Research Article

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Screening for breast cancer with Breast-CT in a ProHTA simulation

Aims: The potential of dedicated breast computed tomography is evaluated by simulating its impact onto the performance of the German breast cancer screening program. Attendance rates, cancer detection and economic implications are quantified. **Methods:** Based on a prospective health technology assessment approach, we simulated screening in different scenarios. **Results:** In the simulation, attendance rates increase from 54 to up to 72% due to reduced pain. Breast cancers will be detected earlier while nodal positives and distant recurrences decrease. Assuming no additional cost, cost savings of up to €55 million in one screening period are computed. **Conclusion:** The simulation indicates that earlier cancer detection, fewer unnecessary biopsies and less pain are potential benefits of Breast-computed tomography resulting in cost savings and higher attendance.

Keywords: breast cancer • computed tomography • health economics • health technology assessment • mammography screening • simulation

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Background

Breast cancer is the most frequent cancer and causes the most cancer deaths among women worldwide [1]. The provision of breast cancer screening programs (BCSP), the diagnostic examination of asymptomatic women in regular screening intervals, is an established strategy to reduce the disease burden by detecting breast cancer at an earlier stage. The German healthcare system provides BCSP.

In current BCSP, digital mammography (DM) is applied to identify suspicious cases. Yielding sensitivity rates of 46–93% and specificity rates of 88–99% [2], DM is limited. Many breast cancers are missed and/or false-positive diagnoses generated.

A computed tomography (CT) system dedicated to cancer diagnosis of the female breast has been developed at the Institute of Medical Physics (IMP) Erlangen in Germany. Based on the results of early trials at IMP, this Breast-CT (BCT) system could surpass DM both in terms of patient comfort and diagnostic performance potentially without increasing patient dose related to radiation exposure [3,4], and could be suited for screening applications.

Aims

In this study, the potential of the application of BCT in breast cancer screening is evaluated by simulating its impact onto the performance of the German BCSP in a prospective health technology assessment (ProHTA) simulation. In our analysis we consider two major drivers of program effectiveness, the attendance and the diagnostic performance. A health economic evaluation is performed from the perspective of the German healthcare system.

Breast cancer screening attendance

Program attendance is a critical success factor in any cancer screening program. In Germany, BCSP attendance has been 54% in 2010 [5]. According to EU guidelines, this is significantly below the acceptable rate of 70% [6]. A survey in Germany showed that one major impediment for women to attend

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BCSP is fear of the painful breast compression [7]. Improving patient comfort of BCSP examinations would be one strategy to raise BCSP attendance rates. By screening for breast cancer using BCT no breast compression will be necessary [4,8,9]. Therefore the use of BCT in BCSP is expected to lower women's fear of a potentially painful diagnostic procedure, and could have a positive impact on BCSP attendance.

Diagnostic performance of breast cancer screening

Since the rationale for breast cancer screening is detecting breast cancer at an earlier stage, the diagnostic performance of the applied imaging technology plays a key role in the effectiveness of the program. Advances in breast imaging technologies and related technological innovations bring about improvements in cancer diagnosis [10].

Although modern DM systems are able to display very small structures and to indicate microcalcifications, a significant share of breast cancers remains undetected. A main reason for 'missed' cancers lies in the limitations of 2D imaging. Superimposed structures 'hide' the actual lesion from even the most experienced observer [11]. Hence, researchers argue that only 3D representation of the breast volume can more accurately detect breast cancers [12].

The more recent development of breast tomosynthesis (BT) has promised improved breast cancer detection. BT allows the synthetic reconstruction of 3D volume data of the breast using 2D projection images acquired over a limited angle. Studies indicate superior performance of BT against 2D mammography, suggesting benefits of 3D imaging [13,14].

Whereas the range of images acquired by BT is limited, BCT is a full 3D imaging modality. It is capable of displaying superposition-free slices throughout the entire breast volume, thereby potentially overcoming the limitations of conventional 2D mammography [15]. BCT systems provide image and structural detail comparable to DM in all three spatial dimensions. With the additional benefit of contrast-enhanced imaging, they could improve diagnostic performance in early breast cancer detection.

Introduction to Breast-CT

This study focuses on a novel CT system dedicated to imaging the female breast. This BCT is being developed under the lead of WA Kalender in a project cooperation of IMP and CT Imaging GmbH. The project is part of the National Leading-Edge Cluster Medical Technologies 'Medical Valley EMN (European Metropolitan Region Nuremberg),' funded by the German Ministry of Education and Research (BMBF).

While standard clinical whole-body CT scanners already serve as complementary imaging modality for breast cancer related diagnostic tasks at specific medical indications [16], the development of BCT is dedicated to imaging the breast exclusively. BCT prototype devices have been developed already in the 1970s by General Electric in USA [17–19]. The manufacturer abandoned BCT in the late 1970s due to concerns over radiation dose and performance limitations [15]. Two decades later, the advent of digital flat-panel detectors has inspired the development of what can be called the second generation of BCT [4]. Research projects dedicated to this BCT approach include groups at the University of Rochester, the University of California, Davis and Irvine, the University of Massachusetts, Worcester, Duke University, MD Anderson Cancer Center and Emory University. Subject to this report is a BCT system based on a spiral CT approach and a new detector design. The system design requires no breast compression. More detail on this BCT can be found elsewhere [4].

Modeling in healthcare economic evaluation & ProHTA

In this study, we use a computer simulation model to perform a health economic evaluation of the technology innovation BCT. This model-based evaluation can be defined as a formal quantified comparison of health technologies, synthesizing sources of evidence on costs and benefits, in order to identify the best option for decision makers to adopt [20].

In order to prospectively assess potential benefits of medical technologies already in an early phase of the product life cycle, that is, before market entry, ProHTA provides a systematic framework. ProHTA is also a project within the 'Medical Valley EMN', funded by the BMBF. The primary goal of ProHTA is the evaluation of medical technologies in an early phase of the development process from the perspective of both the health system and the manufacturer. By providing simulations of a new technology's potential effects on medical and organizational processes at the beginning of the concept phase, the innovation processes can be prospectively optimized [21]. The ProHTA simulation model is based on 'hybrid simulation' consisting of system dynamics models for macrosimulation and discrete-event models for microsimulation [22].

Methods

Model overview

Our model simulates the future German BCSP beginning 1 January 2016 until 31 December 2027 so that all women will go through at least five complete biennial screening cycles. In our report, this time period

will be referred to as total time of simulation (TTS), while the last 2 years 2026–2027 will be referred to as final simulation period (FSP). The model simulates the target population, women from 50 to 69 years of age, the predicted future population development and the incident breast cancers therein. Technology diffusion of BCT and the application and diagnostic performance of both, DM and BCT, are simulated. The model outputs cancers by tumor size, false-positive screening results, cost of screening, biopsies and treatment.

Simulations have been performed in three scenarios:

- Reference case: Simulation of the future German BCSP without changes in current program performance characteristics and screening technologies. DM remains the first-line screening imaging modality in this scenario;
- Base case: Simulation of the future German BCSP including the introduction of BCT into screening. DM will still be the dominant imaging modality and screening attendance, technology diffusion and diagnostic performance will improve only slightly in this scenario;
- Best case: Similar to the base case, however, based on stronger effects of BCT on screening attendance and diagnostic performance, as well as on faster technology diffusion.

The base and best cases assume that BCT will be the primary screening imaging modality in a number of screening units that is depending on the simulated diffusion of technology.

Simulation model & input parameters

Modeling the target population & breast cancer incidence

The simulation of the target population in the years 2016–2027 is based on the population predictions published by the German Federal Statistical Office (Destatis) as population forecast 1-W1 [23]. For modeling purposes, breast cancer incidence rates are assumed constant based on 2010 data as reported by the Robert Koch Institute [24].

Modeling BCT technology diffusion

In our simulation, BCT will be introduced into the German BCSP beginning 2016, gradually taking over the role as the primary diagnostic imaging modality. When innovative technologies enter the market, they usually start off from a small diffusion base. Over time, the diffusion expands until it reaches a certain level of saturation. For our model, data on the introduction of DM into BCSP and the gradual transition from Screen Film Mammography to DM in the Dutch BCSP have served as reference [25]. Our model has been adjusted to fit our expectations of slower diffusion and lower saturation levels.

Modeling screening attendance

Attendance is among the core performance indicators of BCSP in Europe [26]. Low attendance levels of 54% in Germany show both, major potential and political demand for improvement of this key performance indicator.

Fear of pain is the most-cited reason for women not to follow their screening invitations [27,28]. Pain during screening has been reported by as many as 91% of women [29]. Thirty-eight percent of women that do not attend the German BCSP (strongly) agreed to the survey statement 'I am afraid of breast compression' [7]. Schnoor *et al.* [30] report that pain is an impediment for attendance for 12% of women.

BCT has been found to be superior to DM in patient comfort in several studies [8,9,31,32]. In the simulation, the proportion of women of the target population attending screening is depending on the availability of BCT as a pain-free screening technology. The reference case scenario without BCT assumes further stable attendance rates of 54%. In the BCT scenarios, the number of women attending screening will increase by the proportion of previously pain-related nonattendees that now have access to BCT screening sites. In the base case scenario, this proportion is modeled at 12%. In the best case scenario, it is expected to be initially 20% and rise up to 30%.

Modeling program sensitivity

In our model, the diagnostic performance of the imaging modality applied for breast cancer screening is reflected by the parameters sensitivity and specificity. Sensitivity is defined here as the proportion of all cancers detected in the screening population that had positive mammographic findings in the 24 months screening interval [33]. All cancers here are the sum of screen-detected cancers (SDC) and the interval cancers (IC) in the screening population. This study consistently refers to this definition when addressing BCSP sensitivity, following the recommendation of the European guidelines [6].

For the reference case reflecting the performance of the German BCSP in the status quo, a program sensitivity of 68% has been selected [34]. Due to data privacy issues, actual data on the program sensitivity of the German BCSP are not yet available [5]. The Dutch BCSP is structurally alike and has served as our reference.

To date, no study on the performance of BCT in an actual screening setting exists. In order to obtain sound estimates on program sensitivity of screening with BCT in the base and best case, we have made assumptions on the diagnostic performance of BCT. Early trials with BCT serve as a source of evidence which these assumptions are based upon. Furthermore, a closer analysis of cancers that had been missed in standard screening with DM allows conclusions onto potentially detectable cancers with BCT.

Kalender *et al.* [35] indicate that high-resolution imaging of microcalcifications in the magnitude of 100 µm and lesions of 2 mm at dose levels similar or slightly higher than standard DM is feasible. These figures indicate the superior performance that has been further elaborated in a subsequent study, where BCT has been found to provide superior visibility of fibers, masses and microcalcifications than DM and BT [3]. Clinical trials assessing the application of cone-beam BCT show improved visualization of structures in BCT against DM [9,31]. The high-dose efficiency of BCT with dose levels similar or only slightly higher than DM has also been reported elsewhere [36,37]. Further improvements are attainable with contrast-enhanced BCT [38]. The novel spiral BCT technology investigated here could be capable to surpass diagnostic performance parameters of the cone-beam system [4].

An advanced imaging technology must have the potential to detect IC that had been missed before. IC can be classified into four subgroups: 48% of IC show normal or benign features in the previous screening mammogram ('true ICs'); 11% of IC show suspicious signs retrospectively seen on a mammogram, missed during screening ('false-negatives'); 18% of IC show nonspecific 'minimal signs' at the previous screening; 24% of IC are 'radiologically occult,' presenting clinical signs but no mammographic abnormalities [39]. In our reference scenario, if 68% of total are SDC, the residual 32% of total are IC, which can be further broken down into these subgroups.

Based on this typology, we have made assumptions on the proportion of IC that will be detectable by improved diagnostic imaging. In the base case we assume that 20% of true IC will be detectable with BCT. Of the radiologically occult, minimal sign and false-negative cancers 30, 70 and 80% will be detected, respectively. This computation results in an increase of program sensitivity from 68 to 80%. In the best case, we computed a program sensitivity of 85%.

Modeling combined effects of increased program attendance & improved diagnostic performance

A stage shift, that is, the earlier detection of cancers that would have been otherwise detected at later stages, is reflected in the higher share of smaller tumor stages within SDC than within cancers detected outside a screening program. In our model, we assume that SDC, IC and nonattendees' cancers (NAC) each have one specific and constant set of stage distributions. In the reference and base cases, these stage distributions are based on actual data from the German BCSP in 2010. In the SDC group, the early tumor stages *in situ* (noninvasive, 16%) and T1 (invasive, size <2 cm, 66%) make up for 84% of cancers [5]. In the groups of IC and NAC, this share is 55 and 56%, respectively [5,40]. IC distribution is based on data published on ICs in the screening region of North-Rhine-Westphalia [40]. For NAC, we use the stage distribution of cancers detected in the reference population of the German BCSP before the implementation of screening [5]. In the best case scenario, we assume 21% of *in situ*, 69% T1 and 10% T2–T4 for SDC.

Modeling BTC specificity & unnecessary biopsies

For the purpose of quantifying unnecessary biopsies in our reference case scenario, we have set specificity to 97% for mammography as reported by Kuhl *et al.* [41]. We assume an improved specificity of BCT based on the fact that in conventional 2D imaging, imaging artifacts due to effects of superposition will frequently be mistaken for lesions [15]. Hence, a reduction of these effects in tomographic imaging is likely to reduce false alarms, unnecessary recalls and biopsies. These benefits have already been observed in screening trials using BT, indicating specificity of up to 99%, despite the limited image range of this technology [14]. Hence, in the base-case- (best-case-) scenario, we assume that screening with BCT has an improved specificity of 98% (99%).

Modeling effects on healthcare cost

Our model uses probabilities of nodal positive cancers and distant recurrences by tumor size as classified in the UICC tumor node metastasis (TNM) classification at diagnosis, based on data provided by the Surveillance, Epidemiology and End Results Program in the variant Derived AJCC-6 [42]. To simulate the economic effect of BCT, we used several relevant cost factors. First, we assume that nodal positive cancers are treated with chemotherapy and nodal negative cases are not. The net cost effect of nodal status positive (N1+) versus negative (N0) is €14,434 [43]. Second, the net cost effect of distant recurrences (M1) against M0 is €39,029 [44]. Third, based on cost and application rates of different biopsies reported by Weining-Klemm [45] and Göttling [46], we calculated mean-weighted cost of biopsies in our model is €238 for the procedure only. Fourth, cost of screening is €45 per screening exami-

nation [47]. The model assumes no differences in cost of screening with DM or BCT. Cost for local and locoregional recurrences, biopsy complications, further assessment as well as indirect cost effects such as the loss of productivity are excluded from our analysis.

Sensitivity analysis

Three univariate sensitivity analysis have been performed in order to test the model output against the negative variation of key input parameters. These parameters reflect key assumptions we made on the performance of BCT in a screening setting. Since the technology is still in the research and development stage, there is not yet sufficient empirical data available. Therefore these assumptions are subject to uncertainty. The varied input parameters and their respective relevant output parameters in the sensitivity analysis are: the proportion of previously pain-related nonattendees that would attend screening if BCT is available in % – tested against the output parameter average screening attendance. Program sensitivity with BCT – tested against total simulated breast cancers (tumor sizes in TNM classification), nodal status, distant recurrences and cost of treatment of distant recurrences and unnecessary biopsies. BCT specificity – tested against the number of biopsies based on false-positive recommendations and cost of biopsies based on false-positive recommendations. In each of the three analysis, a single parameter has been reduced while all other parameters remain unchanged, based on the base case model in FSP.

Results

Screening attendance

In the reference scenario 36.5 million women attend screening during TTS 2016–2027 (Table 1). All screening attendees are screened with conventional DM technology. In contrast, in the base- and best-case scenarios introducing BCT as screening technology, the number of screening examinations increases by roughly 1 million (3 million) in the base case (best case) in TTS. In these scenarios, 7.8 million and 14.2 million women are screened with the new BCT technology and the residual with DM. In FSP 2026–2027, BCT has reached the level of an established screening modality in the simulation. Fifty percent (80%) of screening examinations will be performed with BCT in the base case (best case), with the remainder still performed with DM. BCT will not entirely replace DM within TTS due to an only gradual diffusion of the novel technology in our simulation. Attendance rates start at 54% and climb to 60% in the base case and 72% in the best case in FSP.

Tumors detected by size in target population

The stage shift discussed above is apparent when looking at the tumor size distribution in Table 1. In TTS, more early stage tumors are detected in the target population. In the base-case scenario, the net increase of *in situ* carcinomas against the reference case in TTS is 965 cases or 2%, and in the best case 4141 or 7%, respectively. In FSP, this increase is 330 (1725) in the base case (the best case). T1 carcinomas increase by 1666 or 1% in the base case, and 7573 or 3% in the best case in TTS and 759 (2%) and 3629 (9%) in FSP. Larger invasive tumor sizes (T2–T4) decrease by 2631 in the base case, and 11,714 in the best case in TTS. In FSP, this decrease is 1088 (5354) in the base case (the best case). Figure 1 illustrates the described stage shifts in the best case. The increase of early stage tumors in this scenario is replacing larger tumor sizes over time.

Tumors detected by nodal status & distant recurrences in target population

In the reference case, 330,321 nodal negative (N0) cancers are incident in the target population in TTS (Table 1). This figure increases by 1187 (4851) cases in the base case (best case) along with a respective decrease in nodal positive (N1+) cancers. The number of distant recurrences (M1) will decrease in the base case by 245 from 441,623 in the reference case, and by 833 in the best case in TTS. In FSP, the decrease of nodal positive cancers against the reference case is 488 in the base case and 2215 in the best case. In the same time span, distant recurrences will decrease by 108 (401) cases in the base case (best case).

Cost of treatment & biopsies

Table 2 lists cost of nodal positive cancers and distant recurrences in the reference case, base case and best case, in both TTS and FSP. Total cost in the reference case is €2357 million, with the major share (€1795 million) in chemotherapy treatment of nodal positive cancers. In the base case, total cost of illness decrease by €32 million or 1% in TTS, and €13 million and 3% in FSP. The best case reveals a larger cost-savings effect of €121 million or 5% in TTS, and €55 million and 14% in FSP. The largest relative savings of treatment cost will be realized in the best-case scenario by the 18% drop of the cost of treating distant recurrences in FSP.

The improved BCT specificity results in a reduced number of recommendations for invasive biopsies. Total cost of these biopsies decreases linearly with the decreasing number of performed biopsies in the simulation. In the reference case, the total number of biopsies based on false-positive recommendations is 217,687 in TTS, or 34,740 in FSP. Associated cost is €52 million, or €8 million in FSP. In The base case,

Table 1. Simulated breast cancers in target population from 2016 to 2027.

Simulation model output parameters	Reference case (no innovation)				Base case (moderate innovation scenario)				Best case (stronger innovation scenario)			
	TTS		FSP		TTS		FSP		TTS		FSP	
	n	%	n	%	n	%	n	%	n	%	n	%
Women screened	36,478,110		5,826,671		37,460 091		6,385,346		39,501,024		7,711,988	
Average screening attendance		54		54		56		60		59		72
Screened with BCT	–	0	–	0	7,882,808	21	3,192,038	50	14,200,874	36	6,169,333	80
Increase/decrease versus reference case												
Total simulated breast cancers (tumor sizes in TNM classification)	454,700	100	75,666	100	±0	±0	±0	±0	±0	±0	±0	±0
Tis (*in situ*, noninvasive)	59,827	13	9980	13	+965	+2	+330	+3	+4141	+7	+1725	+17
T1[†]	247,058	54	40,926	54	+1666	+1	+759	+2	+7573	+3	+3629	+9
T2[†]	121,619	27	20,299	27	-1777	-1	-697	-3	-9627	-8	-4282	-21
T3[†]	14,785	3	2509	3	-516	-3	-234	-9	-1106	-7	-572	-23
T4[†]	11,412	3	1952	3	-338	-3	-157	-8	-980	-9	-499	-26
Nodal status (N0):												
– N0	330,321	73	54,897	73	+1187	+0	+488	+1	+4851	+1	+2215	+4
– N1+	124,379	27	20,769	27	-1187	-1	-488	-2	-4851	-4	-2215	-11
Distant recurrences (M0):												
– M0	441,623	97	73,464	97	+245	+0	+108	+0	+833	+0	+401	+1
– M1	13,077	3	2202	3	-245	-2	-108	-5	-833	-6	-401	-18

[†]T1: Tumor >20 mm; T2: Tumor >20 mm >50 mm; T3: Tumor >50 mm; T4: Tumor of any size with direct extension to the chest wall and/or to the skin.
BCT: Breast-CT; FSP: Final simulation period; N0: No chemotherapy treatment; M0: No distant recurrences; TNM: Tumor node metastasis; TTS: Total time of simulation.

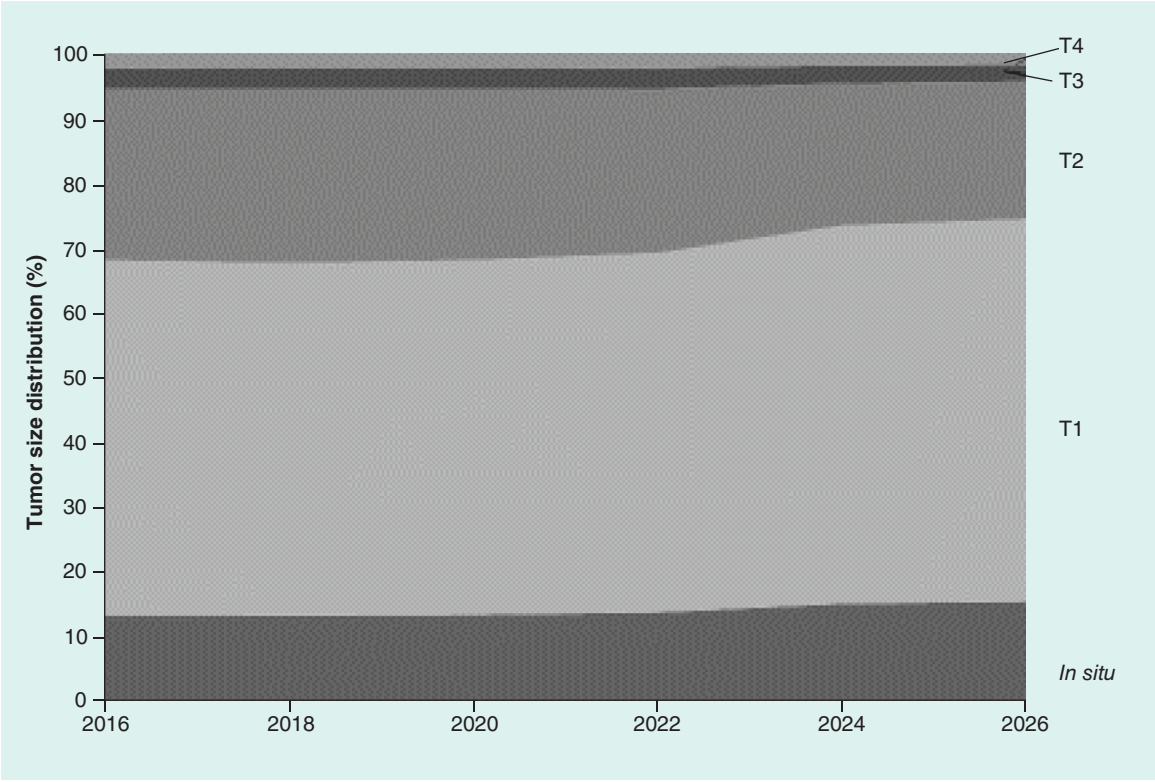

Figure 1. Stage shifts in target population (best case). Proportion of tumors detected in target population by tumor size in TNM classification.
T1: Tumor ≤20 mm; T2: Tumor >20 mm ≤50 mm; T3: Tumor >50 mm; T4: Tumor of any size with direct extension to the chest wall and/or to the skin; *In situ*: noninvasive tumor; TNM: Tumor node metastasis.

22,190 or 10% less biopsies are performed in TTS. In FSP, 7976 or 23% of biopsies can be avoided. In the best case, 75,797 or 35% of biopsies are avoided in TTS, resulting in cost savings of €18 million. In FSP, biopsies and cost decrease by 83% or €7 million.

Cost of screening

Since more women attend screening in the base and best case, total cost of screening (not shown in the tables) increases accordingly. In the reference case, total cost of screening is €1.64 billion in TTS. In the base-case and best-case scenarios, cost of screening is €1.68 billion and €1.77 billion, respectively.

Sensitivity analysis

Tables 3–5 show the results of three univariate sensitivity analysis in three adverse scenarios (1–3) each and the base case as reference.

In Table 3, lowering the proportion of previously pain-related nonattendees that would attend screening if BCT is available results in a decrease in screening attendance. A decrease of this proportion from 12% in base case to 10% (5%) results in a drop in screening attendance to 59% (57%) in the Adverse scenario 1 (2). A reset of this proportion to 0% leaves the screening attendance at the reference case level of 54% without any change (scenario 3). This reflects the model assumption that screening attendance is dependent to a significant degree on the availability of a pain free procedure.

In Table 4, reducing the program sensitivity assumed for BCT screening results in a stage shift toward larger tumor sizes. Program sensitivity has been reduced in 5%-pt. steps from 80% in base case to 65% in adverse scenario 3, which is a lower performance than the 68% assumed for DM in the reference scenario. Hence, in adverse scenario 3, BCT underperforms DM in terms of sensitivity. In contrast to the reference case, both modalities will be applied in adverse scenario 3. The shift toward larger tumor sizes is highest in the T3 class with a 7.1% increase from base case in adverse scenario 3. Along with the increase of tumor sizes, 0.6% (1.2%, 1.6%) more nodal positive tumors are detected in adverse scenarios 1–3, respectively. Distant recurrences appear in 1.3% (1.5%, 2.8%) in adverse scenarios 1–3, respectively. Cost of chemotherapies, treatment of distant recurrences and unnecessary biopsies increase to up to €389 million or up to 2% when BCT program sensitivity drops to 65% in adverse scenario 3.

Table 2. Cost of chemotherapies, treatment of distant recurrences and unnecessary biopsies.

Simulation model output parameters	Reference case (no innovation)		Base case (moderate innovation scenario)					Best case (stronger innovation scenario)				
	TTS	FSP	TTS			FSP		TTS			FSP	
				Δ to ref. -case (%)			Δ to ref.-case (%)		Δ to ref.-case (%)			Δ to ref.-case (%)
Total (million €)	2357	394	2326	-32	-1	381	-13	-3	2237	-121	-5	339	-55	-14
Cost of chemotherapies (million €)	1795	300	1778	-17	-1	293	-7	-2	1725	-70	-4	268	-32	-11
Cost of treatment of distant recurrences (million €)	510	86	501	-10	-2	82	-4	-5	478	-33	-6	70	-16	-18
Cost of biopsies based on false-positive recommendations† (million €)	52	8	47	-5	-10	6	-2	-23	34	-18	-35	1	-7	-83
Number of biopsies based on false-positive recommendations	217,687	34,740	195,497	-22,190	-10	26,763	-7976	-23	141,890	-75,797	-35	5787	-28,953	-83

†Cost of biopsy procedure only, excluding cost of potential complications.
FSP: Final simulation period; TTS: Total time of simulation.

In Table 5, reducing the specificity of BCT from 98% in base case by 1%-pt. steps to 97, 96 and 95% in adverse scenarios 1–3 increases the number of biopsies based on false-positive recommendations by 23.5, 50.1 and 105.1%, respectively. Cost are linear to the number of biopsies and increase accordingly from €6 million in base case to up to €13 million in adverse scenario 3.

Discussion

BCSP based on mammography are increasingly subject to criticism in both, scientific and popular publications. This criticism is based on the high rate of undetected breast cancers despite screening, unnecessary follow-up examinations of unaffected women, overdiagnosis and overtreatment [48–50]. Hence it would be beneficial to enhance the diagnostic performance of screening, expressed by the parameters sensitivity and specificity, in order to improve the effectiveness of the BCSP. In this study we have evaluated the potential of the novel BCT technology as a breast cancer screening modality to provide this improvement and to help raise attendance rates.

The simulated increase of screening attendance from 54 to 60% in the base case or 72% in the best case in 12 years is substantial. Looking at other European countries, the attendance rate of the German BCSP has significant room for improvement, and rates beyond 70% are achievable. Excluding Poland with a very low attendance of 19.4%, the average rate across 25 European programs sending personal invitations was 66.4% in the first decade of the new millennium [51]. In our simulation, the increase is dependent on the assumption that many women that had avoided screening due to fear of pain will attend when they have access to a pain-free procedure. The significant dependency on this assumption of our model has been confirmed in a univariate sensitivity analysis. Even though factors influencing the attitude and behavior of women toward screening remain manifold [30], including logistics and organization of the BCSP, effective pain-reducing interventions are key to strengthen participation [28]. The introduction of BCT could reflect such an intervention. In order to realize this potential and to achieve the simulated improvements in attendance, the advent of the novel technology needs to be accompanied by a reasoned communication strategy addressing and reducing fears of the screening procedure and further related fears such as concerns over radiation dose levels.

In our simulation, program sensitivity increases from 68% when screening with DM to up to 85% with BCT. The application of BCT as a high-resolution 3D imaging modality is causing this assumed leap of

Table 3. Sensitivity analysis 1, based on base case, final simulation period: reducing the model assumption of pain-related nonattendance.

Simulation model parameters	Adverse scenario 3	Adverse scenario 2	Adverse scenario 1	Base case
Input: percentage of previously pain-related nonattendees that would attend screening if BCT is available (%)	0	5	10	12
Average screening attendance (%)	54	57	59	60

BCT: Breast-CT.

screening performance. To put this into perspective, we can refer to magnetic resonance imaging for breast cancer detection. Kuhl *et al.* [41] reported a significantly greater leap of performance from 2D to 3D screening in a study comparing sensitivity of film-screen mammography (32.6%), breast ultrasound (39.5%) and magnetic resonance imaging (90.7%). In our model, sensitivity of BCT screening increased to 80% in the base case and 85% in the best case while specificity increased from 97 to 98 and 99%, respectively. It is often stated that increasing sensitivity in breast cancer screening necessarily comes at the expense of lower specificity [52]. However studies show that both, sensitivity and specificity can increase when comparing different imaging modalities against the reference modality [41].

Due to the detection of cancers in earlier, more favorable stages, healthcare costs decrease in the simulated BCT scenarios. Absolute cost savings are most substantial in the reduced costs of chemotherapies and treatment of distant recurrences, applicable to advanced cancers. The reduction of advanced breast cancers is not only beneficial for the quality of life of the patients, but also an economic demand due to their major budget impact [53].

The highest relative cost savings are achieved by fewer unnecessary biopsies due to the improved specificity of BCT in the simulation. There is only limited research on the economic consequences of false-positive cancer screening results [54,55]. Follow-up assessment of patients tested positive entails costly and invasive biopsies and consequently reduces the cost–effectiveness of screening programs [56]. Our model computes roughly 35,000 biopsies based on false-positive screening in a two-year screening interval with DM. According to the evaluation report of the German BCSP 2008–2009, 1.5% of the screening participants received a biopsy, with a positive result in 0.76% of cases [57]. Based on a screening population of 5.4 m women, these results are well in line with our simulation in the reference case and highlight the savings potential. Follow-up assessment of false-positive recalls also requires costly imaging procedures, mainly through ultrasound. These cost have a strong impact on screening budget [55]. Since they are not included in our model, potential savings could be higher. With the improved specificity, the introduction of BCT into breast cancer screening can have a major impact on the cost–effectiveness of screening, and reduce stress and anxiety of patients due to false alarms of mammography. In addition, this effect can also further help increase attendance rates and should be taken into consideration by healthcare decision makers.

In two univariate sensitivity analysis we have tested the impact on more adverse parameter assumptions on the program sensitivity and specificity of BCT. In the analysis on program sensitivity, even a large negative variation of the parameter assumed for BCT has a relatively limited effect on the output of our model. As in any screening program, the number of detected cancers is small in relation to a large number of screened subjects. Hence, a variation of the detection rate is affecting only a small base of subjects and related cost. In contrast, in the analysis on specificity of BCT, the impact of a parameter variation on cost is relatively strong. Since by definition, diagnostic specificity relates to the large number of healthy subjects, a variation has a stronger relative cost impact. The relatively low impact on cost when reducing program sensitivity and the higher impact when reducing specificity has also been observed by Warmerdam *et al.* in their model analysis of mammographic screening in Germany [58].

While the introduction of BCT into breast cancer screening is causing the highest savings in cancer care cost in the simulation, it is causing cost increases in the healthcare budget for screening. Cost of screening is higher with increasing attendance rates by implication. In fact, additional screening cost of €136 million in the best case versus the reference case seem to cancel the economic benefit. However, we do not draw this conclusion for two reasons. First, the increase of participation in organized screening is likely to cause a parallel decrease of the number of curative mammograms (i.e., nonscreening mammograms performed in women with clinically suspicious signs or at increased risk of breast cancer based on family or personal history)

and associated cost [47]. Curative mammograms have accounted for about €100 million in 2012 [47]. Although curative mammograms are excluded from our simulation, the reduction of cost for curative mammograms is likely to have a substantial impact on total cost of breast cancer diagnostics. Second, high attendance rates are a basic requirement for the screening program to work (cost-)effectively [59]. In addition, the cost associated with achieving the attendance rates required by the European guidelines are to be covered irrespectively of the cost benefits, based on a political imperative.

In our simulation we modeled the introduction of a novel imaging modality into breast cancer screening. Our integrated ProHTA modeling approach allowed us to simulate scenarios in which both, conventional and innovative imaging with distinct performance characteristics are applied for screening. Simultaneously, the effects of gradually introducing pain-free screening on screening attendance rates and associated medical and economical outcomes have been dynamically simulated. The integration of a wide range of multiple diffusion, performance, attendance and cost parameters into a single simulation model is a noteworthy feature of our approach. To our knowledge, only very few studies have reported on the effect of the alteration of multiple screening performance parame-

Table 4. Sensitivity analysis 2, based on base case, final simulation period: reducing the model assumption on Breast-CT performance (diagnostic sensitivity).

Simulation model parameters	Adverse scenario 3	Adverse scenario 2	Adverse scenario 1	Base case
Input: program sensitivity with BCT (%)	65	70	75	80
Total simulated breast cancers (tumor sizes in TNM classification)	75,666	75,666	75,666	75,666
% versus base case	±0.0	±0.0	±0.0	
Tis (*in situ*, noninvasive)	10,062	10,039	10,157	10,310
% versus base case	-2.4	-2.6	-1.5	
T1†	41,192	41,402	41,588	41,685
% versus base case	-1.2	-0.7	-0.2	
T2†	20,121	20,059	19,739	19,601
% versus base case	+2.7	+2.3	+0.7	
T3†	2436	2360	2348	2275
% versus base case	+7.1	+3.7	+3.2	
T4†	1854	1805	1833	1794
% versus base case	+3.3	+0.6	+2.2	
Nodal status (N0)				
N0	55,063	55,146	55,254	55,385
% versus base case	-0.6	-0.4	-0.2	
N1+	20,603	20,520	20,412	20,281
% versus base case	+1.6	+1.2	+0.6	
Distant recurrences (M0)				
No distant recurrences (M0)	73,514	73,541	73,544	73,572
% versus base case	-0.1	-0.0	–0.0	
M1	2152	2125	2122	2094
% versus base case	+2.8	+1.5	+1.3	
Cost of chemotherapies, treatment of distant recurrences and unnecessary biopsies (million €)	389	386	384	381
% versus base case	+2.0	+1.3	+0.8	

†T1: Tumor ≤20 mm; T2: Tumor >20 mm ≤50 mm; T3: Tumor >50 mm; T4: Tumor of any size with direct extension to the chest wall and/or to the skin.
BCT: Breast-CT; M0: No distant recurrences; N0: No chemotherapy treatment; TNM: TNM: Tumor node metastasis.

Table 5. Sensitivity analysis 3, based on base case, final simulation period: reducing the model assumption on Breast-CT performance (specificity).

Simulation model parameters	Adverse scenario 3	Adverse scenario 2	Adverse scenario 1	Base case
Input: specificity of BCT (%)	95	96	97	98
Number of biopsies based on false-positive recommendations	54,905	40,178	33,060	26,763
Cost of biopsies based on false-positive recommendations (million €)	13	10	8	6
% versus base case	+105.1	+50.1	+23.5	

BCT: Breast-CT.

ters or attendance rates on health economic outcomes. Warmerdam *et al.* have simulated the German BCSP based on three distinct sets of screening sensitivity and specificity. Equal to the outcome of our simulation, the authors report significant cost savings due to treating fewer women with advanced disease [58]. De Gelder *et al.* simulated the effect of different settings of screening attendance rates and program performance characteristics in breast cancer screening in Switzerland. In their study, scenarios of organized screening are compared with opportunistic screening [60]. Since we have excluded opportunistic screening from our simulation, our studies are not comparable.

Our model and the interpretation of the simulated outcomes are subject to certain limitations. First, we have not accounted for potentially higher screening cost with BCT. Higher equipment cost, training of staff, longer reading times for BCT images and contrast enhancement can result in additional cost of screening and assessment. Especially in early market stages, this cost can be substantial. The BCT technology presented here is not yet produced in series and market prices at higher equipment production volumes are not available. BT technology can serve as a reference for cost of 3D mammographic screening and equipment. BT equipment cost can run over US$500,000, more than twice the price of DM equipment [61]. In addition, reading 3D mammographic BT images has been found to take more than twice as much time as 2D images which could result in higher screening cost [62]. However, this cost does not necessarily translate into higher screening cost charged by the screening unit. Many US clinics now offer adjunct BT screening at cost of US$50 [61,63]. In our model, screening cost is €45 per examination. Thus cost levels of 3D screening with BCT similar to DM seem to be a realistic long term scenario. Further research is needed to assess the cost–effectiveness of BCT screening in more detail once prices and data are available. Second, our model does not account for potential overdiagnosis when screening asymptomatic women, but rather assumes that all incident cancers need to be treated. Plausible estimates range from 1 to 10% excess incidence of breast cancer due to overdiagnosis [64]. Overdiagnosis is a potential negative side effect of any BCSP which has not been quantified in our model. BCSP are exceedingly subject to criticism for causing overdiagnosis and related harm [65]. Ultimately, the benefit of BCSP is measured by its impact on mortality reduction. Since the end point of our model is cancer detection and related cost, we have not modeled this impact of the new screening modality, which is a further limitation of our study. Instead, with our approach we implicitly assume higher detection rates to be beneficial, without considering overdiagnosis. EU guidelines on BCSP demand the maximization of cancer detection rates and are hence based on the same assumption [6]. While the important debate on potential harms of higher detection rates is ongoing and further informed by new reviews [66], a full review of the evaluation of evidence regarding benefit and harm of BCSP in general was outside of the scope of our study. Third, in our simulation, we have not considered the initial increase of breast cancer incidence when women are attending screening for the first time. Typically, when introducing breast cancer screening, incidence rates peak following the introduction [5]. This effect is leveling out when programs are established and has therefore been excluded from our simulation. Furthermore, our model excludes various cost factors such as treatment of local and locoregional recurrences, biopsy complications, further assessment as well as indirect cost effects. Hence, our model potentially underestimates total savings in assessment and treatment cost, but at the same time underestimates additional screening cost caused by the novel technology. These perspectives will have to be included in further studies on the technology assessment of BCT.

Conclusion

We have presented a ProHTA simulation that indicates the introduction of the novel BCT technology into breast cancer screening to be potentially beneficial for the German healthcare system. In the simulation, women screened with BCT benefit from the earlier detection of cancers and fewer unnecessary biopsies. Our model has computed significant cost savings in the German healthcare system as a direct effect of this improved diagnostic. Due to the pain-free diagnostic procedure, BCT has the potential to increase attendance rates toward a level close to or beyond the level recommended by EU guidelines.

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Executive summary

- Breast cancer screening programs aim to detect breast cancer at early stages by using 2D digital mammography (DM).
- The effectiveness of any screening program strongly depends on attendance and diagnostic performance.
- Painful breast compression necessary for DM potentially limits attendance, while diagnostic performance of this 2D imaging modality is limited particularly due to superimposed structures.
- The introduction of Breast-CT, a dedicated 3D imaging modality for the female breast, into screening could overcome shortcomings of DM.
- A prospective health technology assessment hybrid simulation model has been developed, simulating the impact of BCT on the performance of the German breast cancer screening program.
- In the prospective health technology assessment simulation, the introduction of Breast-CT leads to higher attendance rates due to increased patient comfort (no breast compression), breast cancers detected at earlier stages due to higher sensitivity and a reduction of false-positive recalls.
- By shifting breast cancer detection to earlier stages and reducing unnecessary follow-up assessments, the novel technology can potentially reduce overall healthcare cost.

References

Papers of special note have been highlighted as:
• of interest

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int. J. Cancer* 127(12), 2893–2917 (2010).

2 Souza FH, Wendland EM, Rosa MI, Polanczyk CA. Is full-field digital mammography more accurate than screen-film mammography in overall population screening? A systematic review and meta-analysis. *Breast* 22(3), 217–224 (2013).

3 Kalender WA. Dedicated high-resolution breast CT can outperform digital mammography and breast tomosynthesis at equivalent dose levels. *RSNA* (2013). http://archive.rsna.org

4 Althoff F. Systemdesign und patientenlagerung bei der dedizierten brust-computertomografie (2013). http://opus4.kobv.de

• **Background and technological details on the Breast-CT (BCT) system subject to this research.**

5 Mammographie K. Evaluationsbericht 2010: ergebnisse des mammographie-screening-programms in Deutschland (2014). http://fachservice.mammo-programm.de

• **Reference data on the German breast cancer screening program.**

6 Perry N, Broeders M, De Wolf C *et al.* European guidelines for quality assurance in breast cancer screening and diagnosis fourth edition. Luxembourg office for official publications of the European Communities (2006). http://ec.europa.eu

7 Bund B. Inanspruchnahme des qualitätsgesicherten mammographie-screenings – follow-up studie 2012 (2012). http://fachservice.mammo-programm.de

8 O'Connell A, Conover DL, Zhang Y *et al.* Cone-beam CT for breast imaging: radiation dose, breast coverage, and image quality. *Am. J. Roentgenol.* 195(2), 496–509 (2010).

- **Pilot study (see also** [31]**) to evaluate various performance parameters of Cone-Beam BCT compared with conventional mammography.**

9 Lindfors KK, Boone JM, Nelson TR, Yang K, Kwan AL, Miller DF. Dedicated breast CT: initial clinical experience1. *Radiology* 246(3), 725–733 (2008).

- **Clinical trial comparing BCT images with screen-film mammograms.**

10 Houssami N, Ciatto S. The evolving role of new imaging methods in breast screening. *Prev. Med.* 53(3), 123–126 (2011).

11 Boone JM, Kwan AL, Yang K, Burkett GW, Lindfors KK, Nelson TR. Computed tomography for imaging the breast. *J. Mammary Gland Biol. Neoplasia* 11(2), 103–111 (2006).

12 Chen Z, Ning R. Why should breast tumour detection go three dimensional? *Phys. Med. Biol.* 48(14), 2217 (2003).

13 Bernardi D, Caumo F, Macaskill P *et al.* Effect of integrating 3D-mammography (digital breast tomosynthesis) with 2D-mammography on radiologists' true-positive and false-positive detection in a population breast screening trial. *Eur. J. Cancer* 50(7), 1232–1238 (2014).

14 Houssami N, Macaskill P, Bernardi D *et al.* Breast screening using 2D-mammography or integrating digital breast tomosynthesis (3D-mammography) for single-reading or double-reading – evidence to guide future screening strategies. *Eur. J. Cancer* 50(10), 1799–1807 (2014).

15 Glick SJ. Breast CT. *Annu. Rev. Biomed. Eng.* 9, 501–526 (2007).

- **Overview of BCT developments in the past decades.**

16 Schulz-Wendtland R, Sauer G, Kreienberg R. Präoperative diagnostik. In: *Mammakarzinom interdisziplinär.* Springer Berlin Heidelberg, Germany, 109–122 (2010).

17 Chang C, Sibala JL, Fritz SL, Gallagher JH, Dwyer 3rd S, Templeton AW. Computed tomographic evaluation of the breast. *Am. J. Roentgenol.* 131(3), 459–464 (1978).

18 Gisvold JJ, Reese DF, Karsell PR. Computed tomographic mammography (CTM). *Am. J. Roentgenol.* 133(6), 1143–1149 (1979).

19 Chang C, Sibala JL, Fritz SL *et al.* Computed tomography in detection and diagnosis of breast cancer. *Cancer* 46(Suppl. 4), 939–946 (1980).

20 Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. *Health Econ.* 15(12), 1295–1310 (2006).

21 Kolominsky-Rabas PL, Djanatliev A, Wahlster P *et al.* Technology foresight for medical device development through hybrid simulation: the ProHTA project. *Technol. Forecasting Soc. Change* 97, 105–114 (2015).

22 Djanatliev A, German R. Prospective healthcare decision-making by combined system dynamics, discrete-event and agent-based simulation. Presented at: *Proceedings of the 2013 Winter Simulation Conference* (Piscataway, New Jersey, USA, 2013), Pasupathy R, Kim S.-H., Tolk A, Hill R, Kuhl M, Eds., Institute of Electrical and Electronics Engineers, Inc., IEEE Press, pp. 270–281 (2013).

23 Bundesamt S. Bevölkerung deutschlands bis 2060 – ergebnisse der 12. Koordinierten bevölkerungsvorausberechnung (2009). www.destatis.del

24 Robert Koch Institut. Brustkrebs (mammakarzinom) icd-10 c50 (2014). www.krebsdaten.de

25 Van Luijt PA, Fracheboud J, Heijnsdijk EaM, Den Heeten GJ, De Koning HJ. Nation-wide data on screening performance during the transition to digital mammography: Observations in 6 million screens. *Eur. J. Cancer* 49(16), 3517–3525 (2013).

26 Perry N, Broeders M, De Wolf C, Törnberg S, Holland R, Von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition-summary document. *Ann. Oncol.* 19(4), 614–622 (2008).

27 Aro A, Koning H, Absetz P, Schreck M. Two distinct groups of non-attenders in an organized mammography screening program. *Breast Cancer Res. Treat.* 70(2), 145–153 (2001).

28 Whelehan P, Evans A, Wells M, Macgillivray S. The effect of mammography pain on repeat participation in breast cancer screening: a systematic review. *Breast* 22(4), 389–394 (2013).

29 Kornguth PJ, Keefe FJ, Conaway MR. Pain during mammography: characteristics and relationship to demographic and medical variables. *Pain* 66(2–3), 187–194 (1996).

30 Schnoor M, Hallof A, Hergert-Lüder D, Katalinic A, Waldmann A. Gründe für die nicht-teilnahme am mammographie-screening – eine querschnittsuntersuchung aus schleswig-holstein. *Dtsch. Med. Wochenschr.* 138(45), 2289–2294 (2013).

31 O'Connell AM, Kawakyu-O'Connor D. Dedicated cone-beam breast computed tomography and diagnostic mammography: comparison of radiation dose, patient comfort, and qualitative review of imaging findings in BI-RADS 4 and 5 lesions. *J. Clin. Imaging Sci.* 2, 7 (2012).

- **Pilot study (see also** [8]**) to evaluate various performance parameters of Cone-Beam BCT compared with conventional mammography.**

32 Mckinley R, Tornai M, Tuttle L, Steed D, Kuzmiak C. Development and initial demonstration of a low-dose dedicated fully 3D breast CT system. In: *Breast Imaging* Maidment AA, Bakic P, Gavenonis S (Eds). Springer Berlin Heidelberg, Germany, 442–449 (2012).

33 Yankaskas BC, Cleveland RJ, Schell MJ, Kozar R. Association of recall rates with sensitivity and positive predictive values of screening mammography. *Am. J. Roentgenol.* 177(3), 543–549 (2001).

34 Fracheboud J, Otto SJ, Gelder RD *et al.* Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in nederland. 1990–2007 (xii). Het twaalfde evaluatierapport (2009). repub.eur.nl/pub/26515/LETBxiiEngels.pdf

35 Kalender WA, Beister M, Boone JM, Kolditz D, Vollmar SV, Weigel MC. High-resolution spiral CT of the breast at very low dose: concept and feasibility considerations. *Eur. Radiol.* 22(1), 1–8 (2012).

- **Simulations on spatial resolution and dose efficiency of BCT.**

36 Vedantham S, Shi L, Karellas A, O'connell AM, Conover DL. Personalized estimates of radiation dose from dedicated breast CT in a diagnostic population and comparison with diagnostic mammography. *Phys. Med. Biol.* 58(22), 7921 (2013).

37 Boone JM, Nelson TR, Lindfors KK, Seibert JA. Dedicated breast CT: radiation dose and image quality evaluation. *Radiology* 221(3), 657–667 (2001).

38 Prionas ND, Lindfors KK, Ray S *et al.* Contrast-enhanced dedicated breast CT: initial clinical experience. *Radiology* 256(3), 714–723 (2010).

39 Domingo L, Salas D, Zubizarreta R *et al.* Tumor phenotype and breast density in distinct categories of interval cancer: results of population-based mammography screening in Spain. *Breast Cancer Res.* 16(1), R3 (2014).

40 Heidinger O, Batzler WU, Krieg V *et al.* The incidence of interval cancers in the german mammography screening program: results from the population-based cancer registry in north rhine-westphalia. *Dtsch. Arztebl. Int.* 109(46), 781–787 (2012).

- **Observations and typology of interval cancers in the German breast cancer screening program.**

41 Kuhl CK, Schrading S, Leutner CC *et al.* Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J. Clin. Oncol.* 23(33), 8469–8476 (2005).

42 Surveillance Epidemiology, and End Results Program. SEER research data derived AJCC-6 T.(2013). http://seer.cancer.gov

43 Wagner S, Bani M, Fasching P *et al.* Can we afford a breast center? Calculation of individual services based on the example of the university breast center franconia (UBF). *Geburtshilfe. Frauenheilkd.* 68(12), 1178–1183 (2008).

44 Lux MP, Reichelt C, Wallwiener D *et al.* Results of the Zometa® cost-utility model for the german healthcare system based on the results of the ABCSG-12 study. *Onkologie* 33(7), 360–368 (2010).

45 Weining-Klemm O. Vergleich verschiedener biopsiearten in der mammadiagnostik: feinnadelaspirationszytologie (FNA), feinnadelbiopsie (FNB) und vakuumbiopsie (VB); möglichkeit, grenzen und kosten (2005). http://publikationen.uni-tuebingen.de

46 Göttling A. Minimal-invasive biopsieverfahren im mammographie-screening–stellenwert und ergebnisse (2013). http://edocs.fu-berlin.de

47 Uleer C, Wagner J, Moisidis-Tesch C. Relevance of health economics in the early detection of breast cancer in Germany – the view of the professional association of practicing gynecologic oncologists e.V. (BNGO). *Breast Care* 8(1), 35–39 (2013).

48 Mühlhauser I, Höldke B. Information zum mammographiescreening – vom trugschluss zur enttäuschung. *Radiologe* 42(4), 299–304 (2002).

49 Ripping TM, Verbeek ALM, Fracheboud J, De Koning HJ, Van Ravesteyn NT, Broeders MJM. Overdiagnosis by mammographic screening for breast cancer studied in birth cohorts in the netherlands. *Int. J. Cancer* 137(4), 921–929 (2015).

50 Rea D, Francis A. Breast screening saves lives: now is the time to address overtreatment. *J. Comp. Eff. Res.* 3(2), 111–113 (2014).

51 Giordano L, Von Karsa L, Tomatis M *et al.* Mammographic screening programmes in europe: organization, coverage and participation. *J. Med. Screen.* 19(Suppl. 1), 72–82 (2012).

52 Zwahlen M, Egger M. Mammografie-screening. *Ther. Umsch.* 70(4), 205–213 (2013).

53 Lux MP, Hartmann M, Jackisch C *et al.* Cost-utility analysis for advanced breast cancer therapy in germany: results of the fulvestrant sequencing model. *Breast Cancer Res. Treat.* 117(2), 305–317 (2009).

54 Lafata JE, Simpkins J, Lamerato L, Poisson L, Divine G, Johnson CC. The economic impact of false-positive cancer screens. *Cancer Epidemiol. Biomarkers Prev.* 13(12), 2126–2132 (2004).

55 Comas M, Arrospide A, Mar J *et al.* Budget impact analysis of switching to digital mammography in a population-based breast cancer screening program: a discrete event simulation model. *PLoS ONE* 9(5), e97459 (2014).

56 Grimes DA, Schulz KF. Uses and abuses of screening tests. *Lancet* 359(9309), 881–884 (2002).

57 Mammographie K. Evaluationsbericht 2008–2009: ergebnisse des mammographie-screening-programms in deutschland (2012).

58 Warmerdam PG, De Koning HJ, Boer R *et al.* Quantitative estimates of the impact of sensitivity and specificity in mammographic screening in Germany. *J. Epidemiol. Community Health* 51(2), 180–186 (1997).

59 De Koning HJ. Breast cancer screening; cost-effective in practice? *Eur. J. Radiol.* 33(1), 32–37 (2000).

60 De Gelder R, Bulliard J-L, De Wolf C *et al.* Cost-effectiveness of opportunistic versus organised mammography screening in switzerland. *Eur. J. Cancer* 45(1), 127–138 (2009).

61 Tomosynthesis_Org. Does insurance cover 3D mammography (tomosynthesis)? (2015). www.tomosynthesis.org

62 Bernardi D, Ciatto S, Pellegrini M *et al.* Application of breast tomosynthesis in screening: incremental effect on mammography acquisition and reading time. *Br. J. Radiol.* 85(1020), E1174–E1178 (2012).

63 Lee CI, Cevik M, Alagoz O *et al.* Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. *Radiology* 274(3), 772–780 (2015).

64 Puliti D, Duffy SW, Miccinesi G *et al.* Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. *J. Med. Screen.* 19(Suppl. 1), 42–56 (2012).

65 Barratt A. Overdiagnosis in mammography screening: a 45 year journey from shadowy idea to acknowledged reality. *BMJ* 350, h867 (2015).

66 Lauby-Secretan B, Scoccianti C, Loomis D *et al.* Breast-cancer screening–viewpoint of the IARC working group. *N. Engl. J. Med.* 372(24), 2353–2358 (2015).