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ORIGINAL ARTICLE

Performance of dedicated breast PET in breast cancer screening: comparison with digital mammography plus digital breast tomosynthesis and ultrasound

Shunsuke Yuge[1] · Kanae K. Miyake[2] · Takayoshi Ishimori[1] · Masako Kataoka[1] · Yoshiaki Matsumoto[3,4] · Masae Torii[5] · Masahiro Yakami[3] · Hiroyoshi Isoda[3] · Kyoko Takakura[3] · Satoshi Morita[6] · Masahiro Takada[4] · Masakazu Toi[4] · Yuji Nakamoto[1]

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Abstract

Objective To compare the diagnostic performance of dedicated breast positron emission tomography (dbPET) in breast cancer screening with digital mammography plus digital breast tomosynthesis (DM-DBT) and breast ultrasound (US).

Methods Women who participated in opportunistic whole-body PET/computed tomography cancer screening programs with breast examinations using dbPET, DM-DBT, and US between 2016–2020, whose results were determined pathologically or by follow-up for at least 1 year, were included. DbPET, DM-DBT, and US assessments were classified into four diagnostic categories: A (no abnormality), B (mild abnormality), C (need for follow-up), and D (recommend further examination). Category D was defined as screening positive. Each modality's recall rate, sensitivity, specificity, and positive predictive value (PPV) were calculated per examination to evaluate their diagnostic performance for breast cancer.

Results Out of 2156 screenings, 18 breast cancer cases were diagnosed during the follow-up period (10 invasive cancers and eight ductal carcinomas in situ [DCIS]). The recall rates for dbPET, DM-DBT, and US were 17.8%, 19.2%, and 9.4%, respectively. The recall rate of dbPET was highest in the first year and subsequently decreased to 11.4%. dbPET, DM-DBT, and US had sensitivities of 72.2%, 88.9%, and 83.3%; specificities of 82.6%, 81.4%, and 91.2%; and PPVs of 3.4%, 3.9%, and 7.4%, respectively. The sensitivities of dbPET, DM-DBT, and US for invasive cancers were 90%, 100%, and 90%, respectively. There were no significant differences between the modalities. One case of dbPET-false-negative invasive cancer was identified in retrospect. DbPET had 50% sensitivity for DCIS, while that of both DM-DBT and US was 75%. Furthermore, the specificity of dbPET in the first year was the lowest among all periods, and modalities increased over the years to 88.7%. The specificity of dbPET was significantly higher than that of DM-DBT ($p < 0.01$) in the last 3 years.

Conclusions DbPET had a compatible sensitivity to DM-DBT and breast US for invasive breast cancer. The specificity of dbPET was improved and became higher than that of DM-DBT. DbPET may be a feasible screening modality.

Keywords Dedicated breast PET · Breast cancer · Opportunistic screening

✉ Kanae K. Miyake
kanaek@kuhp.kyoto-u.ac.jp

[1] Department of Diagnostic Imaging and Nuclear Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[2] Department of Advanced Medical Imaging Research, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawahara-Cho, Sakyo-Ku, Kyoto 606-8507, Japan

[3] Preemptive Medicine and Lifestyle-Related Disease Research Center, Kyoto University Hospital, Kyoto, Japan

[4] Department of Breast Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[5] Department of Breast Surgery, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan

[6] Department of Biomedical Statistics and Bioinformatics, Graduate School of Medicine, Kyoto University, Kyoto, Japan

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Introduction

The incidence and mortality rate of breast cancer among Japanese women is rising. Breast cancer was the fourth leading cause of cancer-related deaths among Japanese women in 2020 [1]. According to the Hospital-based Cancer Registries in Japan, the overall 5-year and 10-year relative survival rate for stage 0 or I breast cancer, defined according to the Union for International Cancer Control Tumor–Node–Metastasis classification (7th edition), is > 95% [1]. Therefore, early breast cancer detection is necessary to reduce breast cancer-related deaths.

Mammography is used for population-based screening, because it reduces breast cancer mortality rates [2]. Biennial mammography screening is recommended for women aged ≥ 40 years in Japan. However, an increase in breast density reduces the sensitivity of mammography for breast cancer [3]. Furthermore, common false-positive recalls and radiation exposure are the major harms of mammography screening [4, 5]. Breast ultrasound (US) is another screening modality for breast cancer. Combining the hand-held breast US with mammography ensures a higher sensitivity for breast cancer detection than mammography alone [6]. Nevertheless, breast US screening has several obstacles, such as longer examination time for large breasts, and relatively poor reproducibility of images due to high operator dependency even if experienced breast radiologists perform [7]. In Japan, since 1994, whole-body (WB) [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) or PET/computed tomography (CT) has been used for opportunistic cancer screening, which is performed based on the recommendation made by self-referral of individuals and is offered at their own expense. However, published studies showed that the cancer detection rate of breast cancer in the WB PET or PET/CT screening was 0.18–0.23% [8–10], which is lower than or equal to the acceptable value (0.23%) for population-based screening mammography provided by the Japanese Ministry of Health, Labor, and Welfare in 2008. A Japanese survey showed that the relative sensitivity of WB PET or PET/CT screening for invasive cancers tended to be lower than that of mammography (61.5% vs. 73.1%) and was significantly lower than that of breast US (67.6% vs. 91.2%) when direct comparisons between modalities were performed [11]. Consequently, WB PET and PET/CT are insufficient for breast cancer screening.

Dedicated breast PET (dbPET) with a ring-shaped detector is a breast-specific PET system with high spatial resolution. dbPET improves the contrast of tumor uptake with the background [12] and is significantly more sensitive than WB PET in detecting subcentimetric breast cancer [13–15]. Thus, dbPET is expected to serve as a modality for improving breast cancer screening with PET.

Yamamoto et al. investigated the screening performance of positron emission mammography (PEM) and found it has an excellent diagnostic yield. PEM had an overall recall rate of 8.3%, sensitivity of 100%, specificity of 84.5%, positive predictive value (PPV) of 27.3%, and cancer detection rate of 2.3% [16]. However, their sample size was small for a screening validation study. Furthermore, they included participants with breast symptoms, which might have increased the pre-test probability, thus, contributing to the high PPV and cancer detection rate. The diagnostic performance of breast-specific PET, especially dbPET, in breast cancer screening for asymptomatic women remains unknown.

Since 2016, WB PET/CT cancer screening has been used as an opportunistic screening program at our cancer screening center (HIMEDIC Kyoto University Hospital). For women, dbPET, digital mammography plus digital breast tomosynthesis (DM-DBT), and breast US examinations were added to improve breast cancer detection. The primary aim of this study was to compare the diagnostic performance of dbPET in breast cancer screening during the first 4.5 years with those of DM-DBT and breast US. In addition, we investigated the influence of age, breast density, and the initial or repeated screening on diagnostic performance.

Materials and methods

Study population

This retrospective observational study reviewed 2918 screenings performed following WB PET/CT among 1687 women who participated in our institution's opportunistic cancer screening program from June 2016 to December 2020. To prevent radiation exposure, participants in their 20 s or younger were recommended to avoid PET or DM-DBT examinations. The exclusion criteria were determined according to the previously described [16, 21] as follows: (1) DM-DBT or breast US not performed on the same day as dbPET and (2) unavailability of final results, which were determined pathologically or by follow-up for at least 1 year. The reports issued for each modality were reviewed and analyzed in this study. This study was approved by the Ethics Committee of Kyoto University (Approval No. R1512) and involved individuals who had participated in a preceding study with their consent. Therefore, the requirement for written informed consent was waived. Data collection for eligible participants was performed from February 23 to August 31, 2022.

Image acquisition

[^{18}F]-FDG dbPET. Participants fasted for at least 4 h before administering [^{18}F]-FDG (approximately 3.5 MBq/

kg of body weight). Following WB PET/CT acquisition, dbPET was performed with a ring-shaped dbPET scanner (Elmammo, Shimadzu Corp., Kyoto, Japan) on each breast with the woman in the prone position for approximately 90 min post-injection. The dbPET scanner consisted of 36 detector modules arranged in three contiguous rings with an inner diameter of 195 mm and an axial length of 165.5 mm. The effective transaxial field of view was 185 mm. The intrinsic detector performance evaluated based on NEMA NU4-2008 standards has been reported elsewhere [17]. The dbPET image was reconstructed using a dynamic row-action maximum-likelihood algorithm with one iteration and 128 subsets, a relaxation control parameter of $\beta = 20$, matrix size measuring 236×236 with a post-reconstruction smoothing Gaussian filter (1.17 mm full width at half maximum), and voxel size of $0.78 \times 0.78 \times 0.78$ mm. Scatter correction was performed using the convolution subtraction method [18]. Attenuation correction was applied using a uniform attenuation map with object boundaries obtained from emission data [17]. Maximum intensity projection (MIP) images in the craniocaudal and mediolateral orientations and tomographic images were generated for each breast.

DM-DBT. Craniocaudal and mediolateral oblique views of the two-dimensional (2D) full-field DM and DBT were obtained using a commercial system (Selenia Dimensions, Hologic, USA) for both breasts in each participant.

Breast US. Hand-held breast US examinations of both breasts were performed using a commercially available system (Aplio 500, Canon Medical Systems, Japan) with a 10.0 MHz linear transducer (or 12.0 MHz, if necessary). A registered medical sonographer performed comprehensive breast and axillary lymph node scans. With the woman in the supine position and her upper arms raised and extended in the transverse plane, scanning was conducted from the upper outer quadrant, covering the entire breast in a craniocaudal direction. The probe was rotated into the sagittal plane and swept left to right to scan the entire breast. Doppler US and elastography were performed as required. Each breast quadrant was imaged, and a movie of the entire breast scan was recorded routinely. If a suspicious finding was noted, multiple-plane still images and sweeping movies of the lesion were obtained.

DM-DBT and breast US examination order was not fixed, while dbPET was performed last.

Image interpretation

Two board-certified nuclear medicine physicians interpreted dbPET images on commercial viewers or workstations (Universal Viewer and/or Advantage Workstation, GE Healthcare, USA; Aquarius iNtuition Server, TeraRecon, USA). In previously diagnosed breast cancers, uptake features were described using dbPET lexicon version 1.0 [19]; this was done retrospectively if not performed at the time of screening. DM-DBT images were interpreted on a specialized viewer (mammodite, NetCam Systems Corporation, Japan) by two breast surgeons certified by the Japan Central Organization on Quality Assurance of Breast Cancer Screening for mammography interpretation. Breast US was first evaluated and reported by a sonographer and subsequently re-assessed by a breast surgeon who reviewed the captured US images and movies to confirm the report. Readers were possible to refer to other modalities at the time of image interpretation. Target US or target reviews were often performed when DM-DBT or dbPET detected abnormalities.

Each modality was assessed based on the diagnostic categories proposed by the Japan Society of Ningen Dock. "Ningen Dock" is a private medical checkup system originally established in Japan [20]. Five diagnostic categories were used in the reports: A (no abnormality), B (mild abnormality), C (need for follow-up), D (recommend further examination), and E (under treatment or follow-up). In any modality, the second reader's rating was used as the final assessment of the examination. In cases with category E, images were re-evaluated for this study so that all examinations were classified into A, B, C, or D. In this study, category D was defined as positive. Ningen Dock categories and BI-RADS categories do not exactly match, however, can roughly correspond as follows; Category A = BI-RADS 1, Category B = BI-RADS 2, Category C = BI-RADS 3, and Category D = BI-RADS 4 or 5, respectively.

Diagnostic performance

Screening-detected breast cancer (true positive) was defined as a breast cancer diagnosis with a positive screening, and included invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS), and invasive lobular carcinoma (ILC), confirmed on pathology within 1 year of screening and before the next screening appointment [5]. False positives were defined as positive screenings with no evidence of malignancy based on at least 1 year of clinical or imaging follow-up after screening or pathological confirmation of non-malignant lesions. Negative screenings were regarded as true negatives if there was no evidence of malignancy during the follow-up period or false negatives if breast cancer was diagnosed during the follow-up period.

The cancer detection rate was defined as the number of true positive screenings based on a comprehensive evaluation of all tests divided by the total number of screenings [21]. The cancer detection rates of each modality were not calculated since recommendations for further examinations were determined by considering all the tests and not for each modality.

The recall rate, sensitivity, specificity, and PPV of dbPET, DM-DBT, and breast US were calculated for each modality

to evaluate their diagnostic performance for breast cancer screening. The recall rate was defined as the percentage of screening examinations with a positive assessment (category D). The specificity calculation is difficult in nature in screening with a healthy person, but to overcome this limitation, we defined a 1-year follow-up period for convenience and regarded true negative using pathological diagnosis as the gold standard within that period.

In addition, a retrospective assessment of dbPET, review of WB PET/CT reports, retrospective assessment of WB PET/CT, and evaluations of clinicopathological features were performed in cases of diagnosed breast cancers.

Subgroup analyses were performed to determine the effects of age, breast density, and the initial or repeated screening on diagnostic yields. Participants were divided into two age groups—(1) < 50 years and (2) ≥ 50 years—based on the results of a previous study on the risk–benefit break-even age for PET screening programs [22]. The breast density of each DM-DBT case was categorized into four types according to the criteria of the Japan Central Organization on Quality Assurance of Breast Cancer Screening and the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) [23]. Breast density was grouped into two types for this analysis: (1) dense breast (extremely or heterogeneously dense) and (2) non-dense breast (scattered fibroglandular densities or almost entirely fatty). In the analysis of screening settings, the examinations were divided into (1) initial screening and (2) repeat screening (two or more screening rounds). The screening interval was defined as the number of days between a screening round and the next round. The screening interval was classified as (1) annual (≤18 months), (2) biennial (19−30 months), and (3) triennial or longer (> 30 months) [5].

Statistical analyses

McNemar's test was used for the recall rate, sensitivity, and specificity, and Fisher's exact test was used for PPV to perform multimodality comparisons of the diagnostic yields using paired data. In addition, Fisher's exact test was used to examine the associations between the diagnostic yields and age, breast density, and the initial or repeat screening. Statistical analyses were performed using JMP®Pro 16.0 (SAS Institute Inc., Cary, NC, USA). A p value < 0.05 was considered statistically significant. Continuous data are presented as mean ± standard deviation.

Results

Study population

Among the 2918 screenings among 1687 women, 2156 screenings among 1083 women (mean age, 54.1 ± 10.6 years [range, 30–91 years]) were included in our study. A total of 762 screenings were excluded because of lack of consent in 98, unadministered DM-DBT examinations in 210, and unknown outcomes in 454 (Fig. 1). DM-DBT was not performed in 210 examinations for the following reasons: postmastectomy for breast cancer in 57, after breast surgery for benign lesion or implant surgery in 24, during breastfeeding

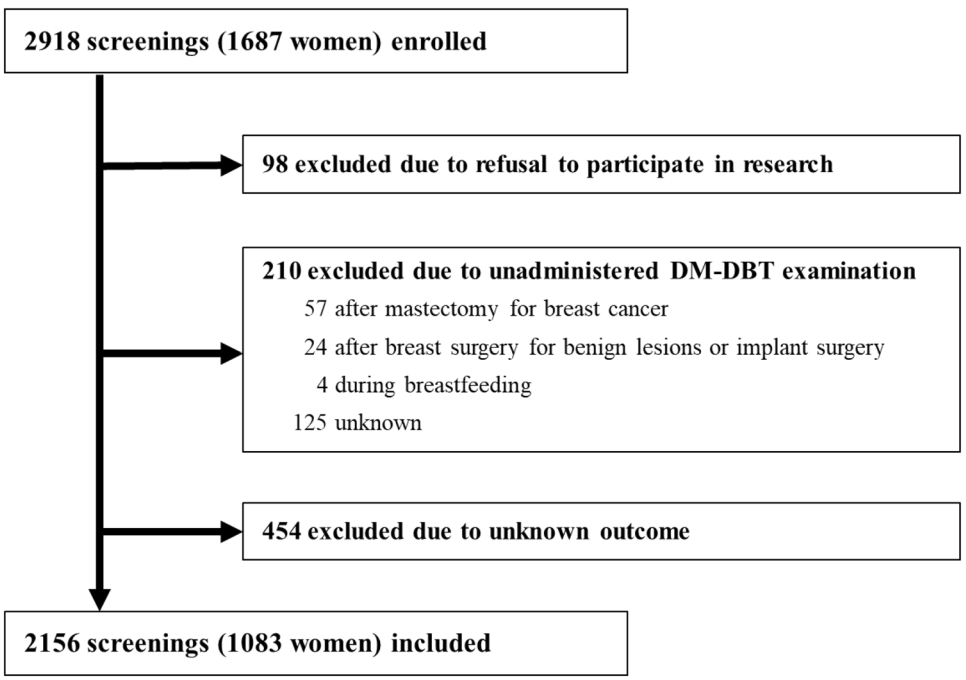

Fig. 1 Flowchart of the inclusion and exclusion of screenings

in four, and unknown reasons in 125. There were no participants with recently diagnosed breast cancer nor those who had a history of breast cancer. With regard to the number of screenings by year, 211 people were examined in 2016, 431 in 2017, 485 in 2018, 531 in 2019, and 498 in 2020. Furthermore, a total of 1083 examinations were performed at the initial screening, and 1073 were performed during the repeat screening. The number of screening rounds per participant during the study period was one in 542, two in 235, three in 148, four in 90, and five in 68. The mean interval between screening rounds was 440 ± 162 days (range 217–1475 days) for repeat screenings (annual screenings in 888, biennial screenings in 166, and triennial screenings in 19).

Breast cancers

Eighteen breast cancer diagnoses were made within the follow-up period: three diagnoses in 2016, two in 2017, nine in 2018, three in 2019, and one in 2020. Nine were IDC, one was ILC, and eight were DCIS. Based on the final comprehensive screening assessment, 17 cases were true positives, while one was false negative. The overall cancer detection rate of our screening program was 0.79%. No breast cancer was overlooked, because it was located in a blind area outside the field-of-view of dbPET.

The clinical, pathological, and imaging features of the 10 identified invasive breast cancer cases are summarized in Table 1. The average size of invasive breast cancers was 16.4 ± 10.4 mm (range 7−45 mm), and the average SUVmax (maximum standardized uptake value) was 4.0 ± 1.5 (range 1.9−6.5). The pathological stage was IA in eight cases and IIA in two cases. All invasive breast cancers were encountered during the initial screening. Invasive cancers were positive on all three imaging modalities except for one case. WB PET/CT detected seven of the 10 (70%) cases, fewer than dbPET. However, the difference was not statistically significant ($p = 0.16$). A representative case of dbPET-positive screening-detected breast cancer is shown in Fig. 2. Figure 3 shows another case of IDC negative on dbPET and breast US and positive on DM-DBT. This cancer was identifiable on dbPET through retrospective review as a mild non-mass uptake. It was luminal A with a Ki-67 index of 2% located deep in the breast.

Of the eight non-invasive cancers (DCIS), four were positive on dbPET, six were positive on DM-DBT, and six were positive on breast US (Table 2). WB PET/CT detected three of the eight (37.5%) cases, which were fewer than dbPET ($p = 0.14$). In retrospect, two of the four DCIS cases with false-negative dbPET results showed an abnormal uptake. Of the four dbPET-negative cases, two were positive on both DM-DBT and US, one was negative on DM-DBT but positive on US, and another was negative on both DM-DBT and US. The last case that resulted in false negatives on all three modalities was previously positive on dbPET and US in the prior-round screening. In the target year, this case was judged as category C (follow-up recommended), defined as negative in this study, as there was no change in the findings. However, following diagnostic magnetic resonance imaging (MRI) and subsequent biopsy, it was diagnosed as DCIS.

Diagnostic yield of dbPET, DM-DBT, and breast US

Overall, the recall rates were 17.8% (384/2156) for dbPET, 19.2% (414/2156) for DM-DBT, and 9.4% (203/2156) for breast US. DbPET had the highest recall rate in the first year; this recall rate subsequently decreased to 11.4%. The sensitivities of dbPET, DM-DBT, and breast US were 72.2%, 88.9%, and 83.3%, respectively. The specificities of dbPET, DM-DBT, and breast US were 82.6%, 81.4%, and 91.2%, respectively. The PPV of dbPET, DM-DBT, and breast US were 3.4%, 3.9%, and 7.4%, respectively. The specificity of dbPET in the first year was the lowest of all periods, but this specificity increased to 88.7% in the final year. Consequently, the specificity of dbPET exceeded that of DM-DBT during the last 3 years. Details of the year-by-year changes in diagnostic yields are presented in Table 3 and Fig. 4.

Table 4 shows the sensitivities according to invasive and non-invasive breast cancers. The sensitivity for invasive cancers was high for all modalities: 90% for dbPET, 100% for DM-DBT, and 90% for breast US. In contrast, the sensitivity for non-invasive cancers was 50% for dbPET and 75% for DM-DBT and breast US.

In the multimodality comparison, there were no significant differences in the sensitivities between dbPET and DM-DBT or between dbPET and breast US in all cancers, invasive cancers, and DCIS (Table 5). Specificity and PPV were not significantly different between dbPET and DM-DBT during the entire study period. However, the specificity of dbPET during the last 3 years of the study was significantly higher than that of DM-DBT ($p < 0.01$). The specificity of breast US was significantly higher than that of dbPET ($p < 0.01$). The PPV of dbPET was not significantly different from that of DM-DBT and breast US.

Subgroup analysis

The results of these subgroup analyses are shown in Table 6.

The age of the participants at dbPET was < 50 years in 789 examinations and ≥ 50 years in 1367 examinations. The recall rate and specificity of dbPET and breast US were significantly higher in the < 50-years subgroup compared with the ≥ 50-years subgroup ($p < 0.01$). However, the sensitivity and PPV of each modality tended to be lower in the < 50 years subgroup than the ≥ 50 years subgroup, although this difference was insignificant.

Table 1 Clinical, pathological, and imaging features of invasive breast cancers

Age	Histological type	Maximal size (mm)	pTNM	pStage	Nuclear grade	ER	PgR	HER2	Ki-67 (%)	Screening dbPET	Retrospective assessment of dbPET	Uptake pattern	SUVmax	WB PET/CT
53	IDC, NST	17	pT1cN0M0	IA	2	+	+	−	24	Positive	−	MU	4.9	Positive
57	IDC, NST	12	pT1cN0M0	IA	1	+	+	+	2	Negative	Positive	n/a	n/a	Negative
63	IDC	8	pT1bN0M0	IA	1	+	+	n/a	20	Positive	−	MU	2.3	Positive
72	IDC, NST	12	pT1cN0M0	IA	1	+	+	−	n/a	Positive	−	MU	2.0	Negative
46	ILC	45	pT2N0M0	IIA	1	+	+	−	n/a	Positive	−	MU	4.2	Positive
57	IDC, scirrhous	10	pT1bN0M0	IA	1	+	+	+	1	Positive	−	MU	6.5	Positive
43	IDC, scirrhous	15	pT1cN0M0	IA	1	+	+	−	n/a	Positive	−	MU	3.6	Positive
58	IDC, NST	7	pT1aN0M0	IA	1	+	+	−	14	Positive	−	Focus	1.9	Negative
55	IDC, NST	20	pT1cN0M0	IA	3	+	+	+	27	Positive	−	MU	5.2	Positive
45	IDC, NST	18	pT1cN1aM0	IIA	2	+	+	−	13	Positive	−	MU	5.0	Positive

Retrospective assessment of WB PET	DM-DBT	Breast density	US	Screening round	Screening assessment
−	Positive	Non-dense	Positive	Initial	Positive
Negative	Positive	Dense	Negative	Initial	Positive
−	Positive	Dense	Positive	Initial	Positive
Negative	Positive	Non-dense	Positive	Initial	Positive
−	Positive	Non-dense	Positive	Initial	Positive
−	Positive	Dense	Positive	Initial	Positive
−	Positive	Dense	Positive	Initial	Positive
Negative	Positive	Non-dense	Positive	Initial	Positive
−	Positive	Non-dense	Positive	Initial	Positive
−	Positive	Dense	Positive	Initial	Positive

dbPET dedicated breast PET, *DM-DBT* digital mammography plus digital breast tomosynthesis, *US* ultrasound, *ER* estrogen receptor, *PgR* progesterone receptor, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *NST* no special type, *n/a* not available, *MU* mass uptake

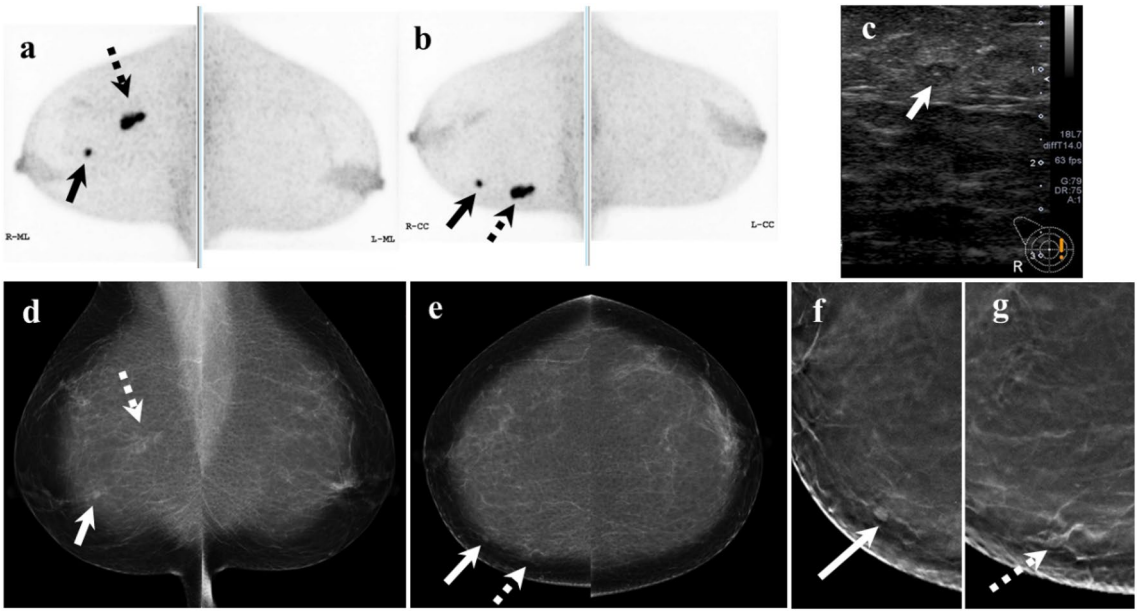

Fig. 2 DbPET-positive invasive ductal carcinoma of the right breast (woman aged in 70 s). Pathological stage IA, luminal B subtype, nuclear grade 3, and Ki-67 27%. The mediolateral (ML) view (**a**) and the craniocaudal (CC) view (**b**) of dbPET with the PET window intensity of SUV 0 to 3, the sagittal view of breast ultrasound (US) (**c**), the mediolateral oblique (MLO) view (**d**) and the CC (**e**) view of digital mammography (DM), and enlarged CC views (**f**, **g**) of digital breast tomosynthesis (DBT). At the screening, DM-DBT and US detected one lesion (solid arrows), which was visualized as intense dot-like uptake on dbPET (solid arrow; SUVmax = 3.4). In addition, dbPET clearly detected another larger lesion (dotted arrow; SUVmax = 5.2) behind it in the upper/inner area of the right breast. All three modalities resulted in true positives per examination; however, this case illustrated that there are breast cancers that are better detected by dbPET than US and DM-DBT

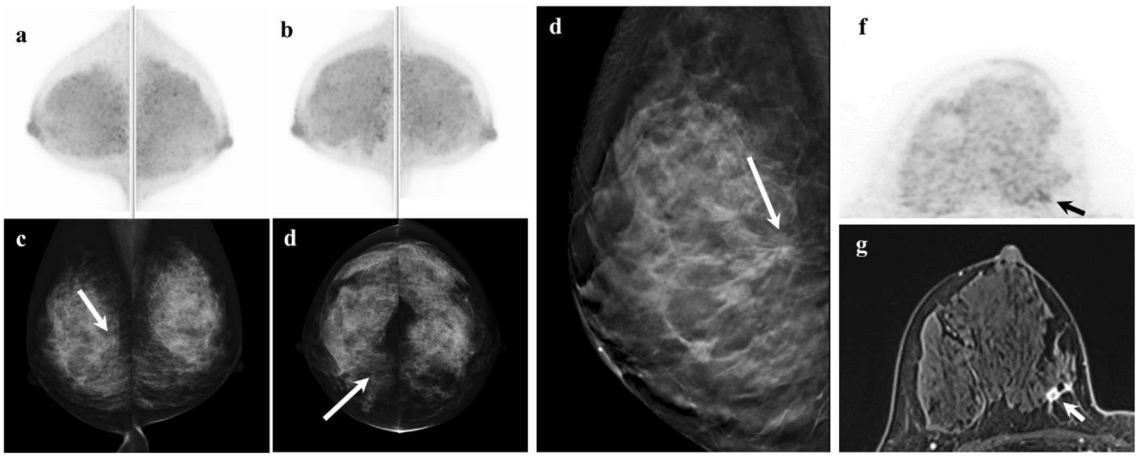

Fig. 3 DbPET-negative invasive ductal carcinoma of the right breast (woman aged in 50 s). Pathological stage IA, luminal A subtype, nuclear grade 1, and Ki-67 2.2%. The mediolateral (ML) view and craniocaudal (CC) view of dbPET MIP (**a**, **b**) with the PET window intensity of SUV 0 to 4, mediolateral oblique (MLO) view and CC view of DM (**c**, **d**), the MLO view of DBT (**e**), axial dbPET image (**f**), and axial early-phase image of diagnostic MRI (**g**). No abnormal uptake was detected on dbPET during screening, but the architectural distortion was identified in the upper/inner area of the right breast on DM-DBT (arrows). Diagnostic MRI (**g**) performed at a later date for further assessment shows a mass with rim-enhancement in the AB area of the right breast, and the corresponding mild focal non-mass uptake (SUVmax = 2.0) was identifiable on dbPET (**f**) retrospectively

Breast density on DM-DBT was dense in 651 examinations (extremely dense in six, heterogeneously dense in 645) and non-dense in 1505 examinations (scattered fibroglandular densities in 1496 and almost entirely fatty in nine). Of the 18 cases of breast cancer, nine women had dense breasts. Of the nine cases with dense breasts, dbPET

Table 2 Clinical, pathological, and imaging features of DCIS

Age	Ductal spread (mm)	Nuclear grade	ER	PgR	HER2	Ki-67 (%)	Screening dbPET	Retrospective assessment of dbPET	Uptake pattern	SUVmax	WB PET/CT	Retrospective assessment of WB PET	DM-DBT	Breast density	US	Screening round	Screening assessment
51	20	1	+	n/a	n/a	n/a	Negative	Negative	n/a	n/a	Negative	Negative	Positive	Dense	Positive	Initial	Positive
71	5	n/a	+	+	−	5	Positive	−	Focus	5.4	Positive	−	Positive	non-dense	Positive	Repeat	Positive
44	7	3	n/a	n/a	n/a	n/a	Negative	Negative	n/a	n/a	Negative	Negative	Negative	Dense	Positive	Initial	Positive
49	n/a	n/a	+	+	n/a	n/a	Positive	−	NMU	n/a	Positive	−	Positive	Dense	Positive	Initial	Positive
81	25	n/a	−	−	+	n/a	Positive	−	Focus	2.3	Positive	−	Positive	Non-dense	Positive	Repeat	Positive
52	40	2	+	−	n/a	n/a	Negative	Positive	n/a	n/a	Negative	Positive	Positive	Non-dense	Positive	Repeat	Positive
48	n/a	2	+	+	n/a	n/a	Negative	Positive	n/a	n/a	Negative	Negative	Negative	Dense	Negative	Repeat	Negative
62	n/a	2	n/a	n/a	n/a	n/a	Positive	−	MU + NMU	5.5	Negative	Positive	Positive	Non-dense	Negative	Initial	Positive

DCIS ductal carcinoma in situ, *dbPET* dedicated breast PET, *DM-DBT* digital mammography plus digital breast tomosynthesis, *US* ultrasound, *ER* estrogen receptor, *PgR* progesterone receptor, *n/a* not available, *MU* mass uptake, *NMU* non-mass uptake, *n/a* not available

Table 3 Diagnostic yield of breast cancer screening

Reference	Screenings (*n*)	Breast cancer (*n*)	Recall rate (%)			Sensitivity (%)			Specificity (%)			PPV (%)		
			dbPET	DM-DBT	US	dbPET	DM-DBT	US	dbPET	DM-DBT	US	dbPET	DM-DBT	US
Total	2156	18	17.8	19.2	9.4	72.2	88.9	83.3	82.6	81.4	91.2	3.4	3.9	7.4
2016	211	3	33.2	19.9	15.6	66.7	100	66.7	67.3	81.3	85.1	2.9	7.1	6.1
2017	431	2	21.6	17.6	9.3	100	100	100	78.8	82.8	91.1	2.2	2.6	5.0
2018	485	9	17.3	21.2	11.8	77.8	88.9	100	83.8	79.8	89.9	8.3	7.8	15.8
2019	531	3	15.1	19.8	9.8	33.3	66.7	66.7	85.0	80.5	90.5	1.3	1.9	3.8
2020	498	1	11.4	17.7	4.2	100	100	0	88.7	82.5	95.8	1.8	1.1	0
2018–2020	1514	13	14.6	19.6	8.6	69.2	84.6	84.6	85.9	81.0	92.1	4.1	3.7	8.5

dbPET dedicated breast PET, *DM-DBT* digital mammography plus digital breast tomosynthesis, *US* ultrasound, *PPV* Positive predictive value of positive screening results

was negative in four, DM-DBT was negative in one, and breast US was negative in two. The recall rate of dbPET was significantly lower in dense breasts compared with non-dense breasts ($p = 0.03$). DM-DBT and breast US recall rate was significantly higher in dense breasts than in non-dense breasts ($p = 0.01$ and < 0.01, respectively). In each imaging modality, the sensitivity tended to be lower, and PPV tended to be higher in dense breasts than in non-dense breasts, although these differences were insignificant. The specificity of dbPET was significantly higher in dense breasts than in non-dense breasts ($p = 0.02$), while the specificity of DM-DBT and breast US was significantly lower in dense breasts than in non-dense breasts ($p = 0.02$ and 0.01, respectively).

All 10 cases with invasive cancers and four of the eight cases with DCIS were detected in the initial screening. The remaining four cases with DCIS were detected in the repeat screening. Significantly higher recall rates and lower specificities were observed in the initial screening compared with the repeat screening for each imaging modality ($p < 0.01$). Figure 5 shows the year-by-year changes in the recall rates of dbPET according to the initial and repeat screenings. The recall rate in the initial screening was significantly higher than that in the repeat screening every year ($p < 0.01$) and progressively decreased year by year from the first year.

Discussion

The present study reviewed 2156 screenings in an opportunistic breast cancer screening program with ring-type dbPET, DM-DBT, and breast US and investigated the diagnostic yield of ring-type dbPET compared with DM-DBT and breast US. To the best of our knowledge, this is the first study to demonstrate the performance of dbPET in detecting breast cancers in a screening setting on a relatively large scale.

In this study, dbPET correctly detected nine out of 10 cases of invasive cancers and misdiagnosed one. The sensitivities of dbPET, DM-DBT, and breast US were 90%, 100%, and 90%, respectively, for invasive cancers. There were no significant differences between dbPET and DM-DBT or between dbPET and breast US. The small number of proven invasive cancer cases may prevent the determination of the most suitable imaging modality for detecting invasive cancer. However, the comparative sensitivity of dbPET to those of DM-DBT and breast US, which were more like diagnostic tests rather than standard screenings, suggests the feasibility of dbPET in detecting invasive breast cancers. One false-negative invasive cancer detected with dbPET was luminal A and had a very low Ki-67; however, it was identifiable as mild uptake in retrospect. Some breast cancers, such as less aggressive tumors or those with low cellularity (i.e., mucinous cancers, invasive lobular carcinomas, and

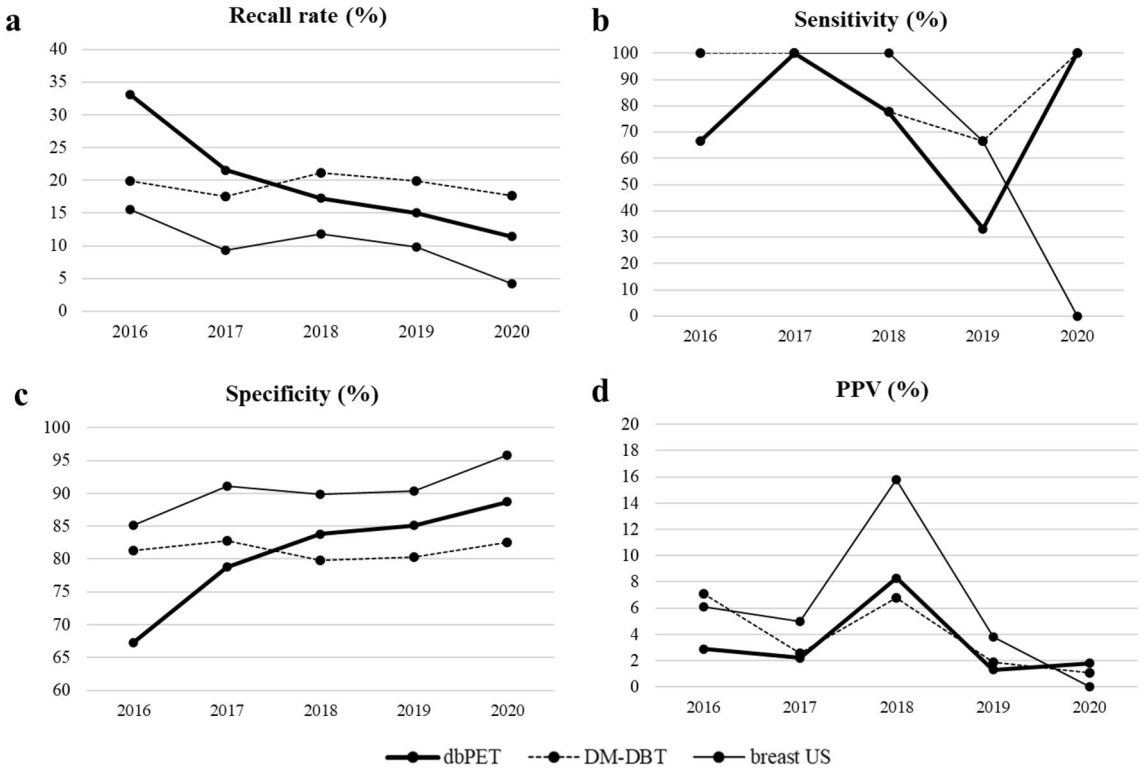

Fig. 4 Changes in the diagnostic yield of three types of breast cancer screening modalities per year. The recall rate (**a**), sensitivity (**b**), specificity (**c**), and positive predictive value (PPV) (**d**) of the dbPET (thick solid line), DM-DBT (broken line), and breast US (thin solid line)

Table 4 Sensitivity of breast cancer screening for invasive cancer or DCIS

Reference	Screenings (*n*)	Invasive cancer				DCIS			
		n	dbPET (%)	DM-DBT (%)	US (%)	n	dbPET (%)	DM-DBT (%)	US (%)
Total	2156	10	90.0	100	90.0	8	50.0	75.0	75.0
2016	211	3	66.7	100	66.7	0	n/a	n/a	n/a
2017	431	2	100	100	100	0	n/a	n/a	n/a
2018	485	4	100	100	100	5	60.0	60.0	100
2019	531	1	100	100	100	2	0	50.0	50.0
2020	498	0	n/a	n/a	n/a	1	100	100	0

dbPET dedicated breast PET, *DM-DBT* digital mammography plus digital breast tomosynthesis, *US* ultrasound, *DCIS* ductal carcinoma in situ, *n/a* not available

scirrhous cancers), can have low or occasionally absent FDG-avidity [24]. Other factors that hinder the detection of cancers include the relatively large blind area of dbPET [25] and possible noise or impaired image quality.

In contrast, the sensitivity of dbPET for non-invasive cancers was low (50%). dbPET had a lower sensitivity than DM-DBT and breast US in detecting non-invasive cancers, although these differences were insignificant. dbPET seems to have limited efficacy for detecting DCIS. However, based on these findings alone, one should not conclude that dbPET has inferior clinical utility than DM-DBT and breast US. The detection and treatment of DCIS are controversial. The advent of screening mammography has increased the incidence rate of DCIS; however, some DCIS cases do not progress to invasive diseases or influence mortality. An active surveillance strategy without surgery has been proposed as a potential alternative management strategy for low-risk DCIS, and several clinical trials, namely the LORD, LORIS, and COMET trials, are ongoing in this regard [26–28]. Grana-Lopez et al. showed that abnormal [^{18}F]-FDG uptake on dbPET (MAMMI, Oncovision, Spain), a similar type of scanner from a different vendor,

Table 5 Comparison of the sensitivity, specificity, and PPV with dbPET vs. DM-DBT or breast US for breast cancer detection

	dbPET	DM-DBT	*p*	dbPET	US	*p*
Sensitivity (%)						
Overall	72.2 (13/18)	88.9 (16/18)	0.08	72.2 (13/18)	83.3 (15/18)	0.31
Invasive cancer	90.0 (9/10)	100 (10/10)	0.31	90.0 (9/10)	90.0 (9/10)	1.0
DCIS	50.0 (4/8)	75.0 (6/8)	0.16	50.0 (4/8)	75.0 (6/8)	0.31
Specificity (%)						
Overall	82.6 (1767/2138)	81.4 (1740/2138)	0.26	82.6 (1767/2138)	91.2 (1950/2138)	< 0.01*
2018–2020	85.9 (1289/1501)	81.0 (1216/1501)	< 0.01*	85.9 (1289/1501)	92.1 (1382/1501)	< 0.01*
PPV (%)						
Overall	3.4 (13/384)	3.9 (16/414)	0.85	3.4 (13/385)	7.4 (15/203)	0.07
2018–2020	4.1 (9/221)	3.7 (11/296)	0.82	4.1 (9/221)	8.5 (11/130)	0.09

dbPET dedicated breast PET, *DM-DBT* digital mammography plus digital breast tomosynthesis, *US* ultrasound, *PPV* positive predictive value of screening results, *DCIS* ductal carcinoma in situ

*$p < 0.05$

was positive in 92% of high-risk DCIS but in only 8% of low-risk DCIS [29]. These results yielded more than 90% sensitivity and specificity in distinguishing high-risk and low-risk DCIS. The relationship between DCIS grades and dbPET positivity was unclear in our study. However, based on the characteristics of [^{18}F]-FDG, which tends to accumulate in more metabolically active tumors, it is not surprising that dbPET is more likely to detect more aggressive DCIS requiring treatment. Further studies are needed to determine whether dbPET screening can be advantageous in detecting hazardous breast cancers and contribute to resolving the overdiagnosis of screening mammography.

Dense breasts are a potential risk factor for breast cancer and are common among Japanese women [30]. Dense breast cancer screening with conventional mammography (2D mammography) is problematic, because it decreases the sensitivity of breast cancer detection [31]. In contrast, except for lactating breasts, the intensity of background fibroglandular uptake on dbPET is usually mild, less commonly moderate or faint, and rarely interferes with cancer detection [32]. We expected dbPET to have better sensitivity than DM-DBT in dense breasts; however, the results showed no superiority of dbPET over DM-DBT. In our study, DM-DBT yielded perfect sensitivity for invasive cancers and was more sensitive to DCIS than dbPET. DM-DBT performs better than 2D mammography in breast cancer detection in heterogeneously dense breasts [33, 34]. The use of DM-DBT and the small number of participants with detected breast cancer might have hindered the expected results.

Regarding specificity, the best performance was obtained with breast US. For dbPET, the specificity was 67.3% in the first year and gradually increased to 88.7% annually. The specificity of dbPET was higher than that of DM-DBT in the last 3 years. This was due to a decrease in false positives, which also decreased the recall rate of dbPET. We believe that the diagnostic performance at the beginning of the dbPET screening program was low as it was the first attempt without any guidance or evidence. However, more experience and our ongoing efforts to improve the interpretation of dbPET might have led to the successful reduction in false positives.

Abnormal uptake on dbPET is not always indicative of breast cancer. Benign lesions, such as complicated cysts, intraductal papillomas, fibroadenomas, and fat necrosis, can accumulate [^{18}F]-FDG, and noise can appear as a dot-like intensity [35], resulting in potential false positives. The dbPET lexicon was implemented at our site to categorize breast uptake comprehensively based on uptake intensity and morphological features [19] and is used in interpreting, reviewing, and feedback cases. In addition, noise discrimination based on reproducibility assessment using a pair of dbPET images reconstructed from list-mode half-time data is applied to differentiate noise from true lesions [36]. The diagnostic performance of dbPET will further improve if interpretative algorithms mature and become established.

Japan population-based mammography screening benchmarks are defined as follows: cancer detection rate $\geq 0.23\%$, recall rate $< 11\%$, and PPV $\geq 2.5\%$. This study showed a high overall cancer detection rate (0.79%), suggesting a high screening yield in our program. The recall rate of dbPET decreased annually to 11.4%. The PPV of dbPET was 4.1% in the last 3 years. A simple comparison between opportunistic screening and population-based mammography screening cannot be made; however, dbPET appears to be an acceptable screening modality with a similar recall rate and better PPV than the benchmarks.

Radiation exposure is a major concern regarding PET cancer screening. Based on Japanese survey data for [^{18}F]-FDG PET cancer screening, the average estimated effective dose for WB PET/CT was 12.8 mSv in women, and

Table 6 Subgroup analysis of the diagnostic yield of breast cancer screening

Reference	Screenings (*n*)	Breast cancer (*n*)	Recall rate (%)			Sensitivity (%)			Specificity (%)			PPV (%)		
			dbPET	DM-DBT	US	dbPET	DM-DBT	US	dbPET	DM-DBT	US	dbPET	DM-DBT	US
< 50 years	789	6	22.6*	21.7	12.5*	66.7	66.7	83.3	77.8	78.7	88.0	2.2	2.3	5.1
≥ 50 years	1367	12	16.2	18.5	7.6	75.0	91.7	83.3	84.3*	82.1*	93.1*	4.1	4.3	9.6
Dense breast	651	9	15.8	22.0*	12.1*	55.6	77.8	77.8	84.7*	78.8	88.8	4.9	4.9	8.9
Non-dense breast	1505	9	19.7*	17.4	8.2	88.9	88.9	88.9	80.7	83.0*	92.2*	2.7	3.1	6.5
Initial screening	1083	14	25.8*	24.8*	13.7*	78.6	92.9*	85.7	74.9	76.1	87.3	3.9	4.8	8.1
Repeat screening	1073	4	11.3	14.4	5.1	50.0	50.0	75.0	88.9*	85.7*	95.1*	1.7	1.3	5.5

dbPET dedicated breast PET, *DM-DBT* digital mammography plus digital breast tomosynthesis, *US* ultrasound, *PPV* Positive predictive value of positive screening results

*Significantly higher than the counterpart ($p < 0.05$) in the comparison of < 50 years vs. ≥ 50 years, dense vs. non-dense breast, or initial vs. repeat screening

the risk–benefit break-even age from the viewpoint of radiation exposure was calculated to be in the 50 s [37]. If the radiation dose is reduced, e.g., by using lower dose CT for PET/CT, the appropriate age can be lowered. When dbPET is performed with WB PET/CT cancer screening as in our study, there is no additional radiation exposure. Recently, there has been a movement to consider screening for breast cancer using only dbPET, without PET/CT. A preliminary study of nine women without breast cancer demonstrated that, compared with full-dose dbPET (3 MBq/kg), half-dose of dbPET (1.5 MBq/kg) provided acceptable image qualities, at least in normal breasts [37]. However, [^{18}F]-FDG administration exposes whole-body organs to ionizing radiation. Estimation studies demonstrated higher lifetime attributable risks of radiation-induced cancer incidence and mortality with PEM than with DM (e.g., 14 times and 23 times higher incidence and mortality risks, respectively, in 40-year-old women with the administration of 370 MBq [^{18}F]-FDG) [38]. Other issues related to dbPET screening include its high cost, the need for fasting and waiting times, and radiation exposure of technologists. Further studies are needed to determine whether screening with dbPET alone is justified in breast cancer screening.

Nevertheless, our results may encourage using dbPET to detect breast cancers, at least in the setting of a [^{18}F]-FDG WB PET opportunistic cancer screening program. DbPET tended to detect more breast cancers than WB PET/CT alone. DbPET does not require additional radiation exposure, whereas DM and DBT need. Since both DM and DBT are obtained in our program, there seems room to simplify the examinations to reduce radiation exposure. The sensitivity of dbPET for invasive cancer was acceptably high, and the sole dbPET-negative invasive cancer was identifiable on dbPET in retrospect (Fig. 3). This suggests that further improvement of the sensitivity of dbPET is possible by adjusting the interpretational methods. Breast US had the most favorable diagnostic performance; however, it was highly operator-dependent. The advantages of dbPET over breast US are that the positioning and image acquisition of dbPET is not technically difficult and that dbPET is easy to read with MIP. Based on the technical and operational advantages of dbPET and its high sensitivity for invasive cancers, dbPET may be a potential alternative to conventional breast screening modalities in WB PET/CT cancer screening programs; however, a discussion on the issues relating to DCIS detection is required. Another advantage of dbPET compared to mammography is that dbPET does not cause pain. Several studies have revealed that 52–75% of women reported experiencing discomfort or pain associated with mammography screening [39–41], and around 30% of women experience moderate or severe pain [40, 42].

Our study has several limitations. First, the number of participants was too small to assess the value of cancer

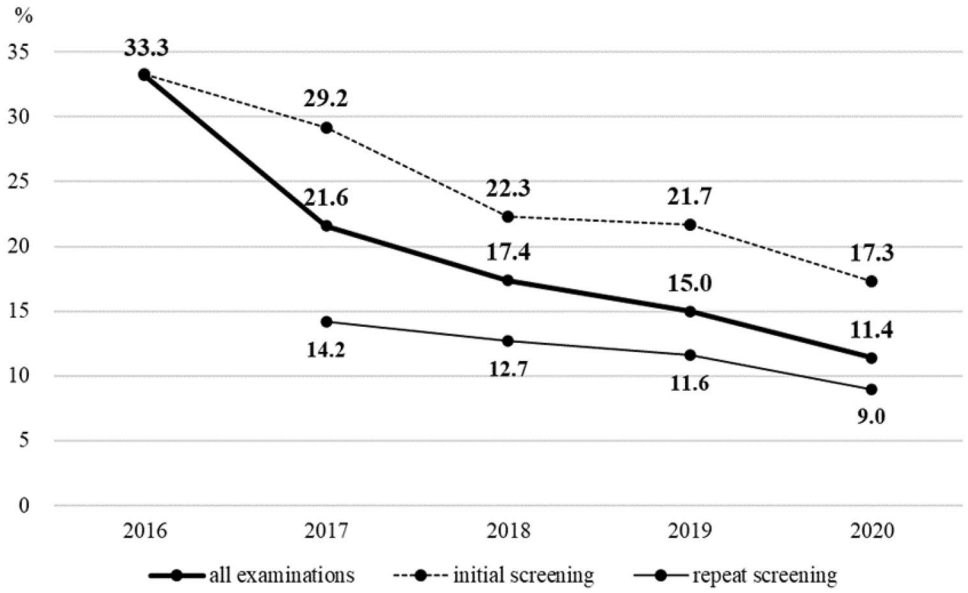

Fig. 5 Yearly changes in the recall rate of dbPET in subgroup analysis according to the initial and repeat screenings. All cancers (thick solid line), the group of initial screening (broken line), and the group of repeat screening (thin solid line)

screening modalities. There were only 18 breast cancer cases, including 10 invasive cancers and eight DCIS. This small number limited the robustness of the sensitivities. Second, the analysis was performed on a per-examination basis and not on a per-lesion basis, because it was not always possible to provide detailed information for each lesion and obtain concordance between modalities and between imaging and pathology findings, especially in women who underwent further examinations and treatment in other hospitals. Third, because dbPET-guided biopsies are currently unavailable, biopsies are usually performed under US-guidance and occasionally under stereo-guidance. Thus, dbPET-positive lesions undetectable on breast US or DM-DBT might not have been biopsied, potentially underestimating the PPV of dbPET. Fourth, there was a potential selection bias among the subjects. The examinees of our screening program usually have higher incomes and greater concerns about their health than the general population, and thus may have had a lower pre-test probability. However, the cancer detection rate of this study was not below, but rather higher than the acceptable value for population-based screening mammography provided by the Japanese Ministry of Health, Labor and Welfare, indicating the good performance of our program in cancer detection. Fifth, this was a retrospective study using real-world data, and it was possible to refer to other modalities at the time of image interpretation. Therefore, the independence of the assessment categories of each modality might not have been maintained. In order to determine the actual value of dbPET among screening modalities, it is necessary to conduct further large-scale studies that blindly and independently evaluate each modality.

Conclusions

DbPET screening detected all invasive cancers except one with a very low Ki-67. The sensitivity of dbPET for invasive cancers was high and not significantly different from those of DM-DBT and breast US. DbPET has low sensitivity for DCIS, but its clinical significance may need further discussion, because the detection of DCIS is controversial. The specificity of dbPET was improved and became higher than that of DM-DBT. Our study demonstrated that dbPET may be a feasible screening modality.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Authors Yoshiaki Matsumoto, Masakazu Toi and Yuji Nakamoto had received research support from Shimadzu Corporation. Kanae K. Miyake is the endowed chair of Industry-Academia Collaboration Project between Kyoto University and Canon Medical Systems Corporation.

Ethics approval This study was conducted following the guiding principles of the Declaration of Helsinki. In addition, approval was granted by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. (Approval number, R1512).

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