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BREAST

Detection of invasive components in cases of breast ductal carcinoma in situ on biopsy by using apparent diffusion coefficient MR parameters

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Abstract
Objectives To evaluate whether apparent diffusion coefficient (ADC) parameters could identify invasive components in cases with ductal carcinoma in situ (DCIS) diagnosed by biopsy.
Methods This retrospective study was approved by the institutional review board and the requirement to obtain informed consent was waived. Sixty-nine consecutive women with 70 lesions diagnosed with DCIS by biopsy underwent breast magnetic resonance (MR) imaging. Multiple regions of interest were placed (as many as possible) within the lesion on ADC maps. The minimum ADC values and the ADC difference values obtained as the difference between minimum and maximum ADCs were evaluated.
Results Surgical specimens revealed 51 lesions with pure DCIS and the remaining 19 lesions with DCIS with invasive components (DCIS-IC). The minimum ADC value for DCIS-IC ($0.99\pm0.04\times10^{-3}$ mm^2/s) was significantly lower than that of pure DCIS ($1.15\pm0.03\times10^{-3}$ mm^2/s) ($P = 0.0037$). The ADC difference value for DCIS-IC ($0.38\pm0.05\times10^{-3}$ mm^2/s) was significantly higher than that of pure DCIS ($0.17\pm0.03\times10^{-3}$ mm^2/s). ROC curve analysis for differentiating DCIS-IC from pure DCIS revealed that the area under the curve was 0.71 for minimum ADC value and 0.77 for ADC difference value.
Conclusions The minimum ADC values and ADC difference values could suggest the presence of invasive components.
Key Points
- *Identification of invasive components in DCIS before treatment is clinically important.*
- *Diffusion-weighted MR imaging can help lesion assessment in breast cancer.*
- *The minimum ADC value may suggest the presence of an invasive component in DCIS.*
- *The ADC difference value also suggests the presence of an invasive component in DCIS.*
- *Preoperative evaluation of diffusion-weighted MR imaging may help surgical planning for DCIS.*

Keywords Breast cancer · DCIS · Invasive carcinoma · Diffusion magnetic resonance imaging · Upgrade

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Introduction

Ductal carcinoma in situ (DCIS) of the breast is defined as the proliferation of malignant epithelial cells localised in ducts without evidence of invasion through the basement membrane [1]. In DCIS diagnosed by biopsy, underestimation of invasive components may occur because of the limited amounts of specimens, and underestimation rates range from 0 % to 59 % [2–6].

The main difference in treatment between patients with pure DCIS and DCIS with invasive components (DCIS-IC) is the management of axillary lymph nodes [7–9]. Sentinel

lymph node evaluation is considered necessary only for patients with a high risk of occult invasive disease [10, 11]. Thus, accurate preoperative differentiation between pure DCIS and DCIS-IC is important for surgical planning.

Studies that have attempted to differentiate between DCIS grades using contrast-enhanced magnetic resonance (MR) imaging have yielded inconsistent results; some studies suggested that morphology and the kinetic curve indicate invasiveness, whereas others did not [12–18].

Several studies have demonstrated the usefulness of diffusion-weighted imaging (DWI) for differentiating benign and malignant breast tumours using apparent diffusion coefficient (ADC) values [19–26]. A few studies have described the relationship between DCIS grade and ADC values [27–29]. However, there have been no studies regarding whether possible invasive carcinoma can be detected by measuring ADC values in lesions initially diagnosed as DCIS by biopsy.

In the field of the grading of brain tumours, high-grade astrocytomas usually result in increased pathological anaplasia and heterogeneity. Based on these histopathological characteristics, some reports have shown that the minimum ADC values corresponding to the sites of highest cellularity within tumours and ADC difference values, i.e. the difference between minimum and maximum ADC values (representing the intra-tumoural heterogeneity on ADC maps), may facilitate accurate grading of astrocytic tumours [30].

Similarly to astrocytic tumours, invasive ductal carcinoma of the breast shows pathological heterogeneity because it is composed of invasive cancer nests, stroma, intra-tumoural fibrosis or necrosis, and intraductal components. Hirano et al. [31] recently reported that the minimum ADC and ADC difference values significantly differentiate malignant breast tumours from benign tumours. DCIS is also heterogeneous with high- and low-grade components coexisting within a single lesion, the grading of which is usually determined on the basis of the highest grade present [32, 33].

The present study was performed to evaluate the usefulness of the minimum ADC and ADC difference values for predicting invasive components in patients with preoperatively diagnosed DCIS by biopsy.

Materials and methods

Patients

Our institutional review board approved the present retrospective study and the requirement to obtain informed consent was waived. In our preliminary investigation of a small number of series, the standard deviation for ADC was estimated to be 0.2×10^{-3} mm^2/s and the significant difference for discriminating DCIS-IC from pure DCIS was estimated to be 0.2×10^{-3} mm^2/s. The necessary number of patients for each group was estimated to be at least 15, applying an α error of 0.05 and β error of 0.2.

Between September 2009 and August 2012, 80 consecutive patients diagnosed with DCIS by biopsy underwent preoperative breast MR imaging. All patients were women and their average age was 54 (range 34–82) years. Bilateral breast lesions diagnosed as DCIS by biopsy were counted as two cases. The following patients were excluded: one patient with neoadjuvant chemotherapy; four patients with no enhancement on dynamic contrast-enhanced imaging or no signal intensity on DWI; two patients with suboptimal images because of incomplete fat suppression; three patients with a too small or thin lesion to place regions of interest (ROIs), thus precluding measurement of ADC values; a patient with huge persistent haematoma after biopsy. Thus, 70 lesions in 69 patients were evaluated in the present study.

All 69 patients first underwent diagnostic mammography and ultrasound with no suspicion of an invasive carcinoma. Amongst 44 lesions detected on ultrasound, 14-gauge core biopsy was performed in 42 lesions and 10-gauge vacuum-assisted biopsy was performed in other two lesions. In the remaining 26 lesions which were not detected on ultrasound and showed microcalcification on mammography, 11-gauge stereotactic vacuum-assisted biopsy was performed.

MR image acquisition

A 3.0-T system (Intera Achieva Quasar Dual; Philips Healthcare, Best, The Netherlands) with single -source radiofrequency transmission was used for MR imaging. All patients were imaged in the prone position with both breasts placed into the four-channel phased array breast coil. MR imaging protocols included the following: bilateral transverse fat-suppressed T2-weighted images (4529/70 [repetition time ms/echo time ms], field of view 320×320 mm, matrix 608×467, section thickness 5 mm, acquisition time 199 s), fat-suppressed diffusion-weighted echo-planar images (8000/96, field of view 340×340 mm, matrix 128×101, section thickness 5 mm, acquisition time 132 s, and application of motion probing gradient pulse along the x, y, and z directions with b values of 0 and 1000 s/mm^2) and gadolinium-enhanced dynamic MR images using a three-dimensional fat-suppressed T1-weighted gradient-echo sequence (5.3/2.6, field of view 350×350 mm, matrix 480×277, section thickness 0.9 mm, acquisition time 68 s) with intravenous infusion of 0.1 mmol/kg gadopentetic acid. The ADC values were calculated using the formula: $ADC = (1/b)\times \ln (S_0/S)$, where S_0 and S are the signal intensities in the ROI, obtained with different gradient factors (b=0 and 1000 s/mm^2).

Image interpretation

Firstly, the extension of lesions was evaluated and measured with the longest diameter using dynamic contrast-enhanced imaging by agreement of two readers blinded to clinical and histological information. Multiple ROIs of 13–45 mm^2 were carefully placed as many as possible so that they covered the entire lesion on all slices of ADC maps traversing the lesion (Fig. 1). Pre-contrast T1-weighted and fat-suppressed T2-weighted images were used to avoid cystic, necrotic or haemorrhagic components. Placement of ROIs was confirmed by agreement of the two readers. The size and number of ROIs in each lesion were recorded. Subsequently, the lowest ADC value was selected from the multiple ROIs as the minimum ADC. The maximum ADC value was also selected, and the difference between maximum and minimum ADCs was recorded as the ADC difference value. Then, we compared the minimum ADC and ADC difference values between DCIS-IC and pure DCIS cases.

Pathological evaluation

All the patients underwent mastectomy or lumpectomy and surgical specimens were prepared for histological evaluation. Specimens were fixed in 10 % formaldehyde solution and sections 5 μm thick were taken every 5 mm. An experienced pathologist evaluated the nuclear grade and presence of necrosis, and determined the DCIS grade. Where invasive carcinoma was identified, the size, number and locations of lesions were recorded.

Statistical analysis

Continuous variables were expressed as means±standard deviation. The lesion size, the minimum ADC values and ADC difference values between pure DCIS and DCIS-IC were compared using Student's *t*-test or Mann–Whitney *U* test. The relationship between the minimum ADC value and ADC difference value was analysed by using correlational analysis (Pearson product moment correlation). The effectiveness of the two ADC parameters in differentiation between DCIS-IC and pure DCIS was evaluated using receiver operating characteristic (ROC) analysis. Statistical analysis was performed with software package JMP Pro 9 (SAS Institute, Cary, NC). Statistical differences with $P < 0.05$ were considered significant.

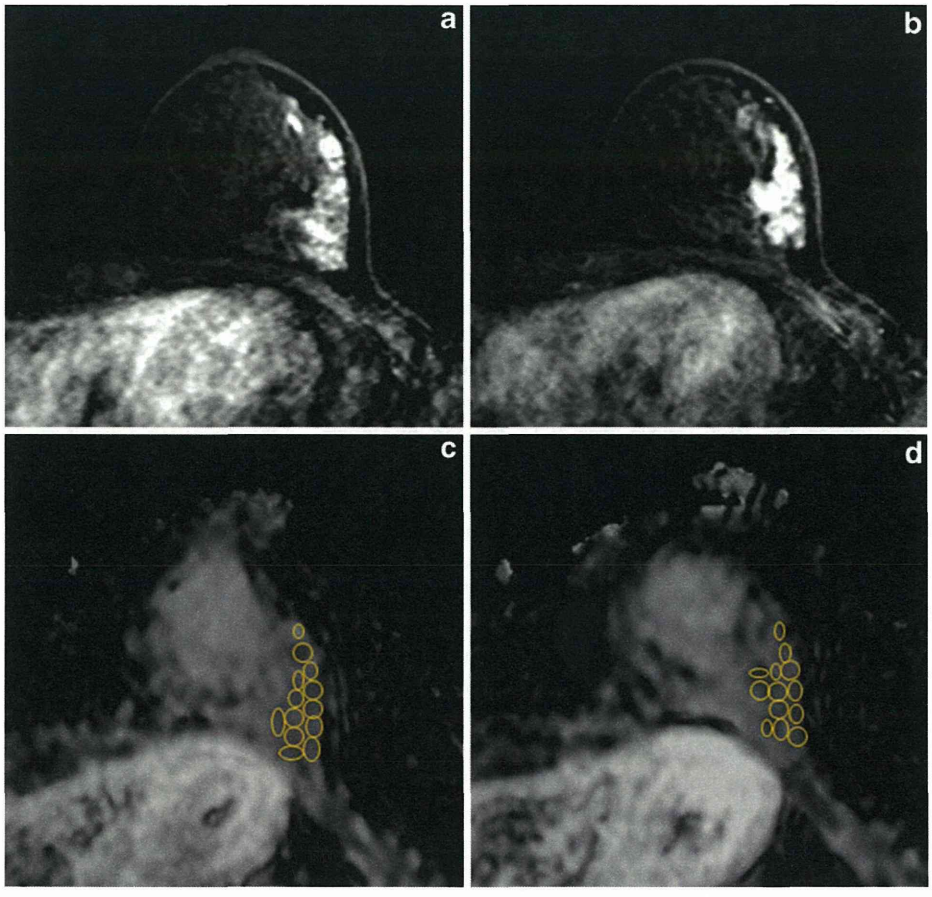

Fig. 1 The method for regions of interest (ROIs) placement on ADC maps. **a**, **b** Dynamic contrast-enhanced imaging shows segmental non-mass-like enhancement. **c**, **d** Multiple round or oval ROIs are carefully placed—as many as possible—so that they cover the entire cross-sectional area of the lesion on ADC maps, avoiding cystic, necrotic or haemorrhagic components or artefact

Results

Eleven lesions were treated with mastectomy and the other 59 lesions were treated with lumpectomy. Pathological diagnosis revealed 51 lesions with pure DCIS and the remaining 19 lesions with DCIS-IC, defined as a tumour in which the dominant lesion was DCIS but with one or more invasive nests. Of the 51 pure DCIS lesions, 24 were low grade, 19 were intermediate grade and the remaining 8 were high grade on pathological evaluation.

Of the 19 lesions with DCIS-IC, two had macro-invasive carcinoma ≥10 mm in diameter; the other17 lesions had invasive carcinoma <10 mm in diameter or minimally invasive carcinoma. Many intraductal components or increased collagen fibres were found to be closely packed around the invasive nests.

The longest diameter was not different between DCIS-IC cases (33.7±17.5 mm) and pure DCIS cases (28.5±16.8 mm) ($P = 0.29$). The mean ROI size was not different between DCIS-IC cases (26.1±5.4 mm^2) and pure DCIS cases (29.4±14.5 mm^2) ($P = 0.33$). The minimum ADC value for DCIS-IC ($0.99\pm0.04\times10^{-3}$ mm^2/s) was significantly lower than that of pure DCIS ($1.15\pm0.03\times10^{-3}$ mm^2/s) ($P = 0.0037$) (Figs. 2a and 4). The ADC difference value for DCIS-IC ($0.38\pm0.05\times10^{-3}$ mm^2/s) was significantly higher than that of pure DCIS ($0.17\pm0.03\times10^{-3}$ mm^2/s) ($P = 0.0007$) (Figs. 2b and 4). The minimum ADC value showed significant negative correlation with ADC difference value (r=0.65; Fig. 2c). ROC curve analysis revealed the most effective threshold of minimum ADC value was lower than 1.1×10^{-3} mm^2/s. Using this threshold for differential diagnosis of DCIS-IC from pure DCIS, the sensitivity and specificity were 72 % and 77 %, respectively. Similarly, the most effective threshold of ADC difference value was higher than 0.23×10^{-3} mm^2/s. Using this threshold for differential diagnosis of DCIS-IC from pure DCIS, the sensitivity and specificity were 68 % and 76 %, respectively. The area under the ROC curve was 0.71 for the minimum ADC value and 0.77 for the ADC difference value (Figs. 3 and 4).

Of the 19 lesions with DCIS-IC, 14 lesions detected as minimum ADC value $<1.1\times10^{-3}$ mm^2/s showed a pathological invasive component ranging from 2 to18 mm in diameter (median, 4 mm) and the remaining five lesions detected as minimum ADC value $\geq1.1\times10^{-3}$ mm^2/s showed an invasive component ranging from1.5 to 6 mm (median, 4 mm) in diameter. Thirteen lesions detected as the ADC difference value $>0.23\times10^{-3}$ mm^2/s showed an invasive component ranging from 1.5 to 18 mm (median, 3 mm) in diameter and the remaining six lesions detected as minimum ADC value $\leq0.23\times10^{-3}$ mm^2/s showed an invasive component ranging from 1.5 to 8 mm (median, 4.5 mm) in diameter. Both lesions with macro-invasive carcinoma (≥10 mm in diameter) were detected as minimum ADC value $<1.1\times10^{-3}$ mm^2/s and the ADC difference value $>0.23\times10^{-3}$ mm^2/s.

Discussion

The results of the present study indicated that the minimum ADC value $<1.1\times10^{-3}$ mm^2/s and the ADC difference value $>0.23\times10^{-3}$ mm^2/s could suggest the presence of invasive carcinoma in cases with DCIS diagnosed by biopsy. In ROC analysis, an almost equivalent detectability of DCIS-IC was obtained for each ADC parameter.

Many studies investigating the DWI appearance and ADC values of various tumours have revealed that the signal pattern on DWI as well as ADC values are generally correlated with the tumour cell density or less extracellular space on histological analysis [34–36]. With regard to DCIS in our study, we could not perform precise radiological-pathological correlation and point-to-point comparison between the findings on images and histological specimens because the breast tissue along with the breast tumour varied in configuration according to patient's positioning. However, we presume that the region with minimum ADC corresponded to the foci with the highest cell density, reflecting the invasive nest sites and the ADC difference value (the difference between the maximum and minimum ADC values) corresponded to heterogeneous cell density, reflecting the presence of various pathological components, such as invasive nests, intraductal components, stroma and fibrosis.

In DCIS-IC cases, small invasive nests <10 mm in diameter within DCIS were detectable in several cases with minimum ADC values $<1.1\times10^{-3}$ mm^2/s in the present study. Heterogeneity of lesions, probably reflecting subtle differences in cell density, was detectable with ADC difference values $>0.23\times10^{-3}$ mm^2/s. One factor contributing to this favourable result might have been that we used a 3.0-T MR imaging system, while most previous studies on the relationship between DWI and breast tumours used 1.5-T systems [37]. The 3.0-T system gives a higher signal-to-noise ratio (SNR) and greater spatial resolution, enabling detection of much smaller lesions than the 1.5-T system, despite some disadvantages, including image distortion and inhomogeneous fat suppression [38]. Furthermore, pathological analysis indicated that invasive nests, even nests <5 mm in diameter, were often accompanied by closely packed intraductal components and dense collagen fibres. Therefore, we presume that the size of the area with minimum ADC values $<1.1\times10^{-3}$ mm^2/s may have represented a larger area than that of the invasive nests themselves, facilitating detection of such small lesions.

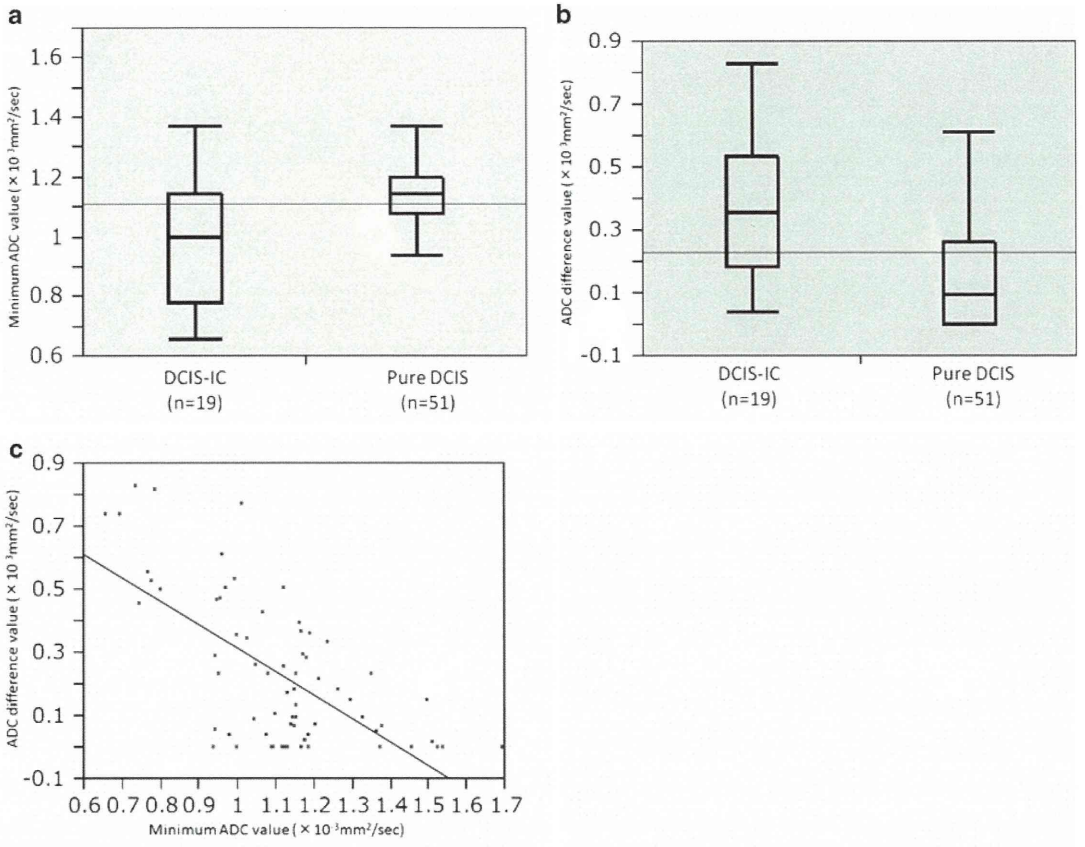

Fig. 2 Apparent diffusion coefficient (ADC) parameters for DCIS with an invasive component (DCIS-IC) and pure DCIS. **a** The box plots of minimum ADC values show that the value for DCIS-IC is significantly lower than that of pure DCIS ($P = 0.0037$). **b** The box plots of ADC difference values show that the value for DCIS-IC is significantly higher than that for pure DCIS ($P = 0.0007$). **c** The scatter diagram shows a significant negative correlation between minimum ADC value and ADC difference value ($r=-0.65$)

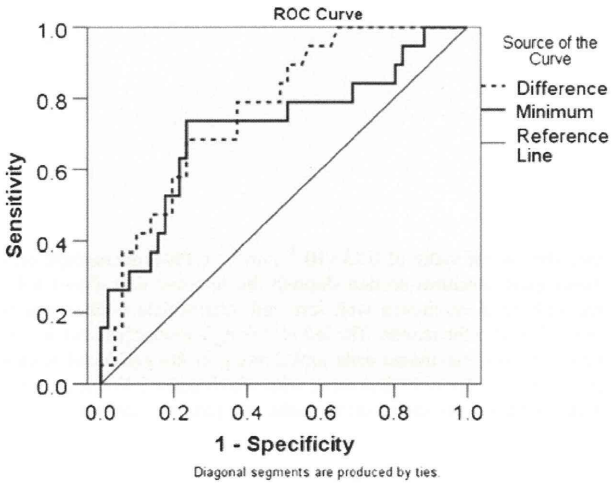

Fig. 3 The receiver operating characteristic (ROC) curves for each apparent diffusion coefficient (ADC) parameter for differentiating DCIS with invasive component (DCIS-IC) from pure DCIS show that the area under the ROC curve is 0.71 for minimum ADC value and 0.77 for ADC difference value

Although the ADC difference value had almost equivalent detectability of DCIS-IC to minimum ADC values, measuring it may not be practical in routine practice because it requires a large number of ROIs to be measured. Instead, a visual evaluation of the heterogeneity of the ADC map may substitute actual measurement, which indicates the need for measuring minimum ADC values in search for possible invasive nests within the tumour.

This study had some limitations. One was the 5-mm thickness of the DWI and fat-suppressed T2-weighted images used. Although we utilised pre-contrast T1-weighted image and fat-suppressed T2-weighted images to prevent contamination of haemorrhage and/or cystic components, minor contamination might not be avoided owing to the relatively large slice thickness of fat-suppressed T2-weighted images, resulting in suboptimal accuracy of the measurement. The small ROI size used for ADC measurement could be another limitation. In this study, we placed multiple ROIs on all slices of ADC maps traversing the lesion. The shape and size of ROIs were restricted by the

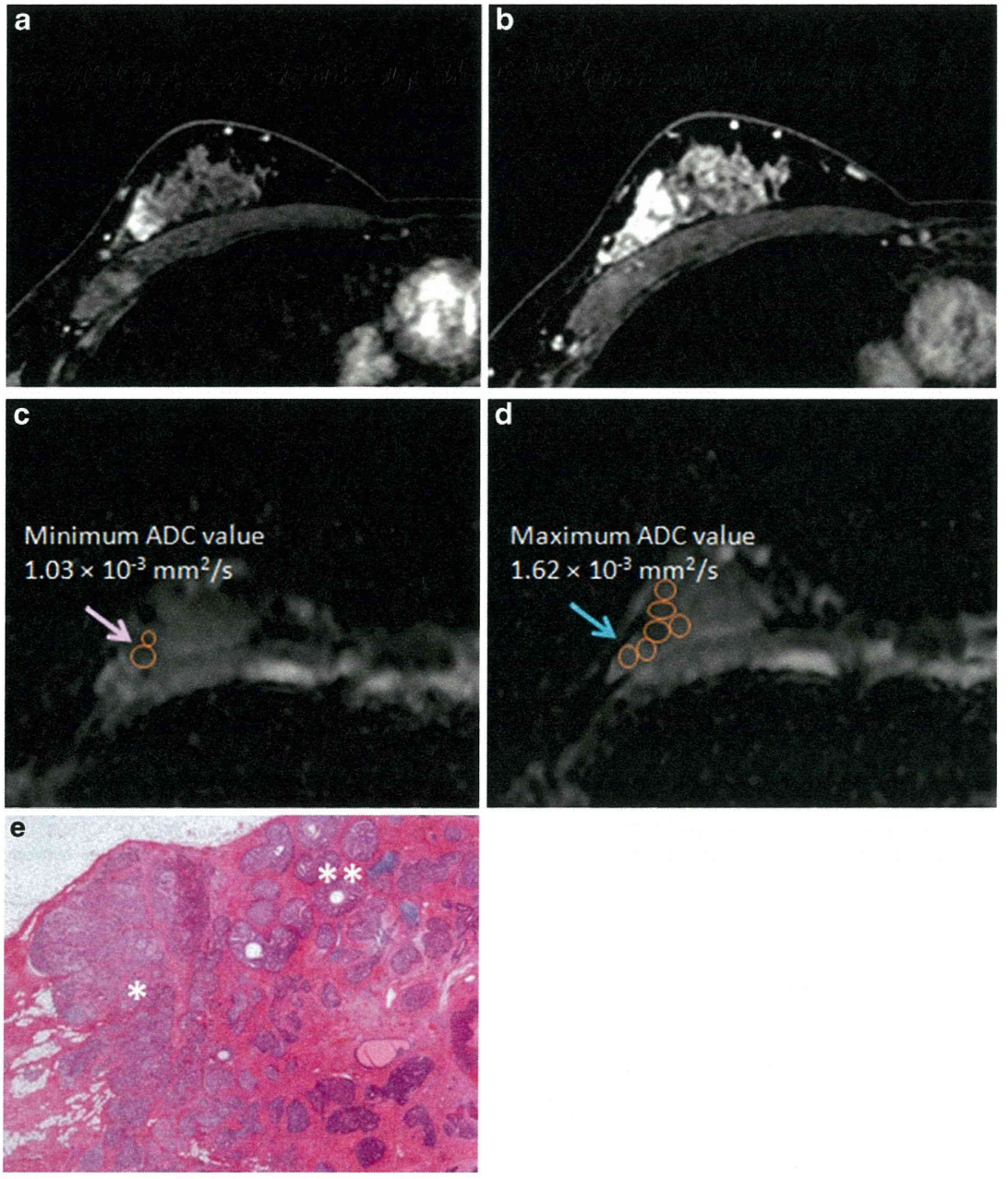

Fig. 4 A 44-year-old woman diagnosed with DCIS preoperatively. **a**, **b** Axial dynamic contrast-enhanced MR images obtained in early phase show a segmental non-mass-like lesion in the right breast. **c** The ADC map shows the ROI with the minimum ADC value (1.03×10^{-3} mm^2/s) (*pink arrow*) lower than the cut-off value of 1.1×10^{-3} mm^2/s. **d** The other ADC map shows the ROI of the maximum ADC value (1.62×10^{-3} mm^2/s) (*blue arrow*), with the resultant ADC difference value being calculated as 0.59×10^{-3} mm^2/s, which is higher than the cut-off value of 0.23×10^{-3} mm^2/s. **e** Photomicrograph of a histological specimen section through the invasive nest shows solid and cribriform carcinoma with low and intermediate nuclear grades protruding into the stroma. The left side (*single asterisk*) shows isolated or grouped carcinoma cells proliferating in the periductal stroma (invasive nest, 4 mm in diameter), with which dense intraductal carcinoma is closely associated on the right side (*double asterisk*)

shape and size of the lesion: the ROIs set in the present study were inevitably limited in size and ranged from 13 to 45 mm^2 (mean, 18 mm^2) with a minimum size of 13 mm^2, which was approximately equivalent to seven pixels.

In conclusion, the minimum ADC and ADC difference value may be useful for detecting the presence of invasive components in DCIS. The information of the presence of invasive component could enable preoperative determination

of the management of sentinel or axillary lymph node evaluation. We suggest that DWI with measurement of these two ADC parameters should be included in the routine MR imaging study of DCIS diagnosed by biopsy.

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Original Article · Originalarbeit

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Cross-National Comparison of Medical Costs Shared by Payers and Patients: A Study of Postmenopausal Women with Early-Stage Breast Cancer Based on Assumption Case Scenarios and Reimbursement Fees

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Keywords
Health care system · Reimbursement · Cost-sharing · Breast cancer

Summary
Background: The objectives of this study were to estimate and cross-nationally compare the medical costs shared by payers and patients and the distributions of medical costs by cost category. **Material and Methods:** We estimated the medical costs covered from definitive diagnosis to completion of treatments of early-stage breast cancer and follow-up, assuming almost identical medical care provided in Japan, the UK, and Germany. The analysis was performed from the payer's perspective. Medical costs were calculated by multiplying the unit costs by the number of units consumed, based on assumption case scenarios. The medical costs incurred by payers or patients were estimated according to the cost-sharing and the cost-bearing systems in each country. **Results:** The total medical costs in Japan were much lower than those in the UK and Germany, and these differences were mainly caused by the low costs of surgery and radiotherapy in Japan. For the base-case scenario, the co-payment in Japan (€ 3,486) was found to be 6.4-fold higher than that in Germany (€ 548). The payers in the European countries paid 2.9-fold more than those in Japan (€ ~25,000 vs. € 8,627). **Conclusion:** Our results will be useful for policy makers in considering how to share medical costs and how to allocate limited resources.

Schlüsselwörter
Gesundheitssystem · Erstattung · Kostenteilung · Brustkrebs

Zusammenfassung
Hintergrund: Ziel dieser Studie war es, die von den Kassen und Patienten geteilten Kosten sowie die Aufteilung der medizinischen Kosten auf verschiedene Kostenkategorien zu schätzen und länderübergreifend zu vergleichen. **Material und Methoden:** Wir schätzten die medizinischen Kosten, die von der definitiven Diagnose bis zur Vollendung der Behandlung von Brustkrebs sowie der Nachbeobachtung abgedeckt werden müssen, unter der Annahme, dass die medizinische Versorgung in Japan, Großbritannien und Deutschland ungefähr gleich ist. Die Analyse wurde aus der Sicht der Kassen durchgeführt. Die medizinischen Kosten wurden kalkuliert, indem basierend auf theoretischen Fallszenarien die Einheitskosten mit der Anzahl der verbrauchten Einheiten multipliziert wurden. Die medizinischen Kosten, die von den Kassen oder Patienten zu tragen waren, wurden entsprechend den Kostenteilungs- und Kostenträgersystemen in jedem Land ermittelt. **Ergebnisse:** Die medizinischen Gesamtkosten waren in Japan wesentlich geringer als die in Großbritannien und Deutschland; diese Unterschiede beruhten zum großen Teil auf den geringen Kosten für Operationen und Radiotherapien in Japan. Für das Basisfallszenario wurde in Japan (3486 €) eine 6,4-fach höhere Zuzahlung als in Deutschland (548 €) ermittelt. Die Kassen der europäischen Länder zahlten 2,9-mal mehr als die in Japan (~25 000 € vs. 8627 €). **Schlussfolgerung:** Unsere Ergebnisse werden für Entscheidungsträger bei ihren Überlegungen zur Verteilung der medizinischen Kosten und der Zuweisung von begrenzten Ressourcen nützlich sein.

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Introduction

In recent years, medical costs have been increasing in developed countries due to the aging population and the availability of highly advanced and costly medical technologies. The increased medical costs pose a serious problem since they impose heavy burdens on the health care systems in the various countries. In Japan, the total medical expenses have been increasing yearly and were estimated as high as ¥ 37.8 trillion (€ 291 billion) in 2011 [1]. Although Japan achieved universal health coverage in 1961, more recently, Japan has been facing a long-term economic recession and changes in the structure of the economy that threaten the sustainability of the social health insurance system [2]. Cross-national comparisons of medical costs among countries with similar economic environments provide policy makers with useful suggestions on how to set reimbursement fees for medical services or drug prices, how to allocate limited resources, and/or how to share medical costs between the third-party payers and patients.

Breast cancer is the most common cancer among women in Japan [3], the USA [4], and Europe [5], and the associated economic burdens are substantial. In the USA, the cost for cancer care was estimated to be $ 124.57 billion (€ 99.6 billion), and among them female breast cancer was the most expensive ($ 16.50 billion or € 13.2 billion) in cancer sites in 2010 [6]. An international consensus on management of this disease has been established by the St. Gallen International Expert Consensus meeting [7], and therefore the majority of the management seems to be unified regardless of treatment location, although domestic clinical practice guidelines also exist in countries apart from the consensus [8]. Treatment approaches are diverse depending on the patients' characteristics, such as clinical stage of the disease, menopausal status, and expression levels of hormone receptors and human epidermal growth factor receptor 2 (HER2), and others [7]. It should be mentioned that a prospective payment system based on a diagnosis-related group (DRG)-like classification, termed diagnosis procedure combination, was implemented with a partly inherited fee-for-service system in Japan in 2003 [9], which led to a shift in medical care for breast cancer from hospitalization to the outpatient setting, to use resources effectively and to gain reimbursements on a fee-for-service basis.

So far, a number of cross-national studies have been conducted to compare medical costs or reimbursements; however, there remain several challenges to comparing such costs. One of these challenges is that different countries have different patterns of clinical practices and, consequently, associated costs are highly varied. In the field of cancer care, the treatment costs for prostate cancer in the first year after diagnosis varied among European countries, despite the common European guidelines available [10]. These differences in treatment costs were explained in some degree by considerable differences in the treatment patterns of prostate cancer among the countries included in the study.

Another challenge is derived from the differences in medical service coding. In other words, there would not always be the same contents of medical services between countries even if the description of a code in a country is the same as in the other country. It has been reported that DRGs actually varied in reimbursements and in contained services among European countries [11, 12]. As far as we know, the *Health*BASKET project in 9 European countries collected cost data at the micro-level for the purpose of overcoming or mitigating these issues [13]. However, despite case vignette approaches applied for the project, there remain differences in treatment approaches for diseases between countries. Thus, the differences in treatment costs were explained to some extent by differences in treatment approaches. Cross-national studies on medical costs are extremely important, but difficult to conduct since these studies require a lot of resources, including collaborators, time etc., and there may be challenges in language and in cultural differences among countries.

Therefore, it seemed that an effective methodology to compare medical costs cross-nationally should be conducted on patients assumed to receive almost identical medical care, where associated costs are estimated by means of a bottom-up approach. In this paper, we estimated the medical costs covered from definitive diagnosis to completion of treatments and follow-up for postmenopausal women with early-stage breast cancer (EBC), based on assumption case scenarios and on reimbursement fees in Japan, the UK, and Germany. The objectives of this study were to estimate and compare the medical costs shared by payers and patients cross-nationally and the distributions of medical costs by cost category.

Methods

Health Care Systems

The health care systems in Japan, the UK, and Germany are briefly introduced below, with a focus on the cost-sharing and cost-bearing systems. In Japan, universal health care coverage has been implemented, and almost every Japanese citizen is insured [2]. A patient co-payment of 30% is basically applied, but there is a cost-bearing limit, termed High Cost Medical Treatment System [14]. This system allows an individual limit per month of ¥ 80,100 (€ 616.28) adding to 1% of the monthly total medical expense of over ¥ 267,000 (€ 2054.28) in the case of a patient aged 69 or younger with a middle income. When the system is applied 3 times within 12 months, the co-payment per month is additionally reduced to ¥ 44,400 (€ 341.61) beginning with the 4th time.

In the UK, coverage and much of the care is provided through the National Health Service (NHS) and there is little or no cost-sharing for medical care and benefits [15]. A prescription charge of £ 7.65 (€ 8.99) is a co-payment as of April 1, 2012, but there are many exemptions to the charge, such as treatments for cancer patients [16]. The NHS is funded at 76% from general taxation, 18% from National Insurance contributions, and the rest of 6% from others including a patient's co-payment [17]. The National Institute for Health and Care Excellence (NICE) appraises the cost effectiveness of health technologies and drugs and makes decisions

on reimbursements under the NHS. Thus, the NICE has a potent influence on drug prices set by manufacturing companies [18].

In Germany, approximately 90% of the population is covered by statutory health insurance (SHI) with or without additional private coverage for supplemental cost-sharing, and the remainder of the population buy a private coverage alternative to an SHI [15]. Reimbursements are provided based on German DRGs for inpatient care or on the uniform value scale (Einheitlicher Bewertungsmaßstab, EBM) for outpatient care. Patients covered by the SHI need to pay € 10 quarterly for physician visits. Patients also need to pay € 10 per hospital day, including drug costs, as a co-payment, but the contribution is limited to a maximum of 28 days in a calendar year [19]. The patient's co-payment is not considered part of the EBM-based accounting system for the outpatient setting [20]. Co-payments for drugs amount to 10% of the prices, but no less than € 5 and no more than € 10 per package. Individual co-payments are capped at 2% of the net income or at 1% for patients with chronic disease [21].

Assumption Case Scenarios

Using the St. Gallen International Expert Consensus [7], national guidelines recommended in the UK, Germany, and other countries [8], Japanese guidelines [22], and expert opinions in Japan, 3 case scenarios were defined in this study as described below. The baseline characteristics of the cases were assumed to be a postmenopausal woman suspected of breast cancer, 60 years of age, 50 kg of body weight, and 1.5 m^2 of body surface area. The menopausal status was required for selecting hormonal agents, and body weight and body surface area were used to calculate the doses of drugs. To simplify calculating costs, we did not consider diagnostic accuracy, additional surgeries or breast reconstruction after a primary surgery, complications and adverse drug reactions occurring associated with medical care, occurrence or recurrence of the disease, etc.

We assumed that the base-case patient received the following medical care from definitive diagnosis to completion of treatments and follow-up of breast cancer. First, the patient underwent clinical examination, mammography, ultrasound, and core biopsy to determine whether the tumor was benign or malignant and the extent of disease. As a result, the patient was diagnosed as EBC with strongly suspected lymph node involvement clinically. The patient was eligible for breast-conserving surgery according to appropriate factors (e.g. small tumor size) for the procedure. The stage of the disease was considered clinical stage IIb or T2N1M0. In addition, estrogen receptor (ER), progesterone receptor (PgR), and HER2 were quantified by immunohistochemistry for the purposes of predicting prognosis and determining treatment approaches. Immunohistochemistry revealed that the hormone receptors were highly expressed whereas HER2 was not overexpressed.

Next, the patient underwent breast-conserving surgery with axillary lymph node dissection. For cost analysis, the durations of hospitalization were assumed 12 days in Japan [23] and 7 days in Germany [24]. Then, the patient was treated with radiation (50 Gy in 25 fractions) and intravenous chemotherapy with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks for 4 courses, followed by paclitaxel (80 mg/m^2) every week for 12 courses. Paclitaxel was selected as a taxane rather than docetaxel because the standard dose of docetaxel is different between Japan and the other countries in the study. A high dose of docetaxel is not utilized by Japanese patients mainly because granulocyte colony-stimulating factor for the purpose of prophylaxis of febrile neutropenia is not covered by public insurances in Japan. Prophylactic antiemetic therapy during chemotherapy, a costly supportive care, was included [25]. Subsequently, the patient received hormone therapy with anastrozole, a representative aromatase inhibitor, for 5 years. The patient was followed up, and received clinical examinations every 3 months in the first 3 years, and then every 6 months for 2 years, and afterwards every year up to 10 years after completion of chemotherapy and/or radiotherapy. In addition, the patient received hormonal agents every 3 or 6 months and was checked for disease recurrence by mammography every 12 months for 10 years after diagnosis.

In addition to this base-case scenario, we included low- and high-cost case scenarios to examine a wide range of medical costs. The low-cost case scenario with negative hormone receptors (i.e. triple-negative breast cancer) was different from the base-case scenario. In association with that, the low-cost case patient did not receive adjuvant hormone therapy. The high-cost case scenario with overexpression of HER2 was different from the base-case scenario. The patient also received anti-HER2 therapy with trastuzumab. Trastuzumab was initially administered at a loading dose of 4 mg/kg of body weight and at maintenance doses of 2 mg/kg every week concurrently with the administration of paclitaxel, followed by 6 mg/kg every 3 weeks. The total duration of trastuzumab treatment was 1 year.

Table 1. Unit costs

		Japan		UK		Germany	
		Cost, €	Reference	Cost, €	Reference	Cost, €	Reference
Investigation							
Mammography	once	39.08	[26]	52.85	[28]	26.29	[33]
Ultrasound	once	38.47	[26]	59.58	[29]	16.30	[33]
Core biopsy	once	50.01	[26]	181.15	[30]	41.88	[33]
ER testing	once	55.39	[26]	38.84	[a]	35.22	[33]
PgR testing	once	53.09	[26]	38.84	[a]	35.22	[33]
HER2 testing	once	53.09	[26]	38.84	[31]	52.05	[33]
Surgery							
BCS with ALND	once	1942.17[b]	[23]	4,022.88[b]	[29]	4103.29[b]	[34]
Radiotherapy							
Planning	once	263.89	[26]	343.47	[29]	11,065.72	[34]
Delivery	25 fractions	2731.23	[26]	10,384.40	[29]		
Drug							
AC plus antiemetics	3-weekly	201.60	[27]	280.86	[32]	335.68	[35]
Paclitaxel	weekly	142.86	[27]	282.36	[32]	498.08	[35]
Anastrozole	daily	2.38	[27]	2.88	[32]	1.13	[35]
Trastuzumab	weekly, 2 mg/kg	287.79	[27]	318.98	[32]	587.58	[36]
	weekly, 4 mg/kg	575.58	[27]	637.96	[32]	1,175.16	[36]
	3-weekly, 6 mg/kg	863.38	[27]	956.94	[32]	1,762.74	[36]

ER = Estrogen receptor, PgR = progesterone receptor, HER2 = human epidermal growth factor receptor 2,
BCS = breast-conserving surgery, ALND = axillary lymph node dissection, AC = anthracycline plus cyclophosphamide.
[a]Not available and assumed same as HER2 testing.
[b]Including hospitalization charges.

Cost Analysis

The analysis was performed from the payer's perspective. The term 'payer' in this study was defined as the third-party payers or the NHS. The costs included in this study were divided into 4 categories: investigation, surgery, radiotherapy, and drug. The following costs were not considered: some direct medical costs (e.g. costs for physician visits), direct non-medical costs (e.g. transportation cost), and indirect costs (i.e. productivity loss). Medical costs were calculated by multiplying the unit costs by the number of units consumed based on assumption case scenarios, followed by summing them up. For pharmaceuticals, the lowest price was used for calculation when more than one price for a drug was available. Drug costs were calculated based on the actual doses, and unused drug in open vials was not included for cost calculation. The time frame for this study was defined from definitive diagnosis to completion of treatments and a 10-year follow-up. In addition, patient co-payments were estimated in each country according to the cost-sharing and cost-bearing systems described above. An annual discount rate of 3% was applied to the costs.

All the unit costs are presented in table 1. The unit costs were derived or estimated from various public data sources or published literature in Japan [23, 26, 27], the UK [28–32], and Germany [33–36]. Most of the costs were obtained from these sources for 2011 (the UK) or 2012 (Japan and Germany). When unit cost data were obtained from the sources prior to those years, the consumer price indexes for the local currency were applied to adjust the price level. All the costs in local currency units were converted to euro (€) using Organization for Economic Co-operation and Development (OECD) purchasing power parities (PPPs) for the gross domestic product (GDP) 2012 to support cross-national comparability throughout this paper [37].

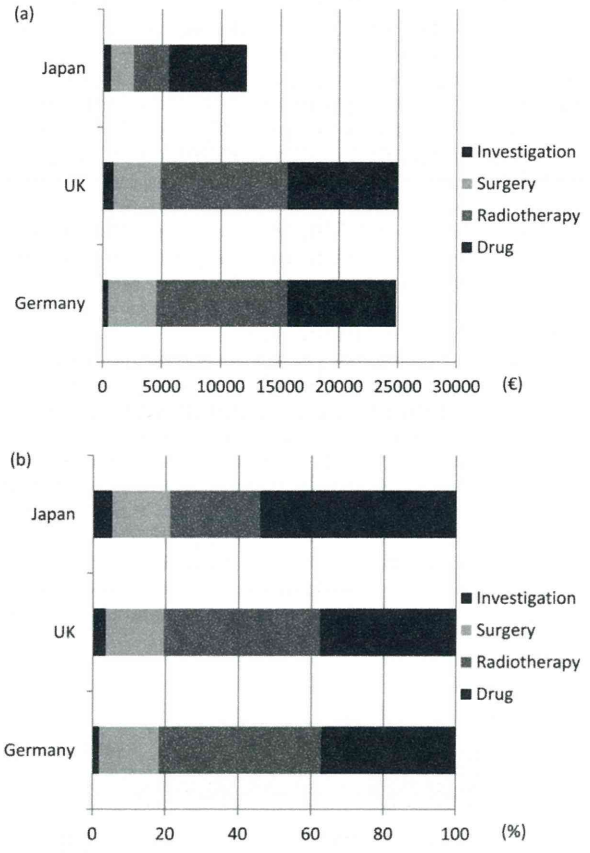

Fig. 1. Medical costs of the base-case scenario. (**a**) The cumulative monetary values in euro (€). (**b**) The percentages of individual cost categories to total medical costs.

Results

Total and Categorical Medical Costs

The total and categorical medical costs consisting of diagnostic and treatment costs for all the cases are shown in table 2, and distributions by cost category for the base-case are illustrated in figure 1. The total medical costs in Japan were much lower than those in the UK and Germany in all the case scenarios, and these differences were mainly caused by the low costs of surgery and radiotherapy in Japan (fig. 1a, table 2). Both of the costs of surgery and radiotherapy in the European countries were 2–3 times as high as those in Japan. Although the total and categorical costs were quite similar in the UK and Germany for the base-case, the total costs in the UK were lower than in Germany for the low- and high-cost scenarios, reflecting the differences of drug costs. The drug costs were highly dependent not only on relative drug prices but also on the availability of low-price generic drugs. In the drug price lists used for this study, generic anastrozole was available in Japan [27] and Germany [35] as of 2012, but only the brand drug was listed in the drug price list as of March 2011 in the UK [32], which affected the costs for the base- and high-cost cases. The costs for the investigations were generally low, at most 5% of the total medical costs in all the countries.

Table 2. Medical costs associated with diagnosis and treatment of EBC: total and by cost category

	Case scenarios[a]	Cost, €		
		Japan	UK	Germany
Investigation	all	622.52	860.90	431.18
Surgery	all	1,942.17	4,022.88	4,103.29
Radiotherapy	all	2,995.12	10,727.86	11,065.72
Drug	low-cost case	2,520.72	4,511.70	7,319.74
	base-case	6,553.61	9,380.29	9,225.47
	high-cost case	20,529.67	24,870.89	37,760.14
Total	low-cost case	8,080.53	20,123.35	22,919.95
	base-case	12,113.41	24,991.94	24,825.67
	high-cost case	26,089.48	40,482.54	53,360.34

[a]All the categorical costs except for drug costs in the low-cost and high-cost scenarios were the same as in the base-case scenario.

Table 3. Cost-sharing

	Japan		UK		Germany[a]	
	Cost, €	%	Cost, €	%	Cost, €	%
Low-cost case						
Payer	5,804.12	71.8	20,123.35	100.0	22,919.95	98.2
Patient	2,276.40	28.2	0	0.0	418.02	1.8
Total	8,080.53	100.0	20,123.35	100.0	23,337.97	100.0
Base-case						
Payer	8,627.14	71.2	24,991.94	100.0	24,825.67	97.8
Patient	3,486.27	28.8	0	0.0	548.41	2.2
Total	12,113.41	100.0	24,991.94	100.0	25,374.08	100.0
High-cost case						
Payer	18,925.04	72.5	40,482.54	100.0	53,360.34	98.9
Patient	7,164.44	27.5	0	0.0	596.96	1.1
Total	26,089.48	100.0	40,482.54	100.0	53,957.30	100.0

The percent values indicate the percentage to the total costs for each case in each country.

[a]The total costs incurred by payer and patients in Germany are different from the total diagnostic and treatment costs presented in table 2 because patient co-payments were set separated from diagnostic and treatment costs.

Cost-Sharing

The patient co-payments are presented in table 3. In the UK, all cases did not have to pay anything since all medical services and drugs were provided free under the NHS. The cost-bearing system in Japan resulted in a co-payment reduction by € 148 for the base-case for the entire time frame. The remaining co-payment in Japan (€ 3486) was still 6.4-fold higher than that in Germany (€ 548). Patient annual co-payments in the first year in Germany were reduced to the individual upper limit of € 200, assuming that these patients' net income after some particular reductions was € 20,000 per year. The patient co-payments for the low- and high-cost cases showed similar trends to the base-case (table 3).

On the other hand, the payers in the European countries paid 2.9-fold more than those in Japan for the base-case (table 3). Similar results were obtained from the low- and high-cost cases. The data suggest that the payers incurred a substantial economic burden for the common disease of EBC in all the countries.

Discussion

In this study, we estimated the medical costs incurred by payers and patients associated with diagnosis and treatment for postmenopausal women with EBC, with the assumption that the patients received almost identical medical care in Japan, the UK, and Germany. The assumption and costing by means of a bottom-up approach were used to enhance cross-national comparability of the costs by removing the differences in treatment patterns. The total medical costs per patient with EBC were estimated to be substantial in all the countries, but varied considerably, reflecting the differences in reimbursement fees for medical services or drug prices even when adjusted by PPPs. The payers paid all or almost all of the medical costs of EBC in both the UK and Germany, in contrast to a little more than 70% of the total costs in Japan.

Regarding patient co-payments, there were no or minimal co-payments in the UK or Germany, and moderate co-payments in Japan despite a cost-bearing system. It should be noted that these results did not always mean that the payers in Japan incurred less costs than those in the UK or Germany because contributions for the payers were not considered. In general, patient co-payments are low in the countries with a high contribution. According to Ikegami et al. [2], the median contribution rate of the society-managed health insurance plans is 7.40%, although the contribution rates are substantially different between the health insurance plans in Japan and the contribution is equally shared between employer and employee. In Germany, the contribution rate is 15.5%, and employees and employers pay 8.2% and 7.3%, respectively [38]. The difference in contribution rate between Japan and Germany might partly explain the differences in co-payments estimated in our study; however, we should consider various other factors such as structure of diseases and socioeconomic characteristics of the citizens. Neugut et al. [39] retrospectively examined the relationship of co-payments and compliance in patients with breast cancer receiving adjuvant hormone therapy with aromatase inhibitors. They showed that higher prescription co-payments were associated with non-compliance to the drugs. We should continue to seek appropriate ways to share medical costs with payers and patients to prevent patients, including ones with financial difficulties, from receiving suboptimal treatments or worse outcomes.

Our results will be useful for resource or financial allocation for medical care, although the proportions of categorical costs might be changed if a more comprehensive cost evaluation were made, including costs for physician visits and additional medical care for complications and adverse drug reactions associated with the treatment of EBC. For example, the validity of the reimbursements for breast-conserving surgery and radiotherapy in Japan should be verified, i.e. whether these reimbursements are set appropriately, reflecting the actual resource consumption. One of the reasonable ways for

achieving effective resource allocation and sound financial management of the health care system is to assess the cost effectiveness of drugs as well as of medical services. More recently, Japan has started to engage in a full-fledged discussion of health technology assessment and to consider the concept of cost effectiveness. At the same time, we should keep in mind the assessment of innovation appropriately.

Our study has 3 major limitations to be considered. First, we may have underestimated the total medical costs per patient with EBC. We did not include the costs of adverse drug reactions except for prophylactic antiemetic therapy, although the costs can be enormous. Our study was based on the assumption that the patients received almost identical medical care among the countries, although the incidences and practices after development of adverse drug reactions must be different, in particular between the two European countries and Japan. Costs for physician visits were not included in our study either, because of the highly varied unit costs, which were perhaps due to the different contents of services or allowances as well as to the frequency of hospital visits among countries. Fees for physician visits were much lower in Japan [26] and in Germany [34] compared to the UK [29].

In addition, the effects of patient body size on the drug costs are important to consider. Assumptions of a body weight of 50 kg and a body surface area of 1.5 m^2 were generally acceptable for women with breast cancer in Japan. However, patients might be larger in Western countries. The mean body surface area of women with breast cancer receiving chemotherapy was reported to be 1.75 m^2 in the UK [40]. In this case, the patients required higher doses of drugs based on patient body size and, subsequently, the drug costs would be increased. Furthermore, when discarded vials were also taken into consideration, the drug costs would be additionally increased.

Second, this study was predominantly based on hypothetical assumptions. Although medical care for patients with EBC is well standardized internationally, in a real-world situation other factors such as completion rates of a series of treatments and other various treatment courses should also be considered. However, since this study focused on the medical costs incurred by payers and patients at the one-patient level, we believe our simple assumptions made to cover a wide range of the medical costs are acceptable. In addition, treatment approaches for breast cancer were diverse as mentioned before; therefore, the financial impact on the health care systems could not be evaluated using only the results of our study with the 3 assumption case scenarios.

Third, the cross-national comparability of costs was limited, even when the local costs were converted by PPPs, as shown previously [37]. PPPs were calculated provided that the real values of goods or services were the same and assuming one perfect market as a whole across countries. The OECD is developing health-specific PPPs for health goods and services, since a limited number of comparisons of health expenditures are made because of the lack of adequate PPPs for health [41]. Such more reliable tools will be helpful for cross-national cost evaluations.

In conclusion, we estimated the medical costs associated with postmenopausal women with EBC, assuming that the patients received almost identical medical care in Japan, the UK, and Germany, by means of a bottom-up approach. Several cross-national differences in cost-sharing of medical costs between payers and patients and distributions of medical costs by cost category were defined. Our results will be useful for policy makers to consider how to share medical costs and how to allocate limited resources. Since this study had some major limitations, the results should be validated by comparing data in depth in a real-world situation. In addition, the results of this study are an investigational estimation, and further studies are needed for establishing future sustainable health care systems.

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Disclosure Statement

We declare that there are no conflicts of interest related to this study.

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