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The Long-Term Effectiveness and Cost-Effectiveness of Organized versus Opportunistic Screening for Breast Cancer in Austria

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ABSTRACT

Background: In 2014, Austrian health authorities implemented an organized breast cancer screening program. Until then, there has been a long-standing tradition of opportunistic screening. **Objectives:** To evaluate the cost-effectiveness of organized screening compared with opportunistic screening, as well as to identify factors influencing the clinical and economic outcomes. **Methods:** We developed and validated an individual-level state-transition model and assessed the health outcomes and costs of organized and opportunistic screening for 40-year-old asymptomatic women. The base-case analysis compared a scenario involving organized biennial screening with a scenario reflecting opportunistic screening practice for an average-risk woman aged 45 to 69 years. We applied an annual discount rate of 3% and estimated the incremental cost-effectiveness ratio in terms of the cost (2012 euros) per life-year gained (LYG) from a health care perspective. Deterministic and probabilistic sensitivity analyses were performed to assess uncertainty. **Results:** Compared with opportunistic screening, an organized program yielded on average additional 0.0118 undiscounted life-years (i.e., 4.3 days) and cost savings of €41 per woman. In the base-case analysis, the incremental cost-effectiveness ratio of organized screening was approximately €20,000 per LYG compared with no screening. Assuming a willingness-to-pay threshold of €50,000 per LYG, there was a 70% probability that organized screening would be considered cost-effective. The attendance rate, but not the test accuracy of mammography, was an influential factor for the cost-effectiveness. **Conclusions:** The decision to adopt organized screening is likely an efficient use of limited health care resources in Austria.

Keywords: breast cancer, cost-effectiveness analysis, mass screening, microsimulation.

Introduction

Breast cancer is the most common malignancy for women in Austria, afflicting 1 in 13 by the age of 75 years. Approximately 5000 invasive breast cancers are diagnosed each year. For women, breast cancer also has the highest cancer mortality, resulting in about 1500 deaths each year [1]. Even though the age-standardized breast cancer mortality rates have been decreasing since the mid-1990s, the incidence rates have been increasing. This increase is correlated with the introduction of opportunistic mammography screening in Austria at the beginning of the 1990s.

Because of a lack of systematic reporting, the quality and performance of opportunistic mammography screening in Austria are difficult to evaluate. European guidelines for quality assurance in breast cancer screening recommend an organized population-based breast screening program [2]. The feasibility of quality-assured organized screening programs within the Austrian health care setting has been demonstrated in small pilot studies as well as in a statewide organized screening program in Tyrol [3,4]. After these studies, in 2014, Austria implemented a national but decentralized organized screening program inviting average-risk women, aged 45 to 69 years, to attend biennial screening involving bilateral two-view mammograms. In dense

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breasts, breast ultrasounds are allowed as an adjunct screening tool.

Nevertheless, evidence on long-term health and economic outcomes is lacking for Austria. The objective of this study was to assess the long-term effectiveness and cost-effectiveness of an organized breast cancer screening program compared with an opportunistic screening approach for women who are at average risk of developing breast cancer within the Austrian health care context.

Methods

Model Structure

We developed a decision-analytic, individual-level (microsimulation) state-transition model [5] that encompassed three main components: 1) a breast cancer natural progression pathway, including clinical diagnosis; 2) opportunistic screening; and 3) an organized screening pathway [6]. The expected health and economic consequences of introducing an organized or opportunistic screening approach for each simulated individual were assessed. The base-case analysis compared a scenario involving organized biennial breast cancer screening with a scenario reflecting current opportunistic screening practice (i.e., status quo in Austria) over the remaining lifetime of average-risk women aged 45 to 69 years. Every 3 months, women transitioned between mutually exclusive and collectively exhaustive health states. This cycle length was short enough to ensure that an event occurred at most once per cycle; half-cycle correction was also applied [7]. We used a health care payer's perspective, and therefore included only direct health care costs. We calculated the incremental cost-effectiveness ratios (ICERs), defined as the additional costs of a strategy divided by the additional life-years, compared with the next most costly strategy, after eliminating dominated strategies [8]. Model outcomes also included the number of cancers diagnosed, stage distribution, and mortality reduction associated with each strategy. We applied an annual discount rate of 3% to both costs and effects [9].

Data from the national statistics bureau, Statistics Austria, categorize breast cancer detection rates by the simplified Tumor, Node, and Metastasis classification [10]. Because of the data structure, we applied ductal carcinoma in situ (DCIS) and invasive tumors defined as local, regional, and distant as relevant health states, which determined the probability of screen detection and affect survival, treatment, and associated costs. Because the in situ stage is a noninvasive cancer that is present only in the layer of cells where it begins, we assumed that only DCIS represented a precursor of invasive breast cancer.

The model schematic, reflecting the natural history of breast cancer, used in this analysis is depicted in Figure 1, which shows the Markov model structure we developed for breast cancer screening with the possible courses of the disease represented by a state-transition ("bubble") diagram as recommended by Siebert et al. [7]. Similar structures have been used in published decision analyses by Rojnik et al. [11] and de Gelder et al. [12]. The blue arrows in the figure indicate possible breast cancer progression pathways during each cycle. Women enter the model at the age of 40 years, and every 3 months, each woman faces a probability of progressing to the next health state, which is based on transition probabilities that vary between cycles and are conditional on the woman's current health states.

We followed international modeling recommendations for building and reporting the model and analysis [7,13]. We performed several validation steps to evaluate face validity, internal validity, external validity, and cross validation according to the International Society for Pharmacoeconomics and Outcomes Research-Society for Medical Decision Making best practice recommendations for validation [14].

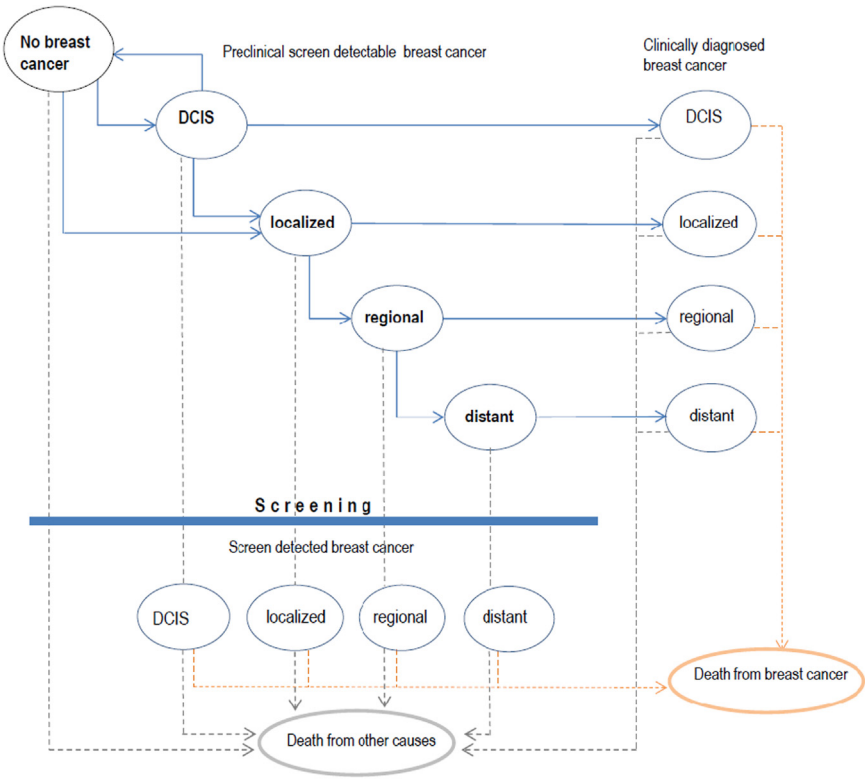

Fig. 1 – Flow diagram representing the natural history of breast cancer in the model. DCIS, ductal carcinoma in situ.

Model Inputs

Data inputs included the prevalence of DCIS and invasive breast cancer stages at age 40 years, the incidence rates of DCIS and invasive breast cancer per 5-year age group, breast cancer–specific and all-cause mortality, stage-specific sojourn times, sensitivity and specificity of the screening tests, and screening attendance rates.

The economic parameter inputs included the cost of the screening program, screening tests, additional diagnostic workup, and treatment for DCIS and invasive cancer.

Clinical data

All data regarding cancer incidence, clinical-stage distribution, and survival were obtained from the Austrian Cancer Registry. The data set included all breast cancer cases, staging information, and age and date at diagnosis together with date and cause of death. From 1983 to 1992, the number of DCIS cases was low and approximately stable with a mean value of 46 cases per year. Since 1993, the number has been steadily increasing, reaching 575 cases in 2009 and 644 cases in 2011 [15]. The small number of DCIS cases in the first 10 years of data collection in the Austrian Cancer Registry may be explained by the absence of any screening mammography during this period. Since the early 1990s, mammography examinations, although unorganized, were available. Data before opportunistic screening (i.e., 1987–1991) were used to estimate the clinical-stage distribution of breast cancer in the absence of intervention, for the calibration of age-dependent incidence and the prevalence at age 40 years. During that period, 46% of breast cancers were clinically detected in the local stage, 42% in the regional stage, and the remaining 12% in the distant stage. Data from 1983 to 1986 were excluded because of the number of death certificate–only cases and cases with unknown stages. The model assumed that the probability of DCIS progression and regression was independent of age.

A key assumption of breast cancer screening is that mammography is able to detect a proportion of cancer cases that would have otherwise gone undetected until clinical symptoms appeared. Therefore, important for screening is the period during which a breast tumor is not palpable and asymptomatic, yet detectable by mammography. This period is called the preclinical phase and its duration is referred to as the sojourn time [16,17], which places an upper limit on the lead time (i.e., the advance in the time of diagnosis achieved by screen detection) [18]. Tumor development was modeled as a process through the consecutive invasive disease stages—local, regional, and distant. Invasive cancer may or may not be preceded by noninvasive DCIS. In each preclinical stage, a tumor may be clinically diagnosed, in the presence of screening detected by mammography, or may grow into the next preclinical stage. The mean sojourn time of DCIS was assumed at 5 years with a range of 3 to 7 years on the basis of time to recurrence for low-grade DCIS reported to recur after 7 years and for high-grade DCIS reported to recur after 3 years [19]. The mean sojourn time of localized preclinical breast cancer was estimated at 2.5 years [11]. We applied a sojourn time of 0.36 to 1.08 years and 0.35 to 1.04 years in preclinical regional and preclinical distant states, respectively [11,20,21] (see Appendix Table A8 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009).

Cost data

All costs were converted to year 2012 euros (€) using the consumer price index for the year of data collection [22]. The average exchange rate in 2012 for €1 to US $1 was 1.29. Only inpatient treatment costs were based on the last available conversion factor of 2011 for the point score. A case flat rate is defined for every procedure-oriented diagnosis-related case group (LDF = leistungsorientierte Diagnosenfallgruppe) in the form of points (LDF points). These are made up of a daily component and a procedure component.

Costs of the screening program including the expenses for the coordinating office, scientific advisory board, public relation efforts and advertising work, screen invitation management, hard- and software, program evaluations and quality assurance initiatives were considered. Relevant cost data were provided by the manager of the Competence Center of Integrated Care of the Viennese Sickness Fund, responsible for organizational issues regarding the Austrian breast cancer screening program [23]. In sum, the annual cost totaled €3,443,920, which was allocated to cover all eligible women aged 45 to 69 years according to the 2012 Austrian population statistics [24].

Austria has two different remuneration categories for mammography: the first for cases screened because of symptoms, referred to as diagnostic mammography, and the second for cases screened as a part of routine physicals for a specific age group within the nationwide “prevention” (Vorsorgeuntersuchung NEU) program [25]. The cost of screening mammography was used in organized screening. For opportunistic screening, the vast majority of mammography screens are labeled as “diagnostic mammography”; therefore, the cost for diagnostic mammography was used in opportunistic screening, in the presence of breast symptoms, and in follow-up assessment after screening.

The costs for a routine mammography screen and for mammography because of clinical suspicion were based on average costs from the catalogue of benefits for all health insurance funds. A similar approach was used for the costs of doctor visits, ultrasound, and magnetic resonance imaging (MRI). The data were provided by the Main Association of Austrian Social Insurance Institutions [26]. To estimate resource use required in opportunistic screening, we calculated the ratio of all reimbursed breast ultrasounds and MRI examinations of the breast, and reimbursed mammograms. All assumptions regarding examination frequency in organized and opportunistic screening, in symptomatic breast cancer cases, as well as for follow-up after 18 months were based on expert opinion.

Unlike other health care systems, Austrian social insurance agencies do not reimburse costs for minimally invasive breast biopsies. Therefore, such biopsies tend to occur in hospitals that conduct the examinations either as inpatient procedures or as outpatient procedures. With the exception of stereotactic breast biopsy, no minimally invasive biopsy is listed in the medical procedure catalogue [27]; therefore, we did not include the costs of minimal invasive biopsies. The cost of performing more clinically invasive biopsy procedures is covered by the hospital diagnosis related group (DRG) system [28].

Linking the records from several databases across different service types was required because of Austria’s fragmented provider payment system and subsequently fragmented registries. A countrywide database, General Approach for Patient-oriented Outpatient-based DRG (GAP-DRG), covering the entire Austrian population was established by the Main Association of Social Insurance Institutions for the years 2006 and 2007. GAP-DRG links the service utilization records, following pseudonymization of the unique patient identifier, by matching methods. The database covers the entire range of health services including hospital, specialized outpatient and primary care, and pharmacies. Semantic interoperability between databases was established [29].

The cost of cancer diagnosis, treatment, and continuing care through 18 months after diagnosis was estimated from the GAP-DRG database. These data do not specify the costs for specific therapies; instead, they provide an average cost for all procedures that women undergo during the period of observation.

Austrian hospitals are financed under the Austrian DRG system, a DRG system adapted to meet the Austrian framework conditions [30]. The Austrian DRG system is a "procedure and diagnosis-related group system," because, in addition to diagnosis, the procedures operate as a primary criterion for allocating patients to case groups. In the DRG model, inpatient hospital stays are grouped into procedure-oriented diagnosis-related case flat rates on the basis of the data collected in hospitals, which include the medical procedure(s) performed, the disease classified by the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, age of the patient, and the hospital department involved. Together, these components determine the LDF points and the flat-rate compensation to be reimbursed [28]. Using the GAP-DRG database, we identified inpatients with newly diagnosed breast cancer. Only patients with a surgical breast procedure (mastectomy or partial mastectomy) were considered for costs.

Because the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, categorizes breast cancer on the basis of topography, no further classification regarding the clinical stage of breast cancer cases was possible [31]. Therefore, to identify women with DCIS, we adopted a pragmatic approach that involved identifying women according to guideline management. For example, women with DCIS are recommended to undergo a surgical breast procedure; in the event of breast-conserving surgery, radiation therapy is recommended, but no chemotherapy is recommended [32]. For women with DCIS, on average 4874 LDF points per woman were accrued for the first hospital stay (SD 2198.2; standard error [SE] 157.8) and 4720 LDF points per woman for the subsequent hospital stays (SD 4483.6; SE 321.9) [33].

Women with invasive breast cancer accrued, on average, 3,041 LDF points per woman for her first hospital stay (SD 2,622.8; SE 118.7) and 14,743 LDF points per woman for the subsequent hospital stays (SD 12,918.7; SE 584.8). Unfortunately, no further delineations of invasive breast cancer stages were possible. To convert the LDF points into monetary costs, the LDF points were multiplied by the average monetary conversion factor, which for 2011 was €1.2417 (H. Ostermann; Gesundheit Österreich GmbH, written communication, April 4, 2013). For services conducted on an outpatient basis, costs for drugs and services related to breast cancer up to 18 months after diagnosis were considered. The estimated drug costs were €4439.90 per woman; over-the-counter drugs and drugs below a certain prescription charge were, however, not considered. Drug costs per medication below the stipulated prescription charge are not reimbursed by the Austrian social security system. The estimated breast cancer–related costs for outpatient services including drugs were €2501.60 per woman. For 19 months through 5 years of follow-up, the annual costs were €130.21. The unit costs are provided in Table 1. The total cost per woman in the organized screening strategy was €85.45, in opportunistic screening €111.47, and in symptomatic breast cancer €132.10 (see Appendix Table A1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009). For each opportunistic mammogram, 0.9 breast ultrasounds were performed, whereas 0.35 of the mammograms in an organized setting were followed by an ultrasound [33] (see Appendix Table A2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009).

Table 1 – Costs of diagnostics and treatment per unit (€).

Unit	Cost per unit (€)
Screen invitation	2.45
Opportunistic screening mammography	75.02
Organized screening mammography	77.70
Diagnostic mammography outside screening	75.02
Doctor visit	16.53
Ultrasound	22.14
MRI	187.37
Costs of therapy including biopsy for DCIS up to 18 mo after diagnosis	18,215.01
Costs of therapy including biopsy for invasive cancer up to 18 mo after diagnosis	29,870.22
Follow-up after 18 mo	130.21

DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging.

Screening attendance

The attendance rate in an organized screening program for women aged 45 to 69 years was based on the data of the state of Tyrol, Austria's only organized screening program, and was estimated to be 60% [3,34]. Age-specific attendance rates for opportunistic screening were extrapolated from billing data from the Austrian social insurance agencies from 2007 and 2008 [26] (see Appendix Tables A3 and A4 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009). These billing data include patients from radiological institutes and radiologist offices (i.e., do not include private or municipal insurance companies or hospital outpatients). Age-specific frequencies for screening participation were not available for Austria. Assuming a 2-year interval, on average, participation rates were estimated to be approximately 45% for women aged 40 to 44 years, 55% for women aged 45 to 69 years, and 30% for women aged 70 to 74 years. No data were available for women older than 75 years. For the model, we assumed that there was no screening before the age of 40 years and after the age of 74 years.

Test characteristics of mammography

Recent studies have shown that the sensitivity of a mammography increases with age, whereas specificity varied little with age [35–37]. Mammography sensitivity is predominantly dependent on breast tissue density [38], and, in general, patient age and mammographic breast density are inversely related [39]. We incorporated age-specific sensitivity values in the model but because of the lack of quality assurance within an opportunistic screening setting, we assumed that the sensitivity and, to a lesser extent, specificity of mammography are lower for opportunistic screening compared with an organized screening setting. This may be in part due to low technical quality assurance, low volume mammography readers, the absence of double reading, and no mandatory training. Model inputs for test characteristics were based on a study comparing mammography performance within an organized screening setting in Norway and from an opportunistic screening setting in Vermont, United States [40] (see Appendix Tables A5 and A6 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009).

Parameterization

We calculated the probability for clinical diagnosis and transition to the next cancer stage in 3-month cycles for each invasive cancer stage on the basis of sojourn times and stage distribution from the Austrian Cancer Registry data [11]. Assuming the mean sojourn time in the DCIS stage to be 5 years and 65% of DCIS progress to invasive cancer, the probability for DCIS progression to invasive breast cancer is 3.25%, the probability that DCIS spontaneously regresses is 1.75%, and the probability of a clinical diagnosis of DCIS during one cycle is 0.237%. Transition

probabilities are presented in Appendix Table A7 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009.

We used 2012 life tables from Statistics Austria to parameterize overall mortality [41]. The annual probabilities in the life table were converted into probabilities for 3-month cycles. No correction was made for the contribution of breast cancer mortality to all-cause mortality because it only represents approximately 3.8% of all-cause mortality within the female general population (i.e., not regarded as a major cause of death in the cohort being modeled) [42].

We calibrated incidence and start-prevalence with data based on clinical diagnoses provided by Statistics Austria using simulation software AnyLogic 6.9.0 (The AnyLogic Company, St Petersburg, Russia). We considered all breast cancer cases of women aged 40 years and older during the years 1987 to 1991, the time period before opportunistic cancer screening. This approach was chosen to limit a potential bias due to screening.

Data from all diagnosed breast cancer cases during 1995 to 2004 were used for the calculation of cancer-specific probability of dying through 15 years of diagnosis. The analysis excluded death certificate–only cases and cases with unknown stages. The calculation of cancer-specific death probabilities was performed separately for each cancer stage (i.e., DCIS, local, regional, and distant cancer) but was not age-specific. To estimate the probability of dying beyond 15 years after a breast cancer diagnosis, we extrapolated the results with a parametric Weibull model through year 20. To adjust for the temporal improvements in treatment, we calculated the mean relative difference between the corresponding probability of dying estimated from 1995 to 1999 and from 2000 to 2004. Subsequently, model inputs reflected the probability of dying in 2000 to 2004 (1–5 years after diagnosis), the adjusted probabilities of dying for diagnoses between 1995 and 1999 (6–15 years after diagnosis), and the corrected and extrapolated probabilities for diagnoses occurring between 1995 and 1999 (16–20 years after diagnosis).

Analysis

The decision-analytic model was developed using TreeAge Pro 2012 software, using versions updated in 2013 and 2014 (TreeAge Software, Inc., Williamstown, Massachusetts). For base-case parameter input values, the model was run for 3 million simulation trials on the basis of a sample size calculation [43].

Parameter uncertainty was captured by one-way deterministic sensitivity analyses. These analyses varied relevant parameter values using plausible ranges or the upper and lower limits of credibility intervals of parameter distributions (see Appendix Tables A9–A14 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009). In addition, two-way sensitivity analysis was performed by varying two parameter input values simultaneously (i.e., attendance rates for different assumptions of test sensitivity). To capture joint parameter uncertainty, we performed a probabilistic sensitivity analysis by running 120,000 Monte-Carlo simulation trials that reflected the relevant distributions for costs and clinical parameters [44] (see Table 2 and Appendix Tables A10–A21 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009).

Table 2 – Distributions in probabilistic sensitivity analysis.

Uncertainty parameter	Distribution
Costs	Lognormal
Sensitivity of mammography	Beta
Specificity of mammography	Beta
Sojourn time	Lognormal
Portion of invasive cancers that are preceded by DCIS	Beta
Portion of DCIS that progresses to preclinical local stage (invasive cancer)	Beta
Portion of clinically detected cancers in local/regional/distant stages	Dirichlet
Attendance rate in organized screening	Beta
Attendance rate in opportunistic screening	Beta

DCIS, ductal carcinoma in situ.

Results

Model Validation

Evaluation of face validity was performed by a panel of decision-analytic modelers at the University for Health Sciences, Medical Informatics and Technology, not involved in constructing the simulation model. Information on the model and supporting documents were provided and presented in several modeling meetings. With regard to the internal validity of the model, each part of the model was tested to examine that the mathematical calculations were precise and consistent with the specifications of the model. Programming accuracy was verified by an independent modeling expert. To verify the internal validity, the adequate natural history pathway of breast cancer, the stage distribution of the modeled no-screening strategy and of the modeled opportunistic screening arm was compared with empirical data provided by Statistics Austria. To compare the no-screening strategy with cancer registry data, prescreening data from 1987 to 1991 were used. The small number of DCIS cases in the Austrian Cancer Registry is indicative of the absence of any screening activity during this period. The comparison of the modeled natural history with cancer registry data showed a good fit for all cancer stages (see Appendix Table A22 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009). To verify the adequacy of the modeled progression to invasive cancer through DCIS, the stage distribution in the opportunistic screening arm was compared with data of the Cancer Registry Statistics Austria. The stage distribution of the model closely resembled the actual average distribution of the year 2000 to 2010, indicating a good fit between predicted and observed stage distribution (see Appendix Table A23 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009).

The cross validation of the model was performed with published results from screening programs in other countries [12,45,46]. Projected reductions in cancer mortality seemed an appropriate parameter for comparison, although breast cancer epidemiology and other factors may differ from the modeled Austrian population. Opportunistic screening was projected to reduce mortality by 14.2%, whereas an organized screening program was projected to increase this reduction to 19.1%. One published study analyzing the cost-effectiveness of opportunistic versus organized mammography screening in Switzerland showed similar reduction rates in breast cancer mortality as our study [12]. In Australia's breast cancer screening program, a mortality reduction of 21% to 28% has been reported [45]. The current screening program targets women aged 50 to 69 years at 2-year intervals; nevertheless, screening women aged 40 to 49 years and 70 years and older is also performed. The decrease in mortality in women aged 50 to 69 years has been attributed, in part, to the early detection of invasive breast cancer through screening, along with advances in the management and treatment of invasive breast cancer. In the Netherlands, a nationwide mammography screening program for women aged 50 to 69 years was gradually implemented between 1989 and 1997. In 2001, the

reported mortality reduction in women aged 55 to 74 years was 19.9% [46]. Reported mortality reductions in meta-analysis of randomized clinical trials fell into the 15% to 21% range [47–49].

Base-Case Analysis

Compared with opportunistic screening, an organized breast cancer screening program yielded on average an additional undiscounted life expectancy of 0.012 years (i.e., 4.3 days) and is expected to cost €41 less per woman, over her remaining lifetime (see Appendix Table A24 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.009). An organized screening program dominates status quo opportunistic screening, yielding 23.955 life-years (discounted) at the cost of €1666.60 versus 23.946 life-years at the cost of €1677.50. These average estimates refer to the overall screening population, that is, women who develop or do not develop breast cancer during their life. This result means that among women who develop breast cancer during their lifetime, an organized screening program yielded an additional undiscounted life expectancy of 0.16 years (i.e., 58.7 days). Assuming 500,000 Austrian women at the age of 45 to 69 years regularly attend organized screening, 10,000 additional life-years are gained during their lifetime.

Compared with no screening (i.e., the only other undominated strategy), organized screening led to population-level gains in life expectancy of 26 undiscounted days. Assuming a screening coverage rate of 60%, an organized screening approach is expected to cost €20,024 per life-year gained (LYG), compared with no screening, as shown in Table 3.

Sensitivity Analyses

We performed 50 different one-way deterministic sensitivity analyses. Regardless of the discount rate applied, the organized screening scenario dominated opportunistic screening. Varying the test sensitivities in opportunistic and organized screening did not alter the dominance of organized screening. Attendance rates in organized screening of less than 55%, the proportion of invasive cancer preceded by DCIS at the lower and upper limits, and cost of diagnostic mammogram at the lower limit resulted in the dominance of opportunistic screening. Higher attendance rates in organized screening resulted in lower ICERs. Decreasing the test sensitivity in organized screening did not influence ICERs substantially compared with no screening. The greatest impact on ICERs compared with base-case analysis was observed with discounting, high treatment costs for invasive cancer and DCIS until 18 months, and low attendance rate in organized screening, whereas sensitivity analyses of both the proportion of invasive cancers preceded by DCIS and the proportion of DCIS progressing to preclinical local stage resulted in ICERs similar to base-case analysis. A scenario analysis with annual opportunistic screening instead of an average interval of 2 years resulted in a higher, unfavorable ICER of opportunistic screening compared with no screening, whereas the organized screening scenario remained dominant. Equal mammography sensitivities in organized screening and opportunistic screening had no influence on ICERs or the dominance of organized screening.

When we simultaneously changed the attendance rate for different levels of mammography sensitivity in all ages in organized screening, we found that attendance rate had a larger impact on ICERs than mammography sensitivity of organized screening when compared with no screening (Fig. 2).

For a maximum acceptable ceiling ratio of €50,000 per LYG, we found that the decision uncertainty surrounding the adoption of the organized screening strategy is approximately 30% (Fig. 3).

Discussion

To our knowledge, this is the first decision analysis to evaluate the long-term effectiveness and cost-effectiveness of breast cancer screening in the Austrian health care context. Until 2014, opportunistic screening was the predominant approach with the exception of several small pilot projects and one statewide organized screening program in Tyrol. Since the beginning of 2014, a nationwide organized screening program has been in effect. We project that additional health benefits in breast cancer outcomes could be achieved for a lower cost by this new organized screening approach. Some uncertainty, however, remains whether organized screening is cost-effective compared with the status quo. We investigated the effect of uncertainty of model input parameters on expected costs and effects, using probability distributions for model parameters. Looking at the distribution of incremental costs and effects in organized screening versus opportunistic screening, most of the points of the cost-effectiveness scatterplot reside symmetrically in the northeast and southeast quadrants, indicating that organized screening has a tendency to be more effective at more or less additional costs when compared with opportunistic screening. The scatterplot showed the overlap in the cost-effectiveness of organized and opportunistic screening.

The additional health benefits of organized screening versus opportunistic screening amount only to a few days of additional life expectancy for all screened women in the lifetime perspective because the vast majority of women who do not develop breast cancer do not benefit from cancer screening at all. For the proportion of women diagnosed with breast cancer by organized screening, the additional life expectancy amounts to around 2 months. Nevertheless, public health relevant numbers show that 10,000 additional life-years are gained in the lifetime perspective when a cohort of 500,000 Austrian women attend organized screening from the age of 45 to 69 years.

A biennial organized mammography screening program, covering 60% of the 45- to 69-year-old Austrian female population, was predicted to reduce breast cancer mortality by 19%. Opportunistic screening with current participation rates was less effective and required higher costs compared with an organized approach. Organized screening was, however, no more dominant if the participation rate in organized screening was lower than 55%. The predicted breast cancer mortality reduction in this study is lower than the reductions observed in national

Table 3 – Predicted effects, costs, and cost-effectiveness (3% discounted).

	No screening	Opportunistic screening	Organized screening
Life-years (n)	23.923	23.946	23.955
Costs (€)	1,015.83	1,677.49	1,666.59
Euro/LYG (ICER)	–	28,893.45	20,023.62

ICER, incremental cost-effectiveness ratio; LYG, life-year gained.

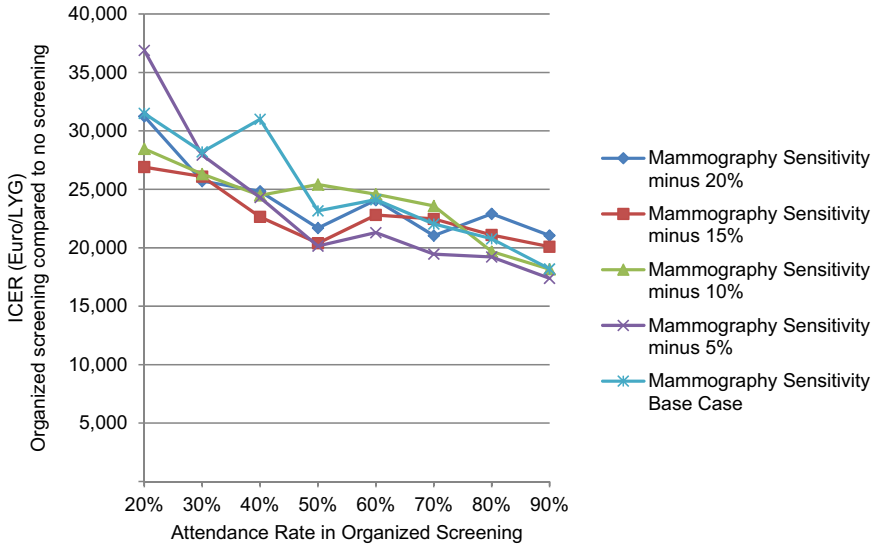

Fig. 2 – ICER of organized screening versus no screening in two-way sensitivity analysis with different levels of mammography sensitivity for all ages and varying attendance rates in organized screening. ICER, incremental cost-effectiveness ratio; LYG, life-year gained.

mammography screening programs [50–52], although some programmatic evaluations predicted reductions of about 19% [46,53,54]. Opportunistic screening was reported to reduce breast cancer mortality by 15% (8%–23%), whereas our model projected a reduction in cancer mortality of 14% [12,55] and supports the findings of de Gelder et al. [12] and Neeser et al. [56] that organized screening is more effective than opportunistic screening. Nevertheless, the ICER of organized breast cancer screening in Austria was higher compared with that of other models. Comparisons should, however, be viewed with caution because of varying target groups, screening intervals, as well as differences in attendance and discount rates. Only a few models have assessed biennial screening of women aged 45 to 70 years, as our study [11,57,58]. The study of Rojnik reported an ICER of €6,290 per LYG compared with our finding of €20,024 per LYG [11]. One study reported an ICER of €4,142 per LYG. This study, however, did not consider DCIS [58]. We expect that including DCIS would have increased the costs of treatment for DCIS cases that would not progress to invasive breast cancer.

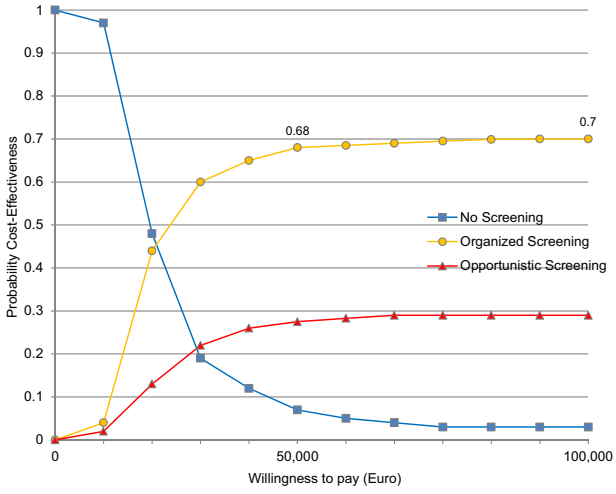

Fig. 3 – Cost-effectiveness acceptability curve of screening strategies (no screening, organized screening, and opportunistic screening).

Despite the unfavorable cost-effectiveness compared with other countries [11,12,58], the ICER (€20,024 per LYG) of the base-case result was cost-effective according to the World Health Organization criteria. Because neither an explicit nor an implicit ICER threshold exists in Austria [59], the willingness-to-pay threshold was chosen on the basis of gross domestic product (GDP) per capita in Austria according to the World Health Organization approach. Cost-effectiveness ratios less than 3 times the GDP per capita are considered cost-effective and ICERs less than the GDP are very cost-effective [60]. In 2014, the GDP per capita in Austria was €38,144.89, implying that Austria should consider interventions less than €114,434.67 to be cost-effective [61]. Moreover, with an ICER of about €20,000 per LYG, organized screening should be considered very cost-effective.

Because of uncertainties in the study's assumptions about test performance and participation rate in opportunistic and organized screening, we performed extensive sensitivity analyses. In the absence of national data, we used publications to determine that opportunistic screening mammograms may have a lower sensitivity compared with mammograms within an organized screening program. Although this may be a result of radiologists having less experience because of fewer readings, lower technical quality control standards, and less specific training, a Danish study showed that opportunistic mammograms were substantially less sensitive than those performed in organized screening [62]. A recent study comparing opportunistic screening in the United States with an organized screening program in Norway revealed lower sensitivity and specificity in opportunistic screening mammograms [40]. Nevertheless, because of the wide use of ultrasounds, some opportunistic screening settings may have equivalent or even improved performance compared with routine use of mammography [63]. A study comparing the performance of organized screening mammograms in the United Kingdom and opportunistic screening mammograms in the United States showed a higher number of cancers detected in the United States, although a large proportion of the increase was in the detection of small invasive and in situ cancers. These countries, however, had very similar numbers for the detection of more severe cancers [64]. Another study found

higher recall rates in opportunistic screening [65]. The reported test sensitivities in opportunistic screening from studies performed in the United States and from the national registry of the Breast Cancer Surveillance Consortium showed a wide range [66–71] overlapping with sensitivity data from organized mammography screenings [37,72,73].

There are several limitations that should be considered when interpreting the findings of this study. Similar to all models, our model relies on empirical data and simplifying assumptions. For example, age-specific participation rates in opportunistic mammography screening were estimated on the basis of data of eligible women in the social insurance system between 2007 and 2008; nevertheless, reliable data on compliance were not available. Because of a lack of systematic reporting, the true underlying test performance of mammography within the Austrian opportunistic screening setting is unknown and had to rely on scarce published data from other settings. In organized screening, we assumed a participation rate of 60% for the age group of 45 to 69 years, on the basis of Tyrolean screening program attendance rates. Because of a lack of data, women were assumed to attend opportunistic screening on average every second year.

We elected to adopt the health care system payer perspective; as such, patient travel costs and productivity loss were not included in our analysis. Treatment costs in this study were based on hospital data that were primarily accounting data, potentially introducing bias. Stage-specific breast cancer costs were available for DCIS and invasive cancers only; a further differentiation of invasive cancers was not possible because of lack of precise classification of breast cancer in hospital data. No data were available for treatment costs at the terminal phase of breast cancer. Including these costs would have led to increased costs, because patients with advanced breast cancer have presumably higher health care costs [74]. In the future, data on cancer stages and their treatment costs would improve our projections of lifetime costs and likely influence our estimates of the cost-effectiveness of organized breast cancer screening.

Screening costs were based on several assumptions regarding the number of additional ultrasounds and MRI examinations after abnormal mammography. We did not include the cost of minimally invasive biopsy. Minimally invasive biopsies are largely performed on an outpatient basis, but the procedure and diagnosis-related group system provides only reimbursement information for more invasive (i.e., open) surgical biopsies. Neither vacuum-assisted breast biopsy nor ultrasound-guided large-core breast biopsies are included [28]. Subsequently, for our analysis, we were limited to including costs for open biopsies.

We did not enumerate potential screening-related harms such as false-positive results that are associated with increased short-term anxiety and unnecessary costs for the health care system. But more importantly, overdiagnosed cancers result in invasive treatment of tumors unlikely to be harmful. Similarly, we focused on the health benefits of breast cancer screening in terms of LYG. Attending screening may also affect the quality of life (QOL) of women. This analysis did not include health-related QOL outcomes because these data are incomplete. Particularly, QOL data on harms due to overdiagnosis and false-positive results are lacking. Reliable data on QOL under various screening scenarios would provide valuable additional information that incorporates both morbidity and mortality changes in the outcome (i.e., quality-adjusted life-years gained).

Our study results reflect assumptions about the underlying natural history process of breast cancer, for which several areas of disease behavior, especially the role of DCIS, are poorly understood. Importantly, we do not know the proportion of invasive cancers preceded by DCIS or the probability of transitioning from DCIS to invasive cancer [21]. We applied the best data available to depict the natural history of breast cancer in the Austrian context, and used rigorous modeling techniques (e.g., calibration and validation) to help overcome these limitations. The validation of our model showed good fit to several important epidemiological end points including stage distribution. Furthermore, we applied a simplified clinical-stage classification to define relevant health states rather than tumor size because of lack of data.

We used a linear progression model in line with almost all publications in this field [75] as opposed to a parallel progression model in which DCIS and invasive cancer progress independently, which may be concluded from genomic expression profiles. In a parallel progression model based on an early metastasis hypothesis, tumor cells disseminate early after transformation and the number of disseminated tumor cells before diagnosis of metastasis is similar for different tumor stages [76]. In contrast, linear progression models assume that tumor cells disseminate from large established primary tumors supported by data about the association of prognosis with tumor size. Alternative hypotheses about the biology of breast cancer should be considered by screening models in the future.

Finally, our assumptions and theory about stage shift, the crucial point in breast cancer screening, may be right or wrong. Screening detects either tumors at earlier stages or other tumors at their usual stage but at an earlier time, both contributing to a better prognosis. But screening may or may not alter the course of disease and time of death, causing harm to women because of living longer with the disease. In addition, screening detects tumors that may not progress to symptomatic and therefore clinically detectable cases, contributing to overdiagnosis and subsequently to improved mortality rates.

In recent years, better breast cancer care and adjuvant cancer treatment have markedly improved the prognosis of breast cancer. Therefore, stage shift may not be solely accountable for the observed reduction in mortality in screening [77,78]. Furthermore, the significance of the increase in the number of screen-detected early-stage breast cancers for the observed mortality reduction in screening remains unclear. It is likely that the effect of screening in stage-shift models is overestimated. To the extent that our assumptions are incorrect, model results can be inconclusive. Our model is valid only if stage shift leads to a real reduction in mortality.

In fact, future analyses can continue to integrate new information from biological models as these data accrue, and our simulation model analyses can be revisited [76,79]. Application of nonlinear mathematics based on chaos theory may potentially aid our understanding of the natural history of breast cancer and support new approaches to modeling [80].

Conclusions

Our decision analysis, which is based on a stage-shift model, indicates that organized breast cancer screening is cost-saving, that is, more effective and less costly than opportunistic screening approaches. Nevertheless, the expected benefits and costs were influenced by assumptions about the screening attendance within the organized program. It is likely that the decision to adopt an organized breast cancer screening program in Austria is an efficient use of limited health care resources. It should be noted, however, that the validity of our model and the reported screening effects rely on the general assumption that screening can lead to cancer detection in earlier stages and that an earlier treatment can improve prognosis.

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Supplementary materials

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