

## Prevalence and Risk of Cancer of Focal Thyroid Incidentaloma Identified by <sup>18</sup>F-Fluorodeoxyglucose Positron Emission Tomography for Cancer Screening in Healthy Subjects

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**Abstract.** The aim of this study was to define the clinical prevalence and rate of malignancy of focal thyroid incidentaloma in a relatively large number of individuals with application of <sup>18</sup>F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) in asymptomatic individuals. The subjects consisted of 4803 physical check-up examinees (2638 men, 2165 women; mean age  $\pm$ SD, 52.8  $\pm$  9 years old) with non-specific medical history. Whole-body FDG PET was performed on all patients. Focal hypermetabolic areas of thyroid, with an intensity equal to or exceeding the level of FDG uptake in the liver, were considered abnormal and interpreted as thyroid incidentaloma. Among the 4803 FDG PET examinations, thyroid incidentaloma was present in 60 examinations, among which, 50 had further examination with ultrasound-guided fine-needle aspiration (FNA), revealing 43 benign lesions and 7 papillary carcinomas. Of 7 examinees diagnosed with cancer, 2 had lymph nodes metastasis. The mean and standard deviation of standard uptake value (SUV) in benign and carcinoma was 2.6  $\pm$  1.01 and 6.7  $\pm$  3.66, respectively. Thyroid incidentaloma identified by FDG-PET occurred with a frequency of 1.2% (60/4803). Of the thyroid incidentalomas that underwent FNA and surgery, 14% (7/50) were found to be malignant. It is possible to differentiate benign from carcinoma of thyroid incidentalomas by the increased rate of glycolysis (SUV) in the carcinoma. The small size and

moderate FDG uptake of thyroid incidentalomas per se cannot guarantee low risk in incidentally found thyroid cancers.

Positron emission tomography (PET) with 2-[<sup>18</sup>F] fluoro-2-deoxy-D-glucose (FDG) is a whole-body imaging technique that exploits the increased rate of glycolysis in tumor cells to detect disease. FDG is a glucose analog that is taken up by cellular glucose transport mechanisms and is phosphorylated by hexokinase. In most malignant cells, FDG-6-phosphate then becomes metabolically "trapped" intracellularly because of the relative lack of glucose-6-phosphatase activity in tumor cells. FDG-PET has a reported sensitivity for detecting thyroid malignancy of 75% to 90% and a specificity of 90% (1, 2). Another clinical value of FDG-PET is in recurrent thyroid cancer with elevated thyroglobulin levels and negative radioiodine whole body scan, and metastatic medullary thyroid cancer (3, 4). FDG-PET is also used for cancer screening in healthy subjects who have no previous history of malignant disease, but the routine use of FDG-PET in this patient population remains controversial (5-7).

Thyroid incidentalomas are defined as newly identified thyroid lesions encountered during imaging study with unknown thyroid lesion. Cohen *et al.* reported, in a retrospective review of FDG-PET studies, that thyroid FDG-PET incidentaloma was found in 2.3 % of a group of patients who underwent FDG-PET for the metastatic evaluation of cancer, and 47% of those incidentalomas, with an available pathological diagnosis, turned out to be malignant (8). Van den Bruel *et al.* and Kang *et al.* also reported a high risk of cancer in a series of thyroid FDG-PET incidentalomas (9, 10). High resolution ultrasound examinations report a prevalence of thyroid nodules ranging from 19-46% in the general population; however, the associated risk of cancer is

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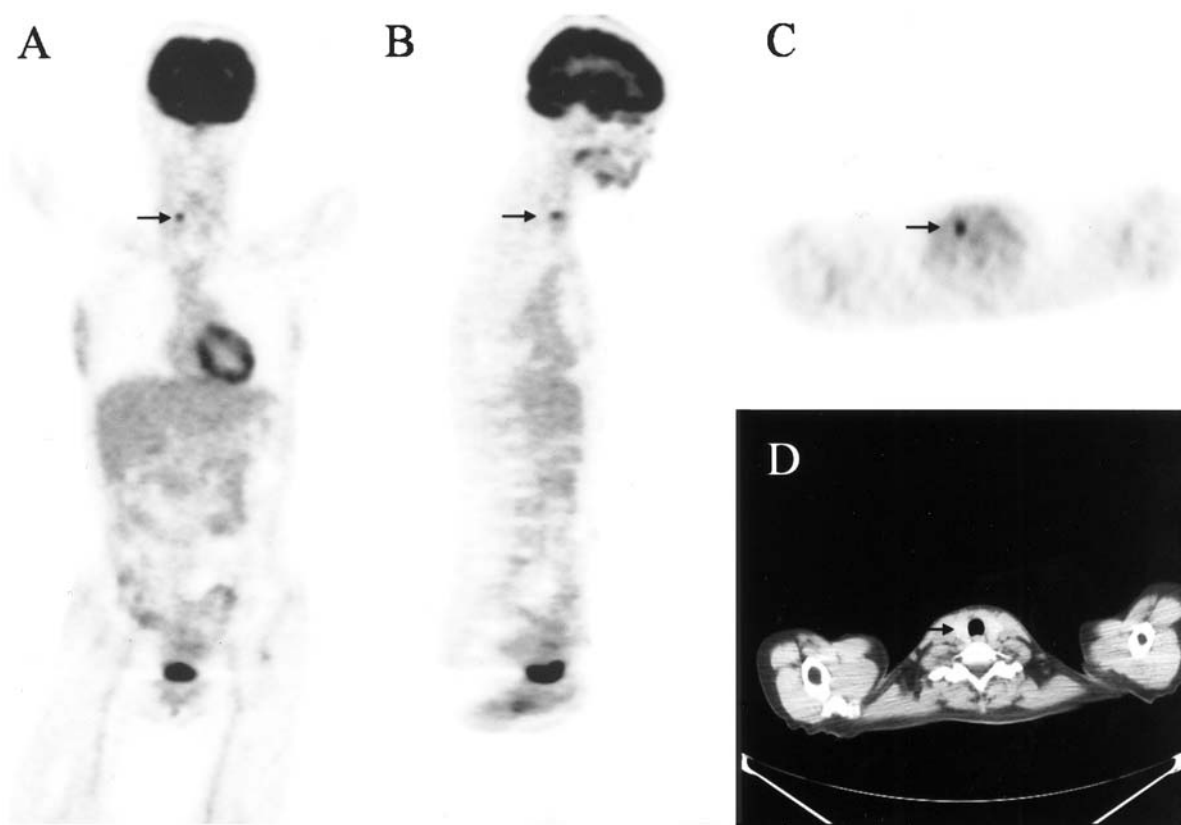


Figure 1. Patient No. 7, FDG PET/CT coronal (A), sagittal (B) and transaxial (C) view of the thyroid. A 35-year-old asymptomatic woman, who underwent PET/CT study performed using a GE discovery LS PET/CT hybrid imaging scanner. Before the study, the subject had fasted for 8 hours. Attenuation-corrected emission images were acquired 60 minutes after the injection of 370 MBq (10 mCi) F-18 FDG. The scan was performed from the upper thigh to the skull base. The arrow points to a moderate focal FDG uptake in the right thyroid gland. Coregistration of the CT (D) scan showed the precise localization of the lesion. Subsequently, fine-needle aspiration cytology of the thyroid revealed suspicion for malignancy. A right total thyroidectomy was then performed and revealed a tumor mass measuring 1.2 x 0.8 x 0.8 cm. Histopathological study showed it to be papillary carcinoma with 2 of the 6 neck lymph node metastases.

very low and ranges from 1.5-10% in these thyroid incidentalomas (11-13). So, in this study, we performed a retrospective review of our institutional experience of thyroid FDG-PET incidentaloma in healthy subjects for voluntary cancer screening. The risk of malignancy of thyroid FDG-PET incidentaloma and its association with the standard uptake value of FDG-PET were evaluated.

### Materials and Methods

**Patient population.** A cross-sectional analysis of asymptomatic adults, who underwent FDG-PET examinations in our health-screening program from February 2001 through July 2003, was performed. The analysis was based on data generated from 5154 examinees accepted for FDG-PET examinations. Among them, 351 examinations were excluded for reasons including the presence of related clinical manifestations (dyspnea, cough, regional lymphadenopathy, vocal cord paralysis), history of cancer, location or size of lesion not defined, or no pathological examination.

Finally, a total of 4803 examinations met the criteria for inclusion in this analysis. Carcinoembryonic antigen (CEA) was determined by the Roche Elecsys 2010 system. A value of 5ng/ml was considered the maximum normal limit. All study subjects gave informed consent according to the guidelines of the local ethics committee and the Helsinki Declaration.

**FDG-PET imaging.** Our PET center was established in February 2001 with a Siemens (ECAT EXACT HR+, model 962, Knoxville, TN, USA) whole body scanner and a GE minitrace cyclotron. The second scanner, a PET-CT system (Discovery LS, GE Medical Systems, Waukesha, WI, USA), was installed in March 2002. Examinees were required to fast for at least 8 hours before the PET scan; furthermore, the examinees had to be well hydrated and avoid strenuous work or exercise for 24 hours before the scan. They were scanned in as many sequential images as necessary to include the entire head, thorax, abdomen and pelvis. Transmission images were obtained for 2 minutes per bed position to correct for photon attenuation using a germanium 68 line source. In the PET/CT scanner, the PET attenuation correction factors were calculated

Table I. Characteristics, intensity of uptake and pathology of patients with thyroid incidentaloma that underwent surgery.

Patient No.	Age (yr/Sex)	Location	Size	Visual uptake intensity	Mean SUV	Pathology	Lymph node metastasis
1	38/M	Left	2.0x1.5x1.0 cm	4+	10	Papillary carcinoma	
2	71/M	Left	2.5x1.2x1.2 cm	3+	3.2	Papillary carcinoma	2/11 (+)
3	55/W	Right	2.1x1.2x1.0 cm	4+	9.8	Papillary carcinoma	
4	27/M	Left	2.0x1.5x1.5 cm	4+	9.7	Papillary carcinoma	
5	73/W	Right	1.0x1.0x1.0 cm	4+	9.1	Papillary carcinoma	
6	48/W	Right	1.2x1.0x1.0 cm	3+	2.2	Papillary carcinoma	
7	35/W	Right	1.2x0.8x0.8 cm	3+	3.1	Papillary carcinoma	2/6 (+)

M, man; W, woman; SUV, standard uptake value.

from the CT images. The transaxial resolution (full width at half maximum) of PET and PET/CT is 4.58 mm and 4.8 mm, respectively. After *i.v.* administration of 370 MBq (10 mCi) of FDG, emission images were acquired for 5 minutes per bed position. The uptake period between FDG injection and the beginning of the emission scan was 60 plus/minus 10 minutes (range 50 to 70). Accurate positioning of the patient between transmission and emission scans was performed using laser marks. Image datasets were obtained using iterative reconstruction (ordered-subset expectation maximization method). Thyroid incidentaloma was defined as thyroid uptake identified on FDG-PET study incidentally, and it was divided into focal and diffuse types according to the thyroid uptake pattern of FDG. Focal uptake was defined as FDG uptake in less than one lobe, while diffuse uptake was defined as FDG uptake in the whole thyroid gland. We did not evaluate the histology of diffuse thyroid FDG-PET incidentaloma, because previous reports indicate that the majority represent chronic thyroiditis or Graves' disease and generally do not need histological diagnosis. The intensity of FDG uptake in the thyroid region was graded subjectively on a five-point scale as follows: 0, no FDG uptake; 1+, less than liver FDG uptake; 2+, FDG uptake as intense as the corresponding physiological liver uptake; 3+, moderately intense FDG uptake, slightly higher than liver uptake; and 4+, intense FDG uptake, markedly higher than liver uptake. The intensity of liver uptake was graded as the middle of the five-point scale, meaning that there were two intensity classes below and two above the intensity of liver uptake. Images acquired were reviewed with consensus by three nuclear medicine specialists. The reviewers had no information about the patients' age, physical examination or laboratory data. The uptake within lesions was quantified by determining the mean activity within a circular region of interest (ROI) of a minimum of 3 x 3 pixels in size placed within the area of maximal activity. The standard uptake value (SUV) was calculated as follows:  $SUV = (\text{mean ROI activity in mCi/mL}) / (\text{injected dose in mCi/patient's weight in kg})$ .

**Ultrasonography-guided fine-needle aspiration (FNA).** FNA was performed with a 21-gauge needle on a 10-ml syringe. Ultrasonography guidance was used to confirm the placement of the needle in the thyroid incidentaloma detected by FDG-PET scan. Two passes were made per nodule. Specimens were smeared on slides, air dried and stained using the Papanicolaou method.

Typically, the procedure was performed by an experienced endocrinologist and the cytological diagnosis was made by an experienced pathologist. All patients with suspicious or malignant cytology were referred for surgery.

**Statistics.** Statistical analysis was carried out for the patient group by computing the mean and standard deviation. Statistical differences were analyzed using one-way analysis of variance (ANOVA) followed by Student's *t*-test. The level of statistical significance was set at  $p < 0.05$ .

## Results

A total of 4803 examinees, including 2638 men and 2165 women, were involved in the cancer screening of asymptomatic individuals. The mean age was  $52.8 \pm 9$  years. Among the 4803 FDG PET examinations, 60 had abnormal focal thyroid uptake of FDG, among which, 10 had no further examination and/or loss of communication. Further examination with ultrasound-guided fine-needle aspiration was undertaken in 50 cases, including 43 benign and 7 cancers. Of 7 examinees diagnosed with cancer, 2 had lymph node metastases (Figure 1) and 1 had elevated CEA. In the 3 men, the cancer was located on the left side and in the 4 women on the right side (Table I). Other pathological findings were made in 4 subjects from 43 examinees with benign lesions, including nodular goiter (Figure 2), nodular hyperplasia and nodular goiter with focal oncocyctic change.

According to the visual uptake intensity of the 50 FDG-PET patients, 17 benign examinees were classified into the 2+ group, whose FDG uptake is as intense as the corresponding physiological liver uptake and no malignancy appeared in this group. Among the 26 examinees in the 3+ group who showed moderately intense FDG uptake, however, 3 examinees had malignancy, whereas among 7 examinees in the 4+ group who showed intense FDG uptake, 4 had malignancy (Table II).

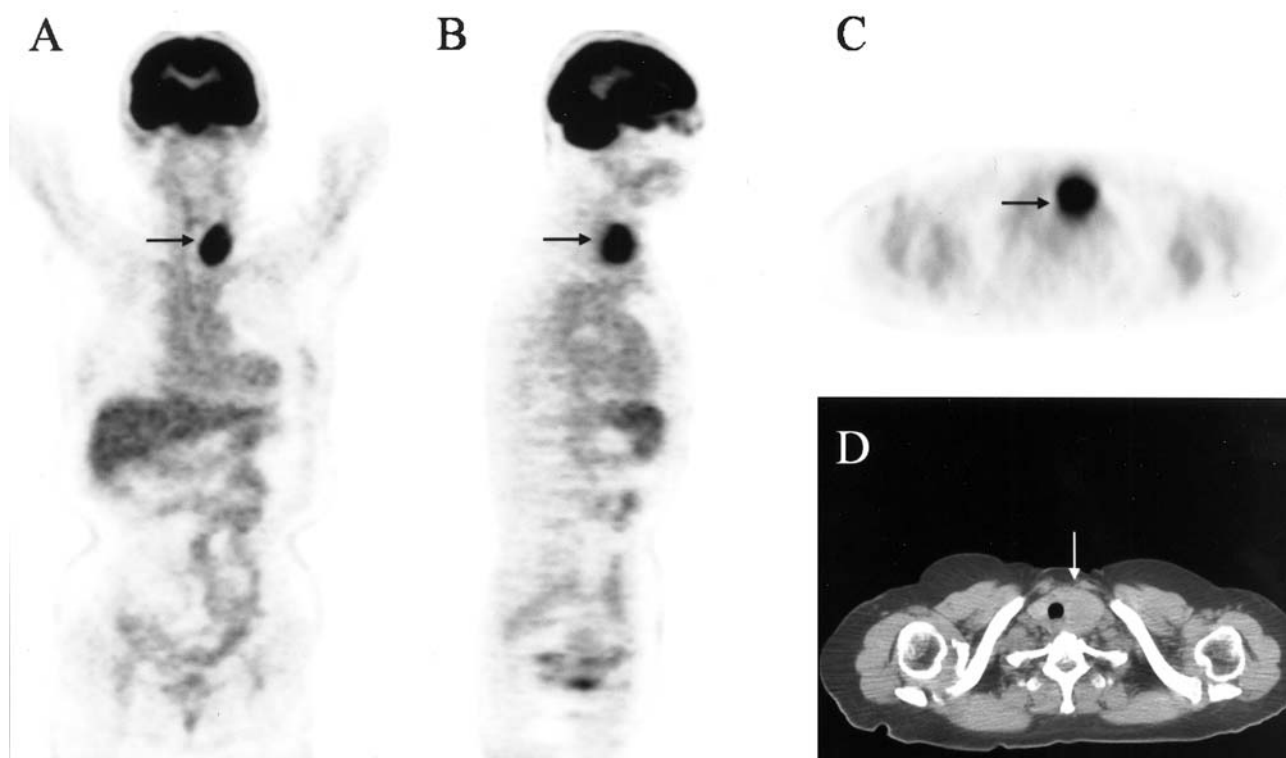


Figure 2. FDG PET/CT coronal (A), sagittal (B) and transaxial (C) view of the thyroid. A 57-year-old asymptomatic woman, who underwent PET-CT study performed using a GE discovery LS PET/CT hybrid imaging scanner. Before the study, the subject had fasted for 8 hours. Attenuation-corrected emission images were acquired 60 minutes after the injection of 370 MBq (10 mCi) F-18 FDG. The scan was performed from the upper thigh to the skull base. The arrow pointed to an intense FDG uptake in the left thyroid gland. Coregistration of the CT (D) scan showed the lesion location. The patient received left total thyroidectomy and histopathological interpretation showed it to be nodular goiter measured as 5.2 x 3.5 x 3 cm in size.

Table II. Visual uptake intensity of physical check-up examinees with thyroid incidentalomas.

	Visual intensity			Total
	2+	3+	4+	
Benign	17	23	3	43
Malignancy	0	3	4	7
Total	17	26	7	50

SUV was measured in focal hypermetabolic lesions in 50 PET patients. The patient number of thyroid incidentalomas of benign and malignancy was 43 and 7, respectively. The mean and standard deviation of standard uptake value (SUV) in benign and malignancy is  $2.6 \pm 1.01$  and  $6.7 \pm 3.66$ , respectively. The Student's *t*-test showed that there was evidence of SUV difference between benign and malignancy ( $p=0.012$ , Figure 3).

## Discussion

Thyroid nodules are commonly encountered in clinical practice. The prevalence of thyroid nodules in the general population is known to be 4-7% by palpation alone (11, 14). Along with the development of modern diagnostic technology, we frequently encounter incidental detection of thyroid nodules during examination of the neck for purposes other than determining thyroid disease. As FDG-PET is widely used in metastasis work-up of cancer patients and cancer screening in healthy examinees without a previous history of cancer, the incidence of thyroid FDG-PET incidentalomas is also increasing. In this study, the prevalence of thyroid FDG-PET incidentaloma was 1.2%.

Although the incidence of thyroid malignancy in the general population is much lower, averaging from 0.004% to 0.1% annually, the risk of finding cancer in a thyroid nodule identified on physical examination is found to be approximately 7.6% and the frequency of cancer in surgically excised nodules ranges from 8% to 17% (13). Most centers use fine-needle aspiration cytology or biopsy,

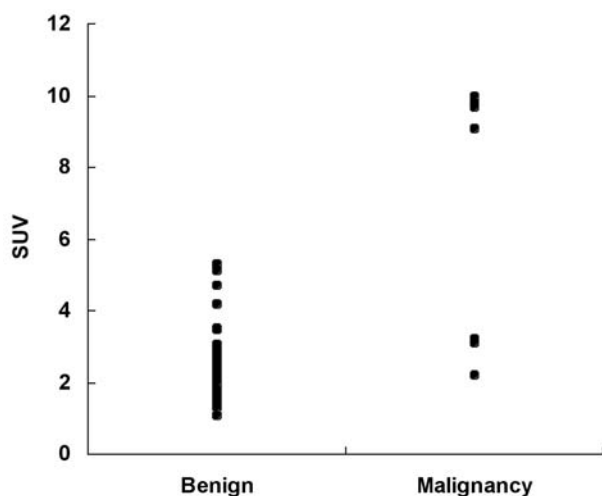


Figure 3. The mean SUV of benign and malignant thyroid incidentalomas.

with or without ultrasonography guidance, as the initial diagnostic method for thyroid nodule. Undoubtedly, fine-needle aspiration (FNA) is the most reliable diagnostic test. However, recently there have been many reports that the diagnostic accuracy of FNA is improved with ultrasonographic guidance, especially for impalpable nodules (15, 16). In this study, all patients with thyroid histology underwent ultrasound-guided FNA. Also, 43 benign lesions were followed-up for more than one year with ultrasound.

Increased FDG uptake may be observed in thyroid carcinoma due to enhanced glycolysis, increased cellular proliferation and augmented expression of glucose transport proteins such as GLUT1 (9, 17). However, FDG also accumulates non-specifically in infectious, inflammatory disease or simply benign nodules secondary to lymphoid tissue activation, increased metabolic activity and rapid iodine turnover. FDG-PET has been shown in several studies to be useful in differentiating benign from malignant thyroid lesions. Both visual and semiquantitative analyses have demonstrated differences in the intensity of uptake between benign and malignant nodules, malignant lesions in general having a significantly higher value. In this study, the SUV for thyroid carcinoma was significantly higher ( $p=0.012$ ) on average than benign lesion, corroborating what other groups have found. Still, there is an overlap of SUV between benign and malignant thyroid incidentalomas. However, FDG-PET may have application in discriminating benign from malignant disease as part of the pre-operative surgical assessment in patients with equivocal FNA results.

According to the visual intensity of FDG uptake in the thyroid incidentalomas, the 2+ group, whose FDG uptake

was as intense as the corresponding physiological liver uptake, comprised 17 examinees and no malignancy appeared in this group; the 3+ group, with moderately intense FDG uptake, comprised 26 examinees, among whom 3 had malignancy (12%); the 4+ group, with intense FDG uptake, was composed of 7 examinees, among whom 4 had malignancy (57%). In the 3+ and 4+ group, correlation of  $^{18}\text{F}$ FDG metabolism, biological aggressiveness and tumor grade varied. Intense FDG uptake in thyroid incidentalomas indicates a higher possibility of malignancy. In this study, all the 7 malignant examinations were papillary carcinoma. Many studies have shown that incidentally detected thyroid papillary carcinomas take an indolent course, but some reports have shown that small thyroid carcinomas can lead to death due to local or distant metastases (18, 19). Two of the 7 papillary carcinomas had lymph nodes metastasis. Although visual intensity 3+ and small size papillary carcinoma were diagnosed in case 7, local lymph nodes metastases also appeared, implying that low risk is not guaranteed by smaller nodule size in thyroid incidentalomas.

Cohen *et al.* analyzed 4525 FDG-PET examinations and found that 102 patients had thyroid incidentalomas (102/4525, 2.3%), 15 patients had thyroid biopsy and 7 thyroid cancer (7/15, 46.7%)(8). The higher prevalence may be due to the small portion of patients with highly suspected thyroid malignancy who underwent thyroid aspiration in the Cohen's study. In addition, Hsieh *et al.* analyzed 477 FDG-PET patients and found 12 patients had thyroid incidentalomas, and only 1 cancer (20). In this study, 7 cancers were found among the 50 FDG-PET thyroid incidentalomas, using further examination with ultrasound-guided FNA and surgery.

In conclusion, the prevalence of thyroid incidentaloma in FDG-PET scan is common. Most of the thyroid incidentalomas are benign lesions, except in the case of moderate and intense uptake of FDG. Semi-quantitative analyses (SUV) have demonstrated differences in the intensity of uptake between benign and malignant nodules. However, there is an overlap of SUV between benign and malignant thyroid incidentalomas. The stronger the visual intensity of FDG uptake, the greater the possibility of malignancy. Further, small size of the nodule cannot exclude the possibility of malignancy with lymph node metastasis.

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