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Calcified carotid artery atheroma and stroke: A systematic review

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Calcified carotid artery atheroma and stroke

A systematic review

Muralidhar Mupparapu, DMD, MDS; Irene H. Kim, DMD, MPH

AImog and colleagues¹ have suggested that the identification of a calcified carotid artery atheroma (CCAA) on a panoramic radiograph (Figure 1) can be a specific risk predictor for stroke when used as a secondary screening tool. It is unclear, however, whether the CCAAs seen on panoramic radiographs represent an increased or decreased risk of stroke or if they are markers for significant risk toward the precipitation of a cerebrovascular event without playing a causal role.² Improperly designed and reported diagnostic studies may trigger the premature dissemination of inappropriate clinical guidelines that lead dentists to make incorrect treatment or referral decisions.

We performed a critical review of the literature to see whether there is evidence to support the claim that CCAAs detected on panoramic radiographs led to the precipitation of cerebrovascular accidents (CVAs). We critically reviewed the literature on this topic using the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) checklist.³

ABSTRACT

Background. Calcified carotid artery atheroma (CCAA) and its identification on panoramic radiographs have been advocated as a predictor of a cerebrovascular accident (CVA).

Types of Studies Reviewed. The authors conducted an electronic search using 11 databases to evaluate the evidence from the literature that links CCAA detection on panoramic radiographs and the precipitation of CVAs among those people. They used the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) checklist to perform this systematic review.

Results. One study of the 54 studies the authors identified satisfied the REMARK criteria in which CCAA was associated with a negligible increased risk of stroke (95 percent confidence interval, 0 to 0.04 percent) in the population studied.

Clinical Implications. This systematic review suggests the data supporting the hypothesis that radiographically detectable CCAA is associated with an increased risk of stroke are incomplete and inconclusive. Further research is needed, as clinical guidelines for risk prediction using panoramic radiographs cannot be established on the basis of the current evidence.

Key Words. Panoramic radiography; calcified carotid artery atheroma; cardiovascular diseases; risk assessment.

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Figure 1. Panoramic radiograph of a 68-year-old man demonstrating a calcified carotid artery atheroma bilaterally (arrows).

MATERIALS AND METHODS

Electronic searching. To help us identify studies that we included or considered for this review, we developed search strategies for each electronic database that we searched (Figure 2). The search strategies used a combination of controlled vocabulary and free text terms. We conducted electronic searches using the following databases: ClinicalTrials.gov, PubMed, Ovid Old MEDLINE, Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Computer Retrieval of Information on Scientific Projects, Evidence Based Medical Reviews (American College of Physicians Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects), Thomsen's ISI Web of Knowledge: Current Contents Connect, OSTMED: The Osteopathic Literature Database and Google Scholar. The phrases we used were "calcified carotid atheromas," "atherosclerosis plus panoramic radiography," "carotid artery disease plus panoramic radiography," "calcinosis plus panoramic radiography" and "carotid arteries plus panoramic radiography."

Data extraction. We independently reviewed and extracted the data using the REMARK checklist (Box, page 486). If we disagreed with one another, we discussed the issue and, if necessary, consulted with a third reviewer. We planned to exclude data if we could not reach an agreement, but we did not have to in this review.

Search results. Our electronic search of 11 databases produced a total of 431 citations, many of which were duplicates. The results for each of the search strategies are summarized in the table (page 487). We eliminated citations that did not include panoramic radiography, CCAAs and CVA or cerebrovascular stroke, giving us 54 articles for this review.

Criteria for excluded and included studies. Our literature search strategies and reasons for study exclusion are summarized in

Figure 2. Most of the publications were case reports, case series, cross-sectional studies and reviews; there was one editorial (Figure 3, page 488). We excluded the case reports, case series, reviews and editorials owing to the lack of rigorous methodology. All of the cross-sectional studies we excluded included prevalence data on the presence of CCAA in various study populations. We excluded them, however, because of the lack of follow-up for outcome assessments. We excluded some articles because they had a different study objective; for example, some studies compared the radiographic detection of CCAA with simultaneous documentation of carotid artery occlusion via Doppler ultrasonography. Although these studies were well-designed, they did not meet our study objective. The lack of follow-up with the patient groups to observe the development of endpoints over time kept the studies with different objectives out of the final analysis. We only included studies that included follow-up with patients with and without CCAAs. We excluded 53 studies and analyzed one using the REMARK checklist.³

RESULTS

The only study that met most of the inclusion criteria was that by Tanaka and colleagues.⁴ They

ABBREVIATION KEY. **AC:** Aortic calcification. **BP:** Blood pressure. **CCAA:** Calcified carotid artery atheroma. **CVA:** Cerebrovascular accident. **IMT:** Intima-media thickness. **REMARK:** Reporting Recommendations for Tumor Marker Prognostic Studies.

evaluated whether CCAA on panoramic radiographs was a predictor of vascular disease among a cohort of 80-year-old Japanese people. In 1998, 659 baseline radiographs of subjects were obtained along with medical histories, and examinations were performed. Thirty-three of the radiographs had CCAA defined as a radiopaque nodular mass or masses adjacent to the cervical vertebrae at or below the intervertebral space between C3 and C4. A second history was taken and a second examination was performed five years after the baseline on 191 of the original subjects. The examination consisted of body height and weight, pulse rate, blood pressure (BP) and heart activity, total blood cholesterol level, fasting blood sugar level and heel bone density. Of the 191 subjects followed up, only eight had CCAA on their baseline panoramic radiographs.

None of the patients with baseline CCAA on their panoramic radiographs had a cerebrovascular event within the five-year follow-up period, whereas 10 patients from the group without any radiographically detectable CCAAs ($n = 183$) had cerebrovascular disease within the five-year follow-up period. The history of vascular diseases, the parameters related to vascular diseases and the occurrence of vascular diseases were recorded and compared between the two groups. No significant difference was found in the incidence of

cerebrovascular diseases between subjects with CCAA and subjects without CCAA ($P = .654$). The cause of death was recorded for the 108 subjects (103 without CCAA, five with CCAA) who died during the five-year period after baseline and was compared between the two groups.

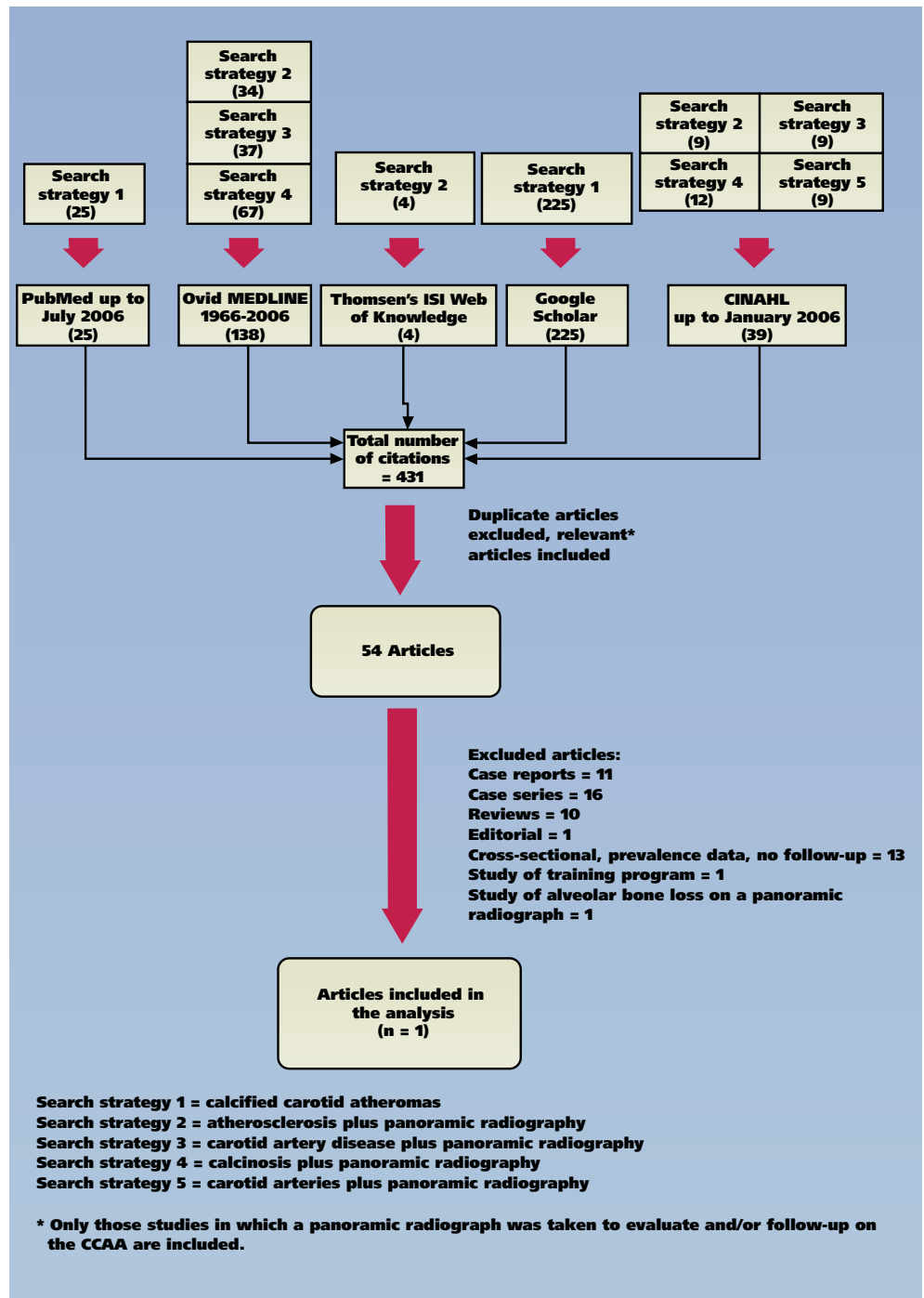


Figure 2. Flowchart of literature search strategies with reasons for inclusion or exclusion of studies. CCAA: Calcified carotid artery atheroma.

BOX

Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK).*

INTRODUCTION

1. State the marker examined, the study objectives, and any prespecified hypotheses.

MATERIALS AND METHODS

Patients

2. Describe the characteristics (e.g., disease stage or comorbidities) of the study patients, including their source and inclusion and exclusion criteria.
3. Describe treatments received and how chosen (e.g., randomized or rule-based).

Specimen characteristics

4. Describe type of biological material used (including control samples) and methods of preservation and storage.

Assay methods

5. Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.

Study design

6. State the method of case selection, including whether prospective or retrospective and whether stratification or matching (e.g., by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.
7. Precisely define all clinical endpoints examined.
8. List all candidate variables initially examined or considered for inclusion in models.
9. Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.

Statistical analysis methods

10. Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.
11. Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.

RESULTS

Data

12. Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the numbers of patients and the number of events.
13. Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including numbers of missing values.

Analysis and presentation

14. Show the relation of the marker to standard prognostic variables.
15. Present univariate analyses showing the relation between the marker and outcome, with the estimated effect (e.g., hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.
16. For key multivariable analyses, report estimated effects (e.g., hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.
17. Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.
18. If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.

DISCUSSION

19. Interpret the results in the context of the prespecified hypotheses and other relevant studies; include a discussion of limitations of the study.
20. Discuss implications for future research and clinical value.

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Causes of death included accidents, malignant tumors, vascular-related events, organ failures, inflammations and other causes. No significant difference was found in the incidence of

the plaque's locations, compared with subjects who do not have carotid plaques.⁶ When the authors looked at the risk associated with plaques in different locations, they observed that there

cerebrovascular-related deaths between subjects with CCAA and subjects without CCAA ($P = .325$). Risk estimates and risk ratios were calculated based on the number of subjects with and without CCAA who were followed. The risk estimate varied from 0 to 0.04 percent, with a 95 percent confidence interval.

No other studies in the literature included follow-up with a study group with CCAA and a control group without CCAA to assess risk strategies.

DISCUSSION

Despite the decline in mortality due to stroke, stroke remains a leading cause of morbidity and mortality in the United States.⁵ It is important to understand all the etiologic factors that predispose the adult population to stroke and to diagnose the atherosclerotic risk appropriately and intervene. It is equally important to measure the relative risk of each these identifiable factors appropriately. Clinicians also must be aware of the recent advances in stroke research, especially in regard to the interpretation of CCAA on panoramic radiographs (Figure 1).

The Rotterdam study of 2002 demonstrated that people with carotid plaques tend to have an increased risk of stroke and cerebral infarction, irrespective of

TABLE

Summary of search strategies developed for electronic database search and their results.

DATABASE	NO. OF CITATIONS OBTAINED VIA DATABASE SEARCH USING SPECIFIC SEARCH CRITERIA				
	Calcified Carotid Atheromas	Atherosclerosis Plus Panoramic Radiography	Carotid Artery Diseases Plus Panoramic Radiography	Calcinosis Plus Panoramic Radiography	Carotid Arteries Plus Panoramic Radiography
ClinicalTrials.gov	0	0	0	0	0
PubMed	25	0	0	0	0
Ovid Old MEDLINE (1950-1965)	0	0	0	0	0
Ovid MEDLINE (1966-June 2006)	0	34	37	67	0
Ovid MEDLINE In-Process & Other Non-Indexed Citations	0	0	0	0	0
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	0	9	9	12	9
Computer Retrieval of Information on Scientific Projects	0	0	0	0	0
EBM Reviews (American College of Physicians Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects)	0	0	0	0	0
Thomsen's ISI Web of Knowledge: Current Contents Connect	0	4	0	0	0
OSTMED: The Osteopathic Literature Database	0	0	0	0	0
Google Scholar	225	0	0	0	0

was no indication that plaques within a turbulent blood flow, such as the carotid bifurcation and internal carotid artery, carried a higher risk than did plaques in the common carotid artery. We do not have any further evidence that these plaques once calcified may lead to increased risk of stroke in the future. Panoramic radiography may demonstrate that CCAAs calcify over time, but there is little evidence-based information that the CCAAs are risk predictors for the diagnosis of cerebrovascular disease.

Clinical examinations, along with other investigatory procedures such as imaging and biochemical and histopathologic diagnostic tests, are

used routinely in medicine and dentistry to diagnose, categorize and monitor the progression of a disease. Each of these procedures can be regarded as a separate diagnostic or screening test.⁷ Systematic reviews of diagnostic tests that are evidence-based and reliable for both the prediction and the outcome of a major debilitating health concern such as stroke are needed. Panoramic radiography is one procedure normally used in dental practice for detecting dental- and maxillo-facial-related disease. There has been a trend toward using panoramic radiographs to identify stroke-prone patients.⁸⁻¹⁰ This issue is complicated because there are many risk factors that predis-

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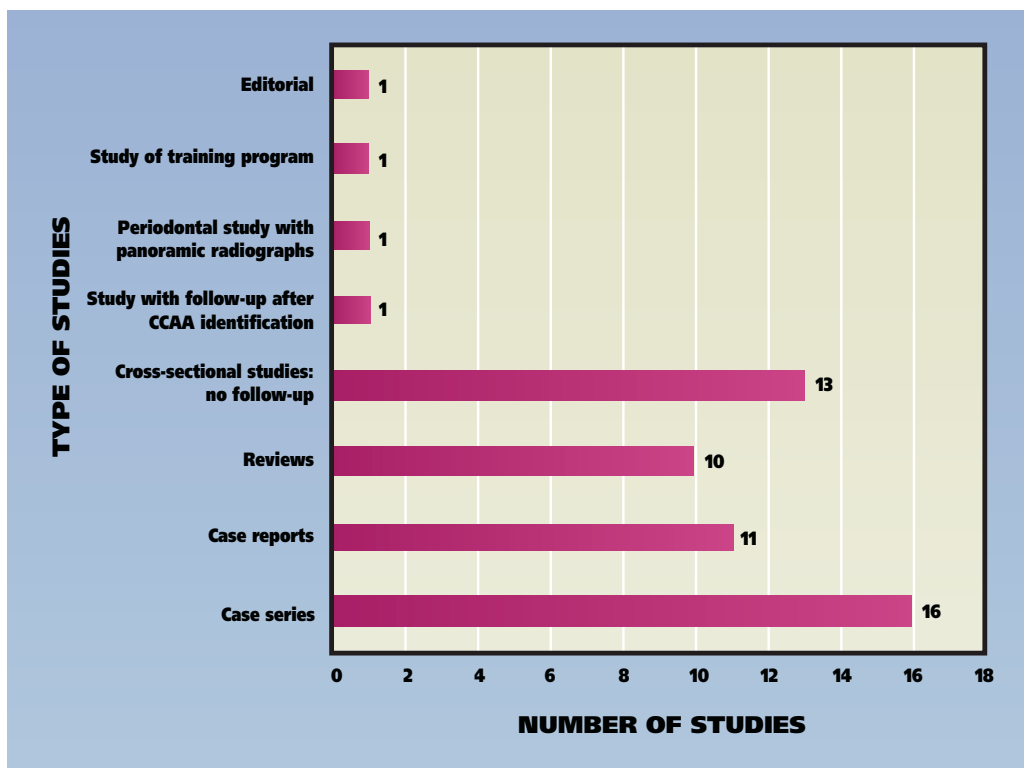


Figure 3. Graph showing the distribution of 54 selected articles that used panoramic radiographs to study calcified carotid artery atheromas. CCAA: Calcified carotid artery atheroma.

pose a person to generalized atherosclerosis and plaque formation that also can promote the risk of cerebrovascular occlusion and stroke. Age, smoking, total cholesterol level, systolic BP or hypertension strongly predict the progression of extracoronary atherosclerosis in elderly people, according to the Rotterdam study of 2003.¹¹ When the study's authors investigated a population-based cohort of adults older than age 55 years to determine which measures of atherosclerosis are strong predictors of the risk of stroke and cerebral infarction, they found that carotid intima-media thickness (IMT) and aortic calcifications (ACs) were the strongest predictors of stroke. A recent study also demonstrated the strong association of metabolic syndrome with the accelerated progression of carotid IMT in elderly women.¹² Such an association could not be determined for the carotid plaques, though the authors considered carotid IMT and ACs to be of additional value in the overall stroke risk assessment. The 2002 Rotterdam study was inconclusive regarding the role of carotid plaques, calcified or not, in the risk assessment strategy for stroke. Despite the observations that calcium frequently is seen in complicated plaques, calcium is not a marker for

subjects. They also reported that the calcified carotid plaques seemed to be more stable than the noncalcified carotid plaques and that the patients with extensive calcification of the carotid plaques were less likely to have symptomatic disease. The plaques that were not calcified, whether demonstrable radiographically or not, most commonly were symptomatic and often had an inflammatory or ulcerative component that was more susceptible to detachment, which eventually could lead to occlusion of the finer carotid vessels. The study showed that there is little evidence to support CCAA as a predictor of stroke. Although this theory needs to be substantiated more convincingly with further research, it has confirmed the findings of Mathiesen and colleagues¹⁴ via the Tromsø study that identified high-risk noncalcified plaques using ultrasonography. According to Mathiesen and colleagues,¹⁴ noncalcified, echolucent plaques have a higher probability of rupture or dislodgement, which can lead to more significant carotid stenosis than do calcified plaques.

In dentistry, one of the tools used for medical risk stratification in patients who are seeking dental treatment and are considered at high risk of experiencing a CVA has been the so-called sec-

unstable or stable plaques. The 2002 Rotterdam coronary calcification study revealed that no definitive conclusions could be drawn concerning the strength of associations between coronary atherosclerosis and atherosclerosis in the carotid artery, peripheral arteries and aorta.

In 2002, Hunt and colleagues¹³ studied the morphological qualities of calcified plaques observed in the carotid arteries. They could not find a direct relationship between the presence of CCAAs and the early occurrence of stroke in the study

ondary screening via panoramic radiography. Friedlander and Lande¹⁵ first reported the radiographic identification of CCAA by using panoramic radiography. Since that first report, many reviews and case series that have attempted to associate CCAA with an increased risk of stroke have been published.^{8-10,16-60} However, there are no adequate population-based cohort studies of the relationship between CCAA that is detectable on panoramic radiographs and the occurrence of cerebrovascular events. In addition, CCAA is not always detectable on panoramic radiographs.⁶¹ Coronary calcifications are similar to CCAAs,⁶² and the calcification that occurs in these atheromatous lesions can be visualized consistently on plain radiographs (skull views, cervical spine series of the neck or lateral cephalometric views^{20,22}). The visualization of CCAAs on panoramic radiographs, however, depends heavily on the position of the film and the width of the focal trough.⁶¹ Moreover, carotid IMT and ACs are independent risk predictors for the occurrence of stroke,⁶³ whereas CCAA lacks the evidence to be an independent risk factor. For the past 25 years, dental health care providers relied on the generally weak and unsubstantiated evidence from the literature^{8-10,16-60} that described a casual association between CCAAs and their radiographic detection as risk markers for CVAs.

In the dental literature, articles about CCAA and panoramic radiographs generally are case reports, case series and cross-sectional studies that report the prevalence of CCAA in various study populations. The prevalence across three studies ranged from 2 to 4.5 percent in a predominantly male study population (age range, 25-88 years)^{15,20,22} and 3.6 percent in a male and female population (age range, 31-86 years).¹⁷ The prevalence in an African-American population was 0.43 percent (age range, 14-77 years).³¹ Among 80-year-old Japanese people, the prevalence of CCAA was 5 percent,⁵⁹ and, in a Thai population, it was 2.5 percent (age range, 50-92 years).⁵² Multiple incidental correlations of the prevalence of CCAA coexisting with systemic medical conditions also have been reported. These systemic conditions included dilated cardiomyopathy,⁴⁹ type 2 diabetes,^{35,39} obstructive sleep apnea syndrome,³⁰ renal disease⁵⁷ and metabolic syndrome.⁵¹ In addition, the prevalence of CCAA also was studied in patients receiving radiation therapy to the neck^{27,28,33} and in postmenopausal women.³⁷ The authors of these studies generally

called for using panoramic radiographs as a secondary screening tool to both increase awareness and increase detection efficiency of these lesions.

In our literature search, only one study met the inclusion criteria and was evaluated, but there were three studies that did include some follow-up with patients with CCAAs.⁵⁸⁻⁶⁰

Cohen and colleagues⁵⁸ sought to determine whether CCAA led to vascular events in a population of male patients with CCAA. The authors followed 71 patients with identifiable CCAA for an average of 3.6 years to determine significant endpoints. Almost two-thirds of the study population had multiple risk factors (73.2 percent), and 86.0 percent of the study population had at least one established vascular risk factor. Seven of the 71 patients who had CCAA had either a stroke or a transient ischemic attack as an endpoint. The authors concluded that it was not clear whether CCAA was a surrogate marker for established vascular risk factors or an independent risk factor for vascular disease. In the end, however, the authors concluded that CCAAs found incidentally on panoramic radiographs would be powerful markers for future cerebrovascular and cardiovascular events and death. This study did not have a control group without CCAA for comparison, and we excluded it from our study.

Ohba and colleagues⁵⁹ evaluated the CCAA detected on panoramic radiographs among 80-year-old Japanese subjects from the Fukuoka prefecture; they found CCAA in 33 of the 659 subjects whose radiographs were selected after excluding 38 radiographs owing to inadequate positioning. The remaining 626 subjects were considered controls. The authors compared BP, electrocardiogram results, total cholesterol level and fasting blood sugar level between the CCAA population and the control population. There was no statistically significant difference in blood pressure, electrocardiogram results, total cholesterol level and fasting blood sugar level between the two groups. At the five-year follow-up of the 33 subjects with CCAA, no CVAs were recorded. We excluded this study because there was no follow-up with the control group.

Tamura and colleagues⁶⁰ conducted a study that explored the relationship between CCAA and the risk of stroke. Over five years, three examiners identified 106 patients with CCAA by using 2,568 radiographs from new patients attending outpatient clinics. All of the patients with CCAA had a significant medical history that included a

history of hypertension; a body mass index greater than 25; hyperlipidemia; cardiovascular disease; thyroid, liver, stomach and kidney disease; smoking; or alcohol consumption. Of the 106 patients with CCAA, only 76 could be followed by a telephone interview for an average of 2.43 years. Only one of these 76 patients (1.3 percent) experienced stroke as a significant endpoint over 3.45 years. There was no follow-up with the group without CCAA for comparison, so we excluded this study.

The significance of Cohen and colleagues⁵⁸ data cannot be assessed without valid control data. Ohba and colleagues⁵⁹ concluded that the panoramic radiographs provide potentially life-saving information for patients who are at risk of experiencing stroke despite having no direct evidence that substantiates their statement. Their conclusion does not match their results. The significance of findings from Tamura and colleagues⁶⁰ is unknown, owing to the lack of a control group in their study.

The study that met all the inclusion criteria was by Tanaka and colleagues.⁴ The investigators studied CCAAs detected on panoramic radiographs among 80-year-old Japanese subjects from the Fukuoka prefecture, the same population initially screened by Ohba and colleagues.⁵⁹ The authors conducted the study to determine if the presence of CCAA on panoramic radiographs of 80-year-old Japanese men and women posed any increased risk of cerebrovascular or cardiovascular events. The authors concluded that CCAA represented a history of vascular disease and the presence or absence of CCAA was not significant in the occurrence of vascular disease–related deaths. This study is unique, as no other studies in the literature followed a population with and without CCAA and re-evaluated both groups for the occurrence of any endpoints. None of the patients who had identifiable CCAA on their panoramic radiographs had cerebrovascular disease. Furthermore, there was no significant difference in the occurrence of vascular disease–related death within five years after the baseline examination among their subjects with and without CCAA ($P = .325$). The authors concluded that CCAAs on panoramic

radiographs are not useful markers for subsequent vascular events and related deaths among 80-year-old Japanese subjects. The negligible risk demonstrated in this elderly Japanese population may not be universal; the risk may differ from population to population, and age and other comorbid factors may alter the outcomes.

As better-designed studies are conducted that report the results of long-term follow-up among patients with CCAA who are compared with those without CCAA, it will become clear as to whether CCAA is an independent risk factor or whether it is associated with future CVAs.

CONCLUSIONS

The preponderance of the literature regarding CCAAs and their significance on panoramic radiographs has become a much-debated health care issue over the past two decades. Stroke is an important and life-threatening vascular endpoint. Panoramic radiography has the potential to be a tool for such a risk prediction. However, unlike the carotid IMT and ACs that are believed to be independent risk predictors for the occurrence of stroke, CCAA does not yet have the same status. Unless case-controlled or cohort studies that include control subjects demonstrate the CCAA leads to an early precipitation of stroke, the association between the two will be unsubstantiated.

Risk factors such as age, smoking history, total cholesterol level, systolic BP and hypertension should be examined closely when assessing a patient at risk of experiencing stroke. We should not estimate the risk of stroke with the incidental finding of CCAA on panoramic radiographs only. Further research is warranted before any recommendations can be made for or clinical guidelines developed regarding using CCAAs detected on panoramic radiographs to predict a cerebrovascular accident. ■

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