men and 56 women) within 1 year after screening. All the malignant tumors were detected during thorough examinations, including FDG-PET. Cancer was not detected during any of the 1-year follow-ups. The number of PET-positive cases without information from whole-body CT scanning totaled 246 from among the 2911 participants. The number of PET-positive cases with information from whole-body CT scanning (PET- and CT-positive cases) totaled 226. True-positive PET findings were obtained for 28 malignant tumors in 12 men and 16 women. The details of the PET-positive cancers are shown in Table 2. The cancers comprised seven colorectal cancers, four lung cancers, four thyroid cancers, three breast cancers, two gastric cancers, two prostate cancers, two small intestinal sarcomas (gastrointestinal stromal tumors), one malignant lymphoma, one head and neck malignancy (nasopharyngeal carcinoid tumor), one thymoma, and one hepatocellular carcinoma. Most of the PET-positive tumors were early stage lesions (stages 0 or I according to the TNM classification). Three of the PET-positive tumors were stage II (one breast cancer and two colorectal cancers), and one was stage III (one gastric cancer).

A total of 129 of the 157 detected cancers were PET-negative. The details of the PET-negative cancers are shown in Table 2. These cancers comprised 28 colorectal cancers, 23 lung cancers, 22 gastric cancers, 20 prostate cancers, 9 thyroid cancers, 8 breast cancers, 7 urologic cancers, 6 esophageal cancers, 4 malignant lymphomas, 1 pancreas cancer, and 1 gallbladder cancer. Four of the participants had double cancers: three participants had colorectal cancer and prostate cancer, and one participant had gastric cancer and prostate cancer. All the PET-negative cancers were early stage lesions (stages 0 or I) according to the TNM classification.

The overall positive rate and the detection rate of FDG-PET for whole-body screening without whole-body CT were calculated to be 7.76% and 0.96%, respectively (Table 3). The positive rate of "PET and CT" diagnosis was 8.58%. The overall sensitivity, specificity, positive predictive value, and accuracy of PET without whole-body CT were estimated as 17.83%, 95.15%, 11.20%, and 87.94%, respectively. Specificity, the positive predictive value, and the accuracy of "PET and CT" diagnosis were 95.20%, 12.39%, and 88.78%, respectively.

Tables 4, 5, 6, and 7 show the details of several kinds of detected cancers such as lung cancer, breast cancer, and colorectal cancer, which are among the main targets of cancer screening. The average tumor diameters of the detected lung cancers, the PET-positive lung cancers, and the PET-negative lung cancers were 15.2 mm (5–32 mm), 16.8 mm (10–24 mm), and 14.9 mm (5–32 mm), respectively. The difference between the mean size of the PET-positive and PET-negative lung cancers was not significant ($P > 0.05$, Table 4). All the PET-positive lung cancers were solid-type nodules and were pathologically identified as adenocarcinomas. The PET-negative lung

Table 2 Detected cancers

	PET-positive cases	PET-negative cases
Lung cancer	4	23
Breast cancer	3	8
Colorectal cancer	7	28
Thyroid cancer	4	9
Malignant lymphoma	1	4
Esophageal cancer		6
Gastric cancer	2	22
Hepatocellular carcinoma	1	
Pancreas caner		1
Gallbladder cancer		1
Prostate cancer	2	20
Renal/bladder cancer		7
Others	4	
Total	28	129

Others in PET-positive cases contain two gastrointestinal stromal tumors, one thymoma, and one nasopharyngeal carcinoid tumor

Table 3 Result of screening value

	PET (%)	PET and CT* (%)
Positive rate	8.58	7.76
Detection rate	0.96	0.96
Sensitivity	17.83	17.83
Specificity	95.15	95.20
Positive predictive value	11.20	12.39
Accuracy	87.94	88.78

*Whole-body CT

Table 4 Size of PET-positive lung nodules

	Cancer	Benign	*P*
Number	4	23	
Average size	16.8 mm	14.9 mm	0.05

Table 5 Detected lung cancers

	Total	Solid nodule	Part-solid nodule	Non-solid nodule
PET-positive case	4	4	0	0
PET-negative case	23	8	12	3

Table 6 Detected breast cancers

	Total	DCIS	IDC
PET-positive case	3	0	3
PET-negative case	8	7	1

DCIS ductal carcinoma in situ, *IDC* invasive ductal carcinoma

Table 7 Detected colorectal cancers

	Depth	*m*	sm1	sm2	mp	ss	se
	Total	18	3	3	0	2	0
PET-positive case	7	4	0	1	0	2	0
PET-negative case	28	23	3	2	0	0	0

m intramucosal tumor, *sm1* slight to moderate submucosal invasion, *sm2* massive submucosal invasion, *mp* invasion to proper muscle layer, *ss* subserosal invasion, *se* serosal invasion

Table 8 Benign focal colorectal accumulations

Physiological uptake	84
Benign adenoma	11
Hyperplastic polyp	2
Hemorrhoid	4
Inflammation (ulcerative colitis)	2
Reactive lymphoid hyperplasia	1
Total	104

Table 9 Focal colorectal accumulations

	Cancer	Benign	*P*
Number	7	104	
Average of SUV_{max}	8.31	5.66	>0.05

SUV_{max} maximum standardized uptake value

cancers comprised 8 solid nodules, 12 part-solid nodules, and 3 non-solid nodules. Pathologically, the PET-negative cancers comprised 18 adenocarcinomas and 5 bronchioloalveolar carcinomas. All the lung cancers were stage I, according to the TNM classification.

Of the breast cancers, all the PET-positive cancers were duct-invasive carcinomas (DIC): two were stage I lesions, and one was stage II. The PET-negative breast cancers comprised four DIC and four ductal carcinomas in situ (DCIS). All the PET-negative breast cancers were at an early stage.

All the detected colorectal cancers were pathologically identified as adenocarcinomas. The PET-positive colorectal cancers comprised four intramucosal tumors, one submucosa-invaded tumor, and two advanced cancers. The PET-negative colorectal cancers comprised 26 intramucosal tumors and 5 submucosa-invaded tumors, respectively.

A total of 104 of the 111 PET-positive cases for the colorectal region were false-positive (Tables 8, 9). The

Table 10 Focal pulmonary accumulations

	Cancer	Benign	*P*
Cancer by CT* diagnosis	4	2	
Benign by CT* diagnosis	0	20	
Average of SUV_{max}	3.76	3.71	>0.05

*Whole-body CT

PET false-positive cases comprised 84 physiological accumulations, 11 adenomas, 2 hyperplastic polyps, 4 hemorrhoids, 2 inflammations (ulcerative colitis), and 1 reactive lymphoid hyperplasia. The average maximal SUVs were 8.31 (3.88–16.25) for the colorectal cancers and 5.66 (2.94–16.77) for the benign accumulations. The difference between the SUVs of the colorectal cancers and the benign uptakes was not significant ($P > 0.05$).

Focal pulmonary FDG uptake was observed in 26 cases, including 4 cancers and 22 inflammations (Table 10). The average maximal SUVs were 3.76 (2.07–4.96) for the lung cancers and 3.71 (1.20–4.39) for the inflammations. The difference between the SUVs of the lung cancers and the lung inflammations was not significant ($P > 0.05$). Of the 26 cases of focal pulmonary uptake, 2 cases of inflammation were misdiagnosed by "PET and CT" diagnosis.

Discussion

FDG-PET is a promising screening modality targeting the whole body. In our study, cancers of many organs were detected, mostly at an early stage, by FDG-PET. A few participants had either a head and neck malignant tumor or a malignant lymphoma that was only detected using FDG-PET. However, the detection of some cancers using FDG-PET is known to be difficult: the detection of urologic cancers is hampered by the renal excretion of FDG [12], and cancers with a low cell density (bronchioloalveolar carcinoma [13], gastric cancer [14], and schirrhous-type breast cancer [8]), small cancers (smaller than 10 mm in diameter) [15], and hypometabolic cancers (renal cell carcinoma [16], and hepatocellular carcinoma [17]) are also difficult to detect. In our study, such cancers were hardly detected as early gastric cancers, small lung cancers containing ground glass opacity on CT scans, DCIS of the mammary gland, intramucosal carcinomas of the colon, prostate cancers. FDG-PET sometimes showed a physiological uptake in the gastrointestinal tract that led to a false-positive PET result [11]. Most of the false-positive PET findings in our study were caused by physiological gastrointestinal uptake. FDG often accumulates in areas of inflammation [10] or in benign

tumors [18]. In our study, a differential diagnosis between tumor and inflammation in the lung or between malignant tumor and benign tumor in the thyroid gland was difficult. Reference to CT images was useful for differentiating lung tumors and inflammation in our study. It has to be kept in mind that FDG-PET has these limitations and some types of cancer are likely to be missed in cancer screenings using only FDG-PET.

The detection rates for PET cancer screening reported by several institutions, including ours, were about 1.0% (from 0.96% to 2.34%) [19]. These detection rates are much higher than the sum of the detection rates for other screening modalities whose efficacies have been already assessed; these other screening modalities include chest X-ray and sputum cytology, MMG and physical examination, upper gastrointestinal (GI) tract X-ray, fecal occult blood test (FOBT), and cytology of the uterine cervix [20, 21]. On the basis of these data, FDG-PET may be considered to be useful in cancer screening. However, a high detection rate is insufficient for an assessment of validity because the detection rate depends on the prevalence of the population [20].

Sensitivity is the most important value in assessing the accuracy of screening, which is relevant to the quality control of screening [20]. However, the sensitivity of PET cancer screening has not been sufficiently measured because of the difficulty in following up PET-negative cancers, which require simultaneous and thorough examinations for each organ or an adequate follow-up system. Each examination conducted as part of the RCCPS program is thorough, and the RCCPS program also has an adequate follow-up system. Therefore, the sensitivity of PET cancer screening targeting the whole body could be measured in the RCCPS program and was estimated to be 17.83%. In an earlier report on PET cancer screening that was based on a large-scale questionnaire survey sent to 99 PET facilities in Japan, the reported sensitivity (79.0%) was higher than that of our data [22]. There are two possible explanations for this difference. First, a large proportion of the population in our study had undergone a prior screening test within 1 year of the present study, according to a report investigating profile of the participants in the RCCPS screening program [1]. Therefore, a considerable proportion of the patients in our study did not have advanced cancers that were easily detected using FDG-PET. Second, the screening sensitivity is a relative value that depends on combined examinations or follow-up systems that affect the detection of PET-negative cancers. These two reasons probably led to the high overall detection rate (5.26%) of the thorough examinations and the low sensitivity by FDG-PET in our study.

The PET sensitivity in our study was considerably lower than the reported sensitivities of examinations that have already been assessed their effectiveness in reducing mortality [20]. However, concluding that FDG-PET is not effective for cancer screening would be hasty because the validity of a cancer-screening modality is not confirmed by a high sensitivity, but rather by a reduction in mortality [20]. Studies to determine the efficacy of FDG-PET for cancer screening of the whole body are underway.

Of note, some cancers with a minimal effect on mortality were included among the PET-negative cancers identified in our study, such as small lung cancer containing ground glass opacity on CT scans, DCIS of the mammary gland, and intramucosal carcinoma of the colon. FDG-PET is presumed to be capable of detecting cancers that are advanced enough to be treated [21]. However, the progression of these PET-negative cancers is not well understood, and further investigation is needed.

To obtain evidence supporting PET cancer screening, the validity of this modality must be assessed. However, assessing reductions in mortality over a short time period is difficult. The United States Preventive Services Task Force (USPSTF) recommends an "analytic framework" that demonstrates a chain of logic in which the evidence supports a link between the preventive service and improved health outcomes [23]. Using such an analytic framework, validity can be assessed not only by using direct evidence, such as a reduction in mortality, but also by using indirect evidence connected to the validity of the modality. Such a framework may enable a shortcut for assessing the validity of PET cancer screening by measuring the relative sensitivity when compared with other modalities such as chest X-ray or FOBT [24] for which sufficient evidence is already obtained.

A few problems regarding PET cancer screening remain; specifically, a risk analysis and economic assessment were not sufficiently investigated in our study. These problems are as significant to the evaluation of a screening modality as the assessment of accuracy [20]. A major risk of PET cancer screening is radiation exposure, which is estimated as 0.7 mSv per 37 MBq of FDG as the effective radiation dose. Although a risk–benefit analysis of PET cancer screening was not sufficiently investigated in this study, efforts to reduce radiation exposure, such as reducing the FDG dose using three-dimensional scans, are needed. From the aspect of the economic assessment of PET cancer screening, no obvious evidence of cost-effectiveness is available, even though PET examinations involve a substantial cost when compared with other screening modalities [19, 21]. At present, PET cancer screening is

categorized as an opportunistic screening modality because the efficacy of PET cancer screening has not been confirmed. Therefore, each subject must pay for the cost of the PET examination by himself or herself, without the support of public funding. If evidence of PET cancer-screening efficacy is obtained in the future, debates surrounding issues of cost-effectiveness will arise.

In conclusion, FDG-PET can detect a variety of cancers at an early stage as part of a whole-body screening modality. The detection rate of PET cancer screening was higher than that of the other screening modalities which had already demonstrated evidence of efficacy. However, the sensitivity of PET cancer screening was lower than that of other thorough examinations performed at our institute. FDG-PET has some limitations, and cancer screening using only FDG-PET is likely to miss some cancers.

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