doctor to receive their cervical screening test results. All women were presented with a hypothetical pathway of a positive HPV screening test, high-grade cytological abnormalities, and diagnosis of CIN2 (see S1).

Framing of regression

Participants were randomised to receive one of two statements differing in the way that resolution of abnormal cells was framed: 1) 'For 5 out of 10 women your age, *the body can naturally clear the HPV infection and abnormal cells itself* within 2 years without the need for treatment ('natural clearance'); or 2) For 5 out of 10 women your age, *the HPV infection and abnormal cells will return to normal* within 2 years without the need for treatment ('normal regression'). We used the term 'natural' in two of the four conditions to try and counterbalance any potential cancer bias and investigate if the use of this discourse influences women's perceived need for invasive treatment.

Overtreatment information

Participants were randomised to receive either a statement about overtreatment or not: 1) *This means that you do not have surgery now and it can help avoid unnecessary treatment, also referred to as overtreatment. But if it stays the same or gets better, surgery would be unnecessary and potentially harmful*; or 2) *This means that you do not have surgery now. But if your cells stay the same or get better, surgery would be not needed*. We included the overtreatment statement in two of the four conditions to investigate whether directly stating that the treatment might be *unnecessary and potentially harmful* would influence women's treatment choice.

Procedure

Consenting participants completed an online survey (S2) hosted on Qualtrics. Firstly, women completed a range of demographic (e.g. age, education) and clinical questions (e.g. family planning status, cervical cancer/cervical abnormalities history). Health literacy (Single Item Literacy Screener) [16] and general numeracy [17] were also measured. Participants were also asked about their perceived risk of cervical cancer (lifetime [18] and relative to a woman of the same age [19]), cancer worry [20], anxiety [21], predisposition for seeking healthcare (medical

minimiser/maximiser) [22], screening intentions, trust in GP [23], tolerance of uncertainty [24] and preferences for involvement in decision-making [25].

Following this, participants were presented with the hypothetical scenario and randomised to receive one of the two framings of abnormal cells resolving, with or without the overtreatment statement. Participants were instructed to keep the diagnosis given in the scenario in mind whilst completing the questionnaire.

The primary outcome was management choice, measured as a direct dichotomous choice between surgery and active surveillance. Participants were also asked to give a reason for their management choice (data reported elsewhere). Secondary outcomes included diagnosis anxiety and treatment choice anxiety [26], perceived seriousness of the diagnosis [18], cancer worry [20], perceived risk of cervical cancer [18,19]; and preferences for frequency of monitoring. More detail of the measures is included in S2. Participants were also asked whether they understood the information presented to them and whether any of this information was new to them.

Analysis

The protocol planned for a sample size of 400 participants in each arm, for an overall total of 1600 women. Sample size was calculated to provide 90% power, at the 5% significance level, to detect a difference in the proportions of women opting for immediate surgery across the four randomised arms assuming these proportions are 65%, 70%, 75% and 80%. The difference in these proportions correspond to a small effect size [27] yet would still be of clinical relevance given around 60% of women diagnosed with CIN2 in Australia prior to the NCSP changes were aged 25-39 [4].

Descriptive statistics (mean and standard deviation for continuous variables, frequency and relative frequency for categorical variables) were calculated for sample characteristics and understanding of information variables. Analyses of primary and secondary outcomes were conducted using regression models, with framing (natural clearance vs normal regression), overtreatment information (provided vs not provided), and their interaction, included in all models. Continuous outcomes were analysed using linear models. Categorical outcomes were analysed using generalised linear models with a modified Poisson approach [28], allowing estimation of relative risks and corresponding confidence intervals by using robust error variances. Exploratory analyses to identify factors associated with choosing active surveillance over surgery included all conceptually plausible study covariates as potential predictors. Age

and education have been included in all models but not reported. All analyses were conducted using Stata/IC v16.1 (Stata Corp., College Station, Texas, US). The study statistician was blinded to randomised allocation until completion of primary data analysis.

The study was registered in the Australian New Zealand Clinical Trials Registry (ACTRN12618002043213, 20/12/2018). This study received ethical approval from The University of Sydney (2018/857).

RESULTS

Sample characteristics

Of 2121 women who clicked through to the survey, 2034 agreed to participate. Of these 2034, 251 were not eligible (too young/old, not female, not living in Australia, previously diagnosed with cervical cancer or a high-grade cervical abnormality, hysterectomy); 116 did not complete the survey to the randomisation point; and 29 did not complete the survey after randomisation (Figure 2). A total of 1638 eligible women participated.

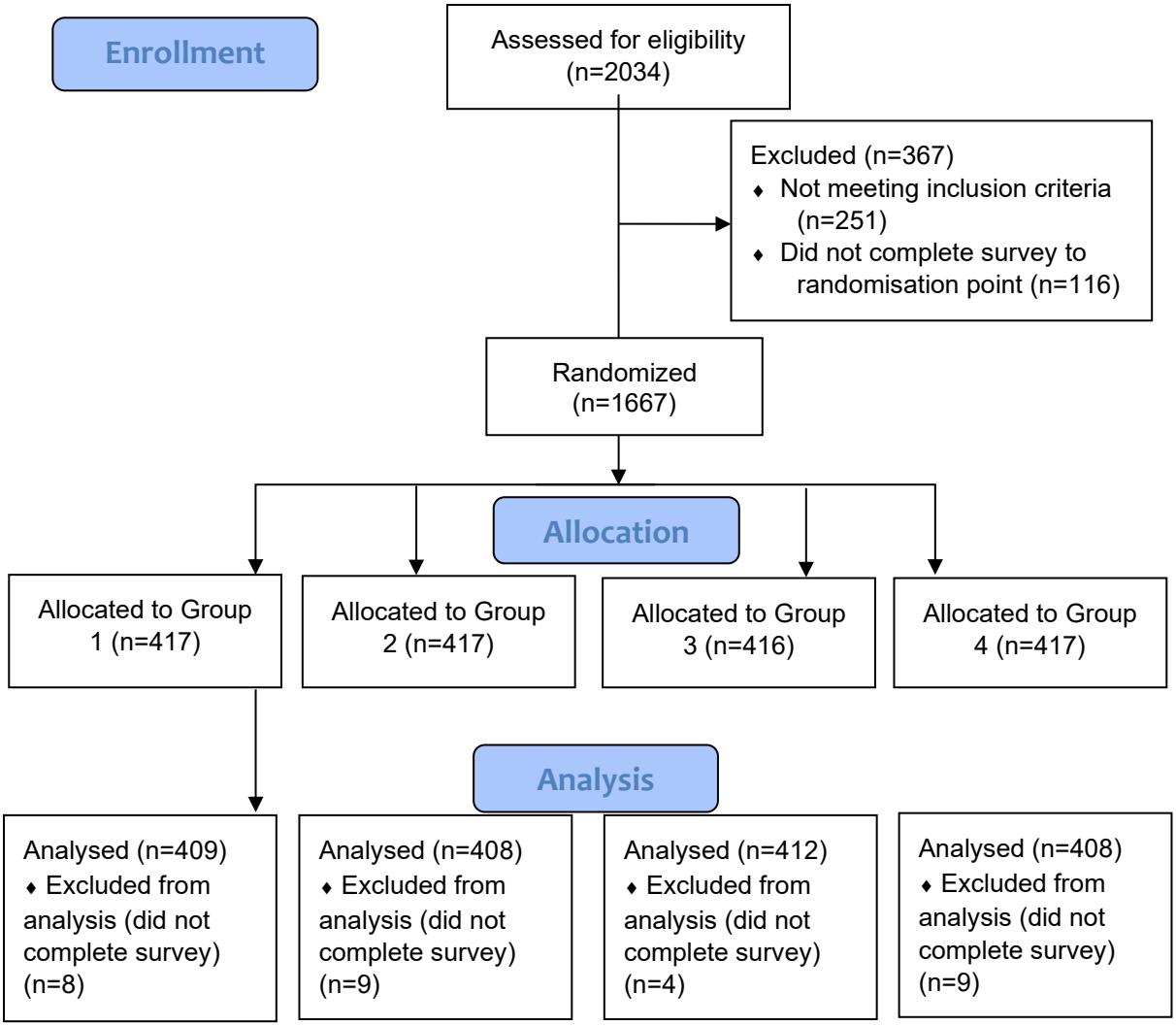

Figure 2: CONSORT Flow Diagram

Table 1 shows the sample characteristics. Comparable to nationally representative data (Australian Bureau of Statistics) for this age group, the majority had a university degree, diploma or certificate (71%; n=1159/1638), were in a relationship (70%; n=1141/1638) and had given birth to one or more biological child (56%; n=913/1638; Table 1). Compared to same-age women in Australia, women who completed the survey were more likely to have been born in Australia, but less likely to and to identify as Aboriginal or Torres Strait Islander, speak a language other than English at home, to have ever tested HPV-positive, and to earn less than $80,000 per year. Almost 50% (n=812/1638) had plans to have biological children in the future. Compared to same-age women in Australia, women who completed the survey were slightly more likely to have received the HPV vaccine, but less likely to have attended cervical screening in the past, and have previously tested positive for HPV. Of the sample, 16.2%

(n=265/1638) reported having previously been diagnosed with low grade abnormal cells or were unsure of what type – women diagnosed with high-grade abnormalities were excluded from the study. A high proportion of the sample preferred to either make the final decision about their treatment or share the decision with their doctor (91%; n=1485/1638) and had adequate health literacy (89%; 1451/1638), and 62% (n=1022/1638) of the sample correctly answered all numeracy scale items.

Table 1: Sample characteristics (n=1638). Data are displayed as n (%) unless otherwise specified.

Sample	Group 1: NC (n=409)	Group 2:NC+O (n=409)	Group 3:NR (n=412)	Group 4:NR+O (n=408)	All sample	Relevant population distribution where available[36,37] (%)
Age (years; SD)	31.86 (4.58)	31.84 (4.41)	32.09 (4.42)	31.90 (4.34)	31.92 (4.44)	32.34
Education[a]						
High	289 (70.7)	291 (71.1)	292 (70.9)	287 (70.3)	1159 (70.8)	65.0
Medium	89 (21.8)	81 (19.8)	81 (19.7)	87 (21.3)	338 (20.6)	23.5
Low	31 (7.6)	37 (9.1)	39 (9.5)	34 (8.3)	141 (8.6)	1.7
Occupation[b]						
Full-time	164 (40.1)	151 (36.9)	174 (42.2)	158 (38.7)	646 (39.5)	Employed full-time: 36.7
Part time	122 (29.8)	113 (27.6)	107 (26.0)	122 (29.9)	464 (28.3)	Employed part-time: 26.0
Studying	29 (7.1)	21 (5.1)	35 (8.5)	30 (7.4)	115 (7.0)	
Other	94 (23.0)	124 (30.3)	96 (23.3)	98 (24.0)	412 (25.2)	37.4
Income						
Less than $80,000 per year	198 (48.4)	201 (49.1)	188 (45.6)	187 (45.9)	774 (47.3)	Negative income to $77,999: 77.8
Between $80,000 and $120,000 per year	96 (23.5)	86 (21.0)	88 (21.4)	103 (25.2)	373 (22.8)	$78,000 to $103,999: 9.3
More than $120,000 per year	92 (22.5)	90 (22.0)	103 (25.0)	91 (22.3)	376 (23.0)	$104,000 to $156,000 or more: 5.4
Prefer not to say	23 (5.6)	32 (7.8)	33 (8.0)	27 (6.6)	115 (7.0)	Not stated: 7.5
Relationship status[c]						
Single	122 (29.8)	113 (27.6)	100 (24.3)	108 (26.5)	443 (27.0)	Not married: 30.0

In a relationship	248 (69.0)	288 (69.5)	306 (74.3)	299 (73.3)	1141 (69.7)	Married or in a de facto relationship: 60.3
Other	5 (1.2)	8 (1.9)	6 (1.4)	1 (0.2)	20 (1.2)	
Born in Australia	329 (80.4)	335 (81.9)	334 (81.1)	325 (79.7)	1323 (80.8)	64.0
Aboriginal/Torres Strait Islander/ Aboriginal and Torres Strait Islander	13 (3.9)	14 (3.4)	13 (3.1)	22 (5.4)	62 (3.8)	2.5
Main language other than English at home: yes	25 (6.1)	27 (6.6)	26 (6.3)	23 (5.6)	101 (6.2)	28.1
Given birth to own biological children: yes	222 (54.3)	242 (59.2)	216 (52.4)	233 (57.1)	933 (57.0)	53.1
Future plans for own biological children: yes	202 (49.4)	191 (46.7)	213 (51.7)	206 (50.5)	812 (49.6)	
Received HPV vaccine: yes	197 (48.2)	202 (49.4)	195 (47.3)	218 (53.4)	812 (49.6)	43.9
Attended cervical screening*: yes	190 (46.5)	192 (46.9)	203 (49.3)	205 (50.2)	790 (48.2)	
2-year screening participation	170 (41.6)	143 (35.0)	152 (36.9)	153 (37.5)	618 (37.7)	48.5[d]
Most recent cervical screening						
Within 6 months	78 (11.7)	57 (13.9)	59 (14.4)	47 (11.5)	241 (14.7)	
6-12 months	38 (9.3)	40 (9.8)	43 (10.4)	45 (11.0)	166 (10.1)	
12-18 months	34 (8.3)	26 (6.4)	30 (7.3)	32 (7.8)	122 (7.5)	
18 months to 2 years	20 (4.9)	20 (4.9)	20 (4.9)	29 (7.1)	89 (5.4)	
2 years plus	41 (10.0)	38 (9.3)	42 (10.2)	48 (11.8)	169 (10.3)	
Unsure	9 (2.2)	11 (2.7)	9 (2.2)	4 (1.0)	33 (2.0)	
Ever tested positive for HPV						Oncogenic HPV (any type) detected
Yes	39 (9.5)	30 (7.3)	33 (8.0)	40 (9.8)	142 (8.7)	13.6[d]
Ever diagnosed with abnormal cells						
Yes – low grade or CIN1	37 (61.7)	48 (72.7)	48 (71.6)	51 (70.8)	184 (69.4)	
Yes – don't know type	23 (38.33)	18 (27.3)	19 (28.4)	21 (29.2)	81 (30.6)	
Preferences for treatment decision-making						

I make the decision about which treatment I will receive	88 (21.5)	99 (24.2)	88 (21.4)	88 (21.6)	363 (22.2)	
I make the final decision about my treatment after seriously considering my doctor's opinion	169 (41.3)	156 (38.1)	166 (40.3)	156 (38.2)	647 (39.5)	
My doctor and I share responsibility for deciding which treatment is best for me	118 (28.9)	114 (27.9)	120 (29.1)	123 (30.1)	475 (29.0)	
My doctor makes the final decision about which treatment will be used, but seriously considers my opinion	26 (6.4)	34 (8.3)	32 (7.8)	31 (7.6)	123 (7.5)	
I leave all decisions regarding my treatment to my doctor	8 (2.0)	6 (1.5)	6 (1.5)	10 (2.5)	30 (1.8)	
Family history of cancer: yes	112 (27.4)	112 (27.4)	114 (27.7)	122 (29.9)	460 (28.1)	
History of Endometriosis	36 (8.8)	32 (7.8)	41 (10.0)	36 (8.8)	145 (8.9)	
Perceived relative risk (/5), mean (SD)	2.59 (0.88)	2.53 (0.92)	2.59 (0.88)	2.57 (0.87)	2.57 (0.89)	
Cancer worry (/4), mean (SD)	1.95 (0.77)	1.78 (0.74)	1.85 (0.78)	1.93 (0.77)	1.88 (0.76)	
STAI[e] Total, mean (SD) (/80)	44.35 (12.89)	44.61 (12.93)	43.45 (12.91)	45.78 (13.57)	44.55 (13.09)	
Trust in GP (/7), mean (SD)	5.51 (1.25)	5.39 (1.36)	5.44 (1.30)	5.58 (1.22)	5.50 (1.26)	
Medical Minimiser / Maximiser[f] (/6), mean (SD)	4.09 (1.15)	4.16 (1.18)	4.16 (1.15)	4.09 (1.20)	4.16 (1.13)	
Health literacy[g]						
Adequate	360 (88.0)	364 (89.0)	371 (90.0)	356 (87.3)	1451 (88.6)	
Inadequate	49 (12.0)	45 (11.0)	41 (10.0)	52 (12.7)	187 (11.4)	
Numeracy						
All four items correct	273 (66.7)	256 (62.6)	240 (58.3)	253 (62.0)	1022 (62.4)	

[a] Education split into high (university degree, diploma or certificate), medium (trade apprenticeship or higher school certificate/ Leaving certificate) and low (school certificate/ Intermediate certificate or less or no school / other qualification). Population data from Census 2016: high (postgraduate, bachelor degree, advanced diploma, certificate 3 and 4), medium (year 10 and above, certificate 1, 2 level) and low (year 9 or below and no educational attainment)

[b] Population data from Census 2016: 'Other' (not in labour force, employed but away from work, unemployed, unemployed looking for full time work, unemployed looking for part time work or not stated)

[c] Population data for relationship status based off 2016 Census 'social marital status' (married in a registered marriage, married in a de facto marriage, not married and not applicable)

[d] Population data from AIHW Cervical Screening monitoring report 2019. Table A1.1; Table A6.1: HPV positivity for women aged 25-39
[e] STAI: State trait anxiety inventory. Higher scores indicate higher levels of anxiety.
[f] Medical Minimiser/Maximiser: Scores between 1-3 indicate medical minimizing and scores between 4-6 indicate medical maximising.
[g] from Single Item Literacy Screener: '*how often do you need to have someone help you when you read instructions, pamphlets or other written material from your doctor or pharmacy?'* Never/Rarely is adequate, and Sometimes/Often/Always is inadequate
NC=natural clearance; NC+O=natural clearance + overtreatment statement; NR=normal regression; NR+O=normal regression + overtreatment statement

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203 **Understanding of information**

204 Most women found the information easy to understand (83.5%) and that there was information
205 new to them (76.9%, Table 2). Of these 76.9%, the information that was most commonly
206 reported as new was that abnormal cells can sometimes clear without treatment (68.3%),
207 followed by that it takes many years for abnormal cells to progress to cancer (56.1%), surgical
208 treatment for abnormal cells can raise the risk of problems in pregnancy (49.3%), and that
209 abnormal cells are not cervical cancer (44.1%).

Table 2: Women's ease of understanding the information and new information

	Total N (%)	Group 1: NC (n=409)	Group 2: NC+O (n=408)	Group 3: NR (n=412)	Group 4: NR+O (n=408)
How easy or difficult was it to understand the information given to you in the scenario?					
Very easy/easy	1069 (65.3)	253 (61.8)	268 (65.6)	281 (68.2)	267 (65.5)
Somewhat easy	298 (18.2)	88 (21.5)	71 (17.4)	73 (17.7)	66 (16.2)
Moderate	227 (35.6)	57 (13.9)	57 (13.9)	47 (11.4)	66 (16.2)
Somewhat difficult	31 (1.9)	6 (1.5)	9 (2.2)	9 (2.2)	7 (1.7)
Difficult/Very difficult	12 (0.7)	5 (1.2)	3 (0.7)	2 (0.4)	2 (0.4)
Was any of the information you read today new to you? (yes)	1259 (76.9)	310 (75.8)	326 (79.7)	314 (76.2)	309 (75.7)
Abnormal cells are not cervical cancer	555 (44.1)	123 (30.1)	144 (35.2)	144 (35.0)	144 (35.3)
It takes many years for abnormal cells to progress to cancer	706 (56.1)	163 (39.9)	182 (44.5)	176 (42.7)	185 (45.3)
Abnormal cells can sometimes clear without treatment	860 (68.3)	219 (53.5)	217 (53.1)	212 (51.5)	212 (52.0)
Surgical treatment for abnormal cells can raise the risk of problems in pregnancy	621 (49.3)	149 (36.4)	158 (38.6)	155 (37.6)	159 (39.0)

NC=natural clearance; NC+O=natural clearance + overtreatment statement; NR=normal regression; NR+O=normal regression + overtreatment statement

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Effect of framing and overtreatment information

Management choice

A high proportion of women indicated they would choose active surveillance over surgery (78.9% overall). We found no evidence that management choice was influenced by the method of framing the information about abnormal cells resolving ($\chi^2(1) = 0.88$, $p = 0.35$), the provision of overtreatment information ($\chi^2(1) = 2.14$, $p = 0.14$), or their interaction ($\chi^2(1) < 0.01$, $p = 0.99$).

Diagnosis and management choice anxiety

There was no evidence that diagnosis anxiety was influenced by method of framing ($F(1,1634) = 0.43$, $p = 0.51$), provision of overtreatment information ($F(1,1634) = 0.38$, $p = 0.54$), or their interaction ($F(1,1634) = 0.11$, $p = 0.74$). No pairwise comparisons between groups were statistically significant (all $p \geq 0.37$). For management choice anxiety, there was also no evidence of an effect of framing ($F(1,1634)=0.17$, $p=0.68$) or overtreatment information provision ($F(1,1634)=1.22$, $p=0.27$), nor interaction ($F(1,1634)=0.07$, $p=0.79$).

Similarly, there was no evidence that the perceived seriousness of the CIN2 diagnosis differed between randomised groups (framing: $F(1,1634)=0.94$, $p=0.33$; overtreatment information: $F(1,1634)=0.01$, $p=0.90$) or an interaction ($F(1,1634)=0.07$, $p=0.79$).

After controlling for baseline perceived lifetime risk, there was still no evidence of an effect of framing ($F(1,1633)=0.01$, $p=0.93$), providing overtreatment information ($F(1,1633)=0.08$, $p=0.78$) or their interaction ($F(1,1633)=1.17$, $p=0.28$). Similarly, after controlling for baseline perceived relative risk, there was no evidence of an effect of framing ($F(1,1633)=0.02$, $p=0.88$), providing overtreatment information ($F(1,1633)<0.01$, $p =0.97$) or their interaction ($F(1,1633)=1.12$, $p=0.29$).

Exploratory associations of choosing active surveillance over surgery

In unadjusted analyses, women who chose active surveillance had lower diagnosis anxiety ($t(1636)=6.42$, $p<0.001$, mean difference [MD]: 0.87, 95% CI 0.60 to 1.13), lower management choice anxiety ($t(1636)=11.78$, $p<0.001$, MD:1.65, 95% CI 01.38 to 1.92), lower perceived seriousness of the condition ($t(1636)=2.09$, $p=0.037$, MD:0.11, 95% CI 0.01 to 0.22) and lower cancer worry ($t(1636)=3.31$, $p<0.001$, MD:0.18, 95%CI: 0.07 to 0.28) compared to women who chose surgery.

After adjusting for age, education and all other model covariates, participants were more likely to choose active surveillance over surgery if they did not already have children (adjusted relative

risk [aRR]=1.14, 95%CI 1.08-1.20), had plans for children in the future (aRR=1.13, 95%CI 1.06-1.21) or were unsure (aRR=1.14, 95%CI 1.06-1.23), had no family history of cancer (aRR=1.08, 95%CI 1.02-1.14), no history of endometriosis (aRR=1.13, 95%CI 1.02-1.27), were less predisposed to seek health care even for minor problems (a medical minimiser) (aRR per unit increase=0.94, 95%CI 0.92-0.96), had adequate health literacy (aRR=1.13, 95%CI 1.06-1.21), and more trust in their GP (aRR=1.02, 95%CI 1.00-1.04) (Table 3).

Table 3: Multivariable model^ examining factors associated with choosing active surveillance over surgery (n=1638)

Factor	Adjusted Relative Risk	95% CI	p-value
Do not already have children (relative to one or more child)	1.14	1.08, 1.20	**<0.001**
Plans for future children (relative to no)			**<0.001**
Yes	1.13	1.06, 1.21	
Don't Know	1.14	1.06, 1.23	
HPV status history[a] (relative to no)			0.75
Ever positive	1.03	0.95, 1.13	
Don't Know	1.01	0.88, 1.16	
No family history of cancer	1.08	1.02, 1.14	**0.014**
No history of Endometriosis[b]	1.13	1.02, 1.27	**0.024**
Perceived relative risk (/unit)	0.99	0.96, 1.02	0.46
Cancer worry (/unit)	0.98	0.95, 1.01	0.14
STAI[c] Total (/unit)	0.998	0.996, 0.999	**0.030**
Trust in GP (/unit)	1.02	1.003, 1.04	**0.025**
Medical Minimiser / Maximiser (/unit)	0.94	0.92, 0.96	**<0.001**
Adequate health literacy	1.13	1.06, 1.21	**<0.001**
Tolerance of uncertainty	1.00	0.99, 1.00	0.13

^ Model controls for intervention received, age and education

[a]No may include those not tested, as the question asked 'Has a doctor ever told you that you have tested positive for the human papillomavirus (HPV)?'

[b] no other reported endocervical condition history was associated with the outcome and therefore was excluded from the model

[c]STAI: State-Trait Anxiety Inventory

Factors associated with continuing to choose active surveillance over surgery at 12 months

Of the 1293 women who initially chose active surveillance, 378 (29.2%) indicated that they would opt for surgery at 12 months if CIN2 had not regressed. After adjusting for all other covariates, women with lower cancer worry (aRR per unit increase = 0.89, 95%CI 0.85-0.93) and who are medical minimisers (aRR per unit increase = 0.96, 95%CI 0.94-0.99) were more likely to continue choosing active surveillance over surgery at 12 months if CIN2 had not regressed.

Table 4: Multivariable model^ examining factors associated with continuing to choose active monitoring over surgery at 12 months (n=1293)

Factor	Adjusted Relative Risk	95% CI	p-value
Do not already have children (relative to one or more child)	1.06	0.98, 1.14	0.15
Plans for future children (relative to no)			0.21
Yes	1.08	0.99, 1.18	
Don't Know	1.05	0.95, 1.16	
HPV status history[a] (relative to no)			0.65
Ever Positive	1.05	0.93, 1.19	
Don't Know	0.97	00.79, 1.18	
No family history of cancer	1.06	0.98, 1.15	0.16
No history of Endometriosis[b]	1.11	0.95, 1.29	0.18
Perceived relative risk (/unit)	1.01	0.97, 1.06	0.51
Cancer worry (/unit)	0.89	0.85, 0.93	**<0.001**
STAI[c] Total (/unit)	1.00	1.00, 1.00	0.41
Trust in GP (/unit)	1.00	0.97, 1.02	0.77
Medical Minimiser / Maximiser (/unit)	0.96	0.94, 0.99	**0.019**
Adequate health literacy	1.01	0.93, 1.10	0.75
Tolerance of uncertainty	1.00	0.99, 1.00	0.34

^ Model controls for intervention received, age and education

[a] No may include those not tested, as the question asked 'Has a doctor ever told you that you have tested positive for the human papillomavirus (HPV)?'

[b] no other reported endocervical condition history was associated with the outcome and therefore was excluded from the model

[c]STAI: State-Trait Anxiety Inventory

Preferences for frequency of active surveillance

Of the 1293 women who initially chose active surveillance, 46.7% (n=604/1293) preferred to be monitored every 6 months, followed by 35.4% (n=458/1293) every 3 months. Of the 915 women who chose to continue active surveillance at 12 months, 43.5% (n=398/915) still preferred to be monitored every 6 months, followed by 38.5% (n=352/915) every 3 months. Of the 378 women opting for surgery at 12 months, 51.1% (n=193/378) said they would need to be monitored every 3 months if they were to consider continuing active surveillance, with 21.4% (n=81/378) every 6 months.

DISCUSSION

Statement of principal findings

This is the first study internationally to investigate the acceptability of active surveillance management of CIN2 to younger women of childbearing age. Overall, 79% of women chose active surveillance when presented with a hypothetical diagnosis of CIN2 and information about

CIN2 regression. We found no effect of framing the regression information or of providing information about the potential for unnecessary treatment (overtreatment) on management choice, diagnosis anxiety or management choice anxiety. Factors associated with choosing active surveillance included not having children at present, had plans for future children, no family history of cancer, a greater trust in GP, being less predisposed to seek health care for minor problems, or higher health literacy. Of the 79% of women who had chosen active surveillance at diagnosis, most (71%) chose to continue with active surveillance if CIN2 persisted at 12 months.

Strengths and limitations

A growing body of evidence suggests that in many cases CIN2 may resolve within 2 years if left untreated. We conducted a large randomised online experimental study to present women with this evidence and investigate the effect of framing and information about overtreatment on women's choice of management. The hypothetical scenario was carefully developed to be easily understood and was extensively pilot tested and expertly reviewed. The HPV type detected was not specified in the scenario and therefore the estimates of regression may be high for some types of HPV. Recruitment through a market research panel helped us to achieve a broad sample which included women who varied in education, relationship status, screening attendance, plans for their own biological children, health literacy, and numeracy. The sample compares closely to the population statistics for 25-40-year-old women in terms of education and relationship status, but were more likely to have been born in Australia, and less likely to be Indigenous, speak a language other than English at home, and to have attended for cervical screening in the last two years. This therefore limits our ability to generalise these findings to some populations, particularly given the large migrant population in Australia who may be less engaged with screening. The hypothetical nature of the experiment limits applicability to women faced with these real decisions, however this is the most appropriate method due to there being ethical issues with discussing management options where some are not currently offered. Although this was generally new information for these women, this is not surprising as these women had never been diagnosed with CIN2 or worse. Our study does not provide evidence on whether or not women who have been treated previously are aware of this information. Hypothetical scenarios also enabled us to test acceptability before further research in a real-life setting of women undergoing cervical screening.

Implications and future research

Previous studies investigating management choice in prostate and thyroid cancer [29–31] have mainly utilised discrete choice experiments to examine trade-offs patients would make between different aspects of active surveillance and surgery. We are not aware of other research investigating factors which may affect women's management choice for CIN2. The purpose of this experimental study was to examine whether active surveillance was an acceptable choice if women were presented with information about regression rates of CIN2 and told that these are not cervical cancer. We were limited by the available data in the estimates of CIN2 regression rates that we could provide; these regression rates should ideally be re-estimated by studies in younger women that take into account both HPV and p16 status. Some trade-offs which could be examined in future research include the frequency of surveillance, costs, and risks associated with treatment, which have been found to be important in previous thyroid and prostate cancer experimental studies [29,30].

As there was no effect of framing or overtreatment information on any primary outcomes, this suggests that the manner in which regression is framed, and the inclusion of overtreatment information, may not impact women's management choice. It may also be that the framing chosen for these scenarios were not different enough to have an effect, and the overtreatment information needs to be stronger and more explicit. However, communicating evidence-based information in a clear and easy to read way is essential to support shared decision making. Almost 80% of women said the information provided in this study was easy to understand, but this was lower for those with lower health literacy (data not shown). It is therefore important that decision aids are developed to also address the needs of adults with lower health literacy [32]. Those with lower health literacy have been previously shown to prefer more invasive treatment options [29]. A previous experiment with patients and urologists for prostate cancer found that although management preferences for active surveillance than surgery/radiotherapy may be similar between patients and urologists, the trade-offs for specific treatment aspects are different [31]. For example, patient's management preferences were not influenced by risk of erectile dysfunction from radiotherapy, yet urologists' management preferences were. This demonstrates the importance of shared decision making for patient treatment decisions.

Understanding women's information needs and preferences, such as acceptability of active surveillance and how to offer the option to women, may be used to support a clinical randomised controlled trial (RCT) comparing active surveillance with surgical treatment in CIN2. Clinicians play an essential role in communicating about the benefits and harms, and monitoring patient's emotional health during active surveillance to address any worries which may lead

patients to seek more intensive treatment even when this is not recommended or required. Therefore, further in-depth research with both women and clinicians is required to explore the information and support needs of both.

Prior to any potential implementation of active surveillance following a RCT, there is a need to consider optimal surveillance strategies that can be applied on a large scale, physician and patient acceptability, which women would be appropriate candidates for active surveillance, and consider how to address patient harm, including patient worry [14]. Our study shows that women who desire children in the future but have not yet started or completed their family may be most willing to consider active surveillance protocols for the management of CIN2. This would potentially optimise the benefit versus harm trade-offs for this group.

Based on previous research for prostate cancer, some factors may increase women's comfort in choosing to continue with active surveillance, such as providing further information and psychosocial support [33]. Considering how to address these may also help uptake and continuance of active surveillance in trials comparing active surveillance with surgery, such as those currently underway for ductal carcinoma in situ [34]. Patients with characteristics of feeling anxious or depressed may prefer immediate treatment, as shown previously in a prostate discrete choice experiment [31]. As active surveillance for CIN2 is an intervention for the prevention of cancer rather than the treatment of cancer, it may be that by making clear the distinction between CIN2 and cervical cancer to these women, active surveillance may be deemed more acceptable than in other situations where patients are diagnosed with cancer, albeit low-risk.

Existing research does not provide data on CIN2 as it is now diagnosed in Australia, through screening positive for HPV and the biomarker p16, as according to LAST. As LAST is now being widely adopted, previous estimates of CIN2 regression are potentially overestimates. Therefore, in order to provide women with accurate information to make an informed choice about their management of CIN2, further research is needed to characterise CIN2 regression in the LAST era.

An additional consideration in the current climate of COVID-19, is that the LLETZ procedure may release SARS-CoV-2 viral particles during its procedures [35], and therefore effective alternatives involving less invasive treatment could reduce harm to clinicians and patients and will have added national and international significance post COVID19.

Conclusions

This experimental study provides evidence from a hypothetical scenario that active surveillance might be acceptable to women diagnosed with CIN2 who are provided with information about the likelihood of it resolving without treatment, paving the way for future clinical trials. Although we found no effect of framing or including information about overtreatment, we could identify women who are most likely to choose active surveillance: women who desire children in the future, have no family history of cancer, greater trust in their GP, and higher health literacy; and those less predisposed to seek health care for minor problems. This exploratory analysis has established a need for further hypothesis generating and testing of causal pathways for choosing active surveillance over surgery, which would help shape shared discussions in clinical practice.

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Data sharing: Study data may be made available on request to accredited researchers who gain ethical approval.

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S1: Scenarios provided for all four groups

Group 1: Natural Clearance

Try to imagine how you would feel if this was you. You have just had the new cervical screening test and returned to the doctor for your results. Your results show that you have HPV. Your cells were checked for physical changes and high-grade abnormalities were detected. This means you have a higher risk of a significant abnormality. You were sent for a colposcopy and it showed that you have grade 2 abnormal cells in your cervix. Abnormal cells are graded from low to high (1 to 3). These are not cervical cancer. If these abnormal cells progress to invasive cervical cancer they could affect your health if left untreated. This is not usual and happens to around 1 out of 200 women, so for the 199 women these cells do not progress to cancer. It can take many years for this to take place. **For 5 out of 10 women your age, the body can naturally clear the HPV infection and abnormal cells itself within 2 years without the need for treatment.** Normal treatment for abnormal cells is surgery to remove the cells. Surgical treatment can raise the risk of problems in pregnancy, such as preterm delivery and late miscarriages. I suggest you consider a new management option called active monitoring. **This means that you do not have surgery now.** Instead I will keep a close eye on your abnormal cells with regular testing every 6 months (same cervical screening test as before and colposcopy) to see if your body naturally clears the virus. If there are any changes the specialist doctor will recommend surgery. **But if your cells stay the same or get better, surgery would be not needed.**

Group 2: Natural Clearance and Overtreatment statement

Try to imagine how you would feel if this was you. You have just had the new cervical screening test and returned to the doctor for your results. Your results show that you have HPV. Your cells were checked for physical changes and high-grade abnormalities were detected. This means you have a higher risk of a significant abnormality. You were sent for a colposcopy and it showed that you have grade 2 abnormal cells in your cervix. Abnormal cells are graded from low to high (1 to 3). These are not cervical cancer. If these abnormal cells progress to invasive cervical cancer they could affect your health if left untreated. This is not usual and happens to around 1 out of 200 women, so for the 199 women these cells do not progress to cancer. It can take many years for this to take place. **For 5 out of 10 women your age, the body can naturally clear the HPV infection and abnormal cells itself within 2 years without the need for treatment.** Normal treatment for abnormal cells is surgery to remove the cells. Surgical treatment can raise the risk of problems in pregnancy, such as preterm delivery and late miscarriages. I suggest you consider a new management option called active monitoring. **This means that you do not have surgery now and it can help avoid unnecessary treatment, also referred to as overtreatment**. Instead I will keep a close eye on your abnormal cells with regular testing every 6 months (same cervical screening test as before and colposcopy) to see if your body naturally clears the virus. If there are any changes the specialist doctor will recommend surgery. **But if it stays the same or gets better, surgery would be unnecessary and potentially harmful.**

Group 3: Normal Regression

Try to imagine how you would feel if this was you. You have just had the new cervical screening test and returned to the doctor for your results. Your results show that you have HPV. Your cells were checked for physical changes and high-grade abnormalities were detected. This means you have a higher risk of a significant abnormality. You were sent for a colposcopy and it showed that you have grade 2 abnormal cells in your cervix. Abnormal cells are graded from low to high (1 to 3). These are not cervical cancer. If these abnormal cells progress to invasive cervical cancer they could affect your health if left untreated. This is not usual and happens to around 1 out of 200 women, so for the 199 women these cells do not progress to cancer. It can take many years for this to take place. **For 5 out of 10 women your age, the HPV infection and abnormal cells will return to normal within 2 years without the need for treatment. Normal treatment for abnormal cells is surgery to remove the cells**. Surgical treatment can raise the risk of problems in pregnancy, such as preterm delivery and late miscarriages. I suggest you consider a new management option called active monitoring. This means that you do not have surgery now. Instead I will keep a close eye on your abnormal cells with regular testing every 6 months (same cervical screening test as before and colposcopy) to see if the HPV infection and abnormal cells have returned to normal. If there are any changes the specialist doctor will recommend surgery. **But if your cells stay the same or get better, surgery would be not needed.**

Group 4: Normal Regression and Overtreatment statement

Try to imagine how you would feel if this was you. You have just had the new cervical screening test and returned to the doctor for your results. Your results show that you have HPV. Your cells were checked for physical changes and high-grade abnormalities were detected. This means you have a higher risk of a significant abnormality. You were sent for a colposcopy and it showed that you have grade 2 abnormal cells in your cervix. Abnormal cells are graded from low to high (1 to 3). These are not cervical cancer. If these abnormal cells progress to invasive cervical cancer they could affect your health if left untreated. This is not usual and happens to around 1 out of 200 women, so for the 199 women these cells do not progress to cancer. It can take many years for this to take place. **For 5 out of 10 women your age, the HPV infection and abnormal cells will return to normal within 2 years without the need for treatment. Normal treatment for abnormal cells is surgery to remove the cells.** Surgical treatment can raise the risk of problems in pregnancy, such as preterm delivery and late miscarriages. I suggest you consider a new management option called active monitoring. This means that you do not have surgery now and it can help avoid unnecessary treatment, also referred to as overtreatment. Instead I will keep a close eye on your abnormal cells with regular testing every 6 months (same cervical screening test as before and colposcopy) to see if the HPV infection and abnormal cells have returned to normal. If there are any changes the specialist doctor will recommend surgery. **But if it stays the same or gets better, surgery would be unnecessary and potentially harmful.**

12-month scenario given to women who had chosen active surveillance at diagnosis

Try to imagine how you would feel if this was you. You have returned to the doctor 12 months after being diagnosed with HPV and CIN2. Your cells were checked again for physical changes and high-grade abnormalities. Your results show that your cells have not changed (i.e., no progression nor regression) and you still have HPV and CIN2. Using this information, show if you would choose active monitoring or immediate surgical treatment.

S2: Detailed description of the measures used

Measure	Description of measure	Response options / range and interpretation
Baseline measures		
Anxiety (STAI-6)	Six-item state trait anxiety inventory short form (STAI-6)	20-80 Score 35: population norm; >44 clinical anxiety
Health Literacy	Single Item Literacy Screener (SILS): *how often do you need to have someone help you when you read instructions, pamphlets or other written material from your doctor or pharmacy?*	5-point Likert scale: never/rarely/sometimes/often/always ('sometimes', 'often' and 'always' considered inadequate health literacy)
Numeracy	*Q1) Which of the following numbers represents the biggest risk of getting a disease?* *Q2/3) If the chance of getting a disease is 10%, how many people would be expected to get the disease:* *Q2) out of 100,* *Q3) out of 1000* *Q4) If the chance of getting a disease is 20 out of 100, this would be the same as having a x% chance of getting the disease*	4 items [correct responses] Q1 response options 1%,10%,5%; Q2 10; (fill in x) Q3 100, (fill in x) Q4 20% (fill in x)
Screening intentions	*How likely are you to go for cervical screening when next invited?*	4-point Likert scale: definitely will not/probably will not/probably will/definitely will
Trust in GP	*All in all, you have complete trust in your doctor.*	7-point Likert scale from strongly disagree to strongly agree
Medical Minimiser Maximiser	Single item Medical Minimiser Maximiser scale (MM1): *In situations where it is not clear do you lean towards taking action or do you lean towards waiting and seeing if action is needed?*	6-point Likert scale: 'I strongly lean toward waiting and seeing' (medical minimiser) to 'I strongly lean toward taking action' (medical maximiser)
Tolerance of uncertainty	12-item Intolerance of uncertainty short form: *Please indicate how much you agree with each statement (how characteristic it is of you)*	5-point Likert Scale: 'not at all characteristic of me' to 'entirely characteristic of me'
Preferences for involvement in decision making	Control preferences scale: *Please indicate how involved you prefer to be when making decisions about your healthcare*	5-point Likert scale: 'I prefer to make the decision about which treatment I will receive' to 'I prefer to leave all decisions regarding my treatment to my doctor'
Secondary outcomes		
Diagnosis anxiety	*How anxious would you feel about this diagnosis of being positive for HPV and having grade 2 abnormal cells?*	Participants moved cursor along Visual Analog Scale with anchored end points and placed it at one of 11 points from 'not at all anxious' to 'extremely anxious'
Treatment choice anxiety	*Thinking about the treatment choice of [active monitoring or surgery] how anxious do you think choosing that would make you feel?*	Participants moved cursor along Visual Analog Scale with anchored end points and placed it at one of 11

		points from ‘not at all anxious’ to ‘extremely anxious’
Perceived seriousness of the condition	*How serious would it be if you tested positive for HPV with grade 2 abnormal cells?*	4-point Likert scale: slightly/moderately/quite a bit/extremely
Cancer worry*	Worry about cervical cancer: *how worried are you of getting cervical cancer in your lifetime?*	4-point Likert scale: not at all worried to very worried
Perceived risk in lifetime*	*What are your chances of developing cervical cancer in your lifetime*	4-point Likert scale: none/low/medium/high
Perceived relative risk*	*What is your lifetime chance of getting cervical cancer compared to a woman of your age and race without any known risk factor?*	5-point Likert scale: much below average to much above average
Preferences for frequency of monitoring: if chose active surveillance	***You chose Active monitoring.*** *If your test results show you are* ***positive for HPV*** *and have* ***grade 2 abnormal cells****, how often would you prefer to be monitored?*	Every 3,6,9,12 or 24 months
Preferences for frequency of monitoring: if chose immediate treatment	***You chose surgery/ immediate treatment.*** *If your test results show you are* ***positive for HPV*** *and have* ***grade 2 abnormal cells****, how often would you need to be monitored before choosing active monitoring over surgery (immediate treatment)?*	Every 3,6,9,12,24 months OR I would still choose surgery

*Cancer worry, perceived risk in lifetime, and perceived risk assessed at baseline post intervention

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