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Association of Patient Age With Progression of Low-Risk Papillary Thyroid Carcinoma Under Active Surveillance
A Systematic Review and Meta-analysis

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IMPORTANCE Active surveillance is sometimes considered as a disease management option for individuals with small, low-risk papillary thyroid carcinoma.

OBJECTIVE To assess whether patient age is associated with progression of low-risk papillary thyroid carcinoma (tumor growth or incident metastatic disease) in adults under active surveillance.

EVIDENCE REVIEW Eight electronic databases (MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Emcare, PsycINFO, Web of Science, and ClincalTrials.gov) were searched from inception to March 2019, supplemented with a hand search. Two investigators independently screened citations, reviewed full-text articles, and abstracted data. Additional data were sought from authors. Random-effects meta-analyses were performed using incidence data (statistically adjusted for confounders and crude rates).

FINDINGS A total of 1658 unique citations were screened, and 62 full-text articles were reviewed, including 5 studies. Three studies included exclusively microcarcinomas and 2 included tumors up to 2 cm in maximal diameter. The mean age of participants was 51.0 to 55.2 years in 4 studies reporting this value. The mean or median follow-up was 5 years or more in 3 studies and approximately 2 years in 2 studies. The pooled risk ratio for tumor growth of 3 mm or more in maximal diameter in individuals aged 40 to 50 years compared with younger individuals was 0.51 when adjusted for confounders (95% CI, 0.29-0.89; 1619 patients, 2 studies), and the unadjusted risk ratio of this outcome for individuals 40 years or older was 0.55 (95% CI, 0.36-0.82; 2097 patients, 4 studies). In adults aged 40 to 45 years, the unadjusted risk ratio for any tumor volume increase compared with younger individuals was 0.65 (95% CI, 0.51-0.83; 1232 patients, 4 studies). The pooled risk ratio for incident nodal metastases in individuals 40 years or older was 0.22 (95% CI, 0.10-0.47; 1806 patients, 3 studies); however, in a secondary analysis, the risk difference was not significantly different. There was no statistically significant heterogeneity in any of the meta-analyses. There were no thyroid cancer–related deaths nor incident distant metastases.

CONCLUSIONS AND RELEVANCE This study suggests that older age may be associated with a reduced risk of primary papillary thyroid carcinoma tumor growth under active surveillance. Incident metastatic disease is uncommon during active surveillance.

Supplemental content

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The incidence rate of thyroid cancer has tripled in the United States during the last 3 decades, although there has been some recent attenuation in this trend, partly associated with changes in diagnostic biopsy thresholds.[1] Given the excellent prognosis for low-risk papillary thyroid carcinoma (PTC) and, in particular, papillary microcarcinoma (≤1 cm in maximal diameter) confined to the thyroid, active surveillance (AS; close follow-up in lieu of surgery) was first proposed as an alternative disease management option by Ito et al[2] and Miyauchi[3] in Japan. Active surveillance is a structured program of follow-up, with specific inclusion criteria as well as criteria for curative-intent treatment (surgery with or without additional treatments) in the event of evidence of disease progression (tumor growth or incident metastatic disease) during follow-up. Patients undergoing AS have the opportunity to undergo surgery in the absence of disease progression at any time during follow-up if it is preferred to continuing follow-up. The longest follow-up AS studies are from Japanese centers, including Kuma Hospital in Kobe and the Cancer Institute Hospital in Tokyo,[3] although, in recent years, research in AS for low-risk PTC has been initiated throughout the world. Initial reports on the association between age at diagnosis and risk of PTC progression in individuals undergoing AS were conflicting.[4] Our aim was to evaluate whether age is associated with disease progression in individuals undergoing AS.

Key Points

Question Is age associated with the risk of tumor progression (ie, tumor enlargement or incident metastatic disease) in individuals with small, low-risk papillary thyroid carcinoma under active surveillance?

Findings In this systematic review and meta-analysis including data from 5 studies, the risk ratio for tumor growth of 3 mm or more in maximal diameter was reduced by about half in individuals aged 40 to 50 years compared with younger individuals. The risk of incident metastatic disease was low at all ages.

Meaning Advancing age may be associated with reduced risk of papillary thyroid tumor enlargement under active surveillance.

Methods

Study Question and Study Eligibility Criteria

We performed a systematic review and meta-analysis to determine whether age is associated with progression of low-risk PTC (tumor growth or incident metastatic disease [lymph nodes or distant]) while undergoing AS. This systematic review was registered on PROSPERO (CRD42019130208). Eligible studies included clinical trials (randomized or observational), systematic reviews, cohort studies, or cross-sectional studies that included adults (aged ≥18 years) undergoing AS for primary management of low-risk PTC. Studies were required to quantitatively report 1 or more of the primary outcomes of interest (ie, change in primary tumor size or incident nodal metastases [ie, clinical nodal metastases detected on imaging, typically prompting a recommendation of surgery due to disease progression]) relative to participant age (at diagnosis or onset of AS). The included studies were required to include patients with low-risk PTC (ie, small tumors confined to the thyroid) who were undergoing AS. Active surveillance jwas defined as close follow-up (typically including clinical assessments and diagnostic imaging, with or without blood tests) in lieu of immediate surgery, in which there are prespecified disease progression criteria for which thyroid cancer surgery with curative intent would be performed. Studies with an absence of surgery in the absence of a planned program of AS or observation (such as delay of surgery or surgery not being performed for specified or unspecified reasons outside of an established AS protocol) were not eligible for inclusion. For overlapping relevant data from the same study, the largest or most recently updated study, preferably reporting a multivariable analysis, was preferred. Owing to limited resources for translation, only English studies were included. We sent an email to corresponding, senior, or primary authors of all studies inquiring about clarification of reported data and additional details of their studies.

Data Sources and Searches

An experienced library information specialist (R.F.) conducted a search of 8 electronic databases (MEDLINE, Embase Classic and Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Emcare, PsycINFO, Web of Science, and ClincalTrials.gov) from inception until March 2019. There was no language restriction on the search. Where available, both the controlled vocabulary terms (eg, *exploded* [where applicable]) and the key words for "papillary thyroid cancer" and "active surveillance" were used in accordance with each database (eAppendix 1 in the Supplement). The electronic search was supplemented by a hand search of relevant cross-references, the personal files of authors (D.P.G. and A.M.S., who had previously conducted a systematic review on AS of PTC),[4] and the recent monthly table of contents of the journal *Thyroid* (from September 2018 to September 2019).

Two of us (A.K. and A.M.S.) independently screened all unique citations for relevance and reviewed full-text articles of relevant electronic citations or those retrieved by the hand search. The 2 reviewers achieved consensus for articles included in the review through discussion (with availability of a third reviewer, D.P.G., in the event of unresolved disagreements). The reasons for excluding any reviewed, full-text articles were reported.

Critical Appraisal of Included Studies and Data Abstraction

Data were abstracted, and the quality of each study was appraised by 2 independent reviewers from a review team (A.K. and A.M.S.) using a customized data abstraction form. The reviews were compared, and consensus was achieved by discussion. The risk of bias of included studies was evaluated using the QUIPS (Quality in Prognostic Studies) tool for prognostic studies.[5] We reported our methods and findings in accordance with PRISMA standards.[6]

Statistical Analysis

We performed random-effects meta-analyses comparing the risk ratios (RRs, also known as relative risks) of disease progression (tumor growth or incident nodal or distant metastatic disease) by comparing older adults with younger individuals. Because we expected to include studies from a variety of geographical regions, we chose to perform random-effects meta-analyses, which incorporate an estimate of the effect variation between studies and study settings, thereby accounting for variation in effects across studies. Meta-analyses were performed, pooling risk estimates that were statistically adjusted for confounders (ie, in a multivariable model or propensity analysis, including a total of ≥2 potential confounders [including age] in the analysis)[7] and crude event rates (cumulative disease progression rates during the entire AS follow-up period). Alternative risk estimates were assumed to be comparable to RRs for uncommon events (ie, <10% cumulative incidence of the event) in adjusted meta-analyses from all included studies.[8] In the adjusted model, we used the inverse-variance calculation method, and the pooled effect was exponentiated so that an RR of less than 1 is interpreted as reduced risk (positive prognostic indicator).[9]

Heterogeneity (variability) of risk estimates among included studies was evaluated using the Cochrane *Q* test[10] and the I^2 measure[11]; 95% CIs were calculated around all effect estimates. We planned to evaluate for publication bias graphically using a funnel plot[12] if 10 or more studies were included in the meta-analysis.[9] We defined statistical significance by an α level of .05 except for the Cochrane *Q* test for heterogeneity, for which an α level of .10 was used.[11] We performed all statistical analyses using Comprehensive Meta-Analysis software, version 2.0 (Biostat Inc).

We planned to investigate possible sources of heterogeneity of meta-analyses using secondary subgroup mixed-effects analyses if statistically significant heterogeneity was observed and if a sufficient number of studies were available for subgroup analyses. Specifically, we planned to explore heterogeneity according to the following characteristics: participant (sex, thyroid-stimulating hormone [TSH] concentration, and use of thyroid hormone or TSH-suppressive therapy), primary tumor (baseline size, characteristics on imaging results [eg, microcalcifications, vascularity, and border appearance], unifocal or multifocal disease, and cytologic diagnosis [suspicious for PTC or PTC]), and study (duration of follow-up and QUIPS criteria for study quality). In rare event outcomes in which 1 or more studies (but not all studies) have zero events in both age comparison groups, we performed a secondary post hoc sensitivity analysis examining the risk difference (because an RR calculation would exclude studies with zero events in both groups).

Results

We identified 2711 citations in the electronic search and 4 from a hand search, yielding 1658 unique citations after exclusion of duplicates (**Figure 1**). We reviewed 62 full-text articles (eAppendix 2 in the Supplement) and included 5 studies in this systematic review (Figure 1).[13-17] Additional information or data about studies were obtained from the original authors for 3 of the included studies.[13,14,16]

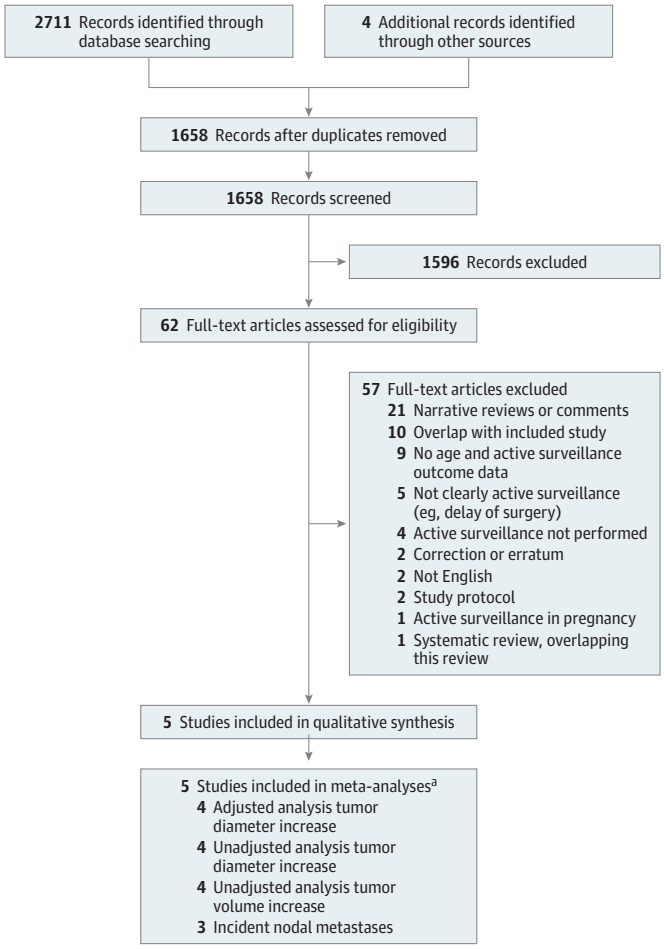
Description of the Included Original Studies

The study characteristics are shown in **Table 1**.[13-18] The studies included in the review were from Japan,[13,14,16] Korea,[15] and the United States,[17] with 3 of 5 studies including only patients with papillary microcarcinoma[13-15] and 2 studies including some patients with PTC with tumors of 1 to 2 cm in diameter.[16,17] The mean or median follow-up period was 5 years or more in 3 studies from Japan,[13,14,16] including 2 studies from the same institution in Tokyo.[13,16] The mean or median duration of follow-up was about 2 years in the study from Korea[15] and in the study from the United States,[17] indicating the later adoption of such research outside of Japan. The characteristics of study participants are described in **Table 2**.[13-17] Most studies included multifocal PTC,[13-16] although 1 study did not report on this feature.[17] The mean or median age of participants ranged from 51.0 to 55.2 years for the 4 studies reporting such an estimate.[13,14,16,17] The percentage of female participants ranged from 75% to 90%.[13-16] Ito et al[14] reported use of TSH-suppressive therapy for 4% (51 of 1235) of patients, and Oh et al[15] reported the use of levothyroxine treatment for 8% of patients (28 of 370), of whom half were taking thyroid hormone replacement (14 of 370 [4%]) and half were taking thyrotropin-suppressive therapy (14 of 370 [4%]). The rate of use of levothyroxine or TSH-suppressive therapy was not reported in the other 3 studies,[13,16,17] although a normal TSH level at baseline was a requirement in 1 of the studies.[17] The evaluation of the risk of bias of the included studies is shown in eAppendix 3 in the Supplement. Most of the features of the included studies were judged to be at low risk of bias, although some confounding was possible for studies that did not include any multivariable or otherwise adjusted analyses (eAppendix 3 in the Supplement).

Qualitative Description of Study Findings

The clinical outcomes of patients undergoing AS relative to age category are shown in **Table 3**. Regarding the outcome of increase in tumor size of 3 mm or more in maximal diameter, of the 4 studies statistically comparing this outcome,[13-15,17] 2 studies[14,17] reported a significantly increased risk among younger individuals compared with older individuals. There was no significant difference observed in univariate[13,15] or multivariate[13] analyses between the other 2 studies comparing data from respective age categories for the outcome of an increase in maximal tumor diameter. For the outcome of tumor volume increase, 2 studies examining this outcome relative to age reported significantly increased risks among younger individuals compared with older individuals in both univariate comparisons.[15,17] Only 1 study reported on a multivariable analysis for this outcome, and the risk of tumor volume increase was reported to be significantly independently increased in younger individuals.[17] Incident nodal metastases were relatively rare events, occurring in 0% to 5% of individuals younger than 40 years and in 0% to 3% of individuals 40 years or older. Given the low incidence rates of clinical nodal

Figure 1. Study Flow Diagram



[a] Not mutually exclusive.

metastases observed in the included studies, an age comparison was performed in only the largest study from Ito et al,[14] which reported a significantly increased risk among younger individuals compared with older individuals in both univariable and multivariable analyses. There were no thyroid cancer-associated deaths or cases of distant metastases reported in any of the included studies. Furthermore, the rates of crossover from AS to thyroidectomy (for disease progression or other reasons) were not compared according to age category in any of the studies.

Results of the Meta-analyses

In a random-effects meta-analysis including data from 2 studies[13,14] with a total of 1619 patients, the RR for tumor growth of 3 mm or more in maximal diameter in individuals aged 40 to 50 years compared with younger individuals was 0.507 (95% CI, 0.288-0.891) when adjusted for confounders (**Figure 2**A). One study was rejected from this model by the statistical analysis program because the reported 95% CI of the risk estimate was not symmetrical[17] and thus could not be combined. There was no statistically significant heterogeneity observed in the meta-analysis for the outcome of a tumor maximal diameter increase of 3 mm or more adjusted for confounders (I^2 = 24.2; Q = 1.32; df = 1; P = .25). The pooled RR for tumor growth of 3 mm or more in maximal diameter in 2097 patients 40 years or older using crude (unadjusted) incidence data was 0.546 (95% CI, 0.364-0.819) in 4 studies.[13,14,16,17] There was also no statistically significant heterogeneity observed in this meta-analysis (I^2 = 0; Q = 0.54; df = 3; P = .91) (Figure 2B). For 1232 patients aged 40 to 45 years, the unadjusted RR for tumor volume increase (>50% or ≥50%) compared with younger individuals was 0.649 (95% CI, 0.505-0.833) in 4 studies.[13,15-17] There was also no statistically significant heterogeneity observed in this meta-analysis examining tumor volume increase (I^2 = 0; Q = 0.26; df = 3; P = .97) (Figure 2C). The pooled RR for incident clinical nodal metastases among 1806 patients 40 years or older was 0.22 (95% CI, 0.10-0.47) in 3 studies[13,14,16] (1 study[17] was excluded owing to zero events observed in each group). There was also no statistically significant heterogeneity in this pooled estimate (I^2 = 0; Q = 0.86; df = 2; P = .65). In a secondary, post hoc sensitivity analysis examining the risk difference of incident nodal metastases that would enable the inclusion of data from a study by Tuttle et al[17] with zero events in each group observed after a mean follow-up period of 29 months, the pooled risk difference between older and younger individuals was −2% (95% CI, −4% to 1%; 2097

Table 1. Characteristics of the Included Studies

Source	Country (institution)	No. of participants and eligibility criteria	Study design	Follow-up duration, mean (SD), [range], mo	Funding
Fukuoka et al,[13] 2016	Japan (Cancer Institute Hospital)	Published: 384 patients with cytopathologically confirmed PMC with no known metastatic disease or extrathyroidal extension, recruited from 1995 to 2013, followed up ≥1 y; updated information: 493 patients, with same inclusion criteria	Cohort study (retrospective analysis of prospectively collected trial data[a])	Published: 82 (52) [12-276]; updated information, including updated data: 90.0 (60.0)	None reported
Ito et al,[14] 2014	Japan (Kuma Hospital)	1235 Patients with cytopathologically confirmed PMC with no known metastatic disease, immediate proximity to or symptoms or signs of invasion of the recurrent laryngeal nerve or trachea, or high-grade malignant neoplasm on cytologic findings; patients recruited from 1993 to 2011	Cohort study (retrospective analysis of prospectively collected trial data[a])	60 [18-227]	None reported
Oh et al,[15] 2018	Korea (multiple sites[b])	370 Patients with PMC (cytologic diagnosis of PTC or suspicious for PTC) with no known metastatic disease or extrathyroidal extension, tracheal or recurrent laryngeal extension, or aggressive variant of PTC from cytologic findings or core biopsy; recruited from 2002 to 2013, followed up ≥1 y	Cohort study (retrospective,[c] published trial protocol reported study to be prospective[18])	Median, 32.5 [IQR, 21.5-47.6]	None reported
Sakai et al,[16] 2019	Japan (Cancer Institute Hospital)	61 Patients with cytopathologically confirmed T1b PTC (ie, 1-2 cm in maximal diameter) with no lymphadenopathy (≥1 cm in maximal diameter on results of ultrasonography) or distant metastases on results of CT imaging of the chest, who requested active surveillance; recruited from 1995 to 2016; surgeon considered patient age, tumor size, and other risk factors, as typically surgery was recommended for this tumor size; updated data: same inclusion criteria for 78 patients	Cohort (retrospective analysis of prospectively collected trial data[a])	95 [12-204]; updated data: 93.6 (63.6)	None reported
Tuttle et al,[17] 2017	United States (Memorial Sloan Kettering Cancer Center)	291 Patients with PTC≤1.5 cm in maximal diameter (PTC or suspicious for PTC on cytologic findings), normal thyroid-stimulating hormone concentration, and no extrathyroidal extension or invasion of local structures and no metastatic disease; minimum follow-up, 6 mo; recruitment period not reported	Cohort (combined prospectively and retrospectively collected data[d])	29 (19) [6-166]	Funding reported as obtained, source not reported

Abbreviations: CT, computed tomography; IQR, interquartile range; PMC, papillary microcarcinoma; PTC, papillary thyroid carcinoma.

[a] Study design confirmed by email correspondence with the original authors.

[b] Multicenter study with the following participating sites in Seoul, Korea: Asan Medical Center, Seoul St Mary's Hospital, and Samsung Medical Center.

[c] Reported by authors in the published reference.

[d] The authors report that they combined prospectively collected data from 249 consenting participants and combined with retrospectively collected data from 42 patients, after obtaining a waiver obtained from the institutional research ethics board for collection of the retrospective data. Given the inclusion of retrospective data, the analysis should be considered, at least in part, retrospective.

Table 2. Characteristics of Study Participants

Source	Exclusively PMC (excluded larger PTCs)	Age at diagnosis	Female sex, No./ total No. (%)	Primary tumor largest dimension size	Inclusion of multifocal papillary thyroid cancer	Prevalence of thyroid hormone use during active surveillance
Fukuoka et al,[13] 2016	Yes	Mean (SD), 54.0 (11.9); range, 23-84 y; updated data: mean (SD), 52.8 (12.7)	331/384 (86); updated data: 434/494 (88)	Not reported	Yes	Not reported
Ito et al,[14] 2014	Yes	Mean not reported; ≥60 y, 496/1235 (40%); 40-59 y, 570/1235 (46%); <40 y, 169/1235 (14%)	1111/1235 (90)	Mean not reported; ≤5 mm, 324/1235 (26%); 5-8 mm, 686/1235 (56%); 8-10 mm, 225/1235 (18%)	Yes	Thyrotropin suppression, 51/1235 (4%)
Oh et al,[15] 2018	Yes	Mean (SD), 51.0 (11.7) (range not reported)	284/370 (77)	Mean (SD), 5.9 (1.7)	Yes	Levothyroxine treatment, 28/370 (8%); including thyroid hormone replacement, 14/370 (4%); thyrotropin suppression, 14/370 (4%)
Sakai et al,[16] 2019	No (T1b)	Mean (SD), 54.4 (10.7) (range not reported); updated data: mean (SD), 55.2 (5.0)	47/61 (77); updated data: 61/78 (78)	Published: mean (SD), 11.7 (1.1); range: 11-16 mm	Not reported; updated data: yes	Not reported
Tuttle et al,[17] 2017	No (T1a and T1b)	Mean (SD), 52 (15); range, 20-86	219/291 (75)	≤1.0 cm, 232/291 (80%); 1.1-1.5 cm, 59/291 (20%)	Not reported	Not reported[a]

Abbreviations: PMC, papillary microcarcinoma; PTC, papillary thyroid carcinoma.

[a] Thyroid hormone–stimulating concentration normal at baseline as an inclusion criterion.

patients in 4 studies).[13,14,16,17] There was also no statistically significant heterogeneity of the meta-analysis examining the risk difference of incident nodal metastases (I^2 = 35.9; Q = 4.68; df = 3; P = .20). These apparently discrepant findings with respect to risk estimates for clinical nodal metastases may be in part a reflection of the rarity of incident nodal metastases

Table 3. Age-Specific Clinical Outcomes of Patients Undergoing Active Surveillance

Source	Event rates in younger and older patients	Results of univariate analysis reported by the authors	Results of multivariable analysis reported by the authors
Tumor maximal diameter increase ≥3 mm			
Fukuoka et al,[13] 2016	Reported by authors: <50 y, 10% at 10 y (No. of subgroup not reported); ≥50 y, 6% at 10 y (No. of subgroup not reported); updated data: <40 y, 10/76 (13%); ≥40 y, 33/417 (8%)	Reported by authors: log-rank test for age cutpoint of 50 y, *P* = .37 (total of 384 patients with PMC)	Reported by authors: multivariable logistic regression model adjusted for age at diagnosis, tumor calcification pattern at last follow-up, and tumor vascularity at last follow-up for all patients: aged ≥50 y at diagnosis: OR, 0.72 (95% CI, 0.33-1.62; *P* = .42) (total of 384 patients with PMC)
Ito et al,[14] 2014	<40 y, 14/169 (8%); ≥40 y, 44/1066 (4%) (of whom 11/496 aged ≥60 y)	Univariate comparison <40 y, 40-59 y, and ≥60 y: *P* = .001	Multivariate analysis adjusted for male sex, TSH suppression, family history, suspected or diagnosed multiplicity, tumor size 5-8 mm, tumor size ≥9 mm, comparing aged <40 y with aged ≥40 y: OR, 2.50 (95% CI, 1.36-4.61; *P* = .003)
Oh et al,[15] 2018	Not reported	Time-to-event comparison for those aged <45 y vs ≥45 y: HR, 1.89 (95% CI, 0.54-6.58; *P* = .32)	Not performed
Sakai et al,[16] 2019	Not reported in article; updated data: <40 y, 0/6 (0%); ≥40 y, 6/72 (8%)	Not performed	Not performed
Tuttle et al,[17] 2017	Reported in the results of the article: <50 y, 27% at 5 y; ≥50 y, 5% at 5 y; extrapolated from reported data in the supplemental appendix: <40 y, 4/65 (6%); ≥40 y, 7/226 (3%)	Time-to-event comparison for those aged <50 y vs ≥50 y: HR, 4.5 (95% CI, 1.2-17.0; *P* = .03); univariate OR of age (years) being associated with this outcome, 0.93 (95% CI, 0.89-0.98)	In multivariable model adjusted for risk category at diagnosis, sex, cytologic classification, and tumor size, the OR of age (years) being associated with this outcome was 0.92 (95% CI, 0.87-0.98; *P* = .006)
Tumor volume increase (any)			
Fukuoka et al,[13] 2016	Not reported in article; updated data: <40 y, 22/76 (29%); ≥40 y, 79/417 (19%)	Not performed	Not performed
Ito et al,[14] 2014	Not reported	Not reported	Not performed
Oh et al,[15] 2018	Tumor volume increase ≥50% from baseline: <45 y, 35/110 (32%); ≥45 y, 51/260 (20%)	Time-to-event comparison of those aged <45 y vs ≥45 y: HR, 2.18 (95% CI, 1.34-3.55; *P* = .002)	Not performed
Sakai et al,[16] 2019	Not reported in article; updated data: tumor volume increase ≥50% from baseline: <40 y, 1/6 (17%); ≥40 y 8/72 (11%)	Not performed; tumor volume increase >50% above baseline, univariate analysis using age (years): OR, 0.97 (95% CI, 0.94-0.99)	Not performed
Tuttle et al,[17] 2017	Tumor volume increase >50% above baseline: <40 y, 10/65 (15%); ≥40 y, 26/226 (12%)		In multivariable model adjusted for risk category at diagnosis, sex, cytologic classification, and tumor size, the OR of age (years) being associated with tumor volume enlargement >50% was 0.97 (95% CI, 0.94-0.99; *P* = .01)
Incident clinical nodal metastases			
Fukuoka et al,[13] 2016	Not reported in article; updated data: <40 y, 2/76 (3%); ≥40 y, 4/417 (1%)	Not performed	Not performed
Ito et al,[14] 2014	<40 y, 9/169 (5%); ≥40 y, 10/1066 (1%) (of whom 2/496 were aged ≥60 y)	Univariate comparison <40 y, 40-59 y, and ≥60 y: *P* < .001	Multivariate analysis adjusted for male sex, TSH suppression, family history, suspected or diagnosed multiplicity, tumor size 5-8 mm, tumor size ≥9 mm, comparing those aged <40 y with ≥40 y: OR, 6.76 (95% CI, 2.73-16.95; *P* < .001)
Oh et al,[15] 2018	Not reported	Not performed	Not performed
Sakai et al,[16] 2019	Not reported in article; updated data: <40 y, 0/6 (0%); ≥40 y, 2/72 (3%)	Not performed	Not performed
Tuttle et al,[17] 2017	Extrapolated from reported data: <40 y, 0/65 (0%); ≥40 y, 0/226 (0%)	Not performed	Not performed

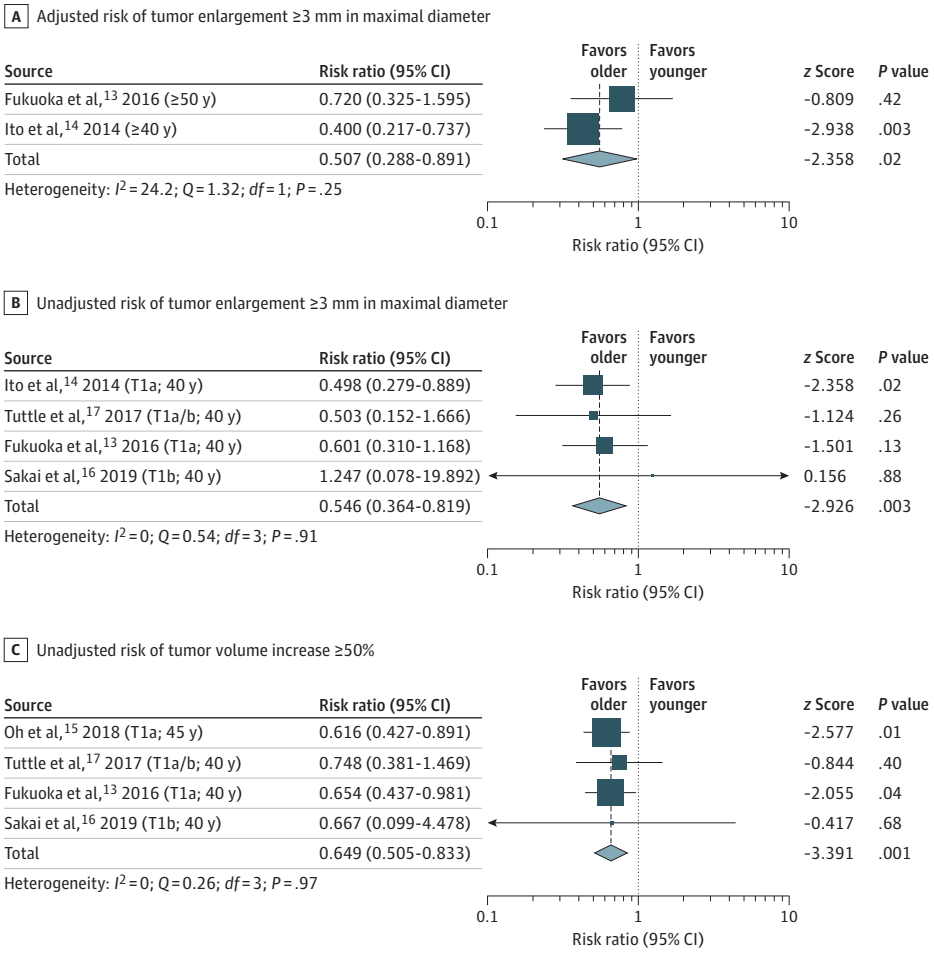
Abbreviations: HR, hazard ratio; OR, odds ratio; PMC, papillary microcarcinoma; TSH, thyroid-stimulating hormone.

among the included studies, with event rates ranging from 0% to 5% in the younger groups and 0% to 3% in the older groups included in the calculation of the risk difference,[13,14,16,17] such that the inclusion of studies with event rates of zero in both groups may be associated with the results, particularly in the context of studies with limited follow-up periods. Because we did not observe any statistically significant heterogeneity in any of the meta-analyses and because a limited number of studies were included, we did not perform any further sensitivity analyses exploring subgroup effects. Furthermore, given that fewer than 10 studies were included, analysis for publication bias could not be meaningfully interpreted and was not performed.

Discussion

On reviewing the data from 5 studies of AS of small, low-risk PTC, we observed a reduced risk of tumor enlargement (both a maximal diameter increase of ≥3 mm and a tumor volume >50% or ≥50% from baseline) with increasing age. Although not included in this review, the tumor volume doubling time for PTC in patients undergoing AS was also reported to be inversely associated with age in 2 recent studies examining this outcome.[19,20] Incident clinical nodal metastases were generally uncommon in our review, limiting the interpretation of the meta-analyses.

Figure 2. Forest Plot of Pooled Risk Ratios of Tumor Enlargement Relative to Age



A, Forest plot of the risk of tumor enlargement of 3 mm or more in maximal diameter, statistically adjusted for confounders. B, Forest plot of the risk of tumor enlargement of 3 mm or more in maximal diameter (crude, unadjusted data). C, Forest plot of the risk of a tumor volume increase of 50% or more (crude data, unadjusted). Age was the cutpoint used in the analysis.

Decision-making about the management of low-risk PTC in elderly individuals may be complex. Age is known to be a factor negatively associated with outcomes for patients with surgically treated PTC.[21,22] However, the risk of surgical complications after thyroidectomy is also significantly associated with advanced age.[22-24] Miyauchi et al[25] have estimated, based on data from patients with papillary microcarcinomas undergoing AS, the following lifetime disease progression probability percentages according to age at diagnosis: 49% (for patients in their 20s), 25% (for patients in their 30s), 21% (for patients in their 40s), 10% (for patients in their 50s), 8% (for patients in their 60s), and 4% (for patients in their 70s) (from "hypothesis C," which the authors believe is the best model approximating actual probabilities). In considering an elderly patient with small, low-risk PTC for surgery or AS, the potential heightened risk of complications in the context of comorbidities and the competing risk of death must be weighed against the risk of the disease itself, which, in the case of patients with papillary microcarcinoma undergoing AS, appears to be relatively low. However, the risk of disease progression, and particularly incident nodal metastatic disease in patients undergoing AS, appears to be relatively low as well, and this option may be acceptable to middle-aged or even younger patients depending on their attitudes about thyroidectomy, concerns about the disease, and willingness to be closely clinically followed up.

Strengths and Limitations

This study has some strengths, including completion of a comprehensive electronic database search by a library information specialist experienced in database searching, independent duplicate reviews of citations and articles in the selection of eligible studies, and independent duplicate data abstraction and critical appraisal of included studies. We also made an effort to contact the authors of the primary studies to clarify methodological questions and to enable the authors of 2 of the studies[13,16] to include updated data in the meta-analyses.

This study also has some limitations, including a limited number of studies and patients available for inclusion in the review, limited follow-up periods for some of the included studies, the inability to evaluate publication bias or subgroup effects (owing to too few available studies), the limited statistical power to detect heterogeneity in meta-analyses (also owing to limited numbers of studies), and a limited ability to search the gray literature. Furthermore, the findings in this review are applicable only to adult patients with low-risk PTC (mostly patients with pap-

illary microcarcinoma) and should not be generalized to pediatric patients with PTC or those with more advanced disease.

Conclusions

In this systematic review and meta-analysis, we found that advancing age was associated with a reduced risk of tumor enlargement for adult patients undergoing AS for small PTC. Most of these data were collected from patients with papillary microcarcinomas. More research is needed, including data on more patients from different populations with longer follow-up, to confirm these findings, including data on the observed differences in outcomes according to age as well as on the low incidence rates of metastatic disease.

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REFERENCES

1. Morris LG, Tuttle RM, Davies L. Changing trends in the incidence of thyroid cancer in the United States. *JAMA Otolaryngol Head Neck Surg*. 2016;142(7):709-711. doi:10.1001/jamaoto.2016.0230

2. Ito Y, Uruno T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid*. 2003;13(4):381-387. doi:10.1089/105072503321669875

3. Miyauchi A. Clinical trials of active surveillance of papillary microcarcinoma of the thyroid. *World J Surg*. 2016;40(3):516-522. doi:10.1007/s00268-015-3392-y

4. Alhashemi A, Goldstein DP, Sawka AM. A systematic review of primary active surveillance management of low-risk papillary carcinoma. *Curr Opin Oncol*. 2016;28(1):11-17. doi:10.1097/CCO.0000000000000244

5. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158(4):280-286. doi:10.7326/0003-4819-158-4-201302190-00009

6. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269, W64. doi:10.7326/0003-4819-151-4-200908180-00135

7. Voils CI, Crandell JL, Chang Y, Leeman J, Sandelowski M. Combining adjusted and unadjusted findings in mixed research synthesis. *J Eval Clin Pract*. 2011;17(3):429-434. doi:10.1111/j.1365-2753.2010.01444.x

8. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol*. 2003;157(10):940-943. doi:10.1093/aje/kwg074

9. Megens MR, Churilov L, Thijs V. New-onset atrial fibrillation after coronary artery bypass graft and long-term risk of stroke: a meta-analysis. *J Am Heart Assoc*. 2017;6(12):e007558. doi:10.1161/JAHA.117.007558

10. Cochran WG. The combination of estimates from different experiments. *Biometrics*. 1954;101:101-129. doi:10.2307/3001666

11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557

12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629

13. Fukuoka O, Sugitani I, Ebina A, Toda K, Kawabata K, Yamada K. Natural history of asymptomatic papillary thyroid microcarcinoma: time-dependent changes in calcification and vascularity during active surveillance. *World J Surg*. 2016;40(3):529-537. doi:10.1007/s00268-015-3349-1

14. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid*. 2014;24(1):27-34. doi:10.1089/thy.2013.0367

15. Oh HS, Ha J, Kim HI, et al. Active surveillance of low-risk papillary thyroid microcarcinoma: a multi-center cohort study in Korea. *Thyroid*. 2018;28(12):1587-1594. doi:10.1089/thy.2018.0263

16. Sakai T, Sugitani I, Ebina A, et al. Active surveillance for T1bNOMO papillary thyroid carcinoma. *Thyroid*. 2019;29(1):59-63. doi:10.1089/thy.2018.0462

17. Tuttle RM, Fagin JA, Minkowitz G, et al. Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. *JAMA Otolaryngol Head Neck Surg*. 2017;143(10):1015-1020. doi:10.1001/jamaoto.2017.1442

18. Moon JH, Kim JH, Lee EK, et al. Study protocol of Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma (MAeSTro). *Endocrinol Metab (Seoul)*. 2018;33(2):278-286. doi:10.3803/EnM.2018.33.2.278

19. Miyauchi A, Kudo T, Ito Y, et al. Natural history of papillary thyroid microcarcinoma: kinetic analyses on tumor volume during active surveillance and before presentation. *Surgery*. 2019;165(1):25-30. doi:10.1016/j.surg.2018.07.045

20. Oh HS, Kwon H, Song E, et al. Tumor volume doubling time in active surveillance of papillary thyroid carcinoma. *Thyroid*. 2019;29(5):642-649. doi:10.1089/thy.2018.0609

21. Adam MA, Thomas S, Hyslop T, Scheri RP, Roman SA, Sosa JA. Exploring the relationship between patient age and cancer-specific survival in papillary thyroid cancer: rethinking current staging systems. *J Clin Oncol*. 2016;34(36):4415-4420. doi:10.1200/JCO.2016.68.9372

22. Joseph KR, Edirimanne S, Eslick GD. Thyroidectomy for thyroid cancer in the elderly: a meta-analysis. *Eur J Surg Oncol*. 2019;45(3):310-317. doi:10.1016/j.ejso.2018.07.055

23. Sahli ZT, Ansari G, Gurakar M, et al. Thyroidectomy in older adults: an American College of Surgeons National Surgical Quality Improvement Program study of outcomes. *J Surg Res*. 2018;229:20-27. doi:10.1016/j.jss.2018.03.057

24. Zambeli-Ljepović A, Wang F, Dinan MA, et al. Extent of surgery for low-risk thyroid cancer in the elderly: equipoise in survival but not in short-term outcomes. *Surgery*. 2019;166(5):895-900. doi:10.1016/j.surg.2019.05.035

25. Miyauchi A, Kudo T, Ito Y, et al. Estimation of the lifetime probability of disease progression of papillary microcarcinoma of the thyroid during active surveillance. *Surgery*. 2018;163(1):48-52. doi:10.1016/j.surg.2017.03.028