ASSESSMENT OF KEY ELEMENTS TO DETERMINE CAUSATION AND RISK FACTORS IN DENTISTRY

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The hypothesis that an exposure or characteristic is associated with a particular disease outcome can be statistically proven through large population studies. Causation studies usually involve identifying diseases that are caused by or whose natural history is modified by lifestyle choices and environmental exposures. A causal association is one in which a change in the frequency or quality of an exposure or characteristic results in a corresponding change in the frequency or quality of the disease outcome. The causal characteristics associated with an increase in disease are often called risk factors. In 1890, Robert Koch clarified the cause-and-effect relationship of infectious disease when he postulated that a bacterium was the cause of a single disease entity. He stated that the specific organism should be present in all hosts suffering from a specific disease, the microorganism should be isolated from the diseased host and grown in pure culture in the laboratory, inoculation of the cultured organism into a healthy host should cause the disease, and the microorganism should be reisolated from the inoculated host. Although not all of Koch's postulates have proved true for all bacteria, viruses, and prions, Koch's postulates marked a milestone for cause-and-effect thinking in health care science.

Epidemiologists frequently perform causation studies. When a true cause-and-effect association is determined, this information assists in

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formulating global strategies for controlling disease based on population issues such as living conditions, nutrition, personal behavior, lack of health care education, absence of immunity, and so forth. Clinicians are interested in the cause of disease so that they may test therapeutic strategies to prevent or cure the disease. Clinicians are interested in prevention and therapy for individual patients and smaller patient populations. For clinicians, strategies are tailored to individual patient characteristics that will allow the clinician to modify therapy prescribed to the patient afflicted with the target disease.

Although most dentists may view dentistry as a clinical and therapeutic science, many global population issues of causation are related to dentistry. Some examples are public water fluoridation, a possible association of amalgam restorations with multiple sclerosis, and smoking as a risk factor for periodontal disease and dental implant loss. Dentistry has recently begun to examine the association of periodontal disease and cardiovascular disease.[1, 4, 8] In these studies, it has been statistically proven that some persons with a diagnosis of heart attack or coronary heart disease are more likely than the general population to have a diagnosis of periodontal disease. The question arises whether this association is a valid cause-and-effect relationship: does periodontal disease cause cardiovascular disease? To some, this cause-and-effect relationship seems outlandish. So did the hypothesis generated by Oliver Wendall Holmes (professor of anatomy and physiology and later dean of Harvard medical school) in 1843 that maternal fevers after childbirth were communicated from mother to mother by obstetricians who did not practice hand washing between births. Learned colleagues stated that they suspected the disease was ''accident or providence'' rather than any process that could be stemmed by hygiene.[5] It was almost 40 years before Koch set forth the postulates that an infectious agent causes disease.

KEY ELEMENTS FOR EVALUATING CAUSATION

Just as Koch formulated postulates that shaped the assessment of the validity of the causal association of a specific organism and a disease, scientists have formulated key elements that assist in judging the scientific evidence for causation. These elements involve chance, bias, confounding variables, biologic credibility, temporal relationship, strength of the relationship, and a dose-response gradient. Making judgments as to whether associations are causal associations involves an evaluation of the totality of evidence taken from a number of sources that document the cause-and-effect relationship. The ultimate test of causation is the successful use of intervention strategies that therapeutically alter the risk factor or characteristic, thereby altering or curing the disease.

RESEARCH STUDIES TO EVALUATE CAUSATION

The methodologies of research an epidemiologist uses to study cause-and-effect relationships are different from those used by a clini-

cian. Causation studies usually include large sample populations, are carried out by epidemiologists, and are observational in nature; the subjects are observed, queried, and measured, without the investigators' offering or testing any interventions. The study is often hypothesis-driven: the investigators are gathering data to determine if the characteristic and the outcome can be found together (associated) in the patient population, with the statistical analysis supporting the association beyond mere chance. Today, health care researchers understand that, unlike Koch's simple assessment of "bacteria cause disease," the cause of disease is often multifactorial. Multiple characteristics affect the host's susceptibility to disease, and how the characteristics come together in the host affects the magnitude of the disease. Therefore, observational studies often examine multiple characteristics of the population to determine associations. Observers record the natural course of events, noting which subject has or does not have the risk factor and who does or does not develop the outcome of interest. Different observational study designs can be used, but some designs offer an improved opportunity to control bias and confounding variables, thereby increasing the likelihood that these studies report a valid causal association. The two types of observational studies most often employed are cohort or case-control studies. Either may be used, but the decision to use one rather than the other is often based on features of the exposure or risk factor and the disease, current knowledge of the disease, and considerations of time and resources.

How is the Magnitude of a Risk Factor Reported?

Depending on the study design, the magnitude of the causal association is often described as a ratio, either an odds ratio or a relative risk. This mathematical analysis considers the ratio of subjects in the exposed or unexposed group that have or do not have the outcome of interest. Because this relationship is a ratio, an odds ratio or a relative risk of 1 denotes that there is no difference in outcomes between the two groups. Relative risks barely above 1 describe a weak association of the risk factor with the outcome. As the ratio becomes higher than 1, it is an estimate of the increased risk of having the outcome if the risk factor is present, as compared with having the outcome if the risk factor is not present. A relative risk of 1.5 means that the subject with the risk factor is 50% more likely to have the disease outcome than a subject without the risk factor. As in all studies, the test population serves only as a representative population to predict how similar populations would respond. When testing a subpopulation, one can only estimate how similar populations would respond. Statistical maneuvers can assure the precision of the estimate by using a 95% confidence interval. A relative risk and confidence interval might be written as 2.2 (C.I. 1.3–4.4) This expression states that, given the data from this representative study, the best estimate of the relative risk is 2.2, but if the study were performed

100 times, in 95% of those studies the true risk estimate would fall somewhere between 1.3 and 4.4.[7, 9, 15]

Prospective Cohort Studies

Cohort studies observe large populations with and without the exposure and observe the subjects forward in time to determine if there is a difference in the populations as to the incidence of the disease outcome. The observation process often begins with descriptive statistics that reveal a difference in prevalence of a disease in a defined population, such as a geographic area. A hypothesis then arises that the increased prevalence of the disease in one geographic population versus another is caused by some environmental factor. For instance, in 1942 a low prevalence of dental decay was demonstrated to correlate with a high fluoride concentration in the natural water supply. These descriptive correlations came from a study of 4425 children, 12 to 14 years of age, in 13 cities located in four states.[14] Understanding this correlation, a subsequent prospective comparison of the dental status of children in a city without natural fluoride (Kingston, New York) and a city that had fluoride added to its water supply (Newburgh, New York).* The children were examined for decayed, missing, and filled teeth at baseline and again in 10 years. In the 6- to 9-year-olds who had drunk fluoridated water for all of their lives, a 57% relative reduction of dental caries was seen. The older children experienced a 41% relative reduction.[2, 6, 7] Another observational study compared decayed, missing, and filled tooth surfaces at baseline and years after fluoridation was removed from the water supply in Antigo, Wisconsin. This study revealed that the caries index rose significantly, from 2.1 to 4.8 surfaces per person in the fourth-grade population and from 0.5 to 2.0 surfaces per person in the second-grade population.[7, 11] This observational study added to the totality of the evidence that fluoride acts to prevent dental caries. In these studies, fluoride is a preventive factor or a negative risk factor for dental caries.

These two studies exemplify some of the elements that quantify the strength of a causal association. In the New York study, the observations were conducted in a prospective fashion and showed that the exposure occurred first, and the outcome followed. This demonstration satisfies the temporal relationship required in causation. In the second study, the negative risk factor (fluoride) was withdrawn, and the disease incidence increased. This demonstration satisfies the dose-response gradient of causation. The strength of the causal evidence is also enhanced by the magnitude of the causal effect in both studies.

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*The addition of fluoride to the water supply could be considered a therapeutic or interventional trial; however, because the subjects were not randomized but were considered as two distinct, self-selected populations who were not balanced for other population characteristics, the methods are similar to those used in an observational trial.

Dental research has since satisfied biologic credibility by explaining the mechanism of fluorappetite and how it decreases acid dissolution of enamel. Finally, multiple therapeutic trials evaluating administration of fluoride in the water supply, in the diet, and through pharmaceutic supplements have demonstrated a decrease in caries incidence.

Case-control Studies

Case-control studies differ from cohort studies in that the exposure or risk factor and outcome have already occurred. There is no following of the subjects over time, waiting for the outcome to occur. A case-control study usually includes a fixed population from which the investigator selects a population with the outcome of interest (cases). In a systematic fashion, the investigator identifies another subject from the fixed population that is as similar in as many characteristics as possible except for the outcome (control). This type of study is often called a matched case-control trial. Both these groups are then evaluated to determine how many of them have the exposure or risk factor. The data concerning the characteristics and exposures are almost always gathered retrospectively from chart reviews, patient questionnaires, and other documentation. Examinations may be performed to confirm some of the data, such as the outcome. The retrospective data and examination data are collected at this one point in time. If the final analysis confirms that the outcome of interest occurs more frequently in the group with the exposure, an association exists. This type of study is sometimes preferred to the cohort study because it allows evaluation of rare outcomes and outcomes that may take many years to manifest. It is also less costly than longitudinal studies.[5, 7, 10, 15] A cross-sectional study is similar to a case-control study in that the outcomes and exposures have occurred before the study, and the interface with the investigator is at one point in time, without longitudinal follow-up. The population is a fixed population, but usually only a representative sample, a cross-section of the fixed population, is evaluated.

The associations between periodontal disease and coronary heart disease have been reported through case-control studies and cross-sectional convenience samples.[1, 12, 13] The multifactorial causality of coronary heart disease, the various criteria defining heart disease outcomes, the various methods of defining periodontal disease, and the large number of microorganisms in the oral cavity have made it difficult to evaluate the evidence in these studies. From a statistical standpoint, the multifactorial causality of heart disease requires statistical adjustments for as many as 13 different causal variables, besides periodontal disease. One study categorized attachment loss in one quadrant of the oral cavity, compared with a self-reported history of a heart attack, in 5564 persons older than 40 years of age. After adjustment of other risk factors for heart attack, the odds ratio for heart attack in persons with attachment loss of 3 mm or greater in 67% of measurements was 3.8 (C.I. 1.5–9.7)

compared with persons without attachment loss. The odds ratio for persons with attachment loss of 3 mm or greater in 33% to 67% of measurements was 2.3 (C.I. 1.2–4.4). There was no statistically significant difference in odds ratio with attachment loss in less than 33% of measurements.[1] A second study of 85 persons referred to a hospital for angiography, matched with persons without coronary heart disease selected from public records, revealed no difference in the dental indices of periapical and periodontal disease. The average age was 56 years, and the author speculated that this group is older than those in previous studies. There may have been an age-selection bias, such that older patients with coronary heart disease are in better general health and have better oral health, because the severely ill patients with coronary heart disease have all ready died.[13] Another one-point-in-time assessment from chart review data and periodontal examination of a sample of 320 Veterans Medical Association dental patients older than 60 years of age was performed to determine dental associations with coronary heart disease. Other risk factors were also considered from data gathered from hospital charts and patient interviews. Use of cardiac medications were considered to represent a diagnosis of coronary heart disease. Multiple analyses were performed on 25 characteristics. The medically recognized risk factors for coronary heart disease did not have significant association in this study. The authors believed the lack of significance in this study was probably caused by to the increased age of the subjects and that those subjects with significant associations may have already succumbed to coronary heart disease. In addition, subjects were being treated for many of the other risk factors, and therefore those risk factors were under control. Statistical associations with coronary heart disease were found for total tooth number up to 14, low salivary levels of *Streptococcus sanguis*, gingival bleeding, positive plaque scores, and a complaint of xerostomia.[12]

A prospective analysis of 9760 persons concluded that persons with periodontitis had a 25% increased risk of coronary heart disease compared with those with minimal periodontal disease. Poor oral hygiene, determined by dental debris and calculus, was also associated with an increased incidence of coronary heart disease, which was defined as a hospital admission or death caused by coronary heart disease. Compared with men without periodontal disease, the highest relative risk for coronary heart disease was for men with periodontitis who were younger than 50 years old, 1.72 (C.I. 1.10–2.68). An even greater relative risk for total mortality was found for this group; those with periodontitis had a relative risk of 2.12 (C.I. 1.24–3.62), and the edentulous subjects had a relative risk of 2.60 (C.I. 1.33–5.07). The authors concluded that a causal association between periodontal disease and coronary heart disease is unclear, and that dental health may be more an indicator of personal hygiene and overall health care practices.[4]

Case-control studies that interface with the subjects at one point in time can suggest an association between a characteristic and an outcome, but they cannot confirm the temporal relationship that the risk factor

came before the outcome. The correct temporal relationship is a primary element in proving causation, but in case-control studies this element is missing. In the evaluations of coronary heart disease and periodontal disease, case-control studies have demonstrated that the two entities occur simultaneously in the population, but one cannot be certain that the coronary heart disease did not in some way cause the periodontal disease. Case-control studies do not control the element of confounding characteristics, that is, the possibility that a third variable or mechanism, not yet isolated or understood, is causing the increase in both coronary heart disease and periodontal disease. Such a confounding element would account for the association of the coronary heart disease and periodontal disease without there being a causal relationship between the two. A confounding characteristic is demonstrated in the study by Loesche and colleagues.[12] There was a significant association of an increase in the complaint of xerostomia in persons with coronary heart disease. One should not assume that xerostomia causes coronary heart disease. It is known, however, that cardiac medications cause xerostomia. Patients with coronary heart disease require cardiac medications. The association of xerostomia and coronary heart disease results from the cardiac medications; the cardiac medications are the confounding factor.

Randomized, Controlled Trials

Randomized, controlled trials (RCTs) are rarely conducted as the first step to determine a causal association. In an RCT, a homogenous population of subjects is randomly assigned to two groups, one that will receive the test intervention and the other that will receive a placebo or standard-of-care intervention. The two groups are followed prospectively for the outcome of the two interventions. The decided advantage of RCTs over all other study designs is the investigators' ability to control multiple aspects of the trial, prospectively thereby decreasing bias and offering the greatest opportunity to arrive at a valid and conclusive answer to a research question.[5, 10, 15] In discussions of causation, the cause is usually harmful, and the outcome is usually a disease. Initially, only descriptive data are available describing a possible harmful cause and effect. Even though the cause-and-effect assumption may be weak, most ethicists and clinicians would not wish to move directly to an RCT in which the investigator purposefully administers a possibly harmful event to determine if it really is harmful. For questions of causation, the initial information to promote the hypothesis and prove an association between an event and an outcome should be gained through observational studies. This data gathering can usually be performed more efficiently and cost effectively in case-control or cross-sectional trials, in which the subjects can be examined at one point in time. If several trials indicate that sufficient association exists and the health care impact is judged appropriate for further time and monies to be expended, several longitudinal, cohort trials could be undertaken.

These studies do not occur in a vacuum, and it is likely that many investigators are examining the same issue in the laboratory and clinically. As a significant body of evidence mounts that a causal association exists, RCTs can be used to evaluate treatments that will modify the harmful cause or risk factor, thereby altering the disease process or curing it.

Bias in Research and Causation Studies

In any research, the validity of the conclusions is negatively affected by bias. One major source of bias in observational studies is the difficulty in assuring a homogenous study population. In observational studies, subjects are usually self-selected in that they experienced an exposure, have an inherent risk factor, or have specific lifestyle behaviors. The investigators must attempt to quantify the other characteristics of the study subjects and to select a comparison population with characteristics as similar to the exposed population as possible. With such ex post facto population selection, bias can easily occur. Given the intricacies of the human body, unknown patient characteristics may affect the outcome. Also, many patients engage in self-directed interventions whereby they wittingly or unwittingly alter the exposure or outcome. These confounding interventions may affect the disease outcome more than the risk factors being assessed. Because the investigator does not know about these confounding entities, they cannot be measured. Nor will the unknown characteristics be uniformly distributed in both comparison groups. Randomized, controlled trials control for these unknown, confounding characteristics by selecting a large homogeneous population before rendering any intervention. The large population is then randomly divided into the two comparison groups. The random assignment of the subjects allows equal assignment of the known and unknown characteristics into both study groups, thereby creating two homogenous populations.

Other biases can occur in observational studies because of the retrospective nature of the data gathering. Investigators must rely on patients to give valid answers on questionnaires and rely on the completeness of medical and dental records to acquire information about a subject's health and exposure status. One cross-sectional study to evaluate fluorosis in a school population required that that the parents complete a questionnaire. Forty-five percent of the questionnaires were not accepted because of invalid responses.[3] Without standard treatment protocols and documentation protocols, difficulties can arise from omission of data or ambiguous interpretation of data to fit a research question. A study that evaluated temporomandibular complications was undertaken as a concurrent evaluation of the efficacy of two orthognathic surgical fixation techniques. The surgeons and other investigators evaluated the temporomandibular complications. The surgeons recorded their data in the patients' charts as part of the treatment record, whereas the trained

temporomandibular examiners documented their data on standardized research forms. It was apparent that the surgeons focused more on efficacy of surgery than on secondary temporomandibular outcomes. In many instances, the surgeons failed to document the temporomandibular findings of pain, oral opening, crepitus, locking, or clicking of the joint. The approximate differences in documentation and disagreement of the various findings between the surgeons and the trained investigators ranged from 20% to 65% for each parameter over the various measurement periods.[16]

Magnitude of the Risk

When the magnitude of risk is great, risk is not easily masked by bias. Even though the original studies in New York on water fluoridation did not use randomized populations or populations selected for like characteristics, the magnitude of the effect in reducing caries was so great that the causal association was accepted. Further studies and examination of the key elements related to causation established the cause-and-effect relationship of fluoride and decrease in caries incidence. When causes are multifactorial, have a long latency period before the effect is demonstrated, and the physiology is complex, as in the risk factors for coronary heart disease, a small increase in risk is not readily observed. When a characteristic has a small influence on the outcome, more subjects are required to demonstrate that influence. The more subjects in a study and the longer the duration of a study, the more likely it is that the study will be tainted by bias, and the more equivocal the conclusions become. Such was the case of smoking and lung cancer. Multiple studies, conducted over many years and from many countries, were necessary to establish this causal relationship by proving a large risk of lung cancer among smokers, and proving both a temporal relationship and a dose-response gradient.

SUMMARY

The best research method for assessing therapeutic modalities is the RCT. The prospective nature and the randomization of the subjects in an RCT provide the greatest opportunity to control bias and offer the most valid answer to the clinical question. Observational studies generate hypotheses about causation and should be viewed as a first step in the continuum of health care delivery. The preponderance of evidence will mount as the hypotheses are tested by additional prospective, longitudinal, observational trials. The clinician's involvement is to design and implement therapeutic strategies to alter the causal exposure, intervene in the dose-response gradient, and block the pathophysiologic mechanisms. Dentistry is an art and a science. Moving through the continuum from causation hypothesis to therapeutic intervention is the science of

dentistry. It is the science of dentistry that will change the scope of the profession in this millennium.

References

1. Arbes SJ Jr, Slade GD, Beck JD: Association between extent of periodontal attachment loss and self-reported history of heart attack: An analysis of NHANES III data. J Dent Res 78:1777–1982, 1999
2. Ast DB, Schlesinger EF: The conclusion of a 10-year study of water fluoridation. Am J Pub Health 46:265–271, 1956
3. Brothwell DJ, Limeback H: Fluorosis risk in grade 2 students residing in a rural area with widely varying natural fluoride. Community Dent Oral Epidemiol 27:130–136, 1999
4. DeStefano F, Anda RF, Kahn HS, et al: Dental disease and risk of coronary heart disease and mortality. BMJ 306:688–691, 1993
5. Fletcher RH, Fletcher S, Wagner EH: Clinical Epidemiology: The Essentials, ed 3. Baltimore, Williams & Wilkins, 1996
6. Friedman GD: Primer of Epidemiology, ed 4. New York, McGraw-Hill, 1994
7. Gordis L: Epidemiology. Philadelphia, WB Saunders, 1996
8. Hujoel PP, Drangsholt M, Spiekerman C, et al: Periodontal disease and coronary heart disease risk. JAMA 284:1406–1410, 2000
9. Hulley SB, Cummings SR: Designing Clinical Research. An Epidemiologic Research, ed 2. Baltimore, Lippincott Williams & Wilkins, 2001
10. Jacob RF, Carr AB: Hierarchy of research design used to categorize the ''strength of evidence'' in answering clinical dental questions. J Prosth Dent 83:137–152, 2000
11. Lemke CW, Doherty JM, Arra MC: Controlled fluoridation: The dental effects of discontinuation in Antigo, Wisconsin. J Am Dent Assoc. 80:782–786, 1970
12. Loesche WJW, Schork A, Terpenning MS, et al: Assessing the relationship between dental disease and coronary heart disease in elderly U.S. Veterans. J Am Dent Assoc 129:301–311, 1998
13. Mattila KJ, Askikainen S, Wolf J, et al: Age, dental infections, and coronary heart disease. J Dent Res 79:756–760, 2000
14. US Public Health Services, 1942, pp 1155–1179, Public Health Report 57
15. Sackett DL, Haynes RB, Guyatt GH, et al: Clinical Epidemiology. A Basic Science for Clinical Medicine, ed 2. Boston, Little, Brown and Co, 1991
16. Scott BA, Clark GM, Hatch JP, et al: Comparing prospective and retrospective evaluations of termporomandibular disorders after orthognathic surgery. J Am Dent Assoc 28:999–1003, 1997

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