EDITORIAL

Evidence base, epidemiology, correlations, and cause and effect: dental caries and head and neck cancer

PREAMBLE

Reader beware. With the ever-increasing number of journals comes an ever-increasing number of publications that require an ever-increasing number of reviewers and fact checkers. However, I am finding that the ever-increasing pace and number of activities authors and reviewers are required to manage is resulting in many examples of less than stellar articles making their way into the publication world. I also am concerned by the fact that many readers may not be aware of the inaccuracies and errors found in publications and would assume that all published findings are accurate. I welcome this editorial from Drs Epstein, Sciubba, and Abt as an example of the importance that health care providers must place on becoming familiar with the principles of evidence-based practice. Otherwise, scientific accuracy and critical analysis will be left to only those who know better.

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It is important that health care professionals be cognizant of the hierarchy of evidence, study designs, methodology, and interpretation of results of studies to evaluate the validity and utility of study outcomes. This requires an evaluation of the study question, the study methods used, and the quality of the study to draw appropriate conclusions from the information presented. A recent publication of potential importance to dental providers stimulated this editorial, which is written to assist health care providers in reading and interpreting the literature.

PRINCIPLES OF CLINICAL STUDIES AND QUALITY OF STUDY DESIGN

Observational studies, including case-control and cohort designs, assessing risk of various conditions are important in developing an understanding of the cause of disease and may lead to the study of disease prevention and improved management. Examples of risk assessment are evidenced by the examination of the effects of obesity on diabetes and cancer and the effects of tobacco on heart disease and cancer. These studies may lead to evidence of causation, but they require very large patient populations, longitudinal study, and

evidence of mechanisms of risk. As a result, evidence builds over many years of comprehensive research, such as has been the case in the example of tobacco use and cancer as well as the association between chronic asbestos exposure and mesotheliomas.[1,2]

It is important to understand the requirements for determination of causation and risk factors for disease and the extensive evidence that is needed. It is also critical to know that "correlation does not prove cause and effect," as evidenced by a recent report that emphasizes a lack of consensus concerning many putative relationships between chronic periodontitis and aspects of systemic health.[3] This is particularly challenging when common conditions (such as gingival/periodontal disease and dental cavities) are assessed in relation to uncommon or rare diseases such as oral cancer. In addition, correlation of 2 common events is also fraught with challenges in determining causation or risk, such as periodontal disease and cardiovascular disease, given that they may share common risk factors.

General principles for evaluating evidence of causation are outlined in Table I.[4] A plausible mechanism should be backed by molecular and cellular studies, animal studies, observational studies, and, in some cases, human trials. This may include the role of chronic inflammation, the role of the innate immune system and epithelial barrier function, and other factors (see Table I), and a dose-response relationship (amount, frequency, and time of exposure increase risk) should be seen. Epidemiologic evidence includes cross-sectional data, prospective longitudinal data, or both. The stated risk factor within these models needs to be assessed as necessary or sufficient or as a cofactor for a specific disease. Exposure to the risk factor is associated with risk, and elimination of exposure that reduces that risk will strengthen or confirm that relationship.

Evidence of causation or effect of therapy must be based on well-designed, well-conducted studies and on a high level of evidence based on multiple evaluations/studies. The nature of the research and other related research can be rated based on the quality of the study and the strength of the evidence.

In reading research-based publications, it is important to recognize that not all published articles are of high quality and that not all journals, websites, or news services are equal. In addition, acceptance or rejection of articles for publication in journals is not a perfect

Table I. Principles in evidence of causation[4]

1. **Strength of association:** The stronger the relationship between the independent variable and the dependent variable, the less likely it is that the relationship is due to an extraneous variable.
2. **Temporality:** It is logically necessary for a cause to precede an effect.
3. **Consistency:** Multiple observations of an association, with different people under different circumstances and with different measurement instruments, increase the credibility of a finding.
4. **Theoretical plausibility:** It is easier to accept an association as causal when there is a rational and theoretical basis for such a conclusion.
5. **Coherence:** The association must be coherent with other knowledge. A cause-and-effect interpretation for an association is clearest when it does not conflict with what is known about the variables under study and when there are no plausible competing theories or rival hypotheses.
6. **Specificity in the causes:** In the ideal situation, the effect has only one cause. Showing that an outcome is best predicted by one primary factor adds credibility to a causal claim.
7. **Dose-response relationship:** There should be a direct relationship between the risk factor (i.e., the independent variable) and people's status on the disease variable (i.e., the dependent variable).
8. **Experimental evidence:** Any related research that is based on experiments will make a causal inference more plausible.
9. **Analogy:** Sometimes a commonly accepted phenomenon in one area can be applied to another area.

science. Peer-reviewed journals may use various numbers of reviewers; each reviewer may have differing points of view; and review of manuscripts may lead to variable results with respect to acceptance or rejection. Although this may be the best available system for assessing manuscripts and associated literature, it is imperfect. Hence, replication of research to support previous findings to prove or substantiate initial claims is needed for verification of principles. Furthermore, if a topic is of interest to the lay press, they may present the information, as is necessary, to the public in simple terminology that is not presented in the article reviewed, and critical implications or nuances may not be mentioned or appreciated, thus potentially leading to invalid conclusions. Simply put, research evidence must be carefully evaluated from the best sources available, including peer-reviewed literature with its own set of limitations that may affect various studies and the quality of literature. Some principles of well-designed studies are listed in Table II. The strength of evidence increases along a gradient of study designs, with systematic reviews of randomized controlled trials having the highest strength (Table III).

DENTAL CARIES AND ORAL CANCER

An example pertinent to dental providers is a recently published single-center case-control study that evaluated dental cavities in patients with cancer and in those without cancer.[5] This study represented an evaluation of risk of oral and oropharyngeal cancer and the relationship to dental caries. One must look at the study methodology, the population studied, the analysis conducted, and the conclusions drawn in light of current and related literature.

Table II. Some principles of well-designed studies

- Definition of a sound and valid research question and prior evidence
- Planning of sample size and outcomes before study conduct (not after study was initiated; the "power calculation")
- If controls are involved: Matched for general findings such as age, gender, and condition (stage of disease)
- If an interventional study: randomized, double-blind design
- Appropriate and defined end points with utilization of laboratory or diagnostic tests and standard clinical or advanced measures
- Whenever possible, use of tools/tests that have been validated in prior studies
- Appropriate statistics
- Careful accounting of those who begin, complete, or discontinue the study
- Multicenter studies can have increased impact/value

Dental caries represents one of the most common infections affecting humankind, whereas oral, oropharyngeal, and laryngeal cancers remain rare diseases (less than 3% of total body cancers; over 40 000 cases per year in the United States).[6] Correlation of a common disease within a population with a rare disease presents study-design and statistical challenges. This report is a small-sample, case-control study, and those features limit the strength of the evidence, which should be considered in drawing conclusions. The methods used to evaluate past dental health, as reflected in current status, are fraught with risk, as panoramic radiographs are not the test of choice for assessing cavities

Table III. Increasing strength of evidence

- In vitro study
- Animal research
- Case report or case series
- Cross-sectional study
- Case-control study
- Cohort study
- Randomized controlled trial
- Systematic review of randomized controlled trials

(only large cavities can be detected, with cavities at the gum margin and roots on the sides of teeth and beneath crowns not consistently detected). As a result, these radiographs are generally not used for the diagnosis of cavities in clinical practice. In this study, a panoramic image was used as the "diagnostic tool." This is justified within the study as being the same diagnostic tool used in the patient population without cancer. The study also used the panoramic image to assess missing teeth and the presence of endodontic therapy or crowns, which are data that it can provide. People with prior endodontic treatment and crown placement are likely to have had a caries-related indication for such; however, the possibility of other non-caries-related events that required crown placement, such as management of a tooth fracture or for esthetic purposes, cannot be defined. Additionally, the choice of treatment may often depend on patient income and the nature (or lack) of reimbursement, if the latter was available at the time of the dental treatment; but this information was not available to the study. The decayed, missing, and filled teeth (DMFT) measure is used in standard epidemiology, but it shows historical changes to the dentition (burden of past dental disease) and, as noted by the authors, does not reflect cause of tooth loss or damage, nor does it represent treatment need (other than the decay subscore). Therefore, the "diagnostic tool," the panoramic film, has significant limitations and is not capable of providing the complete picture of caries risk and caries activity of the individual at the time. Blunt tools that show only the result of the past event of tooth loss, and as used in this study, do not show activity of disease and therefore may show no relation with microbiology or other pathologic processes. Thus, there are limitations in the study design.

However, of real concern in the design are differences noted in the patients with cancer and in the controls who were seen for dental care in the hospital clinic. Randomization is a powerful tool that controls for all known and unknown confounders. Observational studies do not use randomization and are therefore highly susceptible to the effects of confounding variables. Typically, observational studies attempt to mimic randomization either methodologically (by matching control patients to case patients) or statistically (by using logistic regression analysis). Selection of appropriate control patients is critical in case-control studies. This study did not control for age (patients with cancer were older), gender (there were more males in the cancer population), or history of tobacco use and alcohol consumption. Although insurance coverage levels in these cohorts were comparable at the time of the visit, they may or may not have been over time before that visit. These population differences raise concerns including the time when dental caries was active in relation to the diagnosis of cancer. Additionally, adjusted odds ratios should be similar to or greater (further away from the null value) than unadjusted odds ratios. Many of the adjusted odds ratios stated in the study were less than the unadjusted values, raising suspicion that the observed associations may be or are spurious.[7]

The authors note that prior literature has identified increased dental disease (cavities and gum disease, missing teeth) as associated with the risk of cancer. Thus the finding in this report is unique where lower cavity scores were associated with oral cancer risk.

Conclusions in any study must be based on the outcomes of the study. In this study, there was no evaluation of microbiology, and although several hypotheses were presented to explain the findings, these belong only within a hypothetical discussion of the article. Measuring exposure in a case-control study can be difficult, particularly when the measures are not the current clinical standard for assessing dental status, such as the exclusive use of panoramic radiographs for DMFT calculations.

Although this study raises these kinds of questions, it cannot be concluded that low risk of dental cavities, and thus presumed lower lactobacillus counts and possibly other forms of oral microbial colonization, are associated with oral and head and neck cancer risk. This requires much more work, from basic research to observational studies. In addition, and of importance, dental disease must be prevented and managed, because there are local oral health implications in the form of pain, abscess formation (local and regional infection), and the potential effect of oral sources of chronic inflammation and potential systemic effects. Furthermore, there are no other studies that found this correlation, and all others have found that poor dental health may be associated with overall poor health behavior, including tobacco and alcohol use, that presents known increased risk of cancer.

The implication that dental cavities (and possibly associated bacteria) may be protective of oral and oropharyngeal cancer cannot be concluded from the published article based on limitations of design and as proposed for a putative mechanism. Methodologic issues may have led to the reporting of spurious findings.

The implications of the study are important in overall oral health and to dental professionals. This study provides an excellent model for discussion of evidence-based findings and the importance of understanding the methods used in studies and the evidence needed for evaluation of cause and effect.

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