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Trade-off preferences regarding adjuvant endocrine therapy among women with estrogen receptor-positive breast cancer

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Background: There is substantial nonadherence to effective adjuvant endocrine therapy for breast cancer prevention.

We therefore examined patients' trade-offs between the efficacy, side-effects, and regimen duration, and whether tradeoffs predicted nonadherence.

Patients and methods: Trade-offs from 241 women were assessed with an Adaptive Conjoint Analysis (ACA) choice task that was customized to each individual patient. From the estimated ACA utilities, the relative importance of each treatment property was calculated and a benefit/drawback ratio between the importance of the efficacy versus that of the side-effects and other treatment properties. Nonadherence was assessed through composites of validated self-report measures.

Results: Efficacy was most important. The side-effects joint and muscle pain and risk of endometrial cancer were almost as important. The benefit/drawback ratio showed 16% of the women to value the efficacy less than the side-effects and other treatment properties. A higher benefit/drawback ratio was associated with decreased nonadherence [adjusted odds ratio (OR) 0.1, 95% confidence interval 0.03–0.3].

Conclusions: One in six women do not consider the efficacy of endocrine therapy to outweigh its drawbacks. Knowing women's trade-offs is likely to identify women at risk for nonadherence and to help clinicians in tailoring their communication and care to different needs of individual women.

Key words: breast cancer, decision aids, endocrine therapy, patient adherence, patient centered care, patient Preferences

INTRODUCTION

Five years of the adjuvant endocrine therapy tamoxifen reduces the risk of recurrence of estrogen-positive breast cancer by 41% [1]. Despite this efficacy, nonadherence was found to increase from ~20% to 25% [2, 3] in the first years to 30%–40% [3, 4] in the subsequent years of the regimen. However, from the perspective of women with breast cancer, this contradiction is rather unsurprising. The regimen completion takes multiple years and can cause notable side-effects such as libido decrease [5, 6], joint pain [5, 7], and hot flashes [5, 6, 8, 9]. Therefore, women's perceptions of endocrine therapy should be conceived of as trade-offs between its efficacy and its drawbacks. Indeed, Fink et al. found a threefold increase of premature discontinuation for women with a negative decisional balance variable that was calculated by subtracting a woman's perceived risks of endocrine therapy from her perceived benefits [2].

This study examines women's trade-offs with regard to endocrine therapy. Instead of assessing trade-offs with a decisional balance score, we use a conjoint analysis task. Although the decisional balance score is intuitive [2], its main limitation is that it is calculated from independently rated questions about treatment harms and benefits. Conjoint analysis choice tasks better mimic the trade-offs that patients make in the real world regarding treatment benefits and drawbacks.

Patients' trade-off preferences are assessed by asking them to choose between pairs of hypothetical treatment alternatives, in which one of the alternatives is 'more favorable' than the other for one characteristic (e.g. prevents breast cancer recurrence in 5 of 10 versus 3 of 10 women), but 'less favorable' for another (e.g. frequently versus occasionally hot flashes). In this way, conjoint analysis tasks could enhance informed [10] and shared decision-making [11] about treatment. Previously, these tasks have been used for various treatments [11–14]. In addition, we examine relationships between women's trade-offs and demographic and clinical characteristics. Previously, associations between nonadherence and marital status [15], age [8, 15–19], and surgery [16] were found.

Accordingly, the objective was to examine breast cancer patients' trade-offs between the benefit and drawbacks of endocrine therapy, and the associations between demographic and clinical characteristics and nonadherence.

METHODS

patients

Women treated with endocrine therapy were recruited through two hospitals and community pharmacies. Exclusion criteria were terminal illness, psychiatric disorders, or reasons at the discretion of the nurse practitioner or the pharmacist. In addition, women were recruited through two patient organizations. Women participated through filling out an online questionnaire or through a face-to-face interview. Of the 672 women approached, 241 consented to participate (response rate 36%). The medical ethical committee of the Leiden University Medical Center approved the study. Table 1 presents women's clinical and demographic characteristics.

[Table 1]

trade-off preferences for different endocrine therapy attributes

Women's preferences were elicited by an Adaptive Conjoint Analysis (ACA) task [20], showing 15 pairs of hypothetical treatment options 'Endocrine therapy A' and 'Endocrine therapy B', described on two treatment characteristics so-called attributes. Each time, trade-offs had to be made as 'Endocrine therapy A' had a 'more favorable' level of the first attribute (e.g. efficacy) but a 'less favorable' level of the second attribute (e.g. osteoporosis as a side-effect), whereas the opposite was true for 'Endocrine therapy B'. Women had to rate their preference on a 9-point scale (1, strong preference for 'Endocrine therapy A'; 9, strong preference for 'Endocrine therapy B') (see Figure 1). ACA is adaptive because it customizes the presented pairs to an individual's previous choices, and thereby presents trade-offs that are increasingly relevant to that individual.

Selection and definition of endocrine therapy attributes and their levels were based on the literature and online focus groups conducted with women treated with endocrine therapy (manuscript under review).

The following attributes were included (see Table 2 for attribute levels): efficacy [1], libido decrease [5, 6], osteoporosis [21–23], hot flashes [5, 6, 8, 9], risk of endometrial cancer [2, 24, 25], fluid retention [8], joint and muscle pain [5], and regimen duration [1, 21]. To facilitate comprehension of the attributes, we described side-effects in layman's language and numerical attribute levels in words, e.g. '3 out of 10'.

Subsequently, the ACA program (Sawtooth Software, Sequim, WA) [20] estimated, for each individual woman, a utility for each level of every treatment attribute on a scale ranging from −2.5 to +2.5. The higher the utility of an attribute level, the higher the attractiveness of that attribute level for a woman. Based on the utility estimates, a relative importance percentage for each attribute was calculated, which reflected patients' trade-off preferences. Validity analyses showed that for most women utilities reflected conscious and consistent trade-off choosing. See supplement S1, available at *Annals of Oncology* online for the calculation of relative importance percentages and validity analyses.

therapy adherence

Nonadherence was assessed with items from two validated scales [26, 27] and additional questions about forgetting and persistence. Orthogonal factor analysis and internal consistency measures revealed an unintentional nonadherence dimension due to forgetting (six items, observed score range 0–7, $\alpha = 0.77$) and an intentional or conscious nonadherence dimension (three items, observed score range 0–7, $\alpha = 0.81$). See supplement S2, available at *Annals of Oncology* online for factor analytic results and scale calculation.

analysis

Means and standard deviations were calculated for the relative importance score of each treatment attribute.We calculated a benefit/drawback ratio between the relative importance percentage of the efficacy and the sum of the relative importance percentages of the other attributes (≤1: efficacy less or equally important, >1: efficacy more important than other attributes).

Associations between this benefit/drawback ratio and demographic and clinical characteristics were examined with linear regression analysis.

Associations between unintentional nonadherence (score of ≤1 versus >1) and intentional nonadherence or premature discontinuation (score of 0 versus ≥1) as the dependent variables and the benefit/drawback ratio as the independent variable were examined with logistic regression analysis.

[FIGURE 1] [TABLE 2]

RESULTS

Women approached through hospitals and pharmacies were less likely to be treated with cytostatic therapy (66% versus 86%) and were older (M 59 years, SD 11 versus M 53 years, SD 8) than women recruited through patient organizations.Women who were interviewed were less likely to have been treated with cytostatic therapy (49% versus 76%), were more often treated for recurrent cancer (38% versus 22%), were less often higher educated (16% versus 45%), and were older (M 65 years, SD 12 versus M 56 years SD 9) than women who participated online.
Analyses with regard to prediction of nonadherence aretherefore adjusted for site of recruitment and mode of participation.

preferences for different endocrine therapy attributes

Average and spread of utilities and relative importance percentages of the endocrine therapy attributes are shown in Table [2]. Efficacy was the most important attribute. It was on average slightly less important than osteoporosis, but 132 women (55%) considered it most important, whereas 84 women (35%) considered osteoporosis as most important. Surprisingly, the small risk of endometrial cancer was almost as important as the efficacy, which is a 50-fold of the risk of endometrial cancer. Thirteen women (5%) considered the risk of endometrial cancer as most important. Joint and muscle pain as a side-effect was somewhat less important and was considered most important by eight (3%) of the women. Fluid retention, libido decrease, hot flashes, and regimen duration were considered least important.

benefit/drawback ratio and different demographic and clinical variables

The benefit/drawback ratio showed that 39 women (16%) considered the efficacy to be less important than or equally important as the other attributes (ratio ≤ 1). Higher educational level ($\beta = 0.15$, $t = 2.3$, $P = 0.02$) and past treatment with cytostatic therapy ($\beta = 0.19$, $t = 2.9$, $P = 0.004$) were positively associated, whereas age ($\beta = -0.26$, $t = -4.1$, $P = 0.0001$) was negatively associated with the benefit/drawback ratio.

benefit/drawback ratio and nonadherence

Thirty-seven women (15%) reported unintentional nonadherence. Twenty-one women (9%) reported intentional nonadherence or premature discontinuation. There was good agreement between the medication possession ratio (MPR) inferred from the pharmacy refill data (MPR cut-offs 80%–85%– 90%) and self-reported unintentional (85% agreement) and intentional nonadherence or premature discontinuation (90%–92% agreement). Age, educational level, past treatment with radiation therapy, or being treated for cancer recurrence had a univariate association with unintentional nonadherence ($P < 0.10$). No association between the

benefit/drawback ratio and unintentional nonadherence was observed [odds ratio (OR) 1.5, 95% confidence interval (CI) 0.6–3.5,Wald = 0.9, *P* = 0.36], also not after adjusting for the above-mentioned factors, site of recruitment and mode of participation (OR 1.1, 95% CI 0.4–3.1, Wald = 0.05, *P* = 0.8). Marital status, status of use and educational level had a univariate association with intentional nonadherence (*P* < 0.10). A significant association was found between the benefit/drawback ratio and intentional nonadherence (OR 0.2, 95% CI 0.1–0.4,Wald = 14.3, *P* < 0.001), also after adjusting for the above-mentioned factors, site of recruitment, and mode of participation (OR 0.1, 95% CI 0.03–0.3,Wald = 12.9, *P* < 0.001).

DISCUSSION

Our findings demonstrate that from the perspective of women, endocrine therapy represents a real trade-off.Women's trade-off preferences with regard to different treatment characteristics revealed that efficacy was considered most important. Almost as important were several side-effects. The benefit/drawback ratio showed that approximately one in six women considered the efficacy of endocrine therapy to be less than or equally important as its drawbacks. Our finding that the efficacy was most important was consistent with findings by Ravdin et al. [28] who showed high levels of acceptance of even low degrees of efficacy. At the same time, our finding that side-effects were almost as important was consistent with trade-offs previously found by Duric et al. [29], showing for instance that women with more severe side-effects required larger benefits from endocrine therapy. Furthermore, our number of women with a negative or neutral benefit/drawback ratio as well as the association found between the benefit/drawback ratio and intentional nonadherence were comparable to the findings by Fink et al. [2].

For clinical practice, knowledge of women's trade-off preferences is important to improve shared decision-making regarding endocrine therapy and thereby to prevent nonadherence and premature discontinuation. First, for postmenopausal women who consider aggravation of osteoporosis as highly important, tamoxifen should be the primary choice as it reduces the risk of osteoporosis. Second, when a woman considers side-effects to be highly bothersome, switching to another form of endocrine therapy should be considered, as was recommended by the TEAM trialists [30].

Third, an important finding was that women perceived the small risk of endometrial cancer almost as important as the much higher benefit of the efficacy of endocrine therapy, which is a 50-fold of the risk of endometrial cancer. Perhaps many patients find it difficult to understand percentages even when these are put in words. Alternatively, it is not unimaginable, especially for women with breast cancer, that owing to the severity of endometrial cancer, they overestimate its risk.

Regardless of which of these explanations is most important, this finding underlines the need to reassure women by teaching them how to recognize preclinical symptoms or by offering postmenopausal women who remain concerned treatment with aromatase inhibitors as these do not increase the risk of endometrial cancer.

The associations between the benefit/drawback ratio and patient characteristics also have implications for clinical practice. First, the higher educated had a more favorable benefit/ drawback ratio than the lower educated. This could suggest that the higher educated had better comprehension of the efficacy, and that, in turn, the

information about efficacy should be better tailored to the understanding of those with lower education.
Second, the less favorable benefit/drawback ratio observed in older women could suggest that older women value a better quality of life with fewer side-effects over an increased life expectancy brought about by the efficacy of endocrine therapy.
A strength of this study was the use of an ACA choice task.
Currently, trade-offs are usually assessed with a balance score or a subtraction of perceived drawbacks from perceived benefits of treatment [2]. ACA choice tasks, instead, require trade-off comparisons between alternative treatment options both described at more and less favorable attributes. Thereby, ACA choice tasks better mimic the trade-offs that patients make in the real world between the benefits and drawbacks of treatment than a balance score that is calculated from independently rated benefits and drawbacks.
There were also limitations.With regard to the ACA task, the efficacy attribute of breast cancer prevention in 5 of 10 versus 3 of 10 women was an attempt to reflect the relative risk reduction by 41% reported previously [1]. However, in absolute terms, this reduction could have been much higher than it is in reality for many women, especially for those who have a low a priori chance of breast cancer recurrence. Therefore, the rate of 16% of the women who did not consider the benefit to outweigh the drawbacks could have been an underestimation, yet it remains substantial. Also, the ACA task may have been difficult to understand for some of the women, although validity analyses showed this not to be the case for most of the women. Our unintentional and intentional nonadherence dimensions, although derived from validated instruments, are preliminary and need further study.
Moreover, the higher educated may have been over-represented, and some subgroups were too small to permit a detailed analysis. Finally, a suggestion for further research would be to examine whether endocrine therapy preferences change over time, as was previously done for health related quality of life and chemotherapy [31, 32].
Taken together, for an important minority of women, the efficacy of endocrine therapy does not outweigh the drawbacks.
By knowing women's trade-offs, physicians are likely to identify women who are at risk of nonadherence as well as to look at endocrine therapy through the eyes of a woman with breast cancer.

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DISCLOSURE

LVD has the following potential conflicts of interest: two unrestricted grants (BMS and Astra Zeneca). ECGvG is currently employed at the Dutch Kidney Foundation (Nierstichting). All remaining authors have declared no conflicts of interest.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687–1717.
2. Fink AK, Gurwitz J, Rakowski W et al. Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor—positive breast cancer. J Clin Oncol 2004; 22: 3309–3315.
3. Partridge AH, LaFountain A, Mayer E et al. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol 2008; 26: 556–562.
4. Lash TL, Fox MP, Westrup JL et al. Adherence to tamoxifen over the five-year course. Breast Cancer Res Treat 2006; 99: 215–220.
5. Kirk MC, Hudis CA. Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. Clin Breast Cancer 2008; 8: 155–161.
6. Grunfeld EA, Hunter MS, Sikka P et al. Adherence beliefs among breast cancer patients taking tamoxifen. Patient Educ Couns 2005; 59: 97–102.
7. Ziller V, Kalder M, Albert US et al. Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. Ann Oncol 2009; 20: 431–436.
8. Demissie S, Silliman RA, Lash TL. Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older women. J Clin Oncol 2001; 19: 322–328.
9. Guth U, Huang DJ, Schotzau A et al. Target and reality of adjuvant endocrine therapy in postmenopausal patients with invasive breast cancer. Br J Cancer 2008; 99: 428–433.
10. Michie S, Dormandy E, Marteau TM. The multi-dimensional measure of informed choice: a validation study. Patient Educ Couns 2002; 48: 87–91.
11. Pieterse AH, Berkers F, Baas-Thijssen MC et al. Adaptive Conjoint Analysis as individual preference assessment tool: feasibility through the internet and reliability of preferences. Patient Educ Couns 2010; 78: 224–233.
12. Ahmed SF, Smith WA, Blamires C. Facilitating and understanding the family's choice of injection device for growth hormone therapy by using conjoint analysis.
Arch Dis Child 2008; 93: 110–114.
13. Beusterien KM, Dziekan K, Schrader S et al. Patient preferences among third agent HIV medications: a US and German perspective. AIDS Care 2007; 19: 982–988.
14. Fraenkel L, Bogardus ST, Concato J et al. Patient preferences for treatment of rheumatoid arthritis. Ann Rheum Dis 2004; 63: 1372–1378.
15. Hershman DL, Kushi LH, Shao T et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients.
J Clin Oncol 2010; 28: 4120–4128.
16. Owusu C, Buist DS, Field TS et al. Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. J Clin Oncol 2008; 26: 549–555.
17. Kahn KL, Schneider EC, Malin JL et al. Patient centered experiences in breast cancer: predicting long-term adherence to tamoxifen use. Med Care 2007; 45: 431–439.
18. Sedjo RL, Devind D. Predictors of non-adherence to aromatase inhibitors among commercially insured women with breast cancer. Breast Cancer Res Treat 2011; 125: 191–200.
19. Partridge AH, Wang PS, Winer EP et al. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 2003; 24: 602–606.
20. Sawtooth. The ACA/Web v6.0 technical paper, 2007; http://www.sawtoothsoftware.
com (13 May 2013, date last accessed).
21. Silliman RA, Guadagnoli E, Rakowski W et al. Adjuvant tamoxifen prescription in women 65 years and older with primary breast cancer. J Clin Oncol 2002; 20: 2680–2688.
22. Perez EA. Safety profiles of tamoxifen and the aromatase inhibitors in adjuvant therapy of hormone-responsive early breast cancer. Ann Oncol 2007; 18(Suppl 8): viii26– viii35.

23. Lonning PE. The potency and clinical efficacy of aromatase inhibitors across the breast cancer continuum. Ann Oncol 2011; 22: 503–514.
24. Chlebowski RT, Geller ML. Adherence to endocrine therapy for breast cancer. Oncology 2006; 71: 1–9.
25. Amir E, Seruga B, Niraula S et al. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. J Natl Cancer Inst 2011; 103: 1299–1309.
26. Morisky DE, Ang A, Krousel-Wood M et al. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 2008; 10: 348–354.
27. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health 1999; 14: 1–24.
28. Ravdin PM, Siminoff IA, Harvey JA. Survey of breast cancer patients concerning their knowledge and expectations of adjuvant therapy. J Clin Oncol 1998; 16: 515–521.
29. Duric VM, Fallowfield LJ, Saunders C et al. Patients' preferences for adjuvant endocrine therapy in early breast cancer: what makes it worthwhile? Br J Cancer 2005; 93: 1319–1323.
30. Van de Velde CJ, Rea D, Seynaeve C et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 2011; 377: 321–331.
31. Lovrics PJ, Cornacchi SD, Barnabi F et al. The feasibility and responsiveness of the health utilities index in patients with early-stage breast cancer: a prospective longitudinal study. Qual Life Res 2008; 17: 333–345.
32. Jansen SJ, Kievit J, Nooij MA et al. Stability of patients' preferences for chemotherapy: the impact of experience. Med Decis Making 2001; 21: 295–306.

TABLES AND FIGURES

Table 1. Participants' clinical and demographic characteristics

Variables	Statistic
Participants, *n*	241
Recruitment site, *n* (%)	
Hospitals	55 (23)
Community pharmacies	117 (49)
Patient organizations	69 (29)
Demographic characteristics	
mean age (SD) in years	57.2 (10)
Married or living together, *n* (%)	189 (78)
Higher educated, *n* (%)	98 (41)
Status of use, *n* (%)	
Starters or recent users (<3 months)	11 (5)
Users (>3 months)	215 (89)
Discontinued	15 (6)
Duration of use (only users) in years, *n* (%)	
0–1	40 (19)
1–4 years	143 (66)
4 years or longer	32 (15)
Type of Endocrine therapy, *n* (%)	
Tamoxifen	105 (44)
n (%) AI	109 (45)
n (%) Combination/otherwise	27 (11)
Type of surgery[a], *n* (%)	
Lumpectomy	114 (47)
Mastectomy	122 (51)
Cytostatic and radiation therapy and recurrence, *n* (%)	
Cytostatic therapy	173 (72)
Radiation therapy	176 (73)
Recurrent breast cancer	58 (24)

[a]Five (2%) did not (yet) undergo surgery and received neo-adjuvant endocrine therapy.

AI, aromatase Inhibitor.

Figure 1. Example of ACA item.

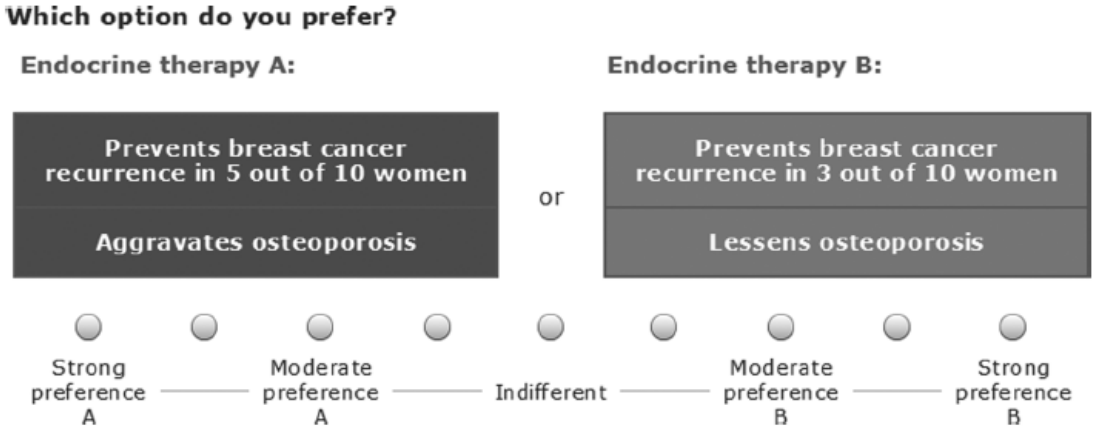

Table 2. Mean and spread of utilities and relative importance of treatment attributes

Treatment attributes and their levels	Utilities[a]		Average importance, (%)[b]	
	M	SD	M	SD
Efficacy				
Prevention of breast cancer recurrence			17.2	4.5
In 3 of 10 women	−0.75	0.55		
In 5 of 10 women	+0.84	0.52		
Side-effects				
Osteoporosis			17.6	2.7
Lessens osteoporosis	+0.82	0.44		
Aggravates osteoporosis	−0.72	0.49		
Risk of endometrial cancer			15.4	3.2
In 1 of 1000 women	+0.73	0.43		
In 5 of 1000 women	−0.64	0.46		
Joint and muscle pain			14.0	2.6
A bit	+0.67	0.37		
Moderate to severe	−0.58	0.42		
Fluid retention			12.7	2.1
A bit	+0.60	0.33		
Moderate to severe	−0.51	0.38		
Libido decrease			10.8	3.0
A bit	+0.53	0.31		
Moderate to severe	−0.43	0.34		
Hot flashes			6.4	1.6
Some per month	+0.32	0.17		
Some per week	−0.23	0.22		
Regimen duration				
Years of endocrine therapy use			5.9	1.9
2 years	+0.31	0.18		
5 years	−0.21	0.22		

[a]Utilities estimated on a scale ranging from ±2.5, the higher the estimated utility value of an attribute level, the more that attribute level is preferred, e.g. a 5-year regimen duration is less preferred than a 2-year regimen duration.

[b]Relative importance is calculated as follows: for each attribute, the difference between the utilities of its levels is divided by the sum of the differences between the utilities for all of the attributes and multiplied by 100.

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