RESEARCH COMMUNICATION

Cancer Screening with Whole-body PET/CT for Healthy Asymptomatic People in Japan: Re-evaluation of its Test Validity and Radiation Exposure

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Abstract

The use of Positron Emission Tomography (PET) or PET/CT for voluntary cancer screening of asymptomatic individuals is becoming common in Japan, though the utility of such screening is still controversial. This study estimated the general test validity and effective radiation dose for PET/CT cancer screening of healthy Japanese people by evaluating four standard indices (sensitivity, specificity, positive/negative predictive values), and predictive values with including prevalence for published literature and simulation-based Japanese data. CT and FDG-related dosage data were gathered from the literature and then extrapolated to the scan parameters at a model PET center. We estimated that the positive predictive value was only 3.3% in the use of PET/CT for voluntary cancer screening of asymptomatic Japanese individuals aged 50-59 years old, whose average cancer prevalence was 0.5%. The total effective radiation dose of a single whole-body PET/CT scan was estimated to be 6.34 to 9.48 mSv for the average Japanese individual, at 60kg body weight. With PET/CT cancer screening in Japan, many healthy volunteers screened as false positive are exposed to at least 6.34 mSv without getting any real benefit. More evaluation concerning the justification of applying PET/CT for healthy people is necessary.

Key Words: PET/CT imaging - mass screening - cancer screening - sensitivity - predictive value - radiation exposure

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Introduction

The use of 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) and a combination of PET and whole-body computed tomography (PET/CT) in clinical practice has expanded over the last few decades. This is because PET/CT provides more accurate anatomical and functional images in a shorter scan time than CT alone (Beyer et al., 2000). In many developed countries, PET or PET/CT is commonly used in the oncology field for the purpose of making a differential diagnosis, staging of tumors, and monitoring the effects of cancer therapy. In Japan, however, there is another unique application of PET or PET/CT, which is its use for mass cancer screening of asymptomatic healthy people. Unselected cancer screening occupies 20% of the whole application of PET or PET/CT, which is the second most common application (Nakamoto, 2003). Radiological installations are now equipped not only in hospitals but also in diagnostic imaging centers next to some hotel resort facilities as certain package tours. The business tie-up between PET/CT imaging centers and travel agents is just like "a social phenomenon". The homepage of the Japan Clinical PET Promotion Council (http://pet.jrias.or.jp/) provides a list of over one hundred cyclotron-equipped PET centers in Japan. More and more healthy Japanese individuals, whether they are at high risk of cancer or not, visit these centers where they can easily undergo PET/CT to try to detect smaller cancer before being clinically diagnosed.

As with whole-body CT, there is some debate about the application of PET/CT for mass cancer screening of healthy asymptomatic individuals (Weckesser et al., 2005, Ide et al., 2005, Rigo et al., 1996). Some researchers emphasize its higher detection rate of small cancers. Others make the argument that there is so far no evidence that cancer screening by PET/CT contributes to public health when applied to healthy asymptomatic individuals. As is well known, a test for cancer screening differs from a diagnostic test. The former is usually applied for healthy asymptomatic individuals; the latter for those who are suspected or already have cancers. Therefore, test validity and risk-benefit should be assessed differently between the two test settings above. Usually, the validity of a diagnostic test is evaluated by calculating four indices, sensitivity, specificity, and positive/negative predictive

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Table 1. Age Distributions of People Undergoing PET/CT at a Model Center in 2005

	Cancer screening		Oncology application	
Age (yr)	Man	Woman	Man	Woman
20-29	1	0	1	5
30-39	30	24	4	5
40-49	86	69	18	20
50-59	206	134	54	61
60-69	132	109	90	59
70-79	57	47	95	81
80-89	6	10	26	19
90-	1	1	1	1
Total	519	394	289	251

values (PPV or NPV). However, for mass cancer screening more appropriate parameters are necessary, by taking into account prevalence of cancer (Stanly, 2001, Kopans et al., 2001, Obuchowski et al., 2001, Harper et al., 2000, NCCP, 2002). Unnecessary radiation exposure and the possibility of cancer induction through accumulated radiation doses are also important concerns, especially in Japan where people have easy access to cancer screenings by radiological equipment. These issues have been well discussed in whole-body CT cancer screening, but not in PET or PET/CT cancer screening.

To evaluate the justification for PET/CT cancer screenings for healthy people, we re-evaluate test validity in published literature and a model PET center, and estimate radiation dose equivalents when a typical, healthy 60kg Japanese person undergoes PET/CT cancer screening.

Materials and Methods

Literature search

We searched for appropriate literature through PubMed, using a combination of the following keywords: FDG-PET, health screening, mass screening, sensitivity, and specificity. Cancer incidence rates in Japan were obtained from a report of the Research Group for Population-based Cancer Registration (Ajiki et al., 2004). The report presented the sex- and age-specific crude incidence rates of all sites of cancers per 100,000 people in Japan in 1999. From their table 3, we used data of cancer rates nearly 0.50% in men and 0.38% in women at the 50~59 age group.

A model PET/CT center

To present a general scenario of the cancer screening practice, we used data provided from a PET/CT Imaging Center of a private hospital in Nagasaki prefecture, Japan. The center is equipped with a cyclotron and two dedicated PET/CT scanning machines, named Discovery ST (GE Yokogawa Medical Systems, Tokyo). The machines integrate a PET scanner using 4 MBq/kg body weight of FDG, and a multi-slice low-dose CT (40mA) capable of 2D and 3D imaging. The whole scanning time takes only 20 minutes in the combined PET/CT mode. About 60% of the workload is for staging of cancer or diagnosis of recurrence, and the remaining 40% is for cancer screening as a part of "the human dry dock (the comprehensive health examination)". Table 1 shows age distributions of people who underwent PET/CT examination in the year 2005, by sex and by application. A total of 1,453 PET/CT scans were performed, of which 913 underwent cancer screening, and the rest were for oncological applications. Age distribution for cancer screening was younger compared to age distribution for oncological application. The highest frequency was the 50-59 years old population for cancer screening (340 people), and the 70-79 years old for oncology application (176 people). Among subjects who underwent cancer screening, 8% had suspicious results indicating possible cancer that required further examination. Unfortunately, we were not able to obtain information of pathological data to confirm how many people had real cancer among the suspicious subjects.

Evaluation for test validity

We evaluated test validity for the accepted literature, or our simulation-based data, using 4 standard indices of sensitivity, specificity, PPV and NPV. Formulas for the standard indices based on a 2 by 2 contingency table were described elsewhere. When articles did not mention indices, we calculated indices using row data. For a simulation-based cancer screening data, a setting when 3,400 healthy subjects aged 50-59 undergo cancer screening by PET/CT with an 8% of detection rate for cancer, we calculated PPVp or NPVp that takes cancer prevalence into consideration using the following formulas. These two formulas are not widely understood, but some articles have already mentioned them (Brenner et al., 1997, Grimes et al., 2002, Altman et al., 1994).

$$PPVp = \frac{\text{Sensitivity} \times \text{Prevalence}}{(\text{Specificity} \times (\text{Prevalence})) + (1-\text{Specificity})(1-\text{Prevalence})}$$

$$NPVp = \frac{\text{Specificity} \times (1-\text{Prevalence})}{(\text{Specificity} \times (1-\text{Prevalence})) + (1-\text{Sensitivity})(\text{Prevalence})}$$

Estimation of exposed Radiation Dose

FDG-dosage data was gathered from literature in which radiation doses for PET and PET/CT examinations were actually calculated. We extrapolated their calculations to the scan parameters at the model PET/CT Center.

Results

Validity of PET or PET/CT cancer screening in literatures

Accepted literature is listed in Table 2. Literature concerning PET cancer screening for healthy asymptomatic people was available from only two countries, Japan and Taiwan (Yasuda et al., 1997, Yasuda et al., 2000, Shen et al., 2003, Chen et al., 2004, Kao et al., 2001). Test validity was not well evaluated in any of the available data. The detected cancer rate ranged from 1.4% to 3.0%. As none of the Japanese reports described numbers of false positives and false negatives, we did not re-calculate test indices. We re-calculated a report from Taiwan (Shen et al., 2003) that reported PET cancer screening in asymptomatic individuals, resulting in a cancer detection rate of 1.4%. For this report the sensitivity, specificity, and simple PPV/NPV were 83.3%, 98.1%, 38.5%, and 99.8%, respectively. Another Data

Table 2. Validity of PET or PET/CT Cancer Screening in the Literature

Reference	Country	Purpose	Target tumour	Age	No. Subjects	No. Cancer (%)	No. TP	No. FN	No. FP	No. TN	Sen.	Spe.	PPV	NPV
Healthy asymptomatic participants														
Yasuda et al. (1997)	Japan	Screening	All	-	1872	26 (1.4%)	15	11	-	-	57.7	-	-	-
Yasuda et al. (2000)	Japan	Screening	All	52.2 (±10.4)	3165	67 (2.1%)	36	31	-	-	53.7	-	-	-
Ide et al. (2005)	Japan	Screening	All	53.6	39785	526 (1.4%)	385	168	-	-	73.2	-	-	-
Kao et al. (2001)	Taiwan	Screening	All	-	299	9 (3.0%)	7	2	3	287	77.8	99.0	70.0	99.3
Shen et al. (2003)	Taiwan	Screening	All	-	1283	18 (1.4%)	15	3	24	1241	83.3	98.1	38.5	99.8
Chen et al. (2004)	Taiwan	Screening	All	52.1	3631	47 (1.3%)	38	9	-	-	80.9	-	-	-
Patients with known or suspected cancer														
Avril et al. (2000)	Germany	Diagnosis	Breast	50.6 (±10.3)	185	133 (71.9%)	85	47	3	50	64.4	94.3	96.6	51.5
Abdel et al. (1998)	USA	Staging	Colon	67.8 (±9.8)	48	37 (84.1%)	37	0	4	3	100	43.0	90.0	100
Dewan et al. (1995)	USA	Diagnosis	Lung	65.2 (41-88)	33	26 (74.0%)	26	0	2	7	100	78.0	100	94.0
Mikosch et al.(2003)	Austria	Restaging	NHL	-	121	61 (50.4%)	48	5	13	55	91	81.0	79.0	92.0
Schirrmeister et al. (2001)	Germany	Staging	Breast	56.8 (28-86)	117	89 (76.0%)	83	6	7	21	94	94	92	96.0

Abbreviations: TP, true positive; FN, false negative, FP, false positive; TN, true negative; Sen, sensitivity (%); Spe, specificity (%); PPV, positive predictive value (%); NPV, negative predictive value (%)

from Taiwan (Kao et al., 2001) reported a detected cancer rate of 3.0%, sensitivity of 77.7%, specificity of 99.0%, simple PPV of 70.0%, and simple NPV of 99.3%. For comparison, we searched literature in which PET or PET/CT was applied for cancer patients or high-risk individuals (Dewan et al., 1995, Adbel-Nabi et al., 1998, Avril et al., 2000, Schirrmeister et al., 2001, Mikosch et al., 2003) and diagnostic validity was evaluated. The detected cancer rate was very high, ranging from 50.4% to 76%. Sensitivity and simple PPV were also higher for cancer screening.

Validity of PET cancer screening in a simulation-based data

Because the most frequent age population for cancer screening was 50-59 years old in a model PET center, we evaluated a simulation-based data of cancer screening for this age group while taking into consideration actual cancer prevalence in Japan. Table 3 explains how PPVp or NPVp would vary by sensitivity and cancer prevalence in a simulation-based cancer screening. When we used the parameters of 0.5% for cancer prevalence (this value was from the Japan Research Group) and an assumption of 53.7% for the sensitivity of PET/CT test (this value was from Yasuda et al., 2000), PPVp would be calculated as 3.3%. When cancer prevalence was 2.0% with the same sensitivity, the PPVp would increase to 11.4%. When cancer prevalence was 0.5% with an assumption of 90% for the sensitivity, PPVp would be calculated at 5.6%. It would be 19.3% at the cancer prevalence of 2.0% with the same sensitivity. In these settings, levels of NPVp remained high.

Estimation of Radiation exposure in PET or PET/CT cancer screening

The homepage of the Japan Clinical PET Promotion Council (http://pet.jrias.or.jp/) states that radiation dose exposure by a PET examination is 2.2 mSv that level is lower than the average annual natural radiation dose. However, we could not find any articles that supported this dose level. Table 4 summarizes the effective radiation

Table 3. Validity of PET/CT Cancer Screening with Simulation-based Data.

Sensitivity=53.7%, Test positive rate=8%

		Cancer +	Cancer -	Total
PET/CT	+	9.1	262.9	272
Test	-	7.9	3120.1	3128
Total		17	3383	3400

Cancer prevalence=0.5%
Specificity=3120.1/3383= 92.2%
PPVp= 3.3% NPVp=99.7%

		Cancer +	Cancer -	Total
PET/CT	+	36.5	235.5	272
Test	-	31.5	3096.5	3128
Total		68	3383	3400

Cancer prevalence=2.0%
Specificity=3096.5/3383=91.5%
PPVp=11.4% NPVp=99.0%

Sensitivity=90%, Test positive rate=8%

		Cancer +	Cancer -	Total
+		15.3	256.7	272
-		1.7	3126.3	3128
Total		17	3383	3400

Cancer prevalence=0.5%
Specificity=3126.3/3383=92.4%
PPVp=5.6% NPVp=99.9%

		Cancer +	Cancer -	Total
+		61.2	210.8	272
-		6.8	3121.2	3128
Total		68	3383	3400

Cancer prevalence=2.0%
Specificity=3121.2/3383=92.3
PPVp=19.3% NPVp=97.8%

Abbreviations: PPVp, positive predictive value that takes prevalence into consideration; NPVp, Negative predictive value that takes prevalence into consideration.

Table 4. The Effective Radiation Dose of PET and CT in the Published Literature

Setting*	Dose (mSv)	Author
18F-FDG isotope related radiation		
MIRD phantom for adult (per MBq)	0.019	ICRP80
MIRD 70 kg (per MBq)	0.029	Deloar
Japanese 60 kg (per MBq)	0.021	Deloar
0.024 mSv / MBq x 260 MBq	6.2	Yasuda
0.029 mSv / MBq x 370 MBq	10.7	Wu
0.019 mSv / MBq x 300 MBq	5.7	Brix
0.019 mSv / MBq x 370 MBq	7.0	Brix
CT related radiation		
High-quality CT	18.97	Wu
High-speed CT	8.81	Wu
Ultra-low-dose CT	0.72	Wu
Low-dose CT	1.3-4.4	Brix
Diagnostic CT with contrast agent	14.1-18.6	Brix

Abbreviations: MIRD, medical internal radiation dose; MBq, mega Becquerel *Radiological Image Setting for whole body

dose of PET and CT in literature. The effective dose equivalent for the FDG-PET scan was estimated to be 0.019-0.029 mSv/MBq by the MIRD (Medical internal radiation dosimetry) method. According to literature from Japanese PET cancer screenings, which reported that the common radiation level of FDG was 260 to 370 MBq (Yasuda et al., 2000), an average whole-body effective dose was calculated to be 6.24 to 8.88 mSv using the parameter of 0.024 mSv/MBq. For the combined equipment of PET and CT, the estimated value of the total effective dose equivalent varies among researchers, quality of CT, and in FDG usage. When we combined FDG related dose with CT related dose, the total effective dose equivalent for a whole body PET/CT would be approximately 23.7-26.4 mSv (Brix et al., 2005) and 8.81-18.97 mSv (Wu et al., 2004). We extrapolated these data to the parameters of a model PET/CT center where a 4 MBq/kg body weight of FDG and a low dose CT were used. The FDG isotope related radiation dose was calculated to be 5.04 mSv, by multiplying 4 MBq/kg and 60 kg Japanese man and 0.021 mSv/MBq. We used 1.3 to 4.4 mSv of dose estimation for a low dose CT (Brix et al., 2005) and consequently the total effective radiation dose is estimated to be 6.34 to 9.48 for an average Japanese of 60 kg body weight of a single PET/CT examination at this center.

Discussion

In this paper, we estimated the more practical PPV of PET/CT cancer screening for asymptomatic Japanese population aged 50-59 years-old whose cancer rate of 0.5% would be only 3.3%, and a total effective radiation dose of a single whole-body PET/CT scan would be 6.34 to 9.48 mSv to the average Japanese individual with 60kg body weight. These results explain that many healthy volunteers might be screened as false positive, might be exposed to at least 6.34 mSv, and suffered from unnecessary further examinations and unnecessary anxiety without getting any real benefit.

We were disappointed that most previous articles reporting test effectiveness of PET cancer screening for health individuals did not calculate PPVp that took cancer prevalence into consideration. Unlike a diagnostic test, a screening test is applied for apparently healthy people; in this situation a more appropriate evaluation of test validity is necessary. Our evaluation for test validity explains that a value of PPVp would be a very low level at 3.3% in population with 0.5% of cancer prevalence. This also explains that 96.7% of people who tested positive were screened as a false positive. Even if PET/CT screenings were performed for population with a cancer rate of 2.0%, a value of PPVp would be still low level at 11.4%. This also explains that 88.6% of people who tested positive were screened as a false positive. Values of NPVp were almost stable even if cancer rate of population increases from 05% to 2.0%. This stability emphasizes the fact that PET/CT screening is more useful for excluding cancer than finding it. Thus, we showed that even very good tests (high sensitivity and high specificity) have poor PPV when they are used for populations with a low-prevalence of cancer.

We know that a combination of PET and CT technologies are very useful for cancer detection. However, justifications for application and technical improvement should be discussed separately. We consider that issues of radiation protection have been of little concern in Japan, partly because PET cancer screening is a leisure activity promoted by travel companies with announcements of low radiation exposure. In this paper, we estimated that a minimum radiation dose equivalent of PET/CT (when using a low dose of the CT) was 6.34 mSv, which value is greater than the advertised dose of 2.2mSv. Specialists in radiation protection have concerns about increasing radiation doses in clinical practice with unproven benefits and the weak ethical justification of repeat examinations for healthy individuals, especially those below 30 years old (Wekesser et al., 2005, Stanrey, 2001).

In addition, PET/CT examinations might be not suitable for cancer screening for the general population because of its high cost, although it might be valuable for those at high-risk of developing cancer. The cost of PET screening per scan is 136,500 yen (about US $ 1,140), but increases to 144,900 yen (about US $ 1,200) for additional screening through laboratory blood tests, and to 166,950 yen (about US $ 1,400) for extra screening by ultrasound and gastroendoscopy. These costs are not covered by health insurance plans in many cases. In contrast, all of onclogical applications of PET are covered by insurances. The monetary cost is increasing considerably for additional diagnostic imaging to further investigate and/or rule out a false positive result.

In conclusion, the estimated positive predictive value of cancer screening based on PET/CT technology in the 50-59 year-old Japanese population is not at an acceptable range for screening purposes, and a large majority of volunteers are exposed to an effective radiation dose of at least 6.34 mSv per examination without getting any real benefit. The use of PET/CT for cancer screening should be regulated in detail by the related guidelines. More evaluation concerning the justification of applying PET/CT for healthy people is necessary.

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