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ORIGINAL REPORT

BRAF V600E Confers Male Sex Disease-Specific Mortality Risk in Patients With Papillary Thyroid Cancer

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ABSTRACT

Purpose
To test whether the prognostic risk of male sex in papillary thyroid cancer (PTC) is determined by *BRAF* V600E and can thus be stratified by *BRAF* status.

Patients and Methods
We retrospectively investigated the relationship between male sex and clinicopathologic outcomes in PTC, particularly mortality, with respect to *BRAF* status in 2,638 patients (male, n = 623; female, n = 2,015) from 11 centers in six countries, with median age of 46 years (interquartile range, 35-58 years) at diagnosis and median follow-up time of 58 months (interquartile range, 26-107 months).

Results
Distant metastasis rates in men and women were not different in wild-type *BRAF* PTC but were different in *BRAF* V600E PTC: 8.9% (24 of 270) and 3.7% (30 of 817; $P = .001$), respectively. In wild-type *BRAF* PTC, mortality rates were 1.4% (five of 349) versus 0.9% (11 of 1175) in men versus women ($P = .384$), with a hazard ratio (HR) of 1.59 (95% CI, 0.55 to 4.57), which remained insignificant at 0.70 (95% CI, 0.23 to 2.09) after clinicopathologic multivariable adjustment. In *BRAF* V600E PTC, mortality rates were 6.6% (18 of 272) versus 2.9% (24 of 822) in men versus women ($P = .006$), with an HR of 2.43 (95% CI, 1.30 to 4.53), which remained significant at 2.74 (95% CI, 1.38 to 5.43) after multivariable adjustment. In conventional-variant PTC, male sex similarly had no effect in wild-type *BRAF* patients; mortality rates in *BRAF* V600E patients were 7.2% (16 of 221) versus 2.9% (19 of 662) in men versus women ($P = .004$), with an HR of 2.86 (95% CI, 1.45 to 5.67), which remained significant at 3.51 (95% CI, 1.62 to 7.63) after multivariable adjustment.

Conclusion
Male sex is a robust independent risk factor for PTC-specific mortality in *BRAF* V600E patients but not in wild-type *BRAF* patients. The prognostic risk of male sex in PTC can thus be stratified by *BRAF* status in clinical application.

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INTRODUCTION

Papillary thyroid cancer (PTC) is a common thyroid malignancy, accounting for 85% to 90% of all thyroid malignancies, and conventional PTC (CPTC) is the main histologic variant.[1,2] PTC is generally indolent but can be aggressive, with high mortality in certain patients.[2] Individualized patient treatment of optimal benefit-harm balance is the core of management of PTC in clinical practice. This relies on appropriate stratification of prognostic risk, particularly mortality risk of patients, which is primarily based on clinicopathologic risk factors, including patient age, tumor size, metastasis, and extrathyroidal extension. These are well-established independent mortality risk factors for PTC, which constitute the cardinal elements in the mortality risk staging system for PTC of the American Joint Committee on Cancer (AJCC).[3,4] The AJCC risk staging system has been consistently adapted in standard clinical practice guidelines for the risk management of PTC.[5-7] Several other mortality risk staging systems for PTC that have emerged over the recent decades are all based on these clinicopathologic risk factors.[8,9]

A prominent but controversial mortality risk factor of PTC is male sex. Some early studies did not show a significant effect of male sex on

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PTC-specific patient survival,[10-12] but others did.[13] A large study showed an independent adverse effect of male sex on PTC-specific survival,[14] whereas a comparably large study conducted at approximately the same time showed no independent effect of male sex.[15] Given these and other early controversial data, the AJCC and virtually all other risk staging systems avoid including sex as a factor in the risk staging of PTC. However, whether this is the correct practice is unclear. An increasing number of recent studies have shown an association between male sex and aggressive PTC tumor behaviors, such as lymph node metastasis,[16,17] although some have not.[18] Recent studies have shown an association between male sex and tumor recurrence[19,20] as well as disease-specific mortality of PTC.[21,22] Recent large entry data analyses have also shown an association between male sex and PTC-specific mortality.[23-25] The recent results, however, have again been inconsistent. For example, the effect of male sex remained after multivariable adjustment for clinicopathologic factors in some large entry data analyses,[26] but it was lost in other large entry data analyses upon clinicopathologic multivariable adjustment.[27] Thus, whether male sex is a true risk factor and how it can be applied in the prognostic risk stratification of PTC remain controversial.

Like other cancers, PTC is a genetically driven disease, and *BRAF* V600E mutation is the most common oncogenic mutation, occurring in 45% of patient cases on average.[28] This mutation is associated with aggressive tumor behaviors,[29] disease recurrence,[30,31] and disease-specific mortality of PTC.[32] Numerous studies have documented oncogenic molecular mechanisms of *BRAF* V600E in driving the aggressiveness of PTC.[33,34] Given these data, in this large international multicenter study, we tested our hypothesis that *BRAF* V600E mutation might constitute a genetic background conferring male sex mortality risk and that *BRAF* status could thus differentiate the prognostic risk of male sex in PTC, reconciling the controversial clinical results from recent decades.

Table 1. Centers, Countries, and Patients Participating in the Study

Medical Center or Country	No. of Patients	Median (IQR) Age at Diagnosis (years)	No. (%) of Male Patients
Medical center			
Johns Hopkins Hospital (Baltimore, MD)	1,051	46 (36-57)	287 (27.3)
University of Pisa (Pisa, Italy)	189	38 (28-51)	47 (24.9)
University of Perugia (Perugia, Italy)	117	49 (37-59)	32 (27.4)
University of Milan (Milan, Italy)	265	45 (36-58)	63 (23.8)
Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology (Gliwice, Poland)	253	47 (35-59)	30 (11.9)
Griffith University (Gold Coast, Queensland, Australia)	76	40 (34-56)	20 (26.3)
University of Padua (Padua, Italy)	135	48 (39-57)	32 (23.7)
University of Pittsburgh (Pittsburgh, PA)	169	52 (38-63)	42 (24.9)
Hospital La Paz Health Research Institute (Madrid, Spain)	66	42 (32-54)	11 (16.7)
University of Sydney (Sydney, New South Wales, Australia)	95	44 (34-59)	20 (21.1)
Institute of Endocrinology (Prague, Czech Republic)	222	47 (31-60)	39 (17.6)
Country			
United States	1,220	47 (37-58)	329 (27.0)
Italy	706	45 (34-56)	174 (24.6)
Poland	253	47 (35-59)	30 (11.9)
Australia	171	43 (34-57)	40 (23.4)
Spain	66	42 (32-54)	11 (16.7)
Czech Republic	222	47 (31-60)	39 (17.6)
Overall	2,638	46 (35-58)	623 (23.6)

Abbreviation: IQR, interquartile range.

PATIENTS AND METHODS

Study patients

A total of 2,638 patients with PTC treated with total or near-total thyroidectomy and therapeutic neck dissection were pooled from 11 medical centers in six countries (Table 1). Pathologic diagnoses of PTC were established following WHO criteria as documented previously.[31,32,35] Postsurgical therapies, including conventional thyrotropin suppression and radioiodine-131 treatments, were pursued as clinically indicated following standard practice. Disease recurrence, including local, regional, and distant recurrences, referred to recurrent or persistent PTC diagnosed per standard histologic, cytologic, radiographic, or biochemical criteria.[5,6] Mortality was defined as PTC-specific patient death. Follow-up time was defined as the time period from initial surgical treatment to time of discovery of disease (for recurrence analyses) or PTC-specific death (for mortality analyses) or to the most recent clinical visit for surviving patients without disease recurrence or death.

Study Design

This was a multicenter retrospective study with institutional review board approval at each center and, where required, informed patient consent for the use of thyroid tumor tissue and collection of clinicopathologic information as described previously.[31,32,35] Genomic DNA isolated from primary PTC tumors was sequenced at exon 15 of the *BRAF* gene to identify *BRAF* V600E mutation as described previously.[31,32] *BRAF* V600E mutation status was retrospectively examined solely for this study and had no impact on the selection of treatment for patients. Data from all the centers were pooled for the analysis of the relationship between patient sex and clinical outcomes with respect to *BRAF* V600E status.

Statistical Analyses

Comparisons of categorical variables were performed using the Pearson χ^2 test and Fisher's exact test when the number of patient cases was $\leq$ five. Wilcoxon Mann-Whitney test for two independent samples in nonparametric statistics was used to compare the median and interquartile range (IQR) of continuous variables. Survival probability was estimated by Kaplan-Meier analysis and log-rank test to compare the differences between Kaplan-Meier curves of men and women. Cox regression and Cox proportional hazards analyses were used to compare the univariable and multivariable effects on disease recurrence and mortality and calculate hazard ratio (HRs) and 95% CIs. SPSS software (version 17.0; SPSS, Chicago, IL) was used for these analyses. All *P* values were two sided, and a value $\leq$ .05 was considered significant.

RESULTS

Effects of Male Sex on Clinicopathologic Characteristics of PTC With Respect to BRAF Status

As summarized in Table 2, a total of 2,638 patients with PTC, of whom 76.4% (2,015) were women and 23.6% (623) were men,

were included in the study, with a median age of 46 years (IQR, 35-58 years) at diagnosis of PTC and a median clinical follow-up time of 58 months (IQR, 26-107 months). CPTC accounted for 71.8% (1,893 of 2,638) of the patient cases. Taking advantage of this large international multicenter cohort, we first examined the effect of male sex on clinicopathologic characteristics of PTC as performed in previous studies. Compared with female sex, male sex was associated with a higher prevalence of several high-risk clinicopathologic characteristics, including older patient age, larger tumor size, extrathyroidal extension, lymph node metastasis, distant metastasis, and advanced disease stages of III or IV. These results were consistent with some previous reports.

The overall prevalence of *BRAF* V600E mutation was 41.8% (1,094 of 2,618) and was not different between men and women

Table 2. Demographic Characteristics and Distribution of Clinicopathologic Characteristics of PTC Among Men and Women

Characteristic	No. (%)			*P*
	Total	Women	Men	
All PTCs*				
Total patients	2,638	2,015 (76.4)	623 (23.6)	
Age at diagnosis, years				< .001
Median	46	45	49	
IQR	35-58	34-57	38-60	
≥ 45	1,408 (53.4) of 2,638	1,027 (51.0) of 2,015	381 (61.2) of 623	< .001
Tumor size, cm				
Median	1.5	1.5	1.8	< .001
IQR	1.0-2.5	1.0-2.5	1.0-3.2	
> 1.0	1,820 (70.0) of 2,601	1,371 (69.0) of 1,987	449 (73.1) of 614	.051
Multifocality	1,000 (38.1) of 2,624	739 (36.9) of 2,004	261 (42.1) of 620	.019
Extrathyroidal extension	668 (25.4) of 2,634	480 (23.9) of 2,012	188 (30.2) of 622	.001
Lymph node metastasis	896 (34.3) of 2,613	632 (31.7) of 1,996	264 (42.8) of 617	< .001
Tumor stage III/IV	614 (23.5) of 2,618	410 (20.5) of 2,000	204 (33.0) of 618	< .001
Distant metastasis	118 (4.5) of 2,615	79 (4.0) of 1,996	39 (6.3) of 619	.014
BRAF mutation	1,094 (41.8) of 2,618	822 (41.2) of 1,997	272 (43.8) of 621	.244
^{131}I treatment†	1,984 (77.5) of 2,559	1,495 (76.4) of 1,957	489 (81.2) of 602	.013
Follow-up time (R), months				.003
Median	51	52	46	
IQR	23-96	24-99	19-91	
Tumor recurrence	423 (16.0) of 2,638	275 (13.6) of 2,015	148 (23.8) of 623	< .001
Follow-up time (M), months				.198
Median	58	58	55	
IQR	26-107	27-107	24-108	
Mortality	58 (2.2) of 2,638	35 (1.7) of 2,015	23 (3.7) of 623	.004
CPTC*				
Total patients	1,893	1,440 (76.1)	453 (23.9)	
Age at diagnosis, years	1,893	1,440	453	< .001
Median	46	45	49	
IQR	35-57	34-57	39-60	
≥ 45	1,002 (52.9) of 1,893	725 (50.3) of 1,440	277 (61.1) of 453	< .001
Tumor size, cm				< .001
Median	1.5	1.5	1.6	
IQR	1.0-2.4	1.0-2.2	1.0-3.0	
> 1.0	1,241 (66.3) of 1,873	931 (65.2) of 1,428	310 (69.7) of 445	.082
Multifocality*	731 (38.7) of 1,888	540 (37.6) of 1,437	191 (42.4) of 451	.070
Extrathyroidal extension	504 (26.7) of 1,890	356 (24.8) of 1,438	148 (32.7) of 452	.001
Lymph node metastasis	690 (36.9) of 1,872	482 (33.8) of 1,425	208 (46.5) 447	< .001
Tumor stage III/IV	445 (23.7) of 1,881	294 (20.5) of 1,432	151 (33.6) of 449	< .001
Distant metastasis	74 (3.9) of 1,885	46 (3.2) of 1,433	28 (6.2) of 452	.004
BRAF mutation	883 (47.0) of 1,879	662 (46.4) of 1,428	221 (49.0) of 451	.327
^{131}I treatment†	1,418 (76.6) of 1,851	1,061 (75.3) of 1,409	357 (80.8) of 442	.018
Follow-up time (R), months				.001
Median	52	54	46	
IQR	24-99	24-102	19-90	
Tumor recurrence	320 (16.9) of 1,893	199 (13.8) of 1,440	121 (26.7) of 453	< .001
Follow-up time (M), months				.134
Median	60	61	57	
IQR	27-110	28-110	25-110	
Mortality	41 (2.2) of 1,893	23 (1.6) of 1,440	18 (4.0) of 453	.002

Abbreviations: CPTC, conventional papillary thyroid cancer; ^{131}I, radioiodine-131; IQR, interquartile range; M, mortality; PTC, papillary thyroid cancer; R, recurrence.
*Data were from medical centers 1 to 11 (Data Supplement), with a total of 2,638 patient cases of PTC, including 1,893 CPTCs. Information on tumor size, multifocality, extrathyroidal extension, lymph node metastasis, tumor stage III/IV, distant metastasis, and *BRAF* mutation was missing in 37 and 20, 14 and five, four and three, 25 and 21, 20 and 12, 23 and eight, and 20 and 14 patient cases in the group of patients with any PTC and the group with CPTC, respectively.
†Data on ^{131}I treatment were from medical centers 1 to 5 and 7 to 11, with a total of 2,562 patient cases, including 1,853 CPTCs, with information missing in three and two patient cases in the group of patients with any PTC and the group with CPTC, respectively.

(Table 2). When dividing the entire cohort into wild-type *BRAF* and *BRAF* V600E groups, the effect of male sex on clinicopathologic characteristics, such as extrathyroidal extension, lymph node metastasis, and stage III to IV, was significant in both wild-type *BRAF* and *BRAF* V600E groups (Table 3). A striking exception was distant metastasis, which is known to be the most robust risk factor for PTC-specific mortality; there was no difference in the distant metastasis rate between men and women with wild-type *BRAF* PTC: 4.3% (15 of 347) and 4.2% (49 of 1,161; $P = .934$), respectively. In contrast, distant metastasis rates were sharply different between men and women with *BRAF* V600E PTC: 8.9% (24 of 270) and 3.7% (30 of 817; $P = .001$), respectively. Similar results were obtained when only CPTC was analyzed (Table 3). Specifically, there was no difference in distant metastasis rate between men and women with wild-type *BRAF* CPTC: 3.5% (eight of 229) and 3.0% (23 of 762; $P = .717$), respectively; however, there

Table 3. Effects of Patient Sex on Clinicopathologic Characteristics of PTC by *BRAF* Status

Characteristic	Wild-Type *BRAF*			*BRAF* V600E		
	No. (%) of Women	No. (%) of Men	*P*	No. (%) of Women	No. (%) of Men	*P*
All PTCs*						
Total patients	1,175 (77.1) of 1,524	349 (22.9) of 1,524		822 (75.1) of 1,094	272 (24.9) of 1,094	
Age at diagnosis, years			< .001			.001
Median	44	47		47	51	
IQR	33-55	37-60		35-59	40-60	
≥ 45	561 (47.7) of 1,175	200 (57.3) of 349	.002	455 (55.4) of 822	180 (66.2) of 272	.002
Tumor size, cm			.001			.001
Median	1.5	1.8		1.6	2.0	
IQR	0.9-2.5	1.0-3.4		1.1-2.5	1.2-3.0	
> 1.0	742 (64.2) of 1,156	232 (67.4) of 344	.267	620 (76.3) of 813	216 (80.6) of 268	.141
Multifocality	412 (35.3) of 1,166	139 (22.9) of 346	.101	318 (38.8) of 820	120 (44.1) of 272	.120
Extrathyroidal extension	191 (16.3) of 1,173	83 (23.8) of 349	.001	284 (34.6) of 821	103 (38.0) of 271	.308
Lymph node metastasis	311 (26.9) of 1,158	138 (39.8) of 347	< .001	312 (38.0) of 820	125 (46.6) of 268	.013
Tumor stage III/IV	166 (14.2) of 1,166	90 (26.0) of 346	< .001	240 (29.4) of 816	113 (41.9) of 270	< .001
Distant metastasis	49 (4.2) of 1,161	15 (4.3) of 347	.934	30 (3.7) of 817	24 (8.9) of 270	.001
^{131}I treatment†	812 (70.7) of 1,148	255 (76.6) of 333	.036	665 (84.1) of 791	232 (86.9) of 267	.267
Follow-up time (R), months			.068			.032
Median	58	52		45	34	
IQR	25-115	24-98		21-85	15-79	
Tumor recurrence	122 (10.4) of 1,175	61 (17.5) of 349	< .001	152 (18.5) of 822	87 (32.0) of 272	< .001
Follow-up time (M), months			.238			.705
Median	64	59		52	48	
IQR	29-119	26-112		24-93	22-102	
Mortality	11 (0.9) of 1,175	5 (1.4) of 349	.384	24 (2.9) of 822	18 (6.6) of 272	.006
CPTC*						
Total patients	766 (76.9) of 996	230 (23.1) of 996		662 (75.0) of 883	221 (25.0) of 883	
Age at diagnosis, years			.003			< .001
Median	44	47		46	50	
IQR	34-55	38-60		34-59	40-59	
≥ 45	365 (47.7) of 766	133 (57.8) of 230	.007	351 (53.0) of 662	143 (64.7) of 221	.002
Tumor size, cm			.045			.003
Median	1.3	1.5		1.5	1.8	
IQR	0.7-2.0	0.7-2.7		1.1-2.5	1.2-3.0	
> 1.0	431 (56.6) of 761	135 (59.7) of 226	.408	496 (75.7) of 655	174 (80.2) of 217	.177
Multifocality	279 (36.5) of 765	89 (39.0) of 228	.482	254 (38.5) of 660	100 (45.2) of 221	.076
Extrathyroidal extension	137 (17.9) of 765	58 (25.2) of 230	.014	216 (32.7) of 661	88 (40.0) of 220	.048
Lymph node metastasis	222 (29.5) of 752	99 (43.4) of 228	< .001	255 (38.6) of 661	108 (49.8) of 217	.004
Tumor stage III/IV	111 (14.6) of 761	58 (24.6) of 228	< .001	180 (27.3) of 659	94 (42.9) of 219	< .001
Distant metastasis	23 (3.0) of 762	8 (3.5) of 229	.717	23 (3.5) of 659	20 (9.0) of 221	.001
^{131}I treatment†	512 (67.7) of 756	167 (74.9) of 223	.041	537 (83.8) of 641	188 (86.6) of 217	.314
Follow-up time (R), months			.052			.007
Median	62	55		47	34	
IQR	28-120	25-96		22-87	14-84	
Tumor recurrence	75 (9.8) of 766	47 (20.4) of 230	< .001	123 (18.6) of 662	74 (33.5) of 221	< .001
Follow-up time (M), months	766	230	.293	662	221	.350
Median	66	62		54	48	
IQR	35-124	30-118		26-97	21-107	
Mortality	4 (0.5) of 766	2 (0.9) of 230	.626	19 (2.9) of 662	16 (7.2) of 221	.004

Abbreviations: CPTC, conventional papillary thyroid cancer; ^{131}I, radioiodine-131; IQR, interquartile range; M, mortality; PTC, papillary thyroid cancer; R, recurrence.
*Data were from medical centers 1 to 11 (Data Supplement), with a total of 2,638 patient cases of PTC, including 1,893 CPTCs. Information on tumor size, multifocality, extrathyroidal extension, lymph node metastasis, tumor stage III/IV, distant metastasis, and *BRAF* mutation was missing in 37 and 20, 14 and five, four and three, 25 and 21, 20 and 12, 23 and eight, and 20 and 14 patient cases in the group of patients with any PTC and the group with CPTC, respectively.
†Data on ^{131}I treatment were from medical centers 1 to 5 and 7 to 11, with a total of 2,562 patient cases, including 1,853 CPTCs, with information missing in three and two patient cases in the group of patients with any PTC and the group with CPTC, respectively.

was a significant difference in distant metastasis rate between men and women with *BRAF* V600E CPTC: 9.0% (20 of 221) and 3.5% (23 of 659; $P = .001$), respectively.

Effects of Male Sex on Recurrence and Mortality of PTC With Respect to BRAF *Status*

In the overall analysis of PTC, disease recurrence and patient mortality rates were 16.0% (423 of 2,638) and 2.2% (58 of 2,638), respectively, which were all higher in men than women, whether in the analysis of all PTCs or CPTCs (Table 2). Corresponding HRs were all significant, and they remained significant except for mortality in the analysis of all PTCs after multivariable clinicopathologic adjustment for patient age at diagnosis, tumor size, multifocality, extrathyroidal extension, lymph node metastasis, and radioiodine-131 treatment (Table 4). These results were consistent with some previous reports. However, a striking finding was the effect of *BRAF* V600E revealed when the cohort was divided into wild-type *BRAF* and *BRAF* V600E groups (Tables 3 and 4). In wild-type *BRAF* patients, although disease recurrence was significantly higher in men than women in univariable analyses of either all PTCs or CPTCs (Table 3), this difference became insignificant after multivariable clinicopathologic adjustment, resulting in insignificant HRs (Table 4). There was no difference in mortality rate between male and female wild-type *BRAF* patients in univariable analyses of all PTCs or CPTCs (Table 3), corresponding to insignificant HRs, which remained insignificant after multivariable adjustment (Table 4). In striking contrast, in patients with *BRAF* V600E PTC, disease recurrence was significantly higher in men versus women, whether in the analysis of all PTCs or CPTCs: 32.0% (87 of 272) versus 18.5% (152 of 822; $P < .001$) in the former and 33.5% (74 of 221) versus 18.6% (123 of 662; $P < .001$) in the latter (Table 3); these corresponded to HRs of 1.89 (95% CI, 1.45 to 2.46; $P < .001$) and 2.04 (95% CI, 1.53 to 2.73; $P < .001$), respectively, which remained significant at 1.50 (95% CI, 1.14 to 1.98; $P = .004$) and 1.54 (95% CI, 1.13 to 2.08; $P = .006$), respectively, after multivariable adjustment (Table 4). Mortality rates in *BRAF* V600E–positive patients were 6.6% (18 of 272) versus 2.9% (24 of 822) in men versus women ($P = .006$) in the analysis of all PTCs and 7.2% (16 of 221) versus 2.9% (19 of 662; $P = .004$) in the analysis of CPTCs (Table 3); these corresponded to HRs of 2.43 (95% CI, 1.30 to 4.53; $P = .005$) and 2.86 (95% CI, 1.45 to 5.67; $P = .003$) in univariable analyses, which remained robustly significant at 2.74 (95% CI, 1.38 to 5.43; $P = .004$) and 3.51 (95% CI, 1.62-7.63; $P = .002$), respectively, upon multivariable adjustment (Table 4).

When dividing the cohort into four groups (women with wild-type *BRAF*, men with wild-type *BRAF*, women with *BRAF* V600E mutation, and men with *BRAF* V600E mutation; Table 5), there was no difference between women and men with wild-type *BRAF*, again demonstrating no effect of male sex in wild-type *BRAF* patients. Compared with women with wild-type *BRAF*, women with *BRAF* V600E mutation had a significant unadjusted HR of mortality, but this significance was completely lost upon multivariable adjustment, suggesting that female sex and *BRAF* V600E mutation had no independent interaction on the mortality. In contrast, compared with women with wild-type *BRAF*, men with *BRAF* V600E mutation had a robust unadjusted HR of mortality, which, upon multivariable analysis, only marginally lost significance in the overall analysis of all PTCs ($P = .079$) but remained significant in the analysis of CPTCs ($P = .009$). The synergy index of mortality risk for the interaction between male sex and *BRAF* V600E was 2.40 (95% CI, 1.00 to 5.74; $P = .050$) for all PTCs and 2.80 (95% CI, 1.19 to 6.59; $P = .018$) for CPTCs. Thus, the interaction between male sex and *BRAF* V600E had an independent effect on mortality, particularly robustly in CPTC, the most common variant of PTC in which *BRAF* V600E is a primary oncogene.

Effect of Male Sex on PTC-Specific Survival Curves of Patients With Respect to BRAF *Status*

As shown in Figure 1, Kaplan-Meier analyses showed no difference in disease-specific survival curves between men and women with wild-type *BRAF* PTC, whether in the analysis of all PTCs ($P = .387$; Fig 1A) or CPTCs only ($P = .521$; Fig 1B); the two lines remained flat without separation. In striking contrast, in *BRAF* V600E patients, the disease-specific survival curve sharply declined in men, whereas the curve for women remained flat, resulting in a significant separation of the two curves, whether in the analysis of all PTCs ($P = .004$; Fig 1C) or CPTCs only ($P = .002$; Fig 1D). These results showed a *BRAF* V600E–dependent effect of male sex on disease-specific survival of patients with PTC.

DISCUSSION

Early studies on the mortality risk of male sex in PTC were controversial.[10-15] Studies in recent years have increasingly shown an adverse effect of male sex on the prognosis of PTC.[16,17,19-25] However, controversy still exists, as exemplified by the fact that the mortality risk of male sex remained after multivariable clinicopathologic adjustment in some large entry data analyses[26] but was lost in other large entry data analyses upon multivariable adjustment.[27] Standard clinical guidelines,[5-7] the AJCC system,[3,4] and other risk staging models[8,9] virtually uniformly avoid including male sex as a mortality factor in the risk stratification of PTC, leaving unresolved the decades-long dilemma of whether male sex is a mortality risk for PTC.

We performed here a large international multicenter study to investigate further the prognostic risk of male sex in PTC, particularly mortality risk. In the overall analysis, irrespective of *BRAF* status, we found a significant association between male sex and poor clinicopathologic characteristics of PTC. Male sex also had an adverse effect on disease recurrence and disease-specific mortality, although the effect on the latter was not independent. We additionally examined only CPTC and made similar observations. These results were consistent with some previous reports,[13,14,16,17,19-25] providing further evidence suggesting that male sex is a risk factor for poor clinical outcomes of PTC, but it may be so only under certain circumstances.

Indeed, a striking finding in our study was the differentiating role of *BRAF* V600E in the effect of male sex on clinical outcomes of PTC. In wild-type *BRAF* patients, male sex was a significant risk factor for disease recurrence in univariable but not multivariable analyses. Male sex had no effect at all on mortality in wild-type *BRAF* patients, whether in univariable or multivariable analyses. Thus, male sex is not an independent risk factor for poor clinical outcomes of wild-type *BRAF* PTC. In contrast, in *BRAF* V600E patients, male sex was strongly and independently associated with

Table 4. HRs of Male Sex– Versus Female Sex–Associated Risk for Recurrence and Mortality of PTC by *BRAF* Status

	Entire Cohort				Wild-Type *BRAF*				*BRAF* V600E			
Tumor Type and Event	HR (95% CI)	*P*	Adjusted HR* (95% CI)	*P*	HR (95% CI)	*P*	Adjusted HR* (95%CI)	*P*	HR (95% CI)	*P*	Adjusted HR* (95% CI)	*P*
All PTC												
Tumor recurrence	1.89 (1.55 to 2.31)	< .001	1.31 (1.06 to 1.61)	.012	1.80 (1.33 to 2.45)	< .001	1.14 (0.82 to 1.57)	.440	1.89 (1.45 to 2.46)	< .001	1.50 (1.14 to 1.98)	.004
Mortality	2.23 (1.32 to 3.77)	.003	1.42 (0.81 to 2.47)	.219	1.59 (0.55 to 4.57)	.391	0.70 (0.23 to 2.09)	.520	2.43 (1.30 to 4.53)	.005	2.74 (1.38 to 5.43)	.004
CPTC												
Tumor recurrence	2.15 (1.71 to 2.70)	< .001	1.47 (1.16 to 1.87)	.001	2.25 (1.56 to 3.24)	< .001	1.47 (1.00 to 2.16)	.050	2.04 (1.53 to 2.73)	< .001	1.54 (1.13 to 2.08)	.006
Mortality	2.64 (1.42 to 4.88)	.002	2.13 (1.09 to 4.18)	.027	1.73 (0.32 to 9.45)	.527	0.86 (0.15 to 4.91)	.864	2.86 (1.45 to 5.67)	.003	3.51 (1.62 to 7.63)	.002

Abbreviations: CPTC, conventional papillary thyroid cancer; HR, hazard ratio; PTC, papillary thyroid cancer.
*Adjusted for patient age at diagnosis, tumor size, multifocality, extrathyroidal extension, lymph node metastasis, and radioiodine-131 treatment.

Table 5. PTC-Specific Mortality, Deaths per 1,000 Person-Years, and HRs

BRAF Status	Mortality		Deaths per 1,000 Person-Years (95% CI)	Unadjusted		Adjusted*	
	No. (%)	*P*		HR (95% CI)	*P*	HR (95% CI)	*P*
All PTCs							
Negative							
Female	11 (0.9) of 1,175	—	1.42 (0.78 to 2.56)	1.00		1.00	
Male	5 (1.4) of 349	.424	2.29 (0.95 to 5.51)	1.59 (0.55 to 4.58)	.39	0.70 (0.23 to 2.10)	.526
Positive							
Female	24 (2.9) of 822	.001	5.28 (3.54 to 7.88)	3.55 (1.73 to 7.26)	.001	0.58 (0.25 to 1.38)	.221
Male	18 (6.6) of 272	< .001	11.95 (7.53 to 18.97)	8.41 (3.97 to 17.83)	< .001	2.10 (0.92 to 4.84)	.079
CPTC							
Negative							
Female	4 (0.5) of 766	—	0.75 (0.28 to 1.99)	1.00		1.00	
Male	2 (0.9) of 230	.626	1.32 (0.33 to 5.30)	1.73 (0.32 to 9.45)	.527	0.86 (0.15 to 4.90)	.862
Positive							
Female	19 (2.9) of 662	< .001	5.00 (3.19 to 7.85)	6.35 (2.14 to 18.80)	.001	1.19 (0.35 to 4.06)	.775
Male	16 (7.2) of 221	< .001	13.00 (7.96 to 21.22)	17.75 (5.92 to 53.28)	< .001	4.89 (1.48 to 16.13)	.009

Abbreviations: CPTC, conventional papillary thyroid cancer; HR, hazard ratio; PTC, papillary thyroid cancer.
*Adjusted for patient age at diagnosis, tumor size, multifocality, extrathyroidal extension, lymph node metastasis, and radioiodine-131 treatment.

both disease recurrence and PTC-specific mortality, particularly the latter, either in univariable or multivariable analyses. All these effects of male sex were similarly observed when only CPTC, the most common and homogenous variant of PTC, was analyzed. In fact, the effects of male sex were generally even more robust in *BRAF* V600E CPTC. Thus, *BRAF* V600E conferred an independent risk of male sex for poor clinical outcomes, particularly disease-specific mortality, in PTC.

It is intriguing that even in patients with wild-type *BRAF* PTC, male sex was associated with several aggressive tumor behaviors, such as lymph node metastasis and extrathyroidal extension. However, these tumor behaviors were mild in wild-type *BRAF* PTC when compared with those in *BRAF* V600E PTC; unlike in the latter, they did not progress to mortality in the former. Similarly, unlike in *BRAF* V600E PTC, recurrent disease of wild-type *BRAF* PTC, which was associated with male sex only in univariable analysis but not in multivariable analysis, was also a mild condition in that it also did not progress to mortality. Thus, male sex is an independent risk factor for poor clinical outcomes, particularly mortality, in *BRAF* V600E PTC but not in wild-type *BRAF* PTC. In fact, there was an independent interaction between male sex and *BRAF* V600E in affecting PTC-specific mortality. These findings may explain and reconcile the controversies of previous studies on the prognostic role of male sex in PTC; depending on the

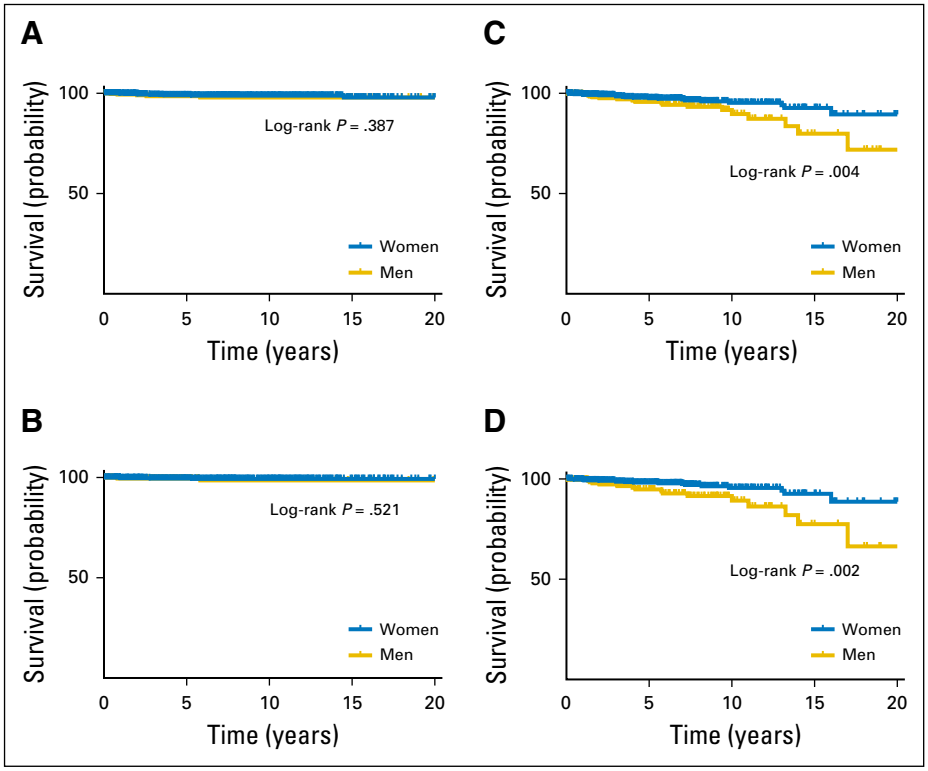

Fig 1. Disease-specific Kaplan-Meier survival curves in men and women with wild-type *BRAF* or *BRAF* V600E papillary thyroid cancer (PTC). Comparison of PTC-specific survival curves between men and women with (A) wild-type *BRAF* in the analysis of patients with any PTC (all PTCs), (B) wild-type *BRAF* in the analysis of only patients with conventional PTC (CPTC), (C) *BRAF* V600E in the analysis of patients with any PTC, and (D) *BRAF* V600E in the analysis of only patients with CPTC.

prevalence and distribution of *BRAF* V600E–positive patient cases among patient cohorts in different studies, results may vary.

It is also intriguing to see a strong association between male sex and distant metastasis in *BRAF* V600E PTC but not in wild-type *BRAF* PTC. This is a pathologic explanation for the mortality risk of male sex in *BRAF* V600E PTC, because distant metastasis is the most robust risk factor for PTC-specific mortality; distant metastasis may practically be treated as equivalent to mortality. This finding is again consistent with the concept that male sex is a strong risk factor for disease aggressiveness of *BRAF* V600E PTC.

The molecular mechanism for male sex–associated risk for the poor prognosis of PTC with *BRAF* V600E remains to be elucidated. *BRAF* V600E has been widely shown to be a prominent oncogene driving aggressive pathogenesis of PTC[33] and poor clinical outcomes.[30-32] It is plausible to speculate that the *BRAF* V600E/mitogen-activated protein kinase (MAPK) pathway might interact with certain male sex–specific molecular or cellular processes to promote aggressiveness of PTC. It has been recently demonstrated that *BRAF* V600E is a robust driver of the mutant *TERT* through a novel MAPK/FOS/GA-binding protein (GABP) pathway.[36] In this process, once phosphorylated and activated by the MAPK pathway, FOS as a novel transcriptional factor of *GABPB* binds and activates the promoter of *GABPB*, promoting its expression. Increased GABPB forms a complex with GABPA to activate specifically the mutant *TERT* promoter, resulting in increased *TERT* expression, leading to aggressiveness of thyroid cancer. FOS thus plays a key role in functionally bridging the two oncogenes in cooperatively promoting oncogenesis, in which *BRAF* V600E is the primary driver. This may be a mechanism for the male sex–associated mortality risk in *BRAF* V600E PTC, particularly given the fact that *BRAF* V600E and *TERT* promoter mutations frequently coexist, cooperatively promote the recurrence and mortality of PTC, and occur more often in men than women.[37-39] It is possible that *BRAF* V600E may drive other male sex–related genetic or epigenetic aberrations in promoting PTC aggressiveness yet to be defined. The prevalence of *BRAF* V600E was not significantly different between women and men, suggesting that the prevalence per se cannot explain male sex–associated mortality risk.

Patient age at diagnosis of disease is a strong mortality risk for PTC. We recently demonstrated that *BRAF* V600E could differentiate patient age–associated mortality risk of PTC; patient age was a significant independent mortality risk in *BRAF* V600E PTC but not wild-type *BRAF* PTC.[35] Our study provides another example that *BRAF* V600E is a genetic background underpinning the mortality risk of some classic clinical factors of PTC.

In summary, in this large international multicenter study, we for the first time to our knowledge demonstrate that male sex is an independent risk factor for poor clinical outcomes of PTC, particularly mortality, in *BRAF* V600E patients but not in wild-type *BRAF* patients. This study helps reconcile previous controversial findings on the role of male sex in the prognosis of PTC and supports its use as an independent risk factor in clinical risk staging, particularly mortality risk, for patients with *BRAF* V600E PTC. In contrast, male sex is not an independent prognostic risk in patients with wild-type *BRAF* PTC.

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Disclosures provided by the authors are available with this article at jco.org.

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BRAF V600E Confers Male Sex Disease-Specific Mortality Risk in Patients With Papillary Thyroid Cancer

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