Differences in the Recurrence and Mortality Outcomes Rates of Incidental and Nonincidental Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-Analysis of 21 329 Person-Years of Follow-up

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Context: There is controversy as to whether papillary thyroid microcarcinoma (PTMC) represents more than one disease entity with different outcomes, requiring different treatment.

Objectives: To compare characteristics, outcomes, and factors associated with prognosis of incidental and nonincidental PTMC.

Setting and Design: Two reviewers performed searches of online databases (1966–2012), reference lists, and conference abstract books. Longitudinal studies of subjects >16 years old receiving any treatments for papillary thyroid cancer ≤10 mm in size were included. Two reviewers independently screened abstracts and articles, extracted data, and assessed quality of studies using National Institute of Clinical Excellence and PRISMA criteria.

Results: Of 1102 abstracts identified, 262 studies were reviewed and 17 studies included, comprising 3523 subjects, with mean follow-up of 70 months and total follow-up of 21 329 person-years. This included 854 subjects with incidental PTMC (follow-up, 4800 person-years; mean tumor size, 4.6 mm [range 3.3–6.7 mm]) and 2669 nonincidental PTMC cases (follow-up, 16 529 person-years; mean tumor size, 6.9 mm [range 5.6–8.0 mm]). The recurrence rate in the incidental group (0.5%; 95% confidence interval [CI], 0–1%, $P < .001$) was significantly lower than that in the nonincidental group PTMC (7.9%; 95% CI, 5–11%), with an OR of recurrence of 14.7 (95% CI, 5.6–54.8, $P < .001$) for nonincidental PTMC, compared with incidental PTMC. Lymph nodes were involved in 80% (126/157) of recurrences. On meta-regression, age, sex, size, tumor multifocality, lymph node involvement, and treatment modality were not significantly associated with recurrence.

Conclusions: Our meta-analysis strongly suggests the existence of at least two distinct entities of PTMC. Incidental PTMC has different clinical characteristics and a much lower recurrence rate than nonincidental PTMC, suggesting that management protocols should be re-considered. Additional studies with standardized data collection are required to explore potential differences between subgroups of nonincidental PTMC. **(*J Clin Endocrinol Metab* 99: 2834–2843, 2014)**

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Abbreviations: 95% CI, confidence interval; OR, odds ratio; PTMC, papillary thyroid microcarcinoma.

The incidence of papillary thyroid microcarcinoma (PTMC), defined by the World Health Organization as papillary thyroid cancer of 10 mm or less in largest dimension (1), has increased considerably during the past two decades (2). Some have attributed this to the increasing identification of thyroid nodules during routine imaging for nonthyroid-related conditions, eg duplex ultrasound for carotid disease or magnetic resonance imaging for cervical disease (3). There is debate regarding the clinical significance of PTMC (4), with many suggesting that it may represent subclinical disease that is nonprogressive and has no effect on morbidity or survival (3). As a result, more conservative strategies for the investigation of thyroid nodules and the treatment of small papillary cancers have been advocated (3–6).

However, there are different clinical presentations of PTMC: those only identified postoperatively on histological examination of thyroid specimens following thyroid surgery for noncancer diagnoses, eg thyrotoxicosis or compressive goiter (termed here incidental papillary carcinoma); and those identified and diagnosed preoperatively, usually either due to clinical presentation of nodal metastasis or alternatively on imaging undertaken for nonthyroid reasons, eg cervical spondylosis, and consequently have a thyroidectomy because of suspicion of cancer, termed here nonincidental PTMC. It is unclear whether these different presentations reflect the same disease or whether there are significant differences in baseline characteristics, behavior and recurrence, and mortality outcomes between incidental and nonincidental PTMCs, that may reflect differences in underlying pathophysiology (7–12). The conflicting results in the literature may reflect the small size of individual studies that are not adequately powered to detect significant differences. Similarly, there is wide variation in the management of these cases. Lin et al (12) consider lobectomy or subtotal thyroidectomy without postoperative radioactive iodine ablation to be adequate for incidental lesions. Carlini et al (14) consider total thyroidectomy to be indicated in all cases of PTMC. Others also recommend postoperative adjuvant radioiodine treatment (15, 16). In contrast, some advocate a risk-stratified management approach, with observation without surgical intervention for PTMC identified after ultrasound-guided fine needle aspiration (17). Recent American Thyroid Association guidelines recommend total or hemi-thyroidectomy with no postoperative radioiodine treatment for PTMC, with subsequent long-term surveillance. The guidelines make no distinction between subtypes or different presentations (6).

Our aim was to compare the recurrence and mortality rates of subjects with incidental and nonincidental PTMC, and to identify risk factors associated with a worse prognosis. Due to low recurrence and death rates from differentiated thyroid cancer (18), large sample sizes with long follow-up periods are required to detect significant differences in outcomes. Consequently, large prospective studies that are adequately powered are difficult to undertake in this field. We therefore carried out a systematic review and meta-analysis of published studies to synthesize data on a large cohort of subjects to enable the investigation of differences in treatment outcomes for patients with incidental and nonincidental PTMC, and the examination of potential risk factors that affect outcomes in these two entities.

Materials and Methods

Definitions

Papillary thyroid microcarcinomas (PTMCs) were defined as any papillary thyroid carcinomas 10 mm or less in size. Incidental PTMCs were defined as cases where suspicious lesions were not identified preoperatively and the PTMC was diagnosed incidentally only on final histopathological examination of a surgical thyroidectomy specimen. The operation was typically performed for benign indications such as compressive multinodular goiter or thyrotoxicosis. This group included cases operated on for suspicious lesions in the thyroid where the suspicious lesion was found to be benign on histological examination but an incidental PTMC, distinct to the index lesion, was discovered. Nonincidental PTMCs were defined as lesions identified preoperatively. This group includes subjects with PTMC who present clinically, for example, due to nodal metastasis. It also includes subjects who have thyroid nodules identified on preoperative radiological examination, usually undertaken for nonthyroid disease, such as carotid duplex scanning for carotid stenosis or magnetic resonance imaging for cervical spinal disease, or undertaken for nonspecific symptoms such as globus. Further investigations might then suggest a suspicion of cancer, usually resulting in a diagnostic thyroidectomy. The presentation of the data in the literature precluded separating the nonincidental PTMC group into further subgroups (eg, those presenting clinically vs those identified on radiological examination).

Search strategy and data sources

Our search was performed of the following databases: Cochrane Oral Health and ENT Groups Trials Register, MEDLINE, PUBMED, Zetoc, CINAHL, and the National Cancer Trials Database. All entries from 1966–2012 were searched. Reference lists of the articles retrieved and previous reviews were manually searched for suitable studies, as were conference abstract books from 2006–2012. The last search was performed on 9 June 2012. Detailed methods are included in the Supplemental Materials section, and a full review protocol is available on request. No language restrictions were made.

Eligibility criteria and study selection

Two trained reviewers (T.A., N.C.) independently screened the abstracts for selection using a priori criteria of reporting on primary outcome data on papillary thyroid cancers 10 mm or less

in diameter. The same two reviewers then reviewed the full articles independently, using the following a priori criteria inclusion criteria: studies had to provide specific data on adult patients older than 16 years using our definition of PTMC. Studies had to include data on patient characteristics, treatment, and outcomes in terms of recurrence and/or mortality. Studies were excluded if they included tumors other than PTMC; reported prevalence of both malignant and benign lesions together; included tumors larger than 10 mm and did not report on them separately; did not mention tumor size in the article, did not specify when the PTMC lesion was identified (ie preoperatively or incidentally on histology) or did not provide details of outcome. Short follow-up less than 3 years, single case reports, and PTMC associated with medullary, follicular, or anaplastic carcinoma were also excluded. If multiple studies used the same data, the most recent study was used if it provided the data required. Where a meeting abstract and a subsequent article reported data on the same cohort, the published article data were used. Any longitudinal study design (whether retrospective or prospective) and studies from all settings were considered, including those that were population based, hospital based, from a cancer registry, or a pathology archive.

Study outcomes

The primary outcomes for this study were recurrence (local, regional, or distant) and all-cause mortality. Secondary outcomes were average size of lesion, incidence of multifocal tumor histology, incidence of lymph node metastases detected clinically and/or radiologically at presentation, and incidence of lymph node metastasis identified histologically.

Data collection

A standardized data-extraction form was piloted and used. A full list of data collected is included in Supplemental Table 1. The two trained reviewers (T.A. and N.C.) independently abstracted data from the selected articles. Where data were missing, the authors of the primary research were contacted to provide the data.

Quality and risk of bias appraisal

The quality assessment and risk of bias of the included studies were appraised by the two reviewers using 11 domains adapted from the National Institute of Clinical Excellence (19), and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (20). At all times, any differences in opinion were resolved by discussion by two reviewers.

Data analysis

Measures of treatment effect

We presented continuous outcomes on the original scale as reported in each individual study and summarized them by the mean. Incidence data were calculated as a proportion and the 95% confidence interval (95% CI) using Fisher's exact test for binomial data.

Assessment of heterogeneity

We assessed clinical diversity by examining the characteristics of the types of participants in studies and interventions. The degree of heterogeneity between studies was assessed using the I^2 statistic, which was reported alongside all meta-analysis.

Data synthesis and meta regression

Two statisticians (E.M. and B.C.) analyzed the data in accordance with the advice in chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (20). A meta-analysis was only carried out if at least three clinically homogeneous studies that investigated similar interventions were identified. A random-effect model was used to pool the data into a meta-analysis (21). Comparisons between baseline-aggregated subgroups' total counts were made using Fisher's exact test (Table 1). We identified a number of potential risk modifiers and, where scientific justification could be made, their influence was assessed using meta-regression (22) (see Supplemental Material for details).

Table 1. Differences in Clinical Characteristics and Outcomes Between Incidental and Nonincidental PTMC Cases

	Incidental	Nonincidental	*P* Values
Clinical Characteristic			
N	854	2669	
Mean age (y), mean (SD)	47.2 (4.51)	49.2 (6.62)	.539
Follow-up period (mo), mean (SD)	67.4 (14.98)	74.3 (23.90)	.364
Number of females/total (%)	735/854 (86.1)	2278/2669 (85.4%)	.655
Tumor size, mm, mean (SD)	4.6 (2.24)	6.9 (2.37)	<.001
Subjects with multifocal tumors (%)[a]	135/728 (18.5)	416/1401 (29.7%)	<.001
Subjects with LN metastases (%)[a] (on postoperative histology)	19/739 (2.6)	739/2460 (30.0%)	<.001
Subjects treated by total or near-total thythyroidectomy (%)[a]	362/716 (50.6)	1578/2656 (59.4%)	<.001
Subjects with treated with RAI (%)[a]	204/620 (32.9)	654/1388 (47.1%)	<.001
Subjects with TSH suppression (%)[a]	441/547 (80.0)	1000/1031 (97.0%)	<.001
Outcomes			
Overall recurrence	4/854 (0.0%)[a]	173/2669 (7.9%)[a]	.001
Recurrences in LN	4/854 (0.0%)[a]	122/2460 (6.0%)[a]	<.001
Mortality	0/854 (0.0%)[a]	17/2669 (0.1%)[a]	.020

Abbreviations: LN, lymph nodes; RAI, radioiodine.

Patient summaries are weighted by cohort size.

[a] Percentage summaries are inverse variance weighted derived from the random effects meta-analysis.

Sensitivity analysis

We carried out sensitivity analyses on larger studies (>50 subjects) compared with smaller ones (<50 subjects), to assess the robustness of the results of this review. This led to exclusion of one study with suspected reporting bias.

Results

Search results and study selection

In total, the search strategy described above yielded 1102 abstracts from the database search and 22 from conference abstract booklets and reference lists. After exclusion of 22 duplicate reports, 1102 abstracts were reviewed. Of these, 262 articles were selected for full review, after which 245 were excluded. Supplemental Figure 1 shows the PRISMA flowchart.

Characteristics of included studies

In total, 17 studies, published between 2003 and 2011 and reporting on 3523 subjects, were selected for inclusion in the meta-analysis. These comprised 12 cohorts of subjects with incidental PTMC and 14 cohorts with nonincidental PTMC. Their characteristics are detailed in Table 2 and Supplemental Table 2 and 3 (online). The average cohort of subjects recruited was 136 (range, 12–1059) from 11 countries across two continents. The average age of subjects was 47.2 years (range, 37–53 years) for incidental cases and 47.9 years (range 32–56) for nonincidental cases. In total, there were 854 subjects with incidental PTMC with a mean tumor size of 4.6 mm (range, 3.3–6.7 mm) and 2669 subjects with nonincidental PTMC with a mean tumor size of 6.9 mm (range, 5.6–8.0) (Table 1).

A total of 1940 subjects had total thyroidectomy (or near-total thyroidectomy), 1458 had lobectomy (or subtotal thyroidectomy), and 858 had postoperative radioiodine ablation. The mean duration of follow-up was 70 months (range, 52–132 mo), with a total follow-up duration of 21 329 person-years. The mean follow-up for incidental cases was 67.4 months, with a total follow-up of 4800 person-years, compared with a mean follow-up of 74.3 months and a total follow-up of 16 529 person-years for nonincidental cases.

Quality assessment and risk of bias

The quality assessment of included studies is detailed in Supplemental Table 4. All 17 included studies were retrospective case series, and all were from hospital clinics. None were population, cancer registry, or pathology archive based. All were single-center studies, and only three stated that they recruited patients consecutively. The average quality assessment score was 7 of 11 (range, 5–9). However, none of these studies was randomized and most were retrospective cohorts studies, therefore all of the included studies had a high risk of bias.

Outcomes

Primary outcomes

Recurrence

All studies reported data on the incidence of recurrence (Figure 1). The overall recurrence rate for subjects with

Table 2. Cohort Characteristics for Included Studies

Study	Year	Country	Cohort Size	No. of Incidental Cases	Mean Age	Male/ Female	Mean Tumor Size, mm	LN Mets, %	Treated With TT/NT, %	Treated With RIA, %	F/U
Wada (37)	2003	Japan	414	155	np	41/373	np	43	8/0	0	58
Lo (7)	2006	China	185	75	45	37/148	5.0	21	63/8	29	98
Roti (38)	2006	Italy	243	52	52	46/197	6.0	13	92/8	97	52
Schonberger (39)	2007	Germany	67	54	52	19/48	7.0	15	63/30	72	56
Pazaitou (40)	2008	Greece	54	30	np	8/46	np	44	np	np	59
Lin (13)	2008	Taiwan	335	126	43	51/284	np	np	57	np	91
Besic (41)	2009	Slovenia	254	107	47	42/212	np	23	84	48	56
Pisanu (42)	2009	France	149	73	np	23/126	np	11	88/0	84	65
Xu (43)	2010	China	177	54	np	26/151	np	29	70	0	60
Dietlein (44)	2005	Germany	20	20	49	12/143	<5 5, ≥5, 15	5	0/25	100	65
Sakorafas (45)	2007	Greece	27	27	45	8/19	4.4	0	100	74	54
Gülben (46)	2008	Turkey	81	81	37	15/66	6.0	12	80/0	37	83
Cappelli (26)	2007	Italy	102	0	55	40/62	7.8	24	100/0	100	102
Abboud (47)	2010	Lebanon	12	0	32	2/10	7.5	100	100	100	60
Sugitani (17)	2010	Japan	56	0	56	28/28	<5 23, ≥5, 33	100	20/80	0	132
Ito (37)	2010	Japan	1059	0	52	95/964	np	14	41	np	76
Moon (48)	2011	Korea	288	0	46	26/262	6.2	34	62/0	40	72

Abbreviations: LN mets, lymph node metastasis detected on histological examination of operative specimen; TT, total thyroidectomy; NT, near-total thyroidectomy; RIA, radioiodine ablation; F/U, follow-up, mean months; np, not provided.

All studies were general, hospital-based, retrospective cohorts.

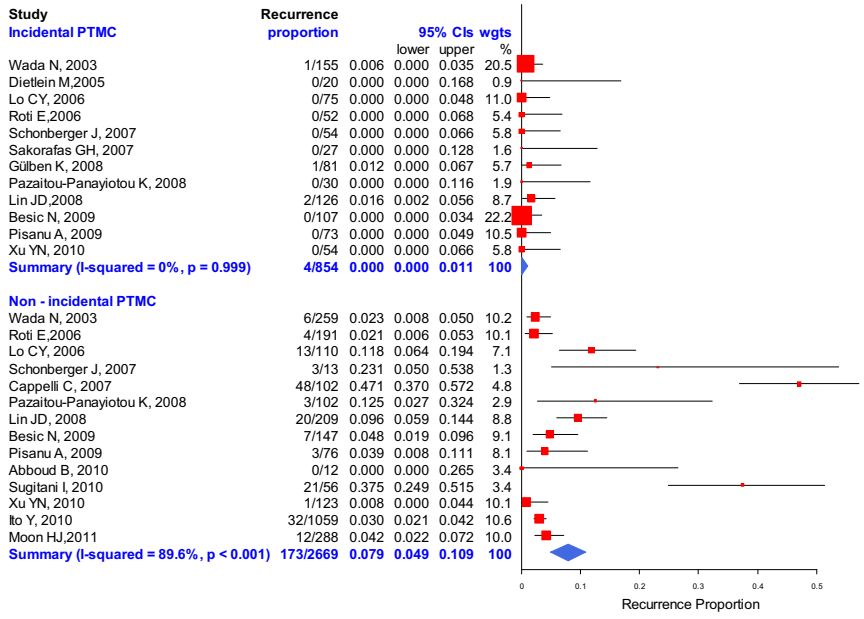

Figure 1. Forest plot for incidence of recurrence for nonincidental and incidental PTMC subjects, using random effects meta-analysis (21). Confidence intervals for proportions were calculated using an exact method for the binomial distribution.

PTMC was 3% (95% CI, 2–5%). There was a clear difference between the two groups: recurrence in the incidental group (0.5%; 4/854; 95% CI, 0–1%) was significantly lower than the nonincidental group (7.9%; 173/2669; 95% CI, 5–11%). The conditional odds ratio (OR) for recurrence in the nonincidental group was 14.7 (95% CI, 5.6–54.8, $P < .001$) compared with the incidental group.

All four recurrences in the incidental group involved lymph nodes. In the nonincidental group, lymph nodes were involved in 80% of recurrences (122/153) (Figure 2). Thyroid recurrences were noted in 23 cases (15%, 23/153), of which six were in the contralateral thyroid lobe. It was not possible to ascertain from the data whether the contralateral lobe recurrences were true recurrences or second primaries due to multifocal disease. Distant metastases were recorded in 21 recurrent cases (13.7%), of which 14 were reported in the same study by Sugitani et al (17).

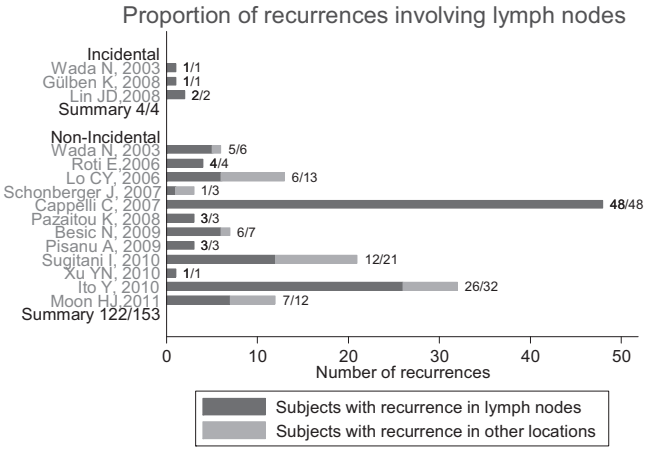

Figure 2. Total number and sites of recurrences (lymph nodes vs other sites) for incidental (upper) and nonincidental (lower) PTMC subgroups. In total, there were 4/854 (0.5%) and 122/2460 (5.0%) recurrences in the incidental and nonincidental subgroups respectively ($P < .001$).

Significant heterogeneity was detected due to the nature of pooling retrospective cohort data ($I^2 = 84.2\%$, $P < .001$). To explore the heterogeneity within the nonincidental group, a sensitivity analysis was performed by removing two studies that seemed to include subjects who were substantially more likely to suffer recurrence (17, 26). Even after excluding these studies, the recurrence in the nonincidental group (4%; 95% CI, 2–5%), remained significantly higher than for the incidental group (0.1%), with an OR = 9.2 (95% CI, 3.5–34.42; $P < .001$).

Mortality

All studies reported all-cause mortality, with an overall incidence of 0.1% (95% CI, 0.0–0.4%). None of the studies of subjects with incidental PTMC reported any deaths among 854 patients. There were deaths reported in only three studies of nonincidental cases, with 17 deaths among 2669 subjects. Although there were statistically significant differences found in mortality between the groups ($P = .02$), the absolute numerical differences were small.

Sensitivity analysis

Further sensitivity analyses were carried out on the two primary outcomes by including those studies with at least 50 subjects, and resulted in similar findings to the previous analyses (plots available from the authors).

Secondary outcomes

Characteristics of subjects with incidental and nonincidental PTMC

Average size of lesion (mm). Only seven studies reported data on the variability of the average lesion size (Figure 3A). The overall pooled estimate of lesion size for all subjects combined was 5.7 mm (95% CI, 4.9–6.5). The average lesion size for the incidental PTMC group was 4.6 mm (95% CI, 4.0–5.2) and the average lesion size for the nonincidental group was 6.9 mm (95% CI, 6.4–7.5). Subgroup analysis suggested there was a clear difference in average lesion size between the two groups ($P < .001$), but

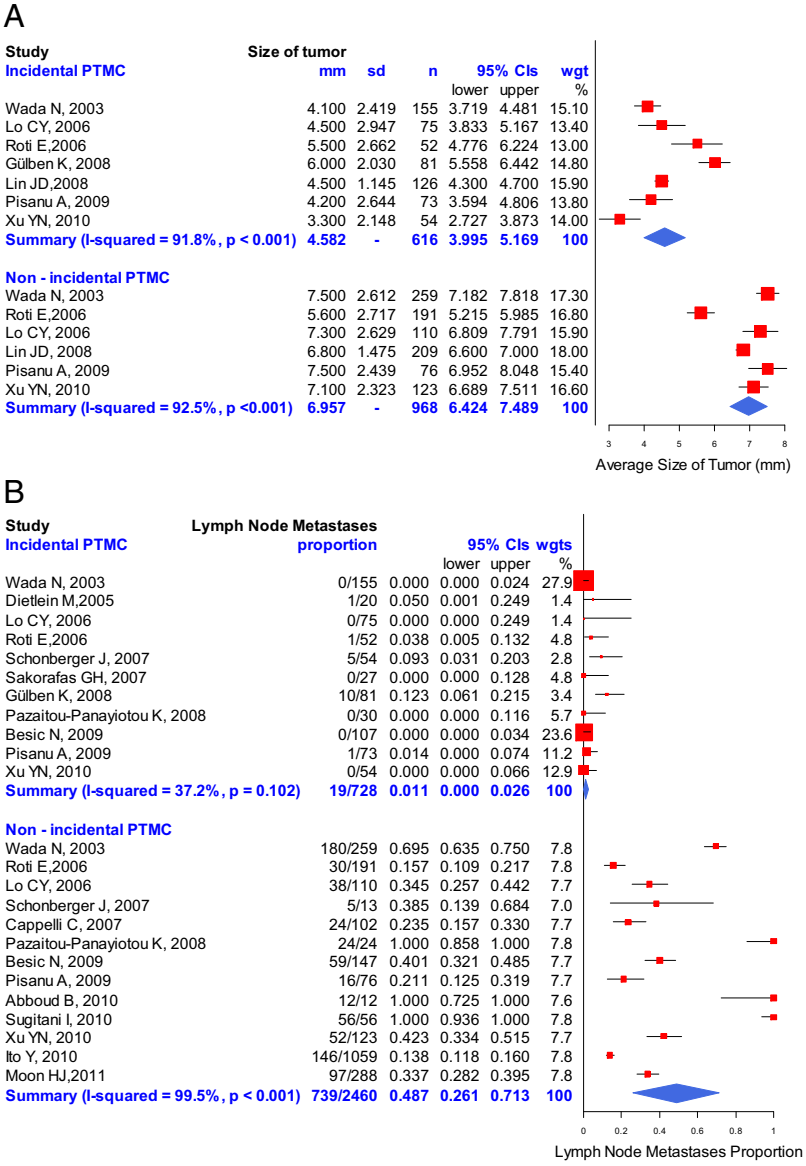

Figure 3. A, Forest plot for average size of lesion (mm) for nonincidental and incidental PTMC groups, using random effects meta-analysis (21). Confidence intervals for proportions were calculated using an exact method for the binomial distribution. B, Forest plot for incidence of lymph node metastases for nonincidental and incidental PTMC groups, using random effects meta-analysis (21). Confidence intervals for proportions were calculated using an exact method for the binomial distribution.

again high heterogeneity was exhibited (I^2=98.2%; $P <$ .001).

Incidence of multifocal tumors on histology. The overall incidence of tumor multifocality was 26.1% (95% CI, 20–32%). The incidence of multifocality in the nonincidental PTMC group was 29.7% (95% CI, 26–44%), and was significantly higher than that in the incidental group at 18.5% (95% CI, 10–22%), with an OR = 2.2 (95% CI, 1.7–2.8; $P <$ .001). There was evidence of severe heterogeneity (I^2=91.8%; $P <$ .001).

Incidence of lymph node metastases at presentation (on postoperative histology). Ten studies reported lymph node metastases at presentation in incidental PTMC cases, and 13 in the nonincidental group (Figure 3B). The overall incidence was 12% (19/728; 95% CI, 11–12%). The incidence of lymph node metastases in the incidental group (2.6%; 95% CI, 0–3%) was significantly lower than the nonincidental PTMC group (30%; 95% CI, 26–71%), ($P <$ .001). The OR for lymph node metastases was 11.1 (95% CI, 4.2–41.5) in nonincidental PTMC compared with incidental cases. There was severe heterogeneity exhibited in the nonincidental group (I^2 = 99.5%; $P <$ .001).

Meta-regression. The meta-regression plotted confounding variables to explore any potential relationship with recurrence, analyzed by subgroup (Figure 4). There was no evidence that subject age, sex, tumor size, or tumor multifocality was associated with the incidence of lymph node metastasis at presentation.

There was also no evidence to suggest that subject age, sex, tumor size, tumor multifocality, lymph node metastases, treatment modality (total thyroidectomy, radioiodine ablation), or TSH suppression by T_4 were associated with recurrence. There was little evidence to suggest that these covariates were associated with lymph node recurrence. There were insufficient data to determine the importance of family history of thyroid cancer, lymphocytic thyroiditis, site of nodal metastasis at presentation, or tumor histologic subtype.

Discussion

Our findings, from a meta-analysis of the outcomes of more than 3500 subjects with PTMC, strongly suggest the existence of at least two distinct disease entities within the current World Health Organization definition of PTMC, a condition that is rapidly rising in incidence in most countries (2). Our findings suggest that incidental PTMC has distinct clinical characteristics and very low recurrence

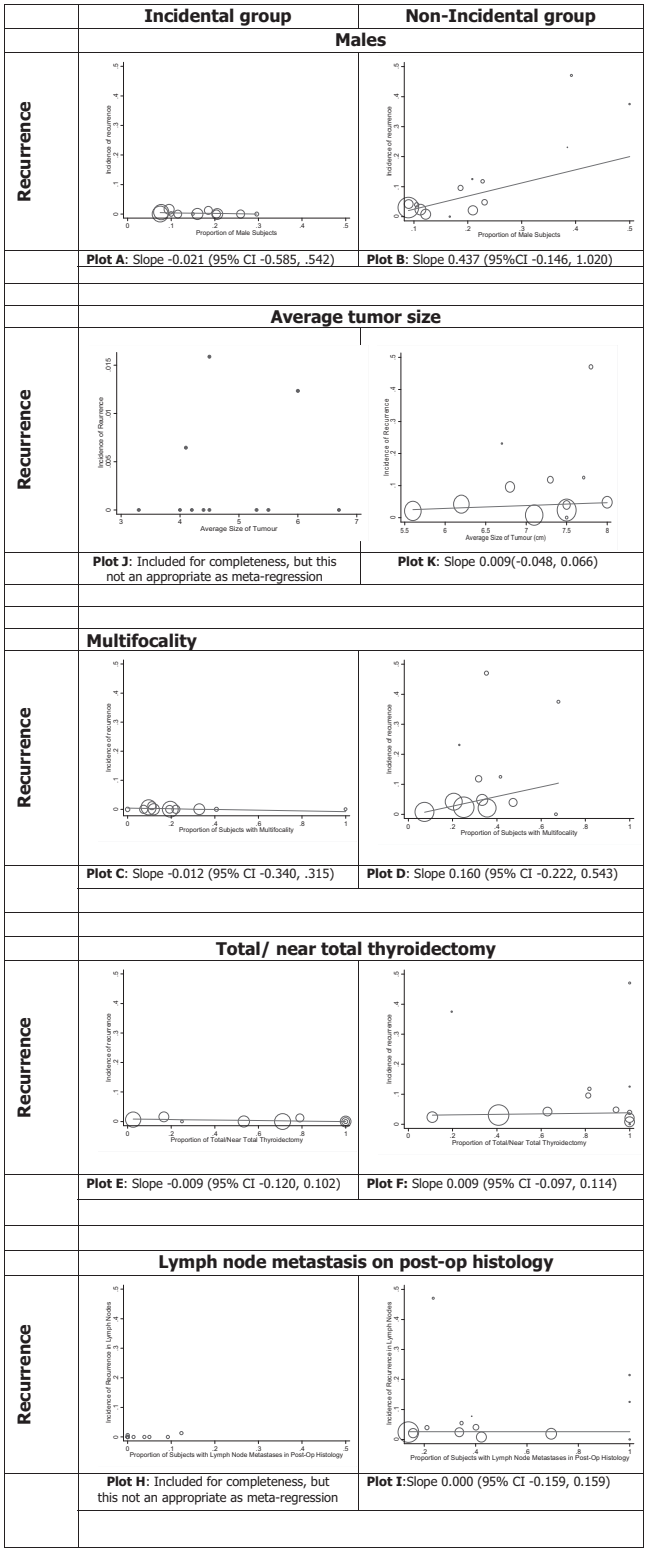

Figure 4. Meta-regression plots of incidence of recurrence (y-axis) against possible confounding factors (x-axis). The association is considered significant if slope of line and the 95% CI > 0. The higher the slope coefficient, the stronger the association.

rate with no mortality, despite receiving less intensive treatment than nonincidental PTMC. However, current treatment guidelines do not make any distinction in the management of PTMC (6, 27). As a result, patients with incidental PTMC are counseled that they have cancer and may undergo further treatment including additional surgery or radioiodine ablation (26), with subsequent long-term follow-up. This may result in inconvenience, physical morbidity, psychological distress, and health care costs (28, 29) despite a very low risk of recurrence and no risk of mortality from their PTMC. Our findings suggest that there may be a need to reconsider patient counseling, management, and follow-up for incidental PTMC.

There seem to be two main modes of presentation of nonincidental PTMC: those identified on radiological investigations undertaken for nonthyroid reasons, and those that present clinically, due to the presence of palpable thyroid nodules or metastatic lymph nodes. It is possible that there may be differences in behavior and/or outcomes between these two groups. Potentially, subjects with nonincidental PTMC confined to the thyroid gland and identified on radiological examination for nonthyroid disorders (sometimes termedthyroid radiological incidentalomas) may have characteristics similar to incidental PTMC identified only on histological examination, as indicated following Sugitani's conservative management of a group of incidental asymptomatic PTMC diagnosed on ultrasound-guided fine needle aspiration cytology (17). Alternatively, radiologically detected nonincidental PTMC may have outcomes in between those of the incidental (histological) PTMC and nonincidental PTMC that presents clinically with lymph nodes. The way data are presented and analyzed in the literature prevents us from separating the nonincidental PTMC group into subgroups to undertake a further analysis.

In the present meta-analysis, subjects with nonincidental PTMC received more extensive treatment including total thyroidectomy operations, postoperative radioiodine ablation, and TSH suppression. Despite this, more recurrences were detected in this group, typically within the nodal basin (in 126/157 recurrent cases). Reasons for the higher recurrence rate are unclear, but it has been postulated that recurrence may be a function of sex (23), the size of the lesion (9, 30), or lymph node metastasis at presentation (31). Our study suggested that while lesion size, tumor multifocality, and lymph node metastases at presentation were all more common in nonincidental PTMC, those physical characteristics were not associated with recurrence, and nor was male sex. This suggests that differences in outcomes may be determined by the fundamental biology of the lesions, with more aggressive or more therapy-resistant biology in nonincidental disease.

For example, over-expression of cyclin D1 on immunohistochemistry is strongly associated with nodal metastasis in PTMC (32). More recently, *BRAF* mutations were found to be significantly more common in cases of aggressive PTMC (extrathyroidal spread or recurrence) compared with nonaggressive cases (33).

The findings of this study help inform debate on the clinical importance of PTMC. Those studies that have cited low recurrence and mortality rates, and high incidence of asymptomatic PTMC in some autopsy studies (34, 35) as evidence that PTMC is not clinically relevant, may have been examining cohorts comprised predominantly of incidental PTMC, possibly as a result of bias in study design or sampling strategy.

Strengths and limitations

Due to the low event rates in PTMC, large sample sizes with sufficient follow-up are required to ensure that significant differences between subgroups can be detected. This has been a major limitation of studies of PTMC, but by undertaking a meta-analysis of 3523 subjects with a total of 21,329 person-years of follow-up, we have mitigated this limitation. Despite the large number of subjects and overall follow-up in the present study, the event rate for incidental cases remained very low, because of the very low recurrence rate of incidental PTMC. This might lead to imprecision in the estimates and wide confidence intervals. However, the confidence intervals between the two PTMC groups were well separated, indicating a likely true difference in recurrence rates between the subgroups.

Subjects were followed up on average for 5.5 years, with similar durations between the two PTMC subgroups. Some may suggest that the smaller, less advanced, differentiated thyroid cancers may require a longer duration to show recurrence. However, both incidental and nonincidental subjects had tumors less than 10 mm in size (ie early tumors of small size, which may be considered to be indolent). Yet despite their similar small size and similar follow-up duration, nonincidental papillary carcinomas demonstrated a significantly higher recurrence and mortality rate than incidental papillary carcinomas, underlining the considerable differences in clinical outcome, behavior, and morbidity arising from the two conditions. These differences may reflect differences in their underlying pathophysiology.

All included studies were retrospective case series drawn from single-center hospital clinics and therefore all were considered to have a high risk of bias. Particular concerns over study design include absence of randomization, small cohort sizes, absence of control for potential cofounders, and a high degree of heterogeneity. The latter may reflect differences in inclusion criteria, treatment, or follow-up strategies and is a limitation that should be considered when interpreting the results. In addition, data on how many subjects had recurrence in the thyroid bed alone or had distant metastases was poorly reported. Importantly, due to lack of data provided in the studies included, subgroup analyses within the nonincidental PTMC group could not be performed. In addition, it was not possible to investigate associations with family history of thyroid cancer or with histologic subtype of papillary carcinoma.

Clinical implications of the study

We found that incidental PTMCs were characterized by lower incidence of tumor multifocality and lower incidence of lymph node metastases. And despite receiving less intensive treatments, subjects with incidental PTMC demonstrated a very low risk of recurrence. Tumor recurrence overwhelmingly occurred in nonincidental PTMCs, and crucially, our study showed nodal recurrence to be the main site.

We therefore propose that subjects with incidental PTMC may be considered differently in terms of management, follow-up, and counseling regarding prognosis compared with those with nonincidental PTMC. Subjects with incidental PTMC should be considered for less aggressive treatment, without the need for comple thyroidectomy or radioiodine ablation. Some have even advocated observation only (without surgery) for incidental asymptomatic PTMC diagnosed on ultrasound-guided fine needle aspiration cytology, with good outcomes (17, 36). Due to the very low risk of recurrence, less frequent and a shorter duration of follow-up may also be considered for incidental PTMC, but with instructions to seek medical assistance should changes occur. Such a conservative follow-up regimen would have to be validated further before implementation in clinical practice. Some have previously advocated management of PTMC according to risk stratification (24), which is usually based on the presence of a combination of risk factors. Our findings suggest that currently for PTMC, one factor—mode of presentation—may be used as an effective surrogate for these risk factors, providing a simplified means of determining further treatment.

Implications for future research

Importantly, there is a need to improve the documentation and reporting of studies on PTMC, to enable further subgroup analysis of nonincidental PTMC groups. We propose that researchers and authors adopt a unified nomenclature and classification system. We propose the following: those with nonincidental PTMC lesions and who presented with clinically evident palpable thyroid nodules or nodal metastasis on presentation might be termed "clin-

ical nonincidental PTMC." Those lesions that did not present clinically and which would have been identified through radiological examination, typically for nonthyroid disease, such as carotid duplex scanning for carotid stenosis or magnetic resonance imaging for cervical spinal disease, might be termed "radiological nonincidental PTMC." Importantly, we propose that authors should report data on the incidence, baseline characteristics, and outcomes for these three subgroups separately. Outcomes should be reported in terms of recurrence rates in the ipsilateral thyroid bed, contralateral thyroid bed, central nodal (level 6) recurrence, and lateral nodal recurrence, as well as distant metastasis and deaths.

Prospective recording in cancer registries of subjects with PTMC with a minimum inclusion of information regarding tumor size, mode of initial presentation, site of recurrence, and time to recurrence may help clarify issues regarding best clinical practice in the future. We also suggest that a pragmatic randomized controlled clinical trial is needed to assess the effects on recurrence, quality of life, and cost-effectiveness outcomes of a more conservative treatment and follow-up regimen for incidental PTMC.

Finally, the differences observed in the baseline characteristics and behavior between incidental and nonincidental PTMCs suggest that there may be a pathophysiological explanation. Well-designed, detailed studies of the molecular biology of the subgroups of PTMC may identify biomarkers leading to personalization of treatment selection for patients with PTMC, and differentiated thyroid cancer in general (4).

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