Preferences of women in deciding about treatment by low-grade DCIS

A hypothetical preference study

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Abstract

INTRODUCTION. Ductal Carcinoma In Situ (DCIS) is a precursor of invasive breast carcinoma. If untreated, it is estimated that 10-15% of low-grade DCIS will develop into invasive breast carcinoma. Because there is little evidence about the prognosis of DCIS, in most cases women detected with DCIS will be treated as if it is invasive breast carcinoma; mastectomy or lumpectomy and radiotherapy. Knowing that a substantial number of DCIS lesions will never form a health hazard, most women with low-grade DCIS might be over treated. Currently, a European randomized inferiority trial (LORD) is set up to test if screen-detected low-grade DCIS can be safely managed by an active surveillance (AS) strategy only. Because future patients may be confronted with this decision option, we studied the preferences of women about low-grade DCIS treatment using a Discrete Choice Experiment (DCE).

METHOD. In a convenient sample of the general population, women between 45 and 75 were invited to complete a questionnaire including socio demographics, the Dutch Cancer Worry Scale (CWS) and the DCE questions. Treatment attributes included interval follow-up; risk of nerve pain; 10 year Ipsilateral invasive breast cancer (iiBC) free rate; level of disfigurement due to choice of intervention. A conditional logistic regression analysis was performed to calculate the coefficients of each attribute level. Subsequently, the relative importance of attributes and predicted choice probabilities were calculated.

RESULTS. From a total of 216 responders, the mean age was 52.6 (SD = 6.5) years. Ninety-two (43%) women scored relatively high on the CWS (>13). The CWS score of respondents was a significant effect modifier for the attribute risk of nerve pain (P=.026). The attribute “Level of disfigurement” had the largest impact (40%) on the predicted choice and stated preference. For women with a high CWS the impact of the attribute “Level of disfigurement” was higher than for women with a low CWS score (relative importance: 51% and 34%, respectively). Women with a high CWS score (>13) had a lower probability to opt for active surveillance than for surgical treatment (47% and 53%, respectively), in contrast women with a low CWS score (≤ 13), they had a higher probability to opt for AS than for surgical treatment (61% and 39%, respectively).

CONCLUSION. Based on the results, the level of disfigurement due to choice of intervention was the most important attribute for choice of low-grade DCIS treatment. Understanding the preferences of women in the general population may help to enhance the informed decision-making process based on the needs of patients.

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Introduction

With the widespread increased rates of screening mammography in the Netherlands introduced in 1998 (Visser, Siesling, & Dijck, 2003) the detection of both DCIS and invasive breast carcinoma has markedly increased (Virnig, Tuttle, Shamliyan, & Kane, 2010). Before 1980 DCIS was rarely diagnosed, around 335 DCIS detections in 1998. Nowadays the detection of DCIS increased to 2387 DCIS detections in 2015 in the Netherlands. (IKNL, 2015)

1.1 Ductal carcinoma in situ

DCIS pathologically refers to a malignant proliferation of neoplastic epithelial cells within the tubulolobular system of the breast (Pang, Gorringe, & Fox, 2016) and is not spread outside the ducts into surrounding breast tissue (non-invasive). Because the heterogeneous group of lesions in the duct(s) vary in their morphology, biology and clinical behaviour, DCIS can be divided into three different grades (Selvi, 2014). This study will specifically focus on the Low-Grade DCIS. Low-grade (Grade I) DCIS can be characterized by the presence of small, regular cells with round nuclei, infrequent mitoses and may have a micro papillary or cribriform and occasionally solid architecture (Selvi, 2014). A more detailed overview of the different grades of DCIS is included in the Appendix (Figure 1).

DCIS itself does not lead to metastatic disease or death, but the abnormal epithelial cells have the morphological features of invasive carcinoma of the breast (Pang, Gorringe, & Fox, 2016). Because of these features, DCIS could be considered as a precursor of invasive breast carcinoma (Selvi, 2014). However, this is not the case for most women detected with DCIS (Timbrell & MRad, 2010). If untreated, it is estimated that in 10-15% (Wesseling, Rutgers, Bijker, Pijnappel, & Elshof, 2015) of the cases low-grade DCIS will develop into invasive carcinoma of the breast. However, there is little evidence about the prognosis of DCIS: it is unclear which DCIS patients would develop invasive breast cancer, over what period of time DCIS could develop into invasive breast cancer (Mannu, Bettencourt-Silva, Ahmed, & Cunnick, 2015) and it is not fully understood which DCIS patients require urgent intervention and which patients can be safely left untreated (Francis, et al., 2015).

1.2 Screening

It is estimated that 80-85% of the DCIS is not palpable, in most cases DCIS is detected by means of mammography, usually on the basis of micro calcifications (Morrow, Schnitt, & Harris, 2000). In the Netherlands screening with mammography is indicated for women from the general population between 50 and 75 years old, with a screening interval of 2 years. For young women associated with a high risk of tumor induction (e.g. gene mutation carriers), it is recommended to start at the age of 30 with screening with a screening interval of 1 year between 30 and 50 years. (IKNL, 2012) Every woman living in the Netherlands between the age of 50 and 75 years old receives an invitation for the mammography. Each year about 1 million women participate in this breast cancer screening program with nationwide a response of approximately 80%, which results in 775 women less dying from breast cancer each year. (RIVM, 2015)

1.3 Treatment

Despite DCIS is not the same as invasive breast carcinoma, in most cases patients detected with DCIS will be treated as if it is invasive breast carcinoma, with treatment options like: lumpectomy, lumpectomy plus radiation, lumpectomy plus radiation and tamoxifen, mastectomy and mastectomy plus tamoxifen (bcaction, 2013). Because there is little evidence about the prognosis of DCIS and no existing test to determine whether or when the DCIS might progress to invasive carcinoma of the breast (Solin, 2012), clinicians generally continue to recommend surgery instead of monitoring in the absence of any available evidence-based strategy (Francis, et al., 2015). Treatment of DCIS is directed

to the prevention of DCIS cells becoming invasive (a locally invasive relapse). Mastectomy – the removal of the whole breast – is mostly performed when the DCIS is widely spread in the breast, and gives the best local control for DCIS, with a nearly 100% survival opportunity (IKNL, 2012). The primary aim of lumpectomy is the complete removal of the DCIS with an optimal cosmetic result, local control would namely be negatively affected by residual tumor tissue. Because in many cases DCIS is not palpable and can be more extensive than is suspected with mammography it is not easy to remove all the DCIS cells with lumpectomy only. Therefore additional radiation is often used after lumpectomy to remove all the DCIS cells (Westenberg, et al., 2003). In the Netherlands the guideline 'Mammacarcinoom (2.0)' is used to determine which treatment option should have the best outcome and it looks at the size and variety of the lesion (IKNL, 2012).

Surgical treatment with or without additional therapy is, however, not without side effects and can greatly affect the quality of life (QoL) of low-grade DCIS patients. The most common side effects are: temporary swelling of the breast tissue, tenderness of breast tissue, formation of hard scar tissue at the surgical site, infection at the surgical site, chronic nerve pain, reduction in arm function and skin burns in case of radiation. Around 25 percent of women which have undergone surgical treatment develop chronic nerve pain due to damage of the nerve as a result of the surgical treatment (Vilholm, Cold, Rasmussen, & Sindrup, 2008). Hart and colleagues (2016) found that women who were diagnosed with DCIS at age 50 years or younger reported lower mental QoL in the 5 years after diagnosis compared with women who were older than 50 years at diagnosis and suggest that women diagnosed at a younger age might benefit from monitoring for low mental QoL. But the difference of QoL by age at diagnosis decreased after 5 years since diagnosis and was similar for all women after 10 or more years since diagnosis (Hart, et al., 2016), this could be because all women experience the long-term effects of anxiety or negative health behaviour changes associated with breast cancer (Sprague, Trentham-Dietz, Nichols, Hampton, & Newcomb, 2010)

1.4 Informed shared decision-making

DCIS patients often face difficulties in the decision making process about which treatment to choose, patients often do not feel prepared to participate in decision making due to the fact that they have limited knowledge about DCIS (Stacey, et al., 2012): women are confused about whether they have the type of cancer that could spread to other parts of the body and have inaccurate beliefs about their breast cancer risk. In Australia less than 15% of the DCIS patients have the knowledge that DCIS alone cannot spread to other parts of the body. (Joseph-Williams, Elwyn, & Edwards, 2014) Most often women get information about their disease and treatment options by their clinician, usually in a single consultation, but some women feel overloaded by the plethora of information given in this single consultation (Vodermaier, et al., 2004).

1.5 Cancer worries

Although DCIS is not an invasive form of cancer, most patients choose their treatment on the same base as invasive cancer patients. Despite the better prognosis of DCIS, women with DCIS often have similar concerns about developing recurrent breast cancer, psychological morbidity (Rakovitch, et al., 2003), and risk perception of recurrence and dying of breast cancer as women with invasive breast cancer (Patridge, et al., 2008). When diagnosed with invasive cancer, patients have to face the decision of what treatment to adopt, in which they often favour active treatment, especially when it is a surgical treatment. This is due to the fact that the diagnosis of cancer is a call to action for many cancer patients, these patients feel a strong need to do something to face up to the cancer. Surgery could fulfil this need by removing the cancer from the body of the patient. Even if a clinician prescribes a less radical treatment or an equally effective treatment with less serious side effects

exists, cancer patients favour the most radical form of surgical treatment that removes most of the cancer cells out of the body (Fagerlin, Zikmund-Fisher, & Ubel, 2005).

1.6 Problem description and aim of research

Knowing that a substantial number of DCIS lesions will never form a health hazard, particularly in the slow-growing low-grade DCIS group, it can be said that many women in the low-grade group might unnecessarily be going through intensive treatment resulting in a decrease of quality of life and an increase in healthcare costs, without any survival benefit (Elshof, et al., 2015).

The uncertainties of the prognosis and nature of DCIS described in section 1.1 needs to be reduced to prevent women from overtreatment. To tackle these uncertainties the LORD (LOw Risk DCIS) trial is set up. The LORD trial is a randomized, international, multicentre Phase III non-inferiority trial, led by the Dutch Cancer Research Group (BOOG) and the European Organization for Research and Treatment of Cancer (EORTC-BBG), that aims to determine whether screen-detected low-grade DCIS can be safely managed by an active surveillance strategy or that the conventional treatment should remain the standard care for low-grade DCIS. (Elshof, et al., 2015) The NKI (Netherlands Cancer Institute) will also provide an Early Stage Technology Assessment next to the LORD trial. If the outcome of the LORD trial is that screen-detected low-grade DCIS can be safely managed by an active surveillance strategy, it could be expected that the guidelines for DCIS patients will change from conventional surgical treatment to a choice for women between surgical treatment or active surveillance. Therefore more support in the informed shared decision making will be needed so that women will be more prepared to make their decision. Before changing the care pathway it is necessary to know what the preferences of low-grade DCIS patients are. With the knowledge of these preferences clinicians are able to design a new guideline / care pathway and improve the informed decision making process for low-grade DCIS patients that suits their preferences.

This study will make clear the preferences of women on low-grade DCIS treatment and is part of the Early Stage Technology Assessment of Active Surveillance (AS) versus standard treatment for screen-detected low-grade DCIS patients. The Early Stage Technology Assessment is separated into different aspects (organizational, economic, ethical-legal and patient-related), this preference study will be part of the patient-related aspect of the Early Stage Technology Assessment.

Global research question *" What determines the preferences of women in the general population in deciding about treatment by low-grade DCIS?"*

Method

This study was set up as a hypothetical preference study, a Discrete Choice Experiment (DCE) was performed in order to get insight in the preferences of women in the general population in deciding about treatment by low-grade DCIS. To compare different groups of women the questionnaire consisted next to the DCE part of the Cancer Worry Scale (CWS) and some additional questions about women's characteristics: age; marital status, children; level of education (with college degree is HBO or higher); knowledge about DCIS; cancer history.

2.1 Study population

Between 21 June 2016 and 28 July 2016 women filled in the questionnaire. The convenient sample method was used to obtain respondents. To select a representative convenient sample that closely resembles the screen-detected low-grade DCIS patients of the LORD trial, women between 45 and 75 were invited for this study via Facebook; the site: watnou60.nl; circle of acquaintances.

2.2 Cancer Worry Scale

The Dutch Cancer Worry Scale (CWS) is an 8-item scale that is used to measure worry about the risk and developing of cancer and the impact of worry on daily functioning among individuals at risk for hereditary cancer. The Dutch CWS is based on the original, English version of the CWS and translated into Dutch, to which Douma and colleagues (2010) added 2 more scales. A 4-point Likert scale is used to rate the 8 items of the CWS and the scale is ranging from 'never' to 'almost always'. The scores could range from 8 to 32, where a higher scores indicate more frequent worries about cancer. (Douma, et al., 2010) The Dutch CWS is shown in figure 2 in the Appendix. The optimal cutoff point for differentiating non-fearful from fearful will be 13 versus 14 based on the findings of Custers and colleagues (2013).

2.3 Discrete Choice Experiment

A DCE is an attribute-driven quantitative technique to elicit stated preferences (Ryan & Farrar, 2000). In a DCE, it is assumed that a medical intervention can be described by their characteristics, the so-called attributes. These attributes can be further specified by variants of that attribute, the so called attribute-levels. The second assumption is that the levels of those attributes can determine an individual's preference for a medical intervention. (Ryan, 2004) The relative importance of attributes and their levels can be assessed by offering the respondents a series of choices/hypothetical scenarios between two or more medical intervention alternatives in which the combination of attribute-levels vary all the time (Hensher, King, Hossain, & Louviere, 2006). After presenting respondents the choice sets, respondents are forced to choose the hypothetical scenario with the most preferred attribute levels (Bridges, et al., 2011).

Attributes and levels

The attributes and the attribute levels of surgical treatment and active surveillance were derived from literature and two focus groups. Thereafter, experts were asked to comment on and complete the list of attributes and related attribute levels that were created form the literature and focus groups and which attributes and levels should be incorporated in the DCE. The experts (psychosocial expert (EB); specialised nurse (VS); pathologist (JW)) were of the opinion that the following attributes should be included: level of disfigurement due to choice of intervention; risk of nerve pain; interval follow-up; 10 year iiBC free rate, with the associated attribute levels shown in the figure below.

Attributes and levels			
Attributes	**Levels**		
Interval follow-up	6 months	1 year	2 years
Risk of nerve pain	0%	10%	25%
10 year Ipsilateral invasive breast cancer (iiBC) free rate	85%	90%	95%
Level of disfigurement due to choice of intervention	Mastectomy	Lumpectomy	AS

2.4 Experimental design

To make more realistic hypothetical scenarios for the respondents this study used restrictions in the DCE design. The level AS of the attribute level of disfigurement due to choice of intervention was restricted to the level 0% of the attribute risk of nerve pain.

With the use of the above mentioned restrictions, the combination of the intervention alternatives, attributes, and their levels resulted in 729 hypothetical scenarios (i.e. 81 scenarios for surgical treatment and 9 scenarios for Active Surveillance (81*9=729)). Because presenting all the 729 scenarios to the respondents would be too burdensome, a subset of scenarios was used. Using the design package R a D-efficient design consisting of 36 choice sets was generated, which were separated in three different versions. So each DCE consisted of 12 choice sets (36/3). The choice sets were unlabelled: women had to choose between option 1 and 2 for each choice set. To keep the choice sets understandable for respondents, the DCE consists of pictures and words alongside all the attribute levels, an example of a choice set can be found in figure 3 in the Appendix.

The questionnaire was pilot tested (n=8) to check for any problems in interpretation. Insight was obtained on the time required to complete the questionnaire (15-20 minutes) and the understanding and the complexity of the questionnaire.

Sample size

There rule-of-thumb formulated by Orme (2010) was used to calculate the needed sample size. Using this method, a minimal number of 63 respondents were needed for reliable statistical analyses of the DCE. The rule-of-thumb (Orme, 2010) and the calculation of the sample size needed is shown in the appendix (figure 4).

2.5 Data collection and statistical analyses

Respondents filled in an online questionnaire or paper version. The online questionnaire was made in LimeSurvey, all paper questionnaires were manually transferred into LimeSurvey and thereafter transferred to IBM SPSS Statistics 22. Respondents had to choose the preferred scenario in each choice set in which each hypothetical scenario had four attribute levels. To analyze these data the hypothetical scenarios were first coded in which a value of 1 was assigned when the respondent preferred scenario option 1 and value 2 was assigned when the respondent preferred scenario option 2. With the use of dummy coding each attribute level was coded to determine the preferences regarding the attribute levels in the scenarios. Descriptive analyses were used to analyze the characteristics of respondents (mean, standard deviation, and frequencies) and to determine the influence of a physician/nurse on the stated preference of women (frequencies).

A conditional logistic regression analysis was performed to determine the stated preferences of the respondents. With this analysis the coefficients of each attribute level were calculated. Each coefficient is a preference weight and represents the relative contribution of the attribute level to the utility that respondents assign to an alternative (Hauber, et al., 2016). After the coefficients for the attribute levels were clear the relative importance of the four attributes were calculated and gives inside into the difference each attribute could make in the total predicted choice probability of respondents. The relative importance/weight (W) of each attribute (i) was calculated by dividing the range of each attribute i (max C_i – min C_i) by the sum of the coefficient ranges of the four attributes (max C_j – min Cj).

$$W_{Attribute\ i} = \frac{\max C_i - \min C_i}{\sum_k (maxC_j - minC_j)}$$

Following, the predicted choice probabilities were calculated and showed the probability of respondents to opt for a certain treatment option. The treatment options used for the calculation of the predicted choice probabilities (based on consultation with the pathologist) were treatment option A (1 year follow-up interval; 0% risk of nerve pain; 85% iiBC free rate; AS), option B (1 year follow-up interval; 25% risk of nerve pain, 95% iiBC free rate, lumpectomy) and option C (1 year follow-up interval; 25% risk of nerve pain, 95% iiBC free rate, mastectomy). The predicted choice probabilities for the three treatment options were calculated with the use of the following formula, where Pset is the percentage of respondents that would choose a particular scenario given the choice between k other scenarios, Ci the sum of coefficients per chosen level of attribute and C_j the sum of the coefficients of the three attributes.

$$Pset = \frac{e^{(\sum C_i)}}{\sum_k e^{\sum C_{ij}}}$$

To study if a high CWS score (>13) had an impact on the stated preferences of respondents the effect modifier analyse was used, were the interaction term was attribute*highCWSscore. For the attributes that showed significant differences (P<.05) the new coefficients were used to calculate the relative importance and predicted choice probabilities between both groups (women with a low- and high CWS score). To study if a history of cancer had impact on the stated preference of respondents again the effect modifier analyse was used with the interaction term attribute*history with cancer. To determine whether there was a significant difference between the respondent characteristics of the two groups an One-Way Anova (F-test) was used.

Results

Between 21 June 2016 and 28 July 2016 a total of 286 women filled in the questionnaire, 70 questionnaires were excluded from the analysis because the women who filled in those questionnaires did not start the with the DCE part (64) or were younger than 45 years (n6) and 3 women were both younger than 45 years and did not start the DCE part.

3.1 Respondents

After exclusion 216 questionnaires could be used for the analysis of which 148 (69%) questionnaires were filled in completely. Respondents had a mean age of 52.6 (SD = 6.5) years, they mainly lived together with a partner (79.2%) and had one or more children (89.4%). Around a quarter of the women (25.9%) had a college degree or higher (Higher professional education or University). The mean score on the CWS was 13.5 (SD = 4.1) and 36 (16.7%) women had a history with cancer of which 22 women had breast cancer (Table 1).

Table 1. Characteristics of respondents	
Demographic characteristics	
Age at the study, in years	52.6 (SD=6.5)
Married of living with a partner	171 (79.2%)
College degree or higher	56 (25.9%)
Children	193 (89.4%)
Knowledge about DCIS	44% (20.4%)
Health characteristics	
History with cancer History with breast cancer	36 (16.7%) 22 (10.2%)
Cancer Worry Scale (CWS)	
Mean of the CWS	13.5 (SD=4.1)
Abbreviations: numbers are Mean (SD) or n (%); SD = Standard Error; n = number of women	

3.2 Discrete choice experiments results

All attributes were significantly related with the choice for treatment, and had a major impact on the stated preferences of respondents (P<.01). On average, respondents had a more negative preference towards an interval of 2 years than towards an interval of 6 months (P<0.01; Table 2), the odds for respondents to prefer an interval follow-up of 2 years was 1.56 times smaller than for an interval of 6 months. Women also had a more negative preference towards a 25% risk of nerve pain than towards 0% risk of nerve pain (P<0.01; Table 2) and the odds for respondents to prefer 25% risk of nerve pain was 1.76 times smaller than for 0% risk of nerve pain. Looking at the iiBC free rate women had a more negative preference towards a 85% iiBC free rate level than towards a 95% iiBC free rate level (P<0.01; Table 2) with an odds that was 1.76 smaller for 25% risk of nerve pain. At least women had a more negative preference to mastectomy and lumpectomy than towards AS (P<0.01; Table 2), with an odds for the preference of respondents that was 3.01 times smaller for mastectomy and 2.18 times smaller for lumpectomy than for AS.

After each DCE question, respondents had to fill in another question whether they would change their stated preference if a physician/nurse should advise another type of treatment. On an average, 36.1% (n= 78) of the women changed their preferred treatment choice.

Table 2. Stated preferences for treatment options of respondents			
Attribute levels	**Coefficient (B)**	**SE**	**Exp(B)**
Interval follow-up (P<.01)			
2 years	-.446[a]	.098	.640
1 year	-.061	.090	.941
6 months (ref level)	0		
Risk of nerve pain (P<.01)			
25%	-.566[a]	.137	.568
10%	-.202	.135	.817
0% (ref level)	0		
10 year Ipsilateral invasive breast cancer (iiBC) free rate (P<.01)			
85%	-.612[a]	.088	.542
90%	-.199	.102	.820
95% (ref level)	0		
Level of disfigurement due to choice of intervention (P<.01)			
Mastectomy	-1.102[a]	.124	.332
Lumpectomy	-.782[a]	.109	.458
AS (ref level)	0		
Abbreviations: CI = confidence interval; ref = reference. Dummy coded used the attributes. [a] Indicates significance at the 1% level			

3.3 Relative importance

More interesting is the difference between coefficients of the attribute levels. The attribute 'Level of disfigurement due to choice of intervention' had the biggest impact (40%, Table 3) on the predicted choice of respondents, and the impact of this attribute was more than two times as high as the impact of the attribute 'Interval follow-up' (16%, Table 3) which was the attribute with the lowest impact on the predicted choice of women. The impacts of the other attributes 'Risk of nerve pain' (21%, Table 3) and '10 year iiBC free rate' (22%, Table 3) were close to the impact of the attribute 'Interval follow-up'.

Table 3. Relative Importance attributes		
Attributes	**Range**	**Importance Weight**
Interval follow-up	.446	16%
Risk of nerve pain	.566	21%
10 year iiBC free rate	.612	22%
Level of disfigurement due to choice of intervention	1.102	40%
Grayscale indicates importance of attribute from dark grey (most important) to white (least important)		

3.4 Predicted choice probabilities

The predicted choice probability is the probability of a women to choose for a specific DCIS treatment. Respondents had a higher probability to opt for AS (option A) than for surgical treatment (option B and C together) (55% and 45%, respectively; Table 4).

Table 4. Predicted choice probabilities women without cancer history					
	Option A		**Option B**		**Option C**
Attribute level	**B**		**B**		**B**
1 year	-.061	1 year	-.061	1 year	-.061
0%	0	25%	-.566	25%	-.566
85%	-.612	95%	0	95%	0
AS	0	Lumpectomy	-1.102	Mastectomy	-.782
Expected Value	-.637		-1.729		-1.409
Exp (EV) $e^{(\text{Expected Value})}$	.5102		.1775		.2444
Share of Preference	55%		19%		26%

3.5 Interaction Effect Modification high CWS score

With the use of the effect modifier analyse, significant interaction was found between a high CWS score and the attribute 'Risk of nerve pain', which means that for women with a high CWS score the effect of the attribute 'Risk of nerve pain' on the stated preference is different from women with a low CWS score.

Respondent characteristics

Looking at the characteristics of respondents, significant difference was found for the characteristic history with cancer (P<0.05) and CWS score (P<0.01). On average, women with a low CWS score had a mean score of 10.7 (SD = 1.7) on the CWS and 10% (n = 12) of these women had a history with cancer (Table 5). Women with a high CWS score had a mean score of 17.2 (SD = 3.5) on the CWS and more than a quarter 26% (n = 24) of these women had a history with cancer (Table 5). 35% of the women (n=44) with a low CWS score and 37% of the women (n=34) with a high SWC score would change their stated preference if a physician/nurse should advise another type of treatment.

Table 5. Characteristics of respondents (comparison of women with a low and high CWS score)

	Women with a low CWS score (n=124)	**Women with a high CWS score (n= 92)**
Demographic characteristics		
Age at the study, in years	53 (SD=6.7)	52 (SD=6.3)
Married of living with a partner	98 (79%)	73 (79%)
College degree or higher	41 (33%)	15 (16%)
Children	116 (94%)	78 (85%)
Knowledge about DCIS	21 (17%)	23 (25%)
Health characteristics		
History with cancer Of which a history with breast cancer	12 (10%) 5	24 (26%) 9
Cancer Worry Scale (CWS)[a]		
Mean of the CWS	10.7 (SD=1.7)	17.2 (SD=3.5)

Abbreviations: numbers are Mean (SD) or n (%); SD = Standard Error; n = number of women
[a] Indicates significance at the 1% level
[b] Indicates significance at the 5% level

Effect modifier analyse

With the use of the effect modifier analyse, significant interaction was found between a high CWS score and the attribute 'Risk of nerve pain'. The coefficient for the level 25% risk of nerve pain for women with a low CWS score was -.922 and for women with a high CWS score -.201 (-.922 + .721, Table 6). The odds for women with a low CWS score to prefer the level 25% risk of nerve pain was 2.51 times smaller than for an 0% risk of nerve pain and the an odds for women with a high CWS score to prefer 25% risk of nerve pain was 1.22 times smaller than for 0% risk of nerve pain. The coefficient for the level 10% risk of nerve pain for women with a low CWS score was -.461 and for women with a high CWS score .091 (-.461 + .552, Table 6). Which means that women with a low CWS score had a more negative preference for 10% risk of nerve pain than towards 0% risk of nerve pain, and in contrast women with a high CWS score had a more positive preference for 10% risk of nerve pain than towards 0% risk of nerve pain.

So on average, women with a high CWS score were more likely to choose for a treatment option where there is a risk of nerve pain than women with a low CWS score. The impact of the coefficients described above on the relative importance of attributes will be described in the next section.

Table 6. Interaction analysis (comparison of women with a low and high CWS score)

Attribute levels	Coefficient (B)	SE	Exp(B)
Interval follow-up (P<.01)			
2 years	-,574[a]	,135	,640
1 year	-,089	,125	,941
6 months (ref level)	0		
Risk of nerve pain (P<.01)			
25%	-,922[a]	,195	,568
10%	-,461[b]	,187	,817
0% (ref level)	0		
10 year Ipsilateral invasive breast cancer (iiBC) free rate (P<.01)			
85%	-,752[a]	,127	,542
90%	-,218	,143	,820
95% (ref level)	0		
Level of disfigurement due to choice of intervention (P<.01)			
Mastectomy	-1,160[a]	,169	,332
Lumpectomy	-,830[a]	,151	,458
AS (ref level)	0		
Interaction terms			
Interaction highCWS*Interval (P= ,387)			
highCWS*2 years	,266	,198	1,305
highCWS*1 year	,063	,182	1,065
Interaction highCWS*Risk of nerve pain (P= ,026)			
highCWS*25%	,721[a]	,278	2,057
highCWS*10%	,552[b]	,272	1,736
Interaction highCWS*10 year iiBC free rate (P=,219)			
highCWS*85%	,267	,178	1,306
highCWS*90%	,025	,205	1,025
Interaction highCWS* level of disfigurement due to choice of intervention (P=,879)			
highCWS*Mastectomy	,116	,251	1,123
highCWS*Lumpectomy	,096	,221	1,101

Abbreviations: CI = confidence interval; ref = reference. Dummy coded used the attributes.
[a] Indicates significance at the 1% level
[b] Indicates significance at the 5% level

Relative importance

The interaction effect of a high CWS on the attribute 'Risk of nerve pain' did influence the relative importance of attributes. For women with a low CWS score the attribute 'Level of disfigurement due to choice of intervention' has the most impact (34.3%; Table 7) on the predicted choice and the attribute 'Interval follow-up' the least impact (16.2%; Table 7) on their predicted choice. For women with a high CWS score the attribute 'Level of disfigurement due to choice of intervention' did also effect the predicted choice of women with a cancer history the most (43.6%; Table 7) but in contrast the attribute 'Risk of nerve pain' did have the least impact (7.5%; Table 7) on the predicted choice of women with a high CWS score. The impact of the attribute 'Risk of nerve pain' on the predicted choice is more than three times as big for women with a low CWS score than for women with a high CWS score.

Table 7. Relative Importance attributes (comparison of women with a low and high CWS score)

	Women with a low CWS score (n=124)		**Women with a high CWS score (n=124)**	
Attributes	**Range**	**Importance Weight**	**Range**	**Importance Weight**
Interval follow-up	.547	16.2%	.547	20.6%
Risk of nerve pain	.922	27.3%	.201	7.5%
10 year iiBC free rate	.752	22.2%	.752	28.3%
Level of disfigurement due to choice of intervention	1.16	34.3%	1.16	43.6%

Grayscale indicates importance of attribute from dark grey (most important) to white (least important)

Predicted choice probability

The group of women with a low CWS score had a higher probability to opt for AS (option A) than for surgical treatment (option B and C together) (61% and 39%, respectively; Table 8). In contrast, women with a high CWS score had a higher probability to opt for surgical treatment than for AS (57% and 43%, respectively; Table 9).

Table 8. Predicted choice probabilities of women with a low CWS

	Option A		**Option B**		**Option C**
Attribute level	**B**		**B**		**B**
1 year	-.089	1 year	-.089	1 year	-.089
0%	0	25%	-.922	25%	-.922
85%	-.752	95%	0	95%	0
AS	0	Lumpectomy	-.830	Mastectomy	-1.160
Expected Value	-.841		-1.84		-2.171
Exp (EV) $e^{(\text{Expected Value})}$	.4313		.1587		.1141
Share of Preference	61%		23%		16%

Table 9. Predicted choice probabilities of women with a high CWS					
	Option A		**Option B**		**Option C**
Attribute level	**B**		**B**		**B**
1 year	-.089	1 year	-.089	1 year	-.089
0%	0	25%	-.201	25%	-.201
85%	-.752	95%	0	95%	0
AS	0	Lumpectomy	-.830	Mastectomy	-1.160
Expected Value	-.84		-1.12		-1.45
Exp (EV) $e^{(\text{Expected Value})}$	.4313		.3263		.2346
Share of Preference	43%		33%		24%

3.5 Interaction Effect Modification a personal history with cancer

With the use of the effect modifier analyse, no significance interaction was found between a history of cancer and the four attributes. Which means that there is no difference between the stated preference of women with- and without a history of cancer.

Respondent characteristics

Looking at the characteristics between women with- and without a cancer history, significance differences were found in their knowledge about DCIS (P<.01) and the score on the CWS (P<.01). Women without a personal cancer history had a mean score of 13 (SD=3.8) on the CWS and 17% of these women (n=30) did know about DCIS (Table 10). Women with a personal cancer history had a mean score of 16 (SD=5.2) on the CWS and 39% of these women (n=14) did know about DCIS (Table 10).

Table 10. Characteristics of respondents (comparison between women with- and without a personal cancer history)

	Women without a personal cancer history (n= 180)	**Women with a personal cancer history (n= 36)**
Demographic characteristics		
Age at the study, in years	52 (SD=6.5)	54 (SD=6.2)
Married of living with a partner	146 (81%)	25 (69%)
College degree or higher	50 (28%)	6 (17%)
Children	161 (89%)	32 (89%)
Knowledge about DCIS *p=.002	30 (17%)	14 (39%)
Health characteristics		
History with cancer History with breast cancer	NA NA	36 (100%) 22 (61%)
Cancer Worry Scale (CWS)		
Mean of the CWS *p=.001	13 (SD=3.8)	16 (SD=5.2)
Abbreviations: numbers are Mean (SD) or n (%); SD = Standard Error; n = number of women; NA not applicable.		

Effect modifier analyse

No significance interaction effect was found between a personal history of cancer and the attributes on the stated preferences of respondents. That no significance difference was found could be due to the fact that the group of women with a history of cancer was just a small group (n=36).

No conclusions can be drawn from the effect modifier analyse, but looking at the coefficients of the levels some implications can be done (Table 11).

Table 11. Interaction analysis (comparison of women with- and without a personal cancer history)

Attribute levels	Coefficient (B)	SE	Exp(B)
Interval follow-up *(P<.01)			
2 years	-,399[a]	,113	,671
1 year	-,000	,102	1,000
6 months (ref level)	0		
Risk of nerve pain * (P<.01)			
25%	-,624[a]	,155	,536
10%	-,274	,153	,761
0% (ref level)	0		
10 year Ipsilateral invasive breast cancer (iiBC) free rate *(P<.01)			
85%	-,609[a]	,101	,544
90%	-,158	,116	,854
95% (ref level)	0		
Level of disfigurement due to choice of intervention *(P<.01)			
Mastectomy	-1,215[a]	,141	,297
Lumpectomy	-,871[a]	,123	,419
AS (ref level)	0		
Interaction terms			
Interaction highCWS*Interval * (P= ,457)			
History with cancer*2 years	-,192	,235	1,278
History with cancer *1 year	-,274	,228	1,291
Interaction highCWS*Risk of nerve pain * (P= ,710)			
History with cancer *25%	,245	,346	,997
History with cancer *10%	,255	,337	,831
Interaction highCWS*10 year iiBC free rate * (P=,670)			
History with cancer *85%	-,003	,215	1,829
History with cancer *90%	-,186	,253	1,626
Interaction highCWS* level of disfigurement due to choice of intervention * (P=,119)			
History with cancer *Mastectomy	,604	,309	1,829
History with cancer *Lumpectomy	,486	,285	1,626

Abbreviations: CI = confidence interval; ref = reference. Dummy coded used the attributes.
[a] Indicates significance at the 1% level
[b] Indicates significance at the 5% level

Relative importance

Looking at the relative importance between women with- and without a personal history of cancer it was found that for women without a personal cancer history the attribute with the most impact on the predicted choice of women is 'Level of disfigurement due to choice of intervention' (43%; Table 12) and has an impact that is around two times as big than the impact of 'Risk of nerve pain' and '10 year iiBC free rate' (22% and 21%, respectively; Table 12) and more than three times as big as the attribute 'Interval follow-up' (14%; Table 12). For women with a personal history of cancer it was found that the attributes '10 year iiBC free rate' and 'Level of disfigurement due to choice of intervention' had the most impact (28%; Table 12) on their predicted choice. And the attribute 'Risk of nerve pain' had the least impact (17%; Table 12) on the predicted choice of women with a personal cancer history.

These results have to be judged with caution, because no significant interaction effect is found between a personal history of cancer and the stated preference of women.

Table 12. Relative Importance attributes (comparison of women with- and without a personal cancer history)

	Women without cancer history		**Women with cancer history**	
Attributes	**Range**	**Importance Weight**	**Range**	**Importance Weight**
Interval follow-up	.399	14%	.591	27%
Risk of nerve pain	.624	22%	.379	17%
10 year iiBC free rate	.609	21%	.612	28%
Level of disfigurement due to choice of intervention	1.215	43%	.611	28%

Abbreviations: grayscale indicates importance of attribute from dark grey (most important) to white (least important)

Discussion

This study gave insight into attributes that are relevant in determining women's choice among treatment options for low-grade DCIS. Results showed that a significance interaction was found between a high CWS score and the attribute 'Risk of nerve pain', which means that for women with a high CWS score the effect of the attribute 'Risk of nerve pain' on the stated preference is different from women with a low CWS score. For both groups of women (women with a low- and high CWS score) the most important attribute was 'Level of disfigurement due to choice of intervention'. Looking at the attribute that had the least impact on the predicted choice, the attribute 'Interval follow-up' had the least impact on the predicted choice of women with a low CWS score and the attribute 'Risk of nerve pain' had the least impact on the predicted choice of women with a high CWS score (>13). Besides the impact of attributes on the predicted choice, results showed differences between the predicted choice of women with a low- and high CWS score. Women with a low CWS score had a higher probability to opt for AS than for surgical treatment (61% and 39%, respectively). In contrast, women with a high CWS score had a higher probability to opt for surgical treatment than for AS (57% and 43%, respectively).

The authors from the Report of the American Cancer Society (ACS) and National Cancer Institute (NCI): Challenges in DCIS Risk Communication and Decision-making (Partridge, Elmore, Saslow, McCaskill-Stevens, & Schnitt, 2012) assumed that it is not surprising that many women with DCIS are anxious about their disease and overestimate the breast cancer risk they face, because of the not-knowing among them about the entity of DCIS, and heterogeneous views among providers. That women with a high CWS score had a higher probability to opt for surgical treatment than for AS, could be explained by the fact that increased anxiety is significantly associated with inaccurate risk perceptions (Partridge, et al., 2008) (Ruddy, et al., 2013). A higher score on the CWS indicates namely more frequent worries about developing cancer (Douma, et al., 2010), therefore it could be that women with a high CWS score do have inaccurate risk perceptions and prefer surgical treatment that removes the DCIS cells from their breast. The outcome that the 'Risk of nerve pain' has the least impact on the stated preference of women with a high CWS score could also imply that women with a high CWS score are more willing to be surgical treated because they think it will lower their risk of developing invasive breast cancer, which is in line with the assumptions made in an article in progress investigating the preferences of women with DCIS about their thoughts of the LORD-trial. The authors of that article suggest that the most important reason to not participate in the LORD was a strong preference for surgical treatment because of the fear that DCIS cells could develop into breast cancer.

Other studies investigated the knowledge of women with DCIS about their disease and decision-making process about treatment, these studies showed that DCIS patients often face difficulties in the decision making process about which treatment to choose, patients often do not feel prepared to participate in decision making due to the fact that they have limited knowledge about DCIS (Berger-Höger, Liethmann, Mühlhauser, Haastert, & Steckelberg, 2015), women are confused about whether they have the type of cancer that could spread to other parts of the body and have inaccurate beliefs about their breast cancer risk. In a cross-sectional survey of 144 women in Australia diagnosed with DCIS, approximately half expressed high decisional conflict when considering treatment options (De Morgan, Redman, D'Este, & Rogers, 2011). In the present study respondents are not asked whether they found it difficult to make a decision or not but were asked if they would change their stated preference if a physician/nurse should advise another type of treatment. That more than one third of the women (35% of the women with a low CWS score, and 37% of the women with a high CWS score) would change their stated preferences could indicated that these women also face difficulties in decision making.

Patient-centred care entails shared decision-making between patients and providers. This is not only incorporating patients perspective in the care planning and delivery, but also aims to provide ongoing support to meet patients' needs as best as possible and implies responsiveness to those needs. Optimizing patient-centred care may be particularly valuable when there is confusion regarding the diagnosis and uncertainty in available knowledge about DCIS. Improving communication styles among physicians and nurses who care for women with DICS could lead to more accurate risk perceptions, more informed decision-making and better psychosocial outcomes. (Partridge, Elmore, Saslow, McCaskill-Stevens, & Schnitt, 2012) A solution for this problem could be a specialized nurse that acts as a decision coach. Some studies have shown that these specialized nurses are able to enhance the patient's decision making (Stacey, et al., 2012). Specialized nurses have the competences in explaining medical information, supporting patients and sharing the information with physicians (Joseph-Williams, Elwyn, & Edwards, 2014) and are able to support the clinician in providing information to the patient in a more open environment all of the time for patients to ask questions. The outcomes of this study may help to give an insight into the needs of women when they have to decide about low-grade DCIS treatment, in particular which attributes are important for women when they have to make a decision and physicians/nurses can respond to this to enhance the decision-making process.

To compare women in the general population with women who had a personal history with cancer, an effect modifier analyse was performed. No significant interaction was found between a personal history of cancer and the stated preferences of women due to the small sample size and therefore no conclusions could be drawn. The hypothesis was that for women without a personal history of cancer the attribute with the most impact on the predicted choice was 'Level of disfigurement due to choice of intervention' and the attribute 'Interval follow-up' has the least impact and their mean CWS scale was low (13). For women with a personal history of cancer it was assumed that the attributes '10 year iiBC free rate' and 'Level of disfigurement due to choice of intervention' had the most impact on the predicted choice. The attribute 'Risk of nerve pain' had the least impact on the predicted choice of women with a personal cancer history and these women had a higher CWS score (16). The hypothesis of the relative importance of women with a personal history of cancer slightly resembles the relative importance of women with a high CWS score. Therefore it could be that the stated preferences of women with a high CWS score could also predict the stated preferences of low-grade DCIS patients. The hypothesis have to be judged with caution and further research is needed to reveal the interaction of a personal history of cancer on the stated preferences of low-grade DCIS treatment.

Limitations

This study has several limitations, the first and major implication is that respondents used for this study were not low-grade DCIS patients and therefore this study only gives inside into the stated preferences of women in the general population, which could be different from the stated and revealed preferences of women with low-grade DCIS. Secondly, the most relevant attributes are selected for this study using literature review, expert interviews and focus groups; however, this careful procedure does not guarantee that attributes not used in this study are irrelevant to the (stated) preferences of women with DCIS. Thirdly, this study does not ensure orthogonality and a balanced choice set because of the use of fixed attribute levels to make more realistic hypothetical scenarios, this might have influenced the outcomes of this study. Lastly, there was only a small group of respondents with a history of cancer and therefore no interaction effect could be found between a history of cancer and the stated preferences of respondents.

Conclusion

In conclusion, for all women the attribute 'Level of disfigurement due to choice of intervention' had the most impact on the stated preference. Women with a low CWS score had a higher probability to opt for AS than for surgical treatment and in contrast women with a high CWS score had a higher

probability to opt for surgical treatment instead of AS. For women with a low CWS score the attribute 'Interval follow-up' had the least impact on their stated preferences and the attribute 'Risk of nerve pain' had the least impact on the stated preferences of women with a high CWS score. More research needs to be done between the stated preferences of women in the general population and the revealed preferences of low-grade DCIS patients.

To enhance the decision-making process and patient-centred care for low-grade DCIS patients more research needs to be done to reduce the lack of information about the prognostic factors of low-grade DCIS and the therapeutic efficacy and safety of treatment options. The outcomes of this study may help to give an insight into the needs of women when they have to decide about low-grade DCIS treatment and may enhance the decision-making process and patient-centred care. But before the decision-making process and patient-centred care could be enhanced more research needs to be done about the prognostic factors of low-grade DCIS and the therapeutic efficacy and safety to reduce the lack of information about low-grade DCIS.

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Appendix

Feature	Low	Intermediate	High
Pleomorphism	Monomorphic	Moderate degree of pleomorphism	Pleomorphic
Size	x1.5-2 the size of a normal red blood cell or a normal duct epithelial nucleus	x2-2.5 the size of a normal red blood cell or a normal duct epithelial nucleus	>x 2.5 the size of a normal red blood cell or a normal duct epithelial nucleus
Chromatin pattern	Diffuse, finely dispersed chromatin	Intermediate	Vesicular with irregular chromatin distribution
Nucleoli	Rare nucleoli	Occasional nucleoli	Prominent, often multiple nucleoli
Mitoses	Occasional	Intermediate	Frequent
Orientation	Polarized towards luminal spaces	Degree of polarization present	Not polarized towards luminal spaces

Figure 1. Features for determining nuclear grade in DCIS grades (Lester, Bose, & Chen, 2009)

8-item scale Dutch Cancer Worry Scale
During the past 6 months: **1.** How often have you thought about your chances of getting cancer (again)? **2.** Have these thoughts affected your mood? **3.** Have these thoughts interfered with your ability to do daily activities? **4.** How concerned are you about the possibility of getting cancer one day? **5.** How often do you worry about developing cancer? **6.** How much of a problem is the worry? **7.** How often do you worry about the chance of family members developing cancer? **8.** How concerned are you about the possibility that you will ever need surgery (again)?

Figure 2. 8-item scale Dutch Cancer Worry Scale (Douma, et al., 2010)

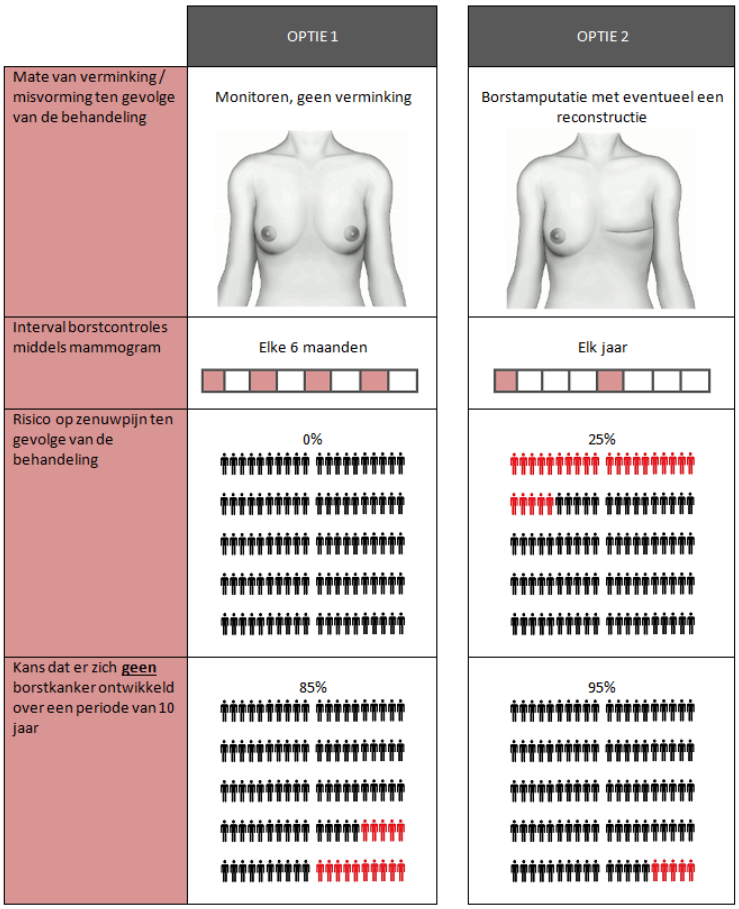

Figure 3. Layout choice set DCE (in dutch)

Rule of Thumb

$$\frac{nta}{c} > 500 \qquad \frac{n * 12 * 2}{3} > 500$$

$$n = 63\ (62{,}5)$$

n: number of respondents
t: number of tasks
a: number of alternatives per task
c: number of analysis cells

Figure 4. Calculation and Rule of Thumb (Orme, 2010)