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Comparison of the clinicopathological behavior of the follicular variant of papillary thyroid carcinoma and classical papillary thyroid carcinoma: A systematic review and meta-analysis

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Abstract. The follicular variant of papillary thyroid carcinoma (FV-PTC) is the second most common type of papillary thyroid carcinoma (PTC), and it has been increasingly diagnosed in recent years. However, whether FV-PTC behaves differently from classical PTC (C-PTC) remains controversial. To address this controversy, a meta-analysis was performed to determine the potential differences between FV-PTC and C-PTC in their clinicopathological behavior. The relevant published studies between January 1, 2003 and August 31, 2014 were reviewed according to the defined selection criteria using the PubMed database. Review Manager was used to calculate the pooled odds ratio (OR) or the mean difference (MD) with a 95% confidence interval (CI), using a random- or fixed-effect model for all analyses. In total, 112 studies were identified and examined; finally, only 36 studies met the inclusion criteria. In the 36 studies, compared to the clinicopathological behavior of patients with C-PTC, patients with FV-PTC had the following parameters: Similar mean age and similar prevalence of gender, tumor size ≥10 mm, multifocality, capsular invasion, vascular invasion, lymphocytic and/or Hashimoto's thyroiditis, and clinical stage; a larger mean tumor size and higher prevalence of age ≥45 years; and lower prevalence of extrathyroidal extensions, lymph node metastases, *BRAF* mutation and recurrence. The meta-analysis suggested that patients with FV-PTC have a more favorable clinicopathological behavior and improved prognosis compared to patients with C-PTC. Thus, patients with FV-PTC and C-PTC may be managed differently, and the two types of PTC should be clearly distinguished in future retrospective or prospective studies.

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Key words: thyroid carcinoma, papillary, follicular, classical, meta-analysis

Introduction

Well-differentiated thyroid cancer is the most common endocrine tumor, and its prevalence is increasing worldwide (1). The majority of thyroid cancer cases (~85%) are papillary thyroid carcinoma (PTC) (2). A number of PTC variants have been described, including classical, follicular, oncocytic, solid, tall cell, columnar cell, diffuse sclerosing and cribriform (3,4). Among these variants, the conventional or classical type is the most common and accounts for ≤54.2% of all PTC cases in certain reported series (5-8). The follicular variant is the second most common subtype and constitutes 4.9-41.2% PTC cases in different series (7-12). Since the follicular variant of PTC (FV-PTC) was first described by Crile and Hazard in 1953 (13), FV-PTC has been increasingly diagnosed and accounts for 41-53% of PTC cases (7,14).

As FV-PTC exhibits a mixed histopathological picture of PTC and follicular thyroid carcinoma (FTC), certain investigators have hypothesized that FV-PTC has specific characteristics from the two types. Numerous studies have since investigated the clinical behavior of FV-PTC and the classical type of PTC (C-PTC) and compared the two; however, certain results were contradictory. In different studies, the incidence of aggressive clinical features was identified as higher, similar or lower in FV-PTC compared to C-PTC (5,7,8,10,12,15-20).

Meta-analysis is a powerful tool for summarizing the results of different studies by producing a single estimate of the major effect with enhanced precision. A major advantage of a meta-analysis is the increase in sample size, which may reduce the probability that a random error will produce false-positive or false-negative associations.

A meta-analysis was performed to quantify and compare the clinical parameters of C-PTC and FV-PTC and provide some guidance on the management and prognosis of FV-PTC. The following clinicopathological parameters were evaluated: Age, gender, tumor size, multifocality, capsular invasion, vascular invasion, extrathyroidal extension, lymph

node metastasis, lymphocytic and/or Hashimoto's thyroiditis, clinical stage, *BRAF* mutation and recurrence.

Materials and methods

Selection criteria. Studies that examined the associations of FV-PTC and C-PTC with clinicopathological parameters were searched for. The following criteria were considered when selecting the studies: i) Studies published in English between January 1, 2003 and August 31, 2014. ii) The criteria of C-PTC include classical, conventional and pure PTC. iii) Clinicopathological parameters with detailed data on C-PTC and FV-PTC tissue were included from the same studies that assessed different types of carcinoma, such as primary, follicular, anaplastic and medullary carcinomas. iv) Only studies analyzing at least two of the above categories of clinicopathological data and containing ≥5 cases reported FV-PTC and C-PTC. v) When multiple studies were published by the same investigators or groups, the newest or most informative single study was selected. The following studies were excluded: i) Review studies without original data; ii) absent or inappropriately reported clinicopathological data; iii) single or pure case reports; iv) animal research; and v) familial research studies.

Collection of published studies. A literature search was carried out using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed). The search term combination was 'follicular variant of papillary thyroid carcinoma' OR 'FV-PTC' OR 'FVPTC' OR 'FPTC' OR 'F-PTC.' Relevant studies were selected on the basis of the summary analysis. Any duplication of data was carefully avoided by examining the names of all the authors and different medical centers involved in each publication. Overlapping studies or data and studies that were unrelated to the meta-analysis were excluded. Two investigators (J. Yang and Y.P. Gong) used the EndNote reference tool to independently screen and select studies. All the procedures conformed to the guidelines for the meta-analysis of observational studies in epidemiology (21).

Data analyses and statistical methods. Review Manager (version 5.1; http://tech.cochrane.org/revman) was used to perform all the statistical analyses, including the calculation of the summary odds ratio (OR) or the mean difference (MD) with a 95% confidence interval (CI), using a random- or fixed-effect model for all the analyses. The choice of each individual statistical method depended on whether the measured event was dichotomous or continuous, whereas the choice of a random- or fixed-effect model depended on the tests for heterogeneity. The heterogeneity of the studies was assessed using the χ^2 test of heterogeneity and the I^2 measure of inconsistency. When the heterogeneity in the χ^2 test showed a P-value of <0.10 or when the I^2 measure was >50%, the random-effect model was chosen, otherwise the fixed-effect model was used. The 95% CI was constructed around the effect size to establish its significance.

For the OR of dichotomous events, if the 95% CI of an OR included 1, the two groups were not considered statistically different, otherwise they were considered statistically different. For the MD of continuous events, if the 95% CI crossed the null point (zero), then the possibility that the difference should be attributed to chance could not be ruled out. When the null point fell outside the 95% CI of an MD, the observed difference was considered statistically significant. The potential publication bias was assessed using Begg's funnel plot and Egger's test by Stata 12.0 software (Stata Corporation, College Station, TX, USA). P<0.05 was considered to indicate a statistically significant difference.

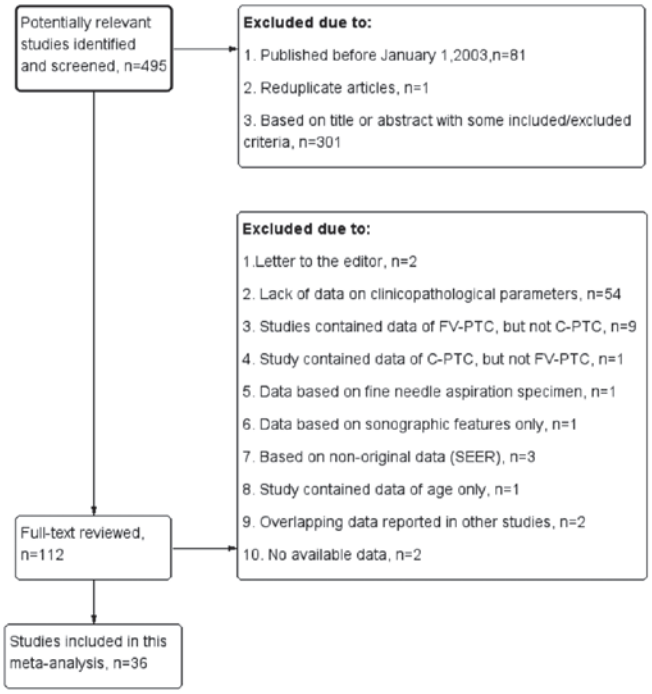

Figure 1. Study selection process. FV-PTC, follicular variant of papillary thyroid carcinoma. C-PTC, classical, conventional or pure papillary variant of papillary thyroid carcinoma; SEER, the Surveillance, Epidemiology and End Results database.

Results

Clinicopathological parameters. Fig. 1 summarizes the study selection process. A total of 495 abstracts and titles were obtained using a PubMed search, of which 81 were published before January 1, 2003 and 1 duplicate study was excluded. Of the remaining 413, 112 full-text studies were deemed relevant and were examined in detail. Eventually, following the application of all the inclusion and exclusion criteria, 36 studies (7,8,10,12,14,16,17,19,20,22-48) fulfilled the eligibility criteria. The main features of the eligible studies are summarized in Table I. In each category of clinicopathological parameters, some heterogeneity was present. In terms of tumor size, multifocality, capsular invasion, vascular invasion, extrathyroidal extension and lymph node metastasis, their heterogeneity was assessed using χ^2 tests and the P-value was <0.10 (or I^2 measures were >50%). The random-effect models were selected, but for the remaining parameters, fixed-effect models were used. The combined results of the meta-analysis and the heterogeneity test are shown in Table II.

Gender. In total, 33 studies were comparable in terms of gender. The prevalence of females among patients with FV-PTC

Table I. Characteristics of individual studies included in the meta-analysis.

First author, year	Country	Patients, no.		Mean age (years) ± SD and/or ≥ (>) 45, no. (%)		Mean tumor size (mm) ± SD and/or ≥ (>)10, no. (%)		(Refs.)
		FV-PTC	C-PTC	FV-PTC	C-PTC	FV-PTC	C-PTC	
Abrosimov, 2007[a]	Japan	34	148	NA	NA	>10±11 (32.4)	>10±71 (47.3)	(22)
Brzezianska, 2007	Poland	8	14	49 (20.4) ≥45±5 (62.5)	47.57 (17) ≥45±7 (50.0)	NA	NA	(23)
Burningham, 2005	USA	46	114	46 (17)[b]	47 (26)[b]	15 (19)[b]	10 (16)[b]	(19)
Chang, 2006	China	85	170	NA	NA	27 (18.4)	23 (13.0)	(10)
Costa, 2008	Portugal	17	16	37 (10)	45 (25)	34 (25)	35 (15)	(24)
Daglar-Aday, 2013	Turkey	36	72	44.94 (15.21)	52.88 (17.11)	NA	NA	(25)
Darr, 2011	USA	6	7	43 (15)	44 (14)	>20±5 (16.7)	>20±6 (14.3)	(26)
Dettmer, 2013	USA	17	27	50.9 (17.73)	47.8 (15.58)	NA	NA	(27)
Di Cristofaro, 2006	France	24	26	38.5 (13)	43.3 (17.3)	21.5 (8.5)	25.7 (11.3)	(28)
Eloy, 2011	Portugal	31	42	42.73 (12.94) ≥45±15 (48.4)	39 (17.75) ≥45±14 (33.3)	22.3 (18) >10±23 (74.2)	22.4 (17.1) >10±32 (76.2)	(29)
Ertek, 2012	Turkey	56	42	39.1 (10.6)	46.7 (12.9)	34.7 (31.7)	13.9 (12.2)	(14)
Espadinha, 2009	Portugal	17	21	35.41 (25.37) ≥45±6 (35.3)	39.24 (25.17) ≥45±14 (33.3)	NA	NA	(30)
Gao, 2012	China	25	84	≥45±13 (52)	≥45±54 (64.3)	>10±20 (80)	>10±61 (72.6)	(31)
Hagag, 2006	Israel	92	99	46 (19.18) ≥45±52 (56.5)	44 (9.95) ≥45±54 (54.5)	22 (19.2)	20 (9.9)	(20)
Hunt, 2004	USA	16	8	50.38 (11.63) ≥45±11 (68.8)	46.75 (11.5) ≥45±5 (62.5)	30.1 (23.7) >10±11 (68.8)	15.6 (13.7) >10±4 (50)	(32)
Igci, 2013	Turkey	10	11	38.5 (12.75) ≥45±5 (50)	50.09 (19.61) ≥45±4 (36.4)	30.6 (16.9) >10±9 (90)	30.6 (16.6) >10±11 (100)	(33)
Igci, 2014	Turkey	25	15	46.76 (13.72) ≥45±15 (60)	48.73 (15.66) ≥45±9 (60)	14.4 (9.7) ≥10±16 (64)	16.4 (10) ≥10±9 (60)	(34)
Ito, 2008	Japan	100	1,313	>55±41 (41)	>55±403 (30.7)	>40±6 (6)	>40±158 (12)	(35)
Lang, 2006	China	67	308	38.5 (14-83)[c]	42.0 (11-81)[c]	25 (10-85)[c]	25 (10-100)[c]	(8)
Lassalle, 2011	France	5	11	39 (8.06)	44.45 (18.05)	22.4 (8.4)	17.7 (7.8)	(36)
Lee, 2011	Korea	30	30	49.27 (12.8)	47.83 (9.65)	17.4 (9.6)	9.7 (6.4)	(37)
Lim, 2013	Korea	85	2,947	45 (13-84)[c]	47 (24-74)[c]	8.2 (0.5-125)[c]	10 (2-65)[c]	(38)
Liu, 2010	USA	73	114	NA	NA	NA	NA	(39)
Min, 2013	Korea	58	312	>45±44 (75.9)	>45±172 (55.1)	>10±15 (25.9)	>10±101 (32.4)	(40)
Nechifor-Boila, 2013	Romania	90	98	27 (6.1)	26.3 (5.5)	27 (16)	21 (11)	(41)
Oler, 2009	Brazil	47	73	≥45±23 (53.5)	≥45±31 (43.7)	≥10±35 (74.5)	≥10±50 (70.4)	(42)
Ozdemir, 2011	Turkey	90	354	43.98 (12.46)	45.82 (12.24)	16.9 (13.9) >10±55 (61.1)	10.6 (9.7) >10±127 (35.9)	(17)
Passler, 2003	Austria	37	117	46.4 (10.9-74.8)[c]	47.5 (18.1-79.3)[c]	17.9 (17.6)	24.2 (21)	(12)
Rivera, 2009	USA	63	43	>45±30 (47.6)	>45±14 (32.6)	≥40±22 (35.5)	≥40±2 (4.7)	(43)
Schulten, 2012	Saudi Arabia	42	115	NA	NA	NA	NA	(44)
Sheu, 2010	Germany	30	10	46.4 (15.4)	48.1 (14.0)	28.5 (18.1)	26.2 (18.8)	(45)
Slosar, 2009	USA	60	37	NA	NA	≥10±56 (93.3)	≥10±30 (81.1)	(46)
Trovisco, 2005	Portugal	54	69	41.5 (19.11)	37.2 (17.44)	27 (13.6)	32 (21)	(47)
Wreesmann, 2004	USA	17	25	40 (25-75)[c]	41 (20-77)[c]	25 (8-65)[c]	20 (6-45)[c]	(48)
Yuksel, 2008	Turkey	41	158	>40±31 (75.6)	>40±37 (23.4)	16.5 (10.8)	13.4 (10)	(16)
Zidan, 2003	Israel	100	143	44 (17-81)[c]	43 (11-78)[c]	35 (3-100)[c]	34 (4-90)[c]	(7)

[a]There were two PTCs with a conventional variant in one patient, two PTCs with conventional and follicular variants in two patients and two microcarcinomas (≤10 mm) with a conventional pattern in one patient; [b]median (IQR, interquartile range reported as the range around the median); [c]continuous data are expressed as median, with the range in parentheses. NA, not available; FV-PTC, follicular variant of papillary thyroid carcinoma; C-PTC, classical, conventional or pure papillary variant of papillary thyroid carcinoma; SD, standard deviation.

Table II. Meta-analyses of the clinicopathological parameters between FV-PTC and C-PTC.

Clinicopathological characteristics	Included study, n	Heterogeneity test			Effects model selection	OR/MD (95% confidence interval)	Combined effect test		Statistical significance	Egger's test
		χ^2	P-value	I^2, %			Z	P-value		P-value
Female	33	29.61	0.59	0	Fixed	1.09 (0.93-1.29)	1.06	0.29	No	0.707
Age, years										
Mean	19	31.36	0.03	43	Fixed	-0.61 (-1.75-0.53)[a]	1.05	0.29	No	0.413
≥45	11	8.90	0.54	0	Fixed	1.45 (1.11-1.90)	2.69	<0.01	Yes	0.754
Tumor size, mm										
Mean	17	50.72	<0.01	68	Random	2.88 (0.26-5.51)[a]	2.15	0.03	Yes	0.485
≥10	10	21.73	0.01	59	Random	1.25 (0.77-2.03)	0.92	0.36	No	0.473
Multifocality	17	40.85	<0.01	61	Random	0.88 (0.64-1.24)	0.77	0.44	No	0.522
CI	6	14.60	0.01	66	Random	0.82 (0.48-1.39)	0.74	0.46	No	0.577
VI	9	31.84	<0.01	75	Random	1.38 (0.56-3.42)	0.69	0.49	No	0.555
EE	18	56.75	<0.01	70	Random	0.40 (0.25-0.64)	3.86	<0.01	Yes	0.609
LNM	23	65.94	<0.01	67	Random	0.35 (0.25-0.49)	6.12	<0.01	Yes	0.450
LT or/and HT	9	13.94	0.08	43	Fixed	0.79 (0.61-1,02)	1.82	0.07	No	0.419
CS (I+II)	12	10.29	0.50	0	Fixed	1.17 (0.90-1.52)	1.16	0.25	No	0.605
BRAF mutation	13	8.15	0.77	0	Fixed	0.19 (0.15-0.24)	13.34	<0.01	Yes	0.247
Recurrence	8	5.46	0.60	0	Fixed	0.52 (0.34-0.80)	2.98	<0.01	Yes	0.991

[a]MD with a 95% confidence interval. FV-PTC, follicular variant of papillary thyroid carcinoma; C-PTC, classical papillary thyroid carcinoma; OR, odds ratio; MD, standardized mean difference; CI, capsular invasion; VI, vascular invasion; EE, extrathyroidal extension; LNM, lymph node metastasis; LT, lymphocytic thyroiditis; HT, Hashimoto's thyroiditis; CS, clinical stage.

and C-PTC was 80.1 (1,136/1,418) and 81.9% (5,627/6,872), respectively, and the difference was not statistically significant (OR, 1.09; 95% CI, 0.93-1.29; P=0.29; Fig. 2A). No statistical heterogeneity was detected among the studies (χ^2=29.61, P=0.59, I^2=0%).

Age. Nineteen studies included mean age in the patient clinical data. The mean age of patients with FV-PTC ranged from 27 to 50.9 years, whereas those of the patients with C-PTC ranged from 26.3 to 52.88 years, and the difference was not significant (MD, -0.61; 95% CI, -1.75-0.53; P=0.29; Fig. 2B). No statistical heterogeneity was identified among the studies (χ^2=31.36, P=0.03, I^2=43%). In addition, 11 studies presented the prevalence of patients aged ≥45 years, which overall was 56.4 (219/388) and 51.5% (371/720) in patients with FV-PTC and C-PTC, respectively, and the difference was statistically significant (OR, 1.45; 95% CI, 1.11-1.90; P=0.007; Fig. 2C). There was no significant statistical heterogeneity among the studies (χ^2=8.90, P=0.54, I^2=0%).

Tumor size. Seventeen studies presented clinical data that included mean tumor size. The mean tumor size of patients with FV-PTC ranged from 14.4 to 34.7 mm, whereas that of patients with C-PTC ranged from 9.7 to 35.0 mm; this difference was statistically significant (MD, 2.88; 95% CI, 0.26-5.51; P=0.03; Fig. 2D). Significant statistical heterogeneity was present among the studies (χ^2=50.73, P<0.0001, I^2=68%). Ten studies presented the prevalence of the tumor size of patients with FV-PTC and C-PTC being ≥10 mm, which overall was 63.4 (251/396) and 45.8% (496/1,084), respectively, and the difference was not significant (OR, 1.25; 95% CI, 0.77-2.03; P=0.36; Fig. 2E). There was significant statistical heterogeneity among the studies (χ^2=21.73, P=0.010, I^2=59%).

Multifocality. In 17 studies that analyzed multifocality, the overall percentage of patients with multifocality in FV-PTC and C-PTC was 31.6 (257/813) and 30.7% (1,411/4,593), respectively, and the difference was not statistically significant (OR, 0.88; 95% CI, 0.64-1.22; P=0.44; Fig. 2F). No statistical heterogeneity was detected among the studies (χ^2=40.85, P=0.0006, I^2=61%).

Capsular invasion. In 6 studies that assessed the capsular invasion of the tumor, the percentages of patients with capsular invasion in FV-PTC and C-PTC were 28.1 (115/409) and 30.2% (281/932), respectively, and the difference was not statistically significant difference (OR, 0.82; 95% CI, 0.48-1.39; P=0.46; Fig. 2G). There was no statistical heterogeneity among the studies (χ^2=14.60, P=0.01, I^2=66%).

Vascular invasion. In 9 studies, the percentages of cases with vascular invasion in FV-PTC and C-PTC were reported; these were 19.8 (85/430) and 12.2% (86/704), respectively, and the difference was not significant (OR, 1.38; 95% CI, 0.56-3.42; P=0.49; Fig. 2H). Significant statistical heterogeneity was detected among the studies (χ^2=31.84, P<0.0001, I^2=75%).

Extrathyroidal extension. Eighteen studies presented the prevalence of cases with extrathyroidal extension in FV-PTC

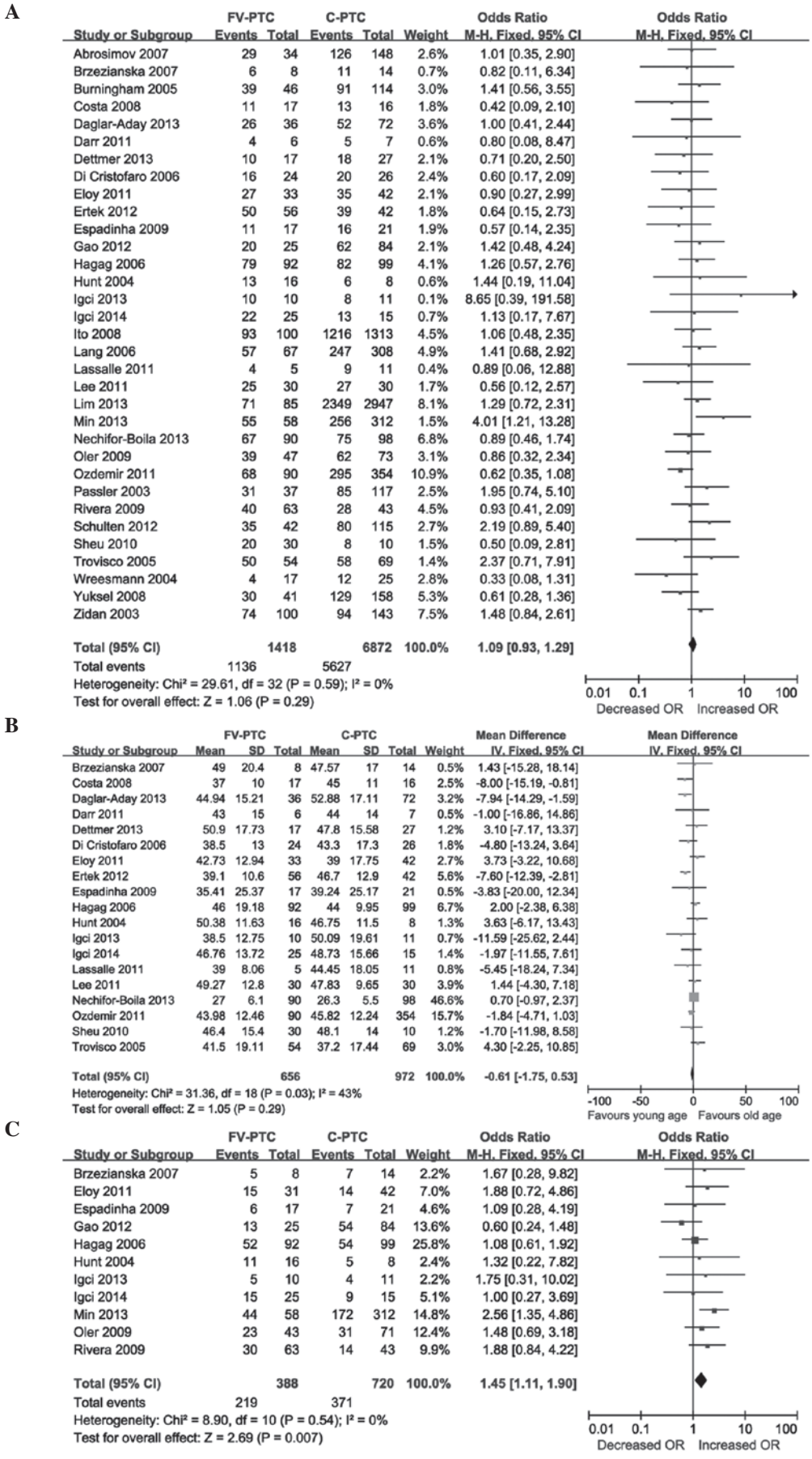

Figure 2. Forest plot for the comparison of (A) female, (B) mean age and (C) aged ≥45 years between follicular variant of papillary thyroid carcinoma (FV-PTC) and classical papillary thyroid carcinoma (C-PTC). ORs or MDs with corresponding 95% CIs of individual studies for comparison of clinico-pathological characteristics are shown. The forest plot shows the effect size and 95% CIs for each study and overall. OR, odds ratio; MD, mean difference; CI, confidence interval.

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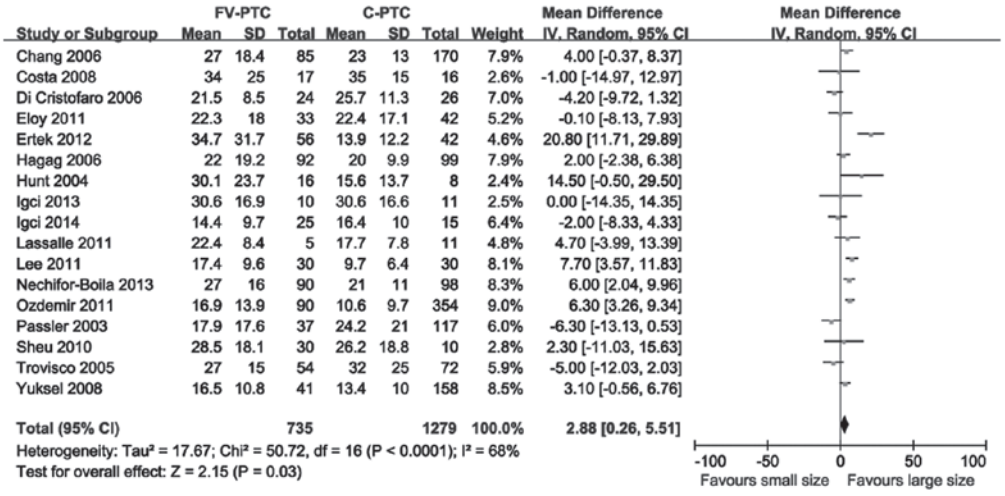

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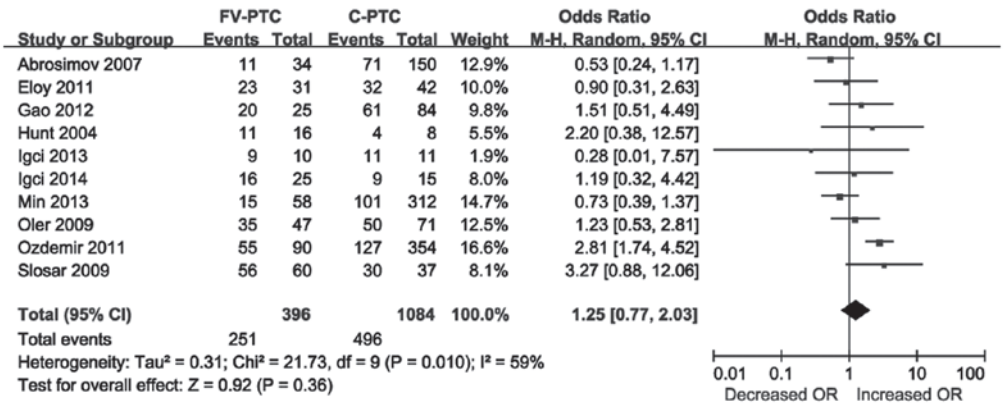

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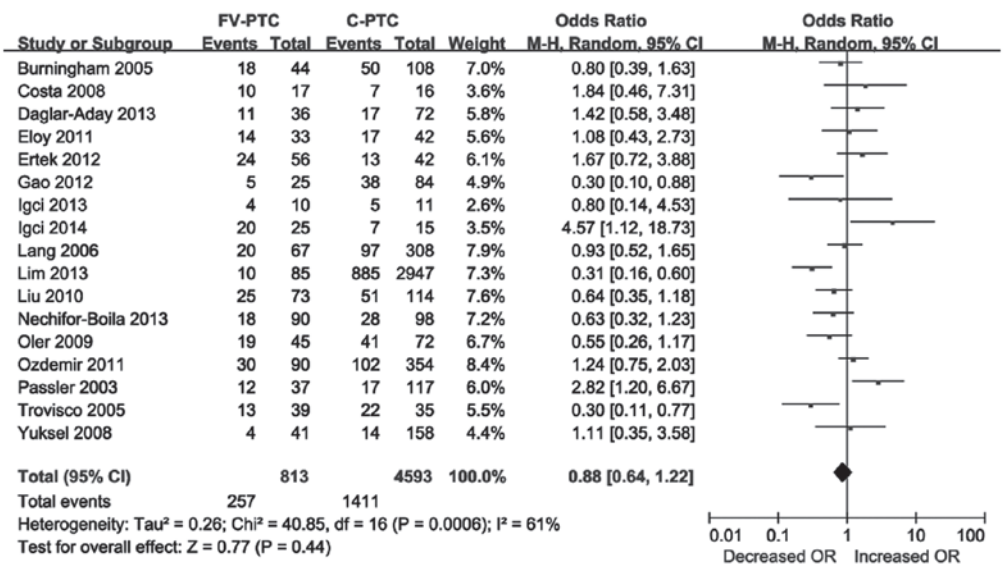

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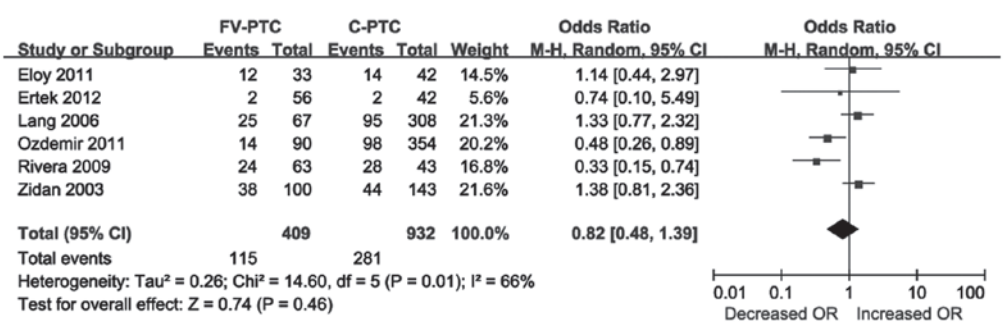

Figure 2. Continued. (D) Mean tumor size, (E) the tumor size being ≥10 mm, (F) multifocality and (G) capsular invasion between follicular variant of papillary thyroid carcinoma (FV-PTC) and classical papillary thyroid carcinoma (C-PTC). ORs or MDs with corresponding 95% CIs of individual studies for comparison of clinicopathological characteristics are shown. The forest plot shows the effect size and 95% CIs for each study and overall. OR, odds ratio; MD, mean difference; CI, confidence interval.

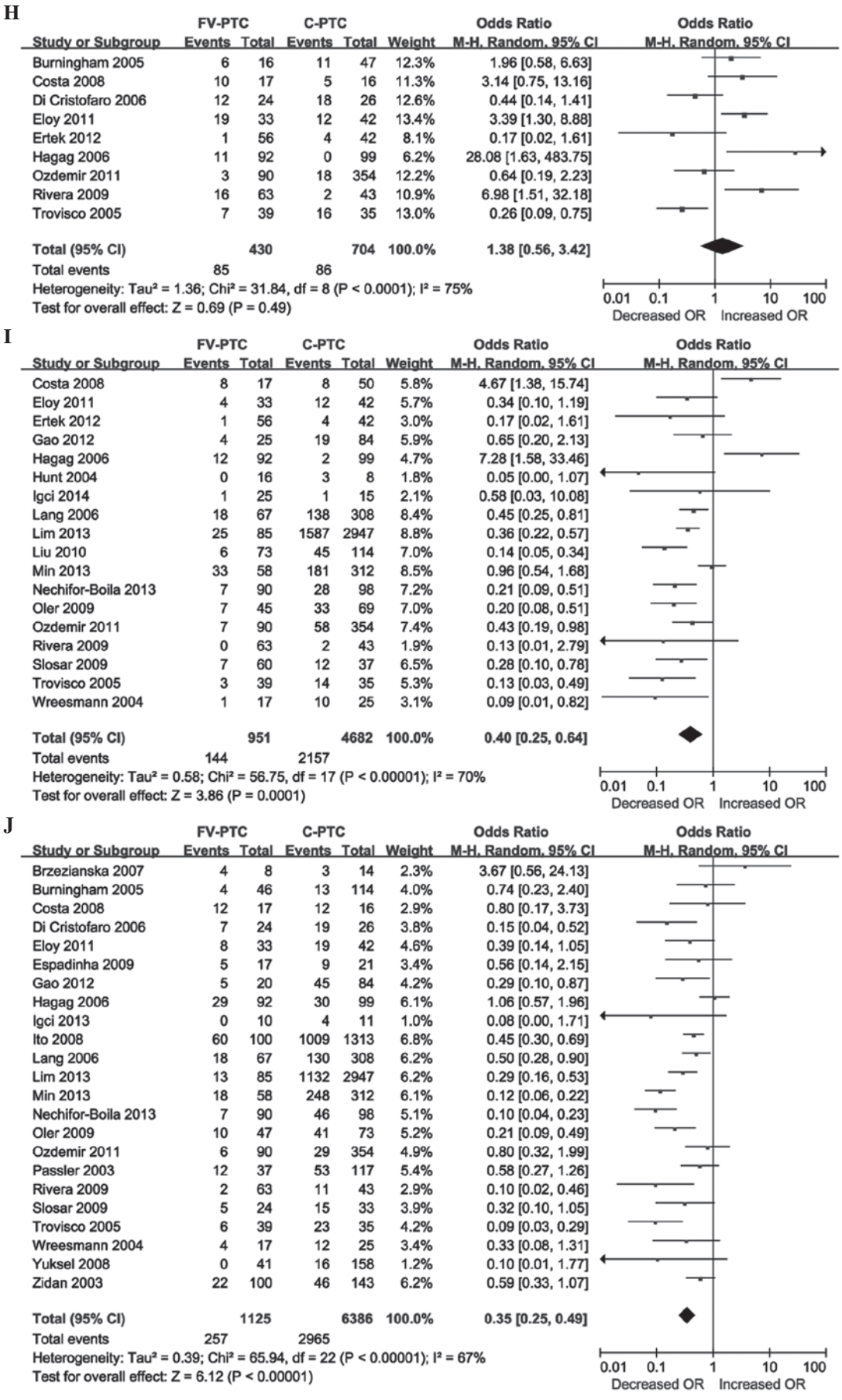

Figure 2. Continued. (H) Vascular invasion, (I) extrathyroidal extension and (J) lymph node metastasis between follicular variant of papillary thyroid carcinoma (FV-PTC) and classical papillary thyroid carcinoma (C-PTC). ORs or MDs with corresponding 95% CIs of individual studies for comparison of clinicopathological characteristics are shown. The forest plot shows the effect size and 95% CIs for each study and overall. OR, odds ratio; MD, mean difference; CI, confidence interval.

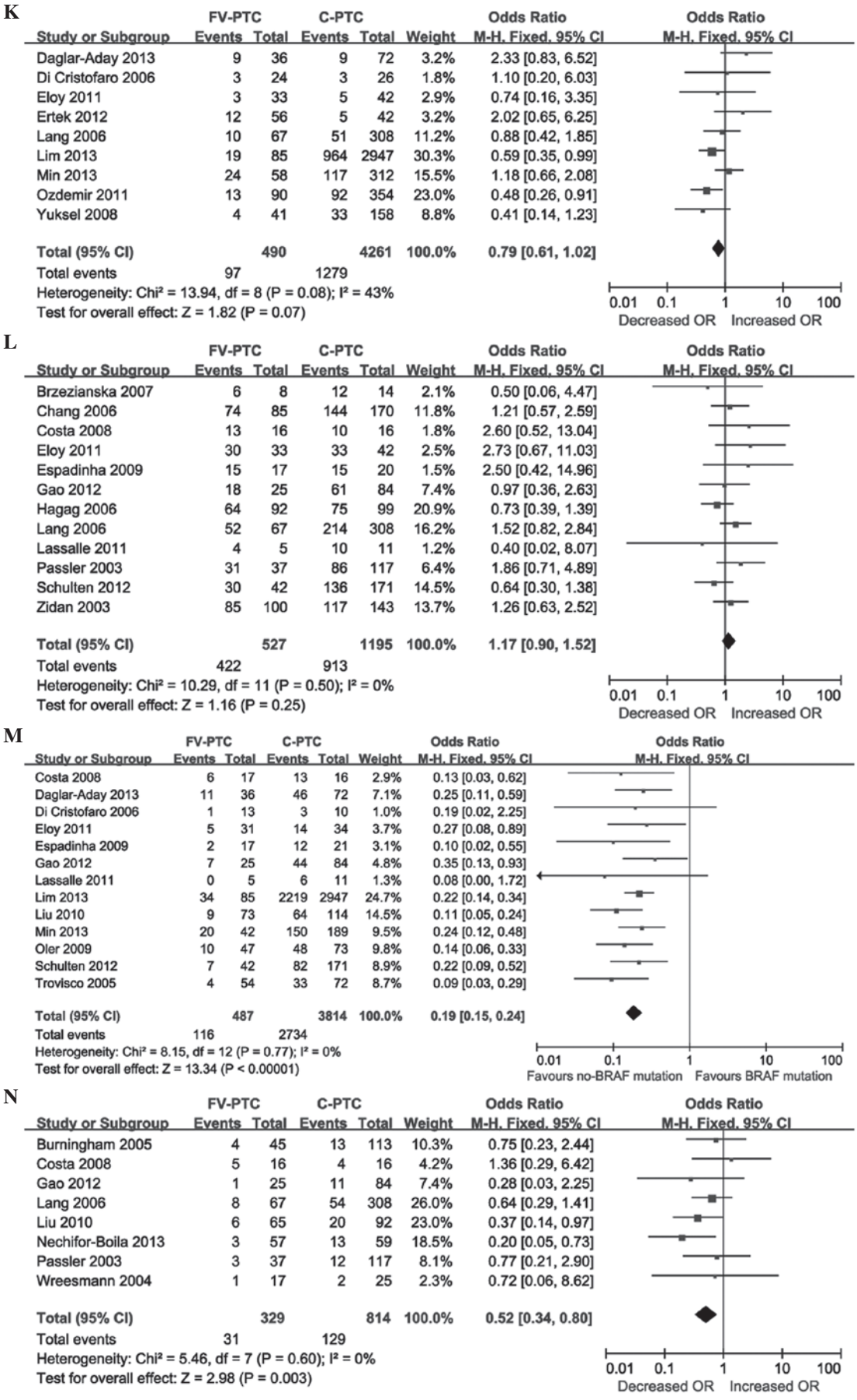

Figure 2. Continued. (K) Lymphocytic and/or Hashimoto's thyroiditis, (L) stages I + II, (M) *BRAF* mutation and (N) recurrence between follicular variant of papillary thyroid carcinoma (FV-PTC) and classical papillary thyroid carcinoma (C-PTC). ORs or MDs with corresponding 95% CIs of individual studies for comparison of clinicopathological characteristics are shown. The forest plot shows the effect size and 95% CIs for each study and overall. OR, odds ratio; MD, mean difference; CI, confidence interval.

and C-PTC, which overall was 15.1 (144/951) and 46.1% (2,157/4,682), respectively, and the difference was statistically significant (OR, 0.40; 95% CI, 0.25-0.64; P=0.0001; Fig. 2I). Significant statistical heterogeneity was detected among the studies (χ^2=56.75, P<0.00001, I^2=70%).

Lymph node metastasis. Twenty-three studies reported the prevalence of lymph node metastasis in patients with FV-PTC and C-PTC, which overall was 22.8 (257/1,125) and 46.4% (2,965/6,386), respectively, and this difference was statistically significant (OR, 0.35; 95% CI, 0.25-0.49; P<0.00001; Fig. 2J). Significant statistical heterogeneity was detected among the studies (χ^2=65.94, P<0.00001, I^2=67%).

Lymphocytic and/or Hashimoto's thyroiditis. Nine studies presented the prevalence of lymphocytic and/or Hashimoto's thyroiditis in patients with FV-PTC and C-PTC. The overall prevalence was 19.8 (97/490) and 30.0% (1,279/4,261), respectively, and the difference was not statistically significant (OR, 0.79; 95% CI, 0.61-1.02; P=0.07; Fig. 2K). There was no significant statistical heterogeneity among the studies (χ^2=13.94, P=0.08, I^2=43%).

Clinical stage. Twelve studies included clinical stage in their analyses. The stage of the tumor was I or II in 422/527 (80.1%) patients with FV-PTC and in 913/1,195 (76.4%) patients with C-PTC; the difference was not statistically significant (OR, 1.17; 95% CI, 0.0-1.52; P=0.25; Fig. 2L). There was no significant statistical heterogeneity among the studies (χ^2=10.29, P=0.50, I^2=0%).

BRAF mutation. Thirteen studies presented the prevalence of *BRAF* mutation in patients with FV-PTC and C-PTC, which overall was 23.8 (116/487) and 71.7% (2,734/3,814), respectively, and the difference was statistically significant (OR, 0.19; 95% CI, 0.15-0.24, P<0.00001; Fig. 2M). There was no significant statistical heterogeneity among the studies (χ^2=8.15, P=0.77, I^2=0%).

Recurrence. Eight studies evaluated the recurrence of tumor while following up patients with FV-PTC and C-PTC for varying periods. The overall percentage of recurrence was 9.4 (31/329) and 15.8% (129/814), respectively, and the difference was statistically significant (OR, 0.52; 95% CI, 0.34-0.80; P=0.003; Fig. 2N). There was no significant statistical heterogeneity among the studies (χ^2=5.46, P=0.60, I^2=0%).

Publication bias. Funnel plots and Begg's test were performed to access the publication bias. All the Begg's funnel plots did not show evident asymmetry (Begg's funnel plots not shown), and the results of Egger's test were confirmed for the comparison of clinical parameters of FV-PTC and C-PTC (all P>0.05 for Egger's test; Table II). The results of Begg's funnel plot and Egger's test did not show any publication bias.

Discussion

Following a systematic review of the recent literature, it was observed that FV-PTC has been increasingly diagnosed in recent years, and an increasing amount of research is being performed concerning FV-PTC. The majority of studies comparing the clinicopathological behavior of FV-PTC and C-PTC have limitations, such as inclusion of relatively few cases, incomprehensive categories of clinical parameters and single-institution bias. Thus, their conclusions were mutually conflicting. Therefore, it is necessary to acquire a more comprehensive view of FV-PTC from population-based studies, and a meta-analysis can achieve this. To the best of our knowledge, this is the first study of a meta-analysis comparing the clinicopathological behavior of FV-PTV and C-PTC.

The findings reveal that the following clinicopathological parameters are significantly different between patients with FV-PTC and those with C-PTC: Patient age (≥45 years), mean tumor size, extrathyroidal extension, lymph node metastasis, *BRAF* mutation and recurrence. By contrast, no significant differences were identified in gender, mean age, tumor size (≥10 mm), multifocality, capsular invasion, vascular invasion, lymphocytic and/or Hashimoto's thyroiditis, and clinical stage.

Patients with FV-PTC and C-PTC have similarly high prevalence of females, and this finding is consistent with nearly all the relevant studies. When analyzing age and tumor size, the meta-analysis was performed in two ways. The mean age of patients with FV-PTC was similar to that of patients with C-PTC, but the former were more likely to be ≥45 years old. The number of patients with FV-PTC and C-PTC in the analysis of mean age was 656 and 972 (total 1,628) respectively, which is a larger population of patients in the analysis of age ≥45 years being 219 and 371 (total 590). Logically, the mean age analysis may be more reliable. The findings were not consistent in the mean tumor size and the prevalence of tumor size ≥10 mm. The mean tumor size of patients with FV-PTC was larger than that of the patients with C-PTC, which is in agreement with the results of studies by Chang *et al* (10), Ozdemir *et al* (17), Burningham *et al* (19), Jain *et al* (49) and Kim *et al* (50). Ozdemir *et al* (17) and Kim *et al* (50) also reported that compared to C-PTC, FV-PTC has more benign sonographic features, a lower incidence of a sonographically malignant grade and a lower diagnostic rate of PTC on fine-needle aspiration biopsy (FNAB). Thus, the lower rate of suspicious findings in FV-PTC lesions may have caused evaluation of larger FV-PTC lesions by FNAB, resulting in the detection of these lesions at a later stage. In addition, FV-PTC lesions may have become larger when patients with FV-PTC underwent surgery. However, the present study identified that the prevalence of tumor size ≥10 mm was similar between the two types. By contrast, Tielens *et al* (5) reported that tumor size of FV-PTC tends to be smaller than that of C-PTC. The present study showed similar prevalence of multifocality, capsular invasion, vascular invasion, lymphocytic and/or Hashimoto's thyroiditis, and clinical stage between patients with FV-PTC and C-PTC.

The prevalence of the above results has been controversial. Passler *et al* (12) suggested that there was a significantly higher prevalence of multifocality in patients with FV-PTC compared to patients with C-PTC, but the opposite was reported by Gao *et al* (31) and Trovisco *et al* (47). Certain studies reported a higher prevalence of capsular invasion and vascular invasion in the FV-PTC (10,20,51), whereas others did not (17,43,47). Although the majority of the C-PTCs do not have a tumor capsule, patients with C-PTC (28.1%) and patients with

FV-PTC (30.2%) showed a similar high prevalence of capsular invasion of tumor in the present meta-analysis. As C-PTC is more inclined to show infiltrative growth, the tumor easily invades the capsule once containing the tumor capsule. When histopathologically comparing the presence of concomitant lymphocytic and/or Hashimoto's thyroiditis in patients with FV-PTC and C-PTC, Tielens *et al* (5) reported a higher rate in the former, whereas Yuksel *et al* (16) reported a higher rate in the latter.

Nearly all the relevant literature on clinical stages shows the same ratio of clinical stage I + II in patients with FV-PTC and C-PTC, thereby suggesting that clinical stages of patients with FV-PTC and C-PTC are similar. The present meta-analysis reveals that the incidence of associated extrathyroidal extension, lymph node metastases, *BRAF* mutation and recurrence is significantly lower in patients with FV-PTC compared to patients with C-PTC. As described in the majority of the studies, the frequencies of extrathyroidal extension and lymph node metastases are lower in patients with FV-PTC compared to patients with C-PTC; however, a few studies reported opposing findings (20,24). Consistently, all the relevant studies on the *BRAF* gene shows the lower ratio of *BRAF* mutation in patients with FV-PTC compared to patients with C-PTC. The majority of meta-analysis studies showed that the *BRAF* mutation was associated with the majority of vital clinicopathological characteristics in PTC, and the *BRAF* mutation may be used as an important prognostic marker of patients with PTC (52-56). However, when analyzing FV-PTC and C-PTC respectively, Gao *et al* (31) and Oler *et al* (42) identified that the *BRAF* mutation was associated with the clinicopathological characteristics in patients with C-PTC, but not in patients with FV-PTC.

After the similar follow-up periods, the rate of recurrence in patients with FV-PTC was significantly lower than that in the patients with C-PTC, which may be associated with the above finding that patients with FV-PTC are at a lower risk of extrathyroidal extension, lymph node metastases or *BRAF* mutation. Aggressive clinicopathological behavior of patients with PTC is associated with old age, and include the following: Presence of extrathyroidal extension, lymph node metastases, advanced clinical stages and *BRAF* mutation. Therefore, poor prognosis in patients with PTC is associated with certain aggressive clinicopathological characteristics. Therefore, patients with FV-PTC have an improved prognosis compared to patients with C-PTC. However, it may be affected by treatment factors such as type of surgery, I-131 ablation and use of external radiotherapy.

Patients with FV-PTC have a lower prevalence of extrathyroidal extension, lymph node metastases, *BRAF* mutation and recurrence compared to patients with C-PTC. The mean tumor size is larger and the incidence of patients aged ≥45 years are higher in the former. Thus, as reported in a previous study (8) and in the present meta-analysis, patients with FV-PTC exhibit a more favorable clinicopathological behavior and improved prognosis compared to patients with C-PTC. Thus, the lower incidence of extrathyroidal extension, lymph node metastases, *BRAF* mutation and recurrence would appear to be distinct clinicopathological behavior of FV-PTC. Patients with FV-PTC and C-PTC are clearly two different groups. As was also reported by Yu *et al* (57) and Chang *et al* (10), the clinicopathological behavior of FV-PTC is unique and represents an intermediate entity between C-PTC and FTC. Different approaches may be used for their clinical management. More invasive treatment strategies, such as total thyroidectomy or central lymph node dissection, may be considered in patients with C-PTC presenting extrathyroidal extension, lymph node metastasis or *BRAF* mutation to decrease recurrence.

The present study has several limitations. One primary limitation is that reporting of FV-PTC is not a standard practice in certain hospitals, leading to a reporting bias. There may be an interpretational difference among pathologists, as FV-PTC may be confused with FTC. Additionally, stratified analyses of summary data from the reported studies could not be performed, and the present study was unable to identify the diverse sources of heterogeneity of the effect size. In addition, multiple outcome variables require cautious interpretation as the outcomes may be interrelated. For instance, the patients with extrathyroidal extension tend to have a more advanced clinical stage and a higher risk of recurrence than those with no extension. However, this limitation is unlikely to have a significant impact on the present study as the sample size in the meta-analysis is sufficiently large.

The meta-analysis suggested that, patients with FV-PTC present more favorable clinicopathological behaviors and improved prognosis than patients with C-PTC. Patients with FV-PTC and C-PTC may be managed differently, and the two types of PTC should be clearly distinguished in future retrospective or prospective studies. For instance, it may not be necessary for patients with FV-PTC to undertake the invasive strategies that are appropriate in patients with C-PTC, if the FV-PTC is diagnosed prior to or during surgery. However, more valuable studies on a large cohort of cases are required to evaluate the clinicopathological behavior in patients with FV-PTC and patients with C-PTC.

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