RESEARCH

Mortality among papillary thyroid cancer patients by detection route: a hospital-based retrospective cohort study

Lan Wu[1], **Salvatore Vaccarella**[2], **Chen-Yang Feng**[3], **Luigino Dal Maso**[4], **Yu Chen**[1], **Wei-Wei Liu**[5], **Miao-Bian Liang**[1], **Zike Zhang**[6], **Jun Yang**[7], **Su-Mei Cao**[1] and **Mengmeng Li**[1]

[1]State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China
[2]International Agency for Research on Cancer (IARC/WHO), Lyon, France
[3]Information Technology Center, Sun Yat-sen University Cancer Center, Guangzhou, China
[4]Unit of Cancer Epidemiology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy
[5]Department of Head and Neck, Sun Yat-sen University Cancer Center, Guangzhou, China
[6]Department of Laboratory Medicine, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China
[7]School of Public Health, Guangzhou Medical University, Guangzhou, China

Correspondence should be addressed to M Li: limm@sysucc.org.cn or to S M Cao: caosm@sysucc.org.cn

Abstract

Background: Incidence rates of papillary thyroid cancer (PTC) have increased rapidly, with incidentally detected cancers contributing a large proportion. We aimed to explore the impact of incidental detection on thyroid cancer-specific and competing mortality among PTC patients.

Methods: We conducted a retrospective cohort study of PTC patients at a cancer center in Guangzhou. Baseline information on detection route and other covariates were collected between 2010 and 2018, and death outcome was followed up for each patient. Cumulative incidence functions were used to estimate the mortality risk of thyroid cancer and competing risk. Cause-specific hazard models were then utilized to explore the association between detection routes and PTC-specific and competing mortality.

Results: Of the 2874 patients included, 2011 (70.0%) were detected incidentally, and the proportion increased from 36.9% in 2011 to 82.3% in 2018. During a median follow-up of 5.6 years, 42 deaths occurred, with 60% of them due to competing causes. The probability of competing mortality at 5 years in the non-incidental group and incidental group was 1.4% and 0.4%, respectively, and PTC-specific mortality in the non-incidental group and incidental group was 1.0% and 0.1%, respectively. After adjusting for covariates, the HRs of incidental detection were 0.13 (95% CI: 0.04–0.46; $P = 0.01$) and 0.47 (95% CI: 0.20–1.10; $P = 0.10$) on PTC-specific mortality and competing mortality, respectively.

Conclusions: Incidental detection is associated with a lower risk of PTC-specific and competing mortality. Under the context of increasing magnitude of overdiagnosis, incorporation of detection route in clinical decision-making might be helpful to identify patients who might benefit from more extensive or conservative therapeutic strategies.

Keywords

- papillary thyroid cancer
- detection routes
- incidental detection
- competing mortality
- overdiagnosis

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Introduction

Thyroid cancer is the most common cancer in the endocrine system, and its incidence rates have increased rapidly worldwide over the past decades, with relatively stable or declining mortality rates (1, 2). The diverging gap between the increasing thyroid cancer incidence and the stable or declining mortality is one of the visible consequences in support of overdiagnosis (3). Overdiagnosis is a phenomenon that labels a person with a disease or abnormal condition that would not have caused them harm if it was left undiscovered (4).

The progressive introduction and wide use of new diagnostic techniques have likely led to increased detection of low-risk tumors (5), particularly papillary thyroid cancer (PTC) subtypes. Incidentally detected cancers, i.e. the detection of cancers on imaging for reasons unrelated to the thyroid (6, 7), have become a large and increasing component of the observed PTC incidence (8, 9). A few studies have shown that incidentally detected thyroid cancers are more frequently low risk and have better progression-free survival (6), but evidence is still lacking on whether the clinical strategies of PTC should also consider the route of detection.

The clinical dilemma is sharpened by the competing causes of death in patients with thyroid cancer. The likelihood of dying from other causes particularly for indolent, regressing, or slow-growing thyroid cancers exceeds that of dying from PTC, especially among older adults (10, 11). The high proportion of competing mortality is particularly relevant in settings where overdiagnosis has become a major public health issue (1). However, deaths due to competing causes are often neglected in previous studies that assessed the association between detection route and thyroid cancer mortality, which could lead to biased results (12).

Therefore, in this study, we aimed to explore the impact of incidental detection on both thyroid cancer and competing mortality among PTC patients, compared to those non-incidentally detected. The findings can provide evidence not only to support clinical decision-making but also to aid for a more in-depth understanding of overdiagnosis in thyroid cancer.

Materials and methods

Data sources and study cohort

We conducted a retrospective cohort study of patients diagnosed with PTC at Sun Yat-sen University Cancer Center (a tertiary health-care center located in Guangzhou, China) between January 1, 2010, and December 31, 2018. The death information of each patient was collected primarily through linking with the death certificate management information system and post-hospital routine follow-up call. These patients were followed until death due to thyroid cancer or competing causes, loss to follow-up, the end of the study period (May 9, 2022), or last contact with the follow-up office if the person could not be linked to the death information system, whichever came first. A total of 3499 patients were diagnosed with PTC during the study period, and then exclusion criteria were applied if (i) there was a coexistence with other thyroid cancer subtypes ($n=7$), (ii) it was not the first time they were diagnosed with thyroid cancer ($n=106$), (iii) follow-up information cannot be obtained ($n=154$), (iv) they were aged less than 18 years ($n=37$), or (v) the detection route was unknown ($n=321$). Finally, 2874 patients were included for further analyses (Fig. 1). Our study involved only secondary analysis of deidentified data and is classified as exempt from institutional review board approval.

Independent variables and outcomes

The exposure of interest in this study is the detection route of thyroid cancer, which were categorized into incidental and non-incidental detection (6). Medical records were reviewed to identify the route of detection: if the detection of thyroid cancer was due to investigations/follow-up for conditions unrelated to the thyroid or through health checkup in asymptomatic people, that was considered to be the incidental group; if a patient was detected from symptoms (such as hoarse voice, difficulty swallowing, and neck pain) or cervical mass which may not be necessarily related to thyroid cancer but lead to further checkup of the thyroid, that was considered to be in the non-incidental group. We also collected other covariates related to TC prognosis based on the availability of data in the electronic medical record system, including baseline age (a continuous variable), sex, employment, smoking status, self-reported history of thyroid diseases, body mass index (BMI) (calculated as weight/height^2, a continuous variable), and stage.

Our primary outcomes were deaths due to thyroid cancer and competing causes. The underlying causes of death in the death certificates were classified into thyroid cancer and other reasons. We defined deaths from any cause other than thyroid cancer as competing mortality.

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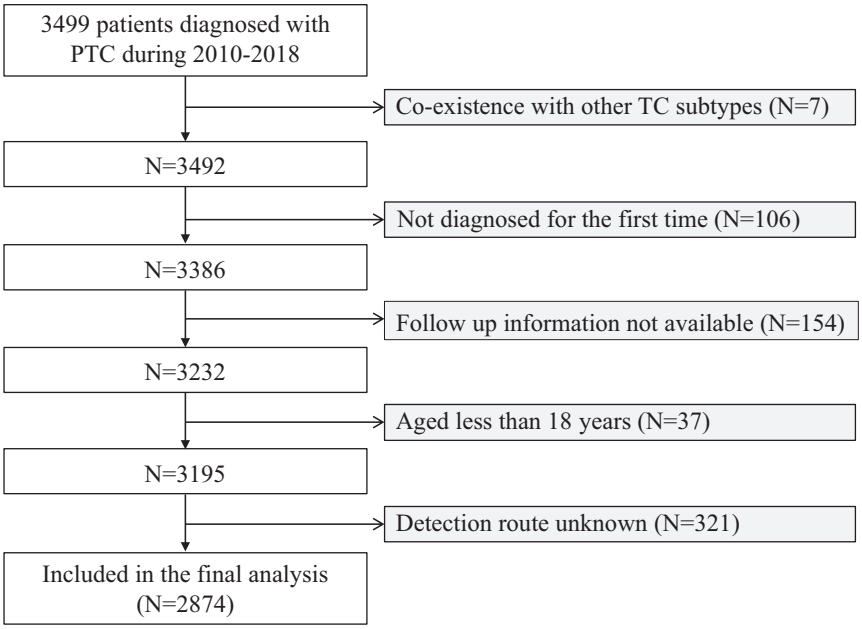

Figure 1
Selection of study population.

Statistical analysis

Baseline characteristics were examined using descriptive statistics, with continuous variables represented as mean (S.D.) and categorical variables as count (%). We then used the ANOVA test for continuous variables and the chi-square test for categorical variables to obtain the *P*-value for the difference test.

The mortality rates were estimated for both thyroid cancer and competing causes by dividing the number of deaths by the person-years. When modeling survival data in the presence of competing risks, the traditional Kaplan–Meier survival function can lead to upward-biased estimates (13); therefore, we used the cumulative incidence functions to estimate the mortality risk of thyroid cancer over time, with deaths from other causes being incorporated as competing risk. We conducted these analyses both for the overall cohort and by detection route and age group (<55 and ≥55 years).

To explore the impact of detection route and other potential risk factors on thyroid cancer and competing mortality, we used the cause-specific hazard models instead of subdistribution hazard models, considering that the regression coefficients from the former models can be interpreted as the effect of the risk factors on the relative increase in mortality rates, which is more appropriate for addressing etiological questions (12). Univariable analyses were conducted for each factor, and then those factors with $P < 0.10$ were further included in the multivariable analysis. Hazard ratios (HRs) of incidental detection on thyroid cancer and competing mortality were estimated after adjusting for potential confounders. We applied the multiple imputation approach by chained equations to impute missing values (14), which ranged from 0.1% (smoking status) to 14.3% (BMI) among the included variables. The process was based on 20 iterations and 5 imputations. The aforementioned modeling analyses were conducted separately before and after imputation by pooling HRs from five imputed datasets.

We also did a stratification analysis by age group (<55 or ≥55 years), sex (men or women), employment (employed or unemployed), smoking status (never or ever smokers), history of thyroid diseases (no or yes), overweight (defined as BMI ≥ 25 kg/m^2, no or yes), and cancer stage (stage I vs stage II–IV). Because most cancer patients were without thyroid diseases and were never smokers, analyses were not conducted for those with thyroid diseases or ever smokers.

All statistical analyses were performed with the R software (version 4.0.3, R Project for Statistical Computing, Vienna, Austria). The 'mice' package was used for the multiple imputation. The 'cmprsk' package was applied to estimate the cumulative incidence functions, and the 'survival' package was used for the cause-specific hazard models.

Results

Among the 2874 patients who met the inclusion criteria (Fig. 1), the mean age at the time of diagnosis was

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41.2 years (S.D. 11.6), and 2001 (69.6%) were female. Of the overall patient cohort, 2011 (70.0%) were detected incidentally, and these patients were slightly younger than those detected non-incidentally. The proportions of men, the employed, and never smokers were higher in the incidental group compared to those in the non-incidental group. Stage I cancers accounted for 93.1% and 85.1% of all incidentally and non-incidentally detected PTC, respectively (Table 1). The numbers (and proportions) of incidentally detected PTC among all patients increased from 31 (36.9%) in 2011 to 601 (82.3%) in 2018 (Fig. 2).

During a total of 16,090 person-years of follow-up, with a median follow-up of 5.1 years, 42 deaths occurred, with 25 (60%) of them due to competing causes. The median (interquartile range) follow-up times were 4.9 (2.7) years for the incidentally detected patients and 6.1 (3.7) for those who were not incidentally detected. The overall mortality rates per 1000 person-years were 1.2 and 5.4 in the incidental and non-incidental groups, respectively. In the incidental group, the mortality rates of competing causes were three times those of thyroid cancer (Supplementary Table 1, see section on supplementary materials given at the end of this article).

The cumulative incidence function curves of the overall cohort show that the probability of dying from thyroid cancer and competing causes was 0.4% and 0.7%, respectively, at 5 years and then reached 1.3% and 2.3% at 10 years (Fig. 3A). The probability of competing mortality at 5 years in the non-incidental group was 1.4% and that of PTC-specific mortality in the non-incidental group was 1.0%; the probability of competing mortality in the incidental group was 0.4% and that of PTC-specific mortality in the incidental group was 0.1%, respectively (Fig. 3B). In age < 55 years group, the probability of PTC-specific mortality in non-incidental detection was 0.4% at 5 years and 1.3% at 10 years. In age ≥ 55 years group, the probability of PTC-specific mortality in non-incidental detection was 4.1% at 5 years and

Table 1 Characteristics of the study population (papillary thyroid cancer patients diagnosed in a tertiary cancer care center in Guangzhou, China, 2010–2018), overall and by detection route. Continuous variables are represented as mean ± S.D., and categorical variables as *n* (%).

Characteristics	Total	Incidental	Non-incidental	*P*
n	2874	2011	863	
Age, years				0.049
<55	2494 (86.8)	1762 (87.6)	732 (84.8)	
≥55	380 (13.2)	249 (12.4)	131 (15.2)	
Sex				0.014
Men	873 (30.4)	639 (31.8)	234 (27.1)	
Women	2001 (69.6)	1372 (68.2)	629 (72.9)	
Employment				<0.001
Employed	2278 (79.3)	1654 (82.2)	624 (72.3)	
Unemployed	591 (20.6)	352 (17.5)	239 (27.7)	
Missing	5 (0.2)	5 (0.2)	0 (0.0)	
Smoking				0.002
Never smoker	2710 (94.3)	1914 (95.2)	796 (92.2)	
Ever smoker	161 (5.6)	95 (4.7)	66 (7.6)	
Missing	3 (0.1)	2 (0.1)	1 (0.1)	
Thyroid diseases				0.178
No	2784 (96.9)	1953 (97.1%)	831 (96.3%)	
Yes	83 (2.9)	53 (2.6)	31 (3.6%)	
Missing	7 (0.2)	6 (0.3)	1 (0.1)	
BMI, kg/m^2	23.1 ± 3.4	23.1 ± 3.5	22.9 ± 3.3	0.128
Staging				<0.001
I	2607 (90.7)	1873 (93.1)	734 (85.1)	
II–IV	209 (7.3)	114 (5.7)	95 (11.0)	
Missing	58 (2.0)	24 (1.2)	34 (3.9)	
Cause of death				<0.001
Thyroid cancer	17 (0.6)	3 (0.1)	14 (1.6)	
Competing causes	25 (0.9)	10 (0.5)	15 (1.7)	
Alive at the end of follow-up (censored)	2832 (98.5)	1998 (99.4)	834 (96.6)	

BMI, body mass index.

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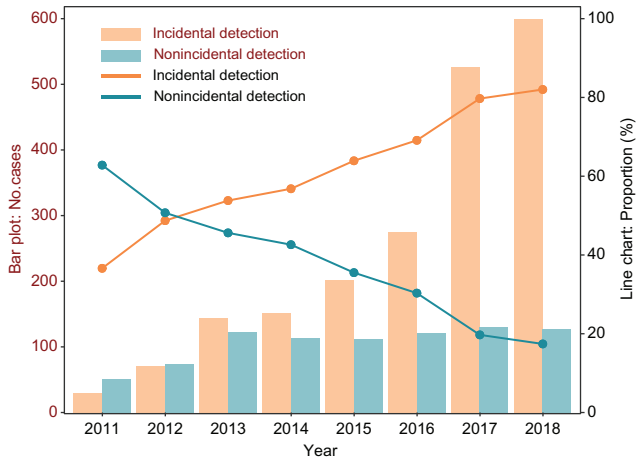

Figure 2
Annual number and proportion of papillary thyroid cancer cases by detection route.

12.5% at 10 years; the probability of competing mortality in incidental detection was 2.3% at 5 years and 3.7% at 10 years; the probability of competing mortality in non-incidental detection was 7.7% at 5 years and 16.1% at 10 years (Supplementary Table 2).

Factors associated with thyroid cancer and competing mortality in univariable and multivariable analyses are shown in Table 2. Detection route, age, and sex were risk factors for thyroid cancer mortality risk, while detection route, age, and BMI were associated with competing mortality risk. After adjusting for covariates, the HRs of incidental detection were 0.13 (95% CI: 0.04–0.46; $P = 0.01$) and 0.47 (95% CI: 0.20–1.10; $P = 0.10$) on thyroid cancer and competing mortality in the cause-specific hazard models. The estimates were similar before and after imputation for missing values of covariates (Supplementary Table 3).

The magnitude of the association between detection route and mortality risk varied substantially by age group. Older patients that are incidentally detected had lower HRs for both cancer-specific mortality (0.07; 95% CI: 0.01–0.56) and competing mortality (0.30; 95% CI: 0.11–0.82) compared with their younger counterparts with HRs of 0.16 and 0.56. The impact of detection route was also larger in men and among those that are unemployed. The HRs for thyroid cancer mortality were similar between stage I and stage II–IV (0.13 vs 0.14). The HRs of incidental detection on competing mortality among those diagnosed with stage I and II–IV were 0.76 (95% CI: 0.23–2.52) and 0.61 (95% CI: 0.16–2.30), respectively (Table 3).

Discussion

In this hospital-based retrospective cohort study, we found that 70% of PTC patients were detected incidentally, and the proportions were higher in more recent years. Over a median of 5.1 years of follow-up, the mortality rates for competing causes were three times those of thyroid cancer, and the 5-year probability of dying from either thyroid cancer or competing causes among those non-incidentally detected far exceeded that among the incidental group. Detection route was strongly associated with mortality risk from both thyroid cancer and other causes, with larger impact among the elderly, men, and the unemployed. To our knowledge, this is the first study investigating the impact of detection route on both thyroid cancer and competing mortality, based in a cancer care center from an economic transitional region where overdiagnosis is causing growing concerns.

Overall, our finding on the proportion of non-incidentally detected PTC is consistent with a multicenter study involving four countries (the USA, Canada,

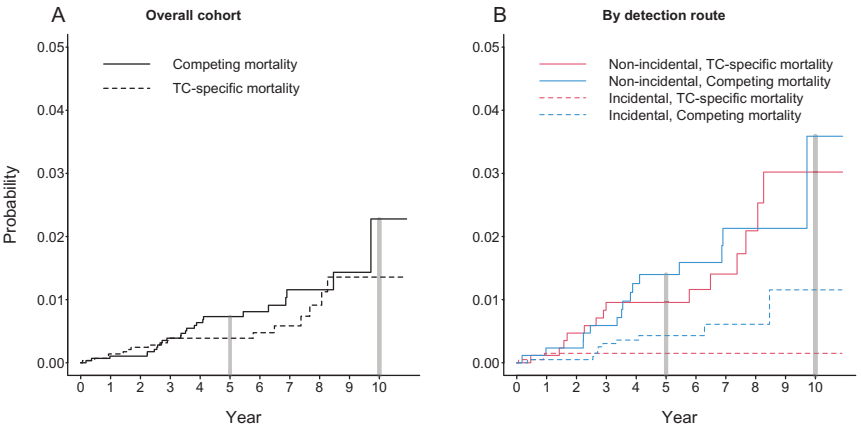

Figure 3
Cumulative incidence functions of thyroid cancer and competing mortality stratified by detection route.

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Table 2 Hazard ratios (95% CI) of risk factors on thyroid cancer and competing mortality.

	Thyroid cancer mortality		Competing mortality	
	Univariable	Multivariable	Univariable	Multivariable
Incidental vs non-incidental	0.11 (0.06, 0.19)	0.13 (0.04, 0.46)	0.34 (0.24, 0.49)	0.47 (0.20, 1.10)
Age, per 1-year increase	1.10 (1.09, 1.12)	1.08 (1.03, 1.13)	1.13 (1.11, 1.15)	1.11 (1.07,1.17)
Women vs men	0.30 (0.19, 0.46)	0.29 (0.10, 0.85)	0.54 (0.38, 0.77)	0.65 (0.26,1.63)
Unemployed vs employed	3.98 (2.57, 6.15)	1.26 (0.37, 4.27)	6.55 (4.51, 9.51)	1.34 (0.48, 3.78)
Ever smoker vs never smoker	2.02 (1.05, 3.89)	0.50 (0.11, 2.38)	2.17 (1.28, 3.65)	0.74 (0.20, 2.80)
BMI, per 1 kg/m^2 increase	1.09 (1.03, 1.15)	1.04 (0.84, 1.28)	1.10 (1.06, 1.15)	1.07 (0.94, 1.23)

BMI, body mass index.

Denmark, and South Africa), which showed that 30% of the thyroid cancer cases were identified through symptoms (15). But the large variation across centers – for example, incidentally detected cases accounted for only 18% male and 11% female cases during 2013–2017 in Ontario, Canada (8) but as high as 62% of all cases during 2013–2016 in Queensland, Australia (16) – highlights the impact of local health-care system and medical practice. With the widespread use of diagnostic imaging and fine-needle aspiration biopsy over the past years, a growing number of thyroid cancers had been discovered incidentally. In our study, the proportion of incidentally detected thyroid cancer increased from 36% in 2011 to 82.3% in 2018. This phenomenon has also been reported in several other countries, such as Japan, Canada, and the USA (8, 9, 17), which suggests that increased imaging and diagnostic scrutiny may have contributed significantly to the upsurge of thyroid cancer incidence observed (18).

Table 3 Hazard ratios (95% CI) of incidental detection on thyroid cancer and competing mortality in different strata. Models did not converge in the strata of ever smokers, history of thyroid diseases, and late stage due to small sample sizes.

	Thyroid cancer mortality	Competing mortality
Age, years		
<55	0.16 (0.03, 0.79)	0.56 (0.14, 2.27)
≥55	0.07 (0.01, 0.56)	0.30 (0.11, 0.82)
Sex		
Men	0.07 (0.01, 0.54)	0.31 (0.07, 1.35)
Women	0.24 (0.05, 1.24)	0.63 (0.22, 1.82)
Employment		
Employed	0.19 (0.04, 0.95)	1.22 (0.29, 5.03)
Unemployed	0.10 (0.01, 0.78)	0.29 (0.09, 0.94)
Smoking status		
Never smoker	0.09 (0.02, 0.40)	0.43 (0.18, 1.02)
Ever smoker	–	–
Thyroid diseases		
No	0.14 (0.04, 0.49)	0.44 (0.18, 1.05)
Yes	–	–
BMI, kg/m^2		
<25	0.13 (0.01, 1.13)	0.52 (0.15, 1.79)
≥25[a]	–	0.24 (0.04, 1.44)
Staging		
I	0.13 (0.03, 0.61)	0.61(0.16, 2.30)
II–IV	0.14 (0.02, 1.20)	0.76 (0.23, 2.52)

[a]Overweight.
BMI, body mass index.

Consistent with other studies showing lower recurrence and higher survival rates among the asymptomatic PTC patients (19, 20), our study also found lower mortality rates among those incidentally detected, after accounting for the high competing mortality. While it remains debatable on whether the management of thyroid cancer should be influenced by the mode of detection, our findings on the very low 5-year cumulative probability of dying from thyroid cancer implies that a more conservative approach might be considered for those cancers that are detected incidentally, such as less intensive surveillance and extensive therapeutic strategies.

Our study finds that the numbers of PTC that are newly diagnosed in our cancer care center has been increasing, especially for those incidentally detected, while mortality rate remains low. The disparity between the incidence and mortality strongly suggests overdiagnosis of thyroid cancer. Furthermore, the mortality rates of competing causes were much higher than those of thyroid cancer, for both the incidental and the non-incidental groups. Two population-based studies also found that deaths from other causes far outnumbered those from thyroid cancer, especially among the elderly (10, 21). Among those incidentally identified patients aged 55 years and above, the probability of dying from competing causes at 5 and 10 years were at least five times those of dying from thyroid cancer mortality, while in the non-incidental group, their relative differences were smaller. These observations imply that under the context of overdiagnosis, competing mortality plays a more important role in overall prognosis regardless of the

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detection route, but its impact may be comparably higher for those incidentally identified cases. It is also important that competing causes of death be considered to aid clinical decision-making.

It is an interesting finding that the association between mode of detection and thyroid cancer mortality varies across populations, with larger impact among the older patients, men, and the unemployed. The reasons underlying this observation are not clear. Increasing age and male sex are risk factors of thyroid cancer mortality (21), which are also found in our study. Studies also found that low socioeconomic status might be associated with poorer survival of thyroid cancer (22). These factors may affect the pathways to the diagnosis of thyroid cancer (16) and therefore indirectly influence the impact of detection route on the mortality outcome.

The strength of our study includes the consideration of competing risk in the association analysis. For cancers with relatively good prognosis, especially for PTCs that are affected by a large magnitude of overdiagnosis, ignoring competing mortality would lead to biased results. By applying the cumulative incidence functions and cause-specific hazard models, the risk of the outcome of interest in the presence of other events could be estimated. We also utilized multiple sources of follow-up data to ascertain the outcome of survival and deaths due to thyroid cancer and other causes and to ensure the accuracy of our estimates.

Several limitations of this study should be noted. First, the sample size and length of follow-up of this study are limited, which disenables the ability to investigate effect-modifying factors and to evaluate longer-term mortality outcomes. Second, as a single-center study, caution should be exercised when generalizing the results to other populations and settings. Third, our analysis may be influenced by lead time bias, as those cancers incidentally detected may still be in an early stage. However, we believe that this impact might be small, considering the fact that stage I cancers accounted for nearly 90% of all patients with stages regardless of the detection route and the robust results when we confined our analysis to those with stage I cancers. Fourth, as our study was mainly based on reviewing the historical medical records, the number of variables that we collected and included in the analyses was restricted. Some of the potential confounders were not available; therefore, the results may be subject to residual confounding.

Conclusion

Based on a retrospective hospital-based cohort of PTC patients, our findings suggest that a growing number and proportion of thyroid cancer patients have been identified incidentally, resembling the global trends of the rapid expansion of overdiagnosis. The comparative risk of dying from competing causes and from thyroid cancer should be evaluated for each individual patient. Incidental detection is an independent risk factor of both PTC-specific and competing mortality. This study implies that the clinical context of PTC patients should be considered in the management of thyroid cancer, and the incorporation of mode of detection in clinical decision-making might be helpful to identify patients who might benefit from more extensive or conservative therapeutic strategies for thyroid cancer.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-23-0127.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policies, or views of the International Agency for Research on Cancer/World Health Organization.

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Author contribution statement

LW: Investigation, Data Curation, Methodology, Writing – Original Draft, Review and Editing. SV: Methodology, Writing – Review and Editing. CYF: Resources, Data Curation. LDM, YC, WWL, ZZ, MBL, and JY: Writing – Review and Editing; SMC: Supervision, Writing – Review and Editing. ML: Conceptualization, Methodology, Investigation, Supervision, Writing – Original Draft, Review and Editing. All authors read and approved the final version of the manuscript.

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