Periodontitis and Premature Death: A Longitudinal, Prospective Clinical Trial

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Periodontal disease is initiated by a biofilm of bacteria on the teeth that trigger an immune–inflammatory response in the adjacent host tissues. It is estimated that 15% to 35% of the adult population in industrialized countries suffers from this multi–factorial illness. In individuals with constitutional proinflammatory traits, the reaction to bacteria may lead to an excessive host response, resulting in general inflammatory reaction. To investigate the relation between periodontitis and general diseases, longitudinal studies spanning several years are recommended to ensure that the time period in which periodontitis develops is taken into account.[1]

In longitudinal studies, individuals are followed over time with monitoring of risk factors or health outcomes. Outcomes such as mortality and incidence of cancer have been related to employment status, and other variables measured. Most longitudinal studies examine associations between exposure to known or suspected causes of disease and subsequent morbidity or mortality. In the simplest design, a sample or cohort of subjects exposed to a risk factor is identified along with a sample of unexposed controls. The 2 groups are then followed up prospectively, and the incidence of disease in each is measured. By comparing the incidence rates, attributable and relative risks can be estimated.

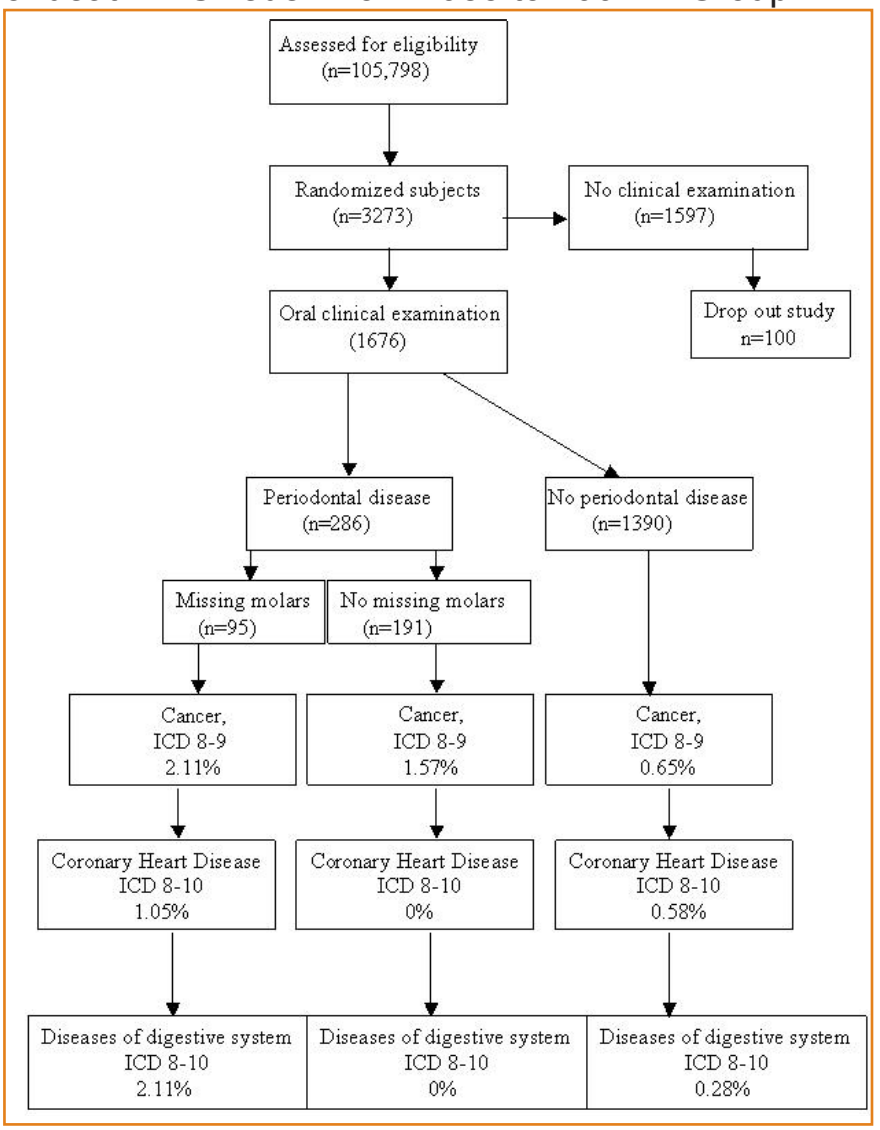
A problem with the cohort method when applied to the study of chronic diseases is that large numbers of people must be followed up for long periods before sufficient cases accrue to give statistically meaningful results. The difficulty is further increased with low grade, silent and long lasting diseases, such as periodontal disease. There is a long induction period between first exposure to a hazard and the eventual manifestation of disease.

Randomized controlled trials are a superior methodology in the hierarchy of evidence, because they limit the potential for bias by randomly assigning patients for prospective clinical trials. This minimizes the chance that the incidence of confounding variables will differ between the groups.

The advantage of prospective cohort study data is the longitudinal observation of the individual through time and the collection of data at regular intervals. However, cohort studies are expensive to conduct, are sensitive to attrition and take a long follow–up time to generate useful data. Nevertheless, the results that are obtained from long–term cohort studies are of substantially superior quality to retrospective/cross–sectional studies, and cohort studies are considered the gold standard in observational epidemiology.

The baseline cohort for the present longitudinal study was selected

Table 1: Proportions (%) of the 3 most frequent causes of death in Sweden from 1985 to 2001 in Group A



in 1985 using the registry file of all inhabitants (n=105,798) of Stockholm County born on the twentieth of any month between 1945 and 1954. Randomized from the file were 3,273 individuals aged 30 to 40 years. In total, 1,676 individuals, 838 women and 838 men, underwent a detailed oral clinical examination.[2] The presence of systemic diseases in the study group were 2,001 compared with data in the following registers from the Swedish National Board of Health and Welfare: the Cancer register, the Hospital register, the Heart Infarct register and the register for Causes of death.

Our hypothesis was that the presence of gingivitis and periodontitis in young adults increases the risk for future life–threatening diseases. Our aim was to evaluate the role of periodontitis in premature death in a prospective study.

The subjects were divided into clinically examined (group A) and dropout (group B). In addition, all age–matched subjects in Stockholm County constituted group Sc and all age–matched subjects in all of Sweden constituted group S. In January 1985, group Sc comprised 105,798 individuals and Group S 1,254,238 individuals.

The present study addresses the issue of periodontal disease as a risk marker for mortality by evaluating the relationship between periodontitis and premature death 16 years after the diagnosis of periodontitis. Our results confirm the hypothesis that periodontitis in young adults with any missing molars is a risk marker for premature death (Figure 1).[3] The prematurely deceased women in the study were expected to live 36.1 years longer and the deceased men 31.6 years longer. The individuals who died were probably infected with periodontitis many years before the baseline registrations. However, the result in present study showed periodontitis as a risk marker for premature death.

Earlier studies have suggested that the reason for mortality could be the combined effect of periodontal diseases, calculus and dental plaque or the severity of caries, periodontitis, periapical lesions and pericoronitis.[4] We have previously shown in a 17–year prospective study that molars were the teeth most affected in subjects with periodontitis.[5]

These results have been confirmed in the present investigation. The missing molars in these young individuals signal a long history of chronic inflammatory and microbial burden of periodontitis, but may also reflect an underlying weakness of the host defense system. A very high bacterial load on tooth surfaces and in gingival pockets over a prolonged period may be responsible for the diseases, subsequently causing death. Therefore, reducing the bacterial burden of affected individuals and identifying the bacteria responsible for the diseases causing death in these subjects are critical.

Our findings have public health consequences and may create a basis for prophylactic measures that, in view of the prevalence and outcome of periodontal diseases and the costs it incurs to society, are well warranted.

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Periodontal Disease and Association with Diabetes Mellitus and Diabetes: Clinical Implications

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Microorganisms in dental biofilms cause periodontal disease. For example, the healthy, normal flora is comprised mainly of Gram–positive and Gram–negative cocci, and it shifts to flora associated with gingivitis (which is mainly Gram–positive and Gram–negative cocci), other Gram–negative forms and Actinomyces. In periodontitis, there is emergence of a more pathogenic flora which is comprised of organisms such as Porphyromonas gingivalis, Tannerella forsythenesis, Treponema denticola and also species of Campylobacteria, Fusobacterium, Prevotella and Peptostreptococci. These pathogens occur in a biofilm which begins at the gingival margin and extends into the gingival sulcus and periodontal pocket. Biofilm organisms have multiple virulence factors such as lipopolysaccharide (LPS), which trigger inflammation and factors which suppress host protection. This inflammation acts locally to induce soft tissue destruction as well as bone resorption. The local inflammation also leads to a chronic level of systemic inflammation characterized by elevated plasma levels of inflammatory mediators such as TNF–alpha, IL–6 and acute phase proteins such C–reactive protein.

In the last 2 decades, investigators have been assessing the role of risk factors for chronic periodontitis. The goal was to determine factors important in increased susceptibility or decreased resistance to periodontal disease to provide a basis for risk factor intervention and to better understand the pathogenic mechanisms by which dental biofilms cause periodontal tissue destruction. In a study population of 1,247 individuals aged 25 to 74 years old from Erie County, New York, we found that of several hundred factors assessed only a few were important risk factors. These include infection with P. gingivalis and T. forsythensis, diabetes, smoking, male gender, chronic stress and inadequate coping and older age. In a U.S. population–based study (NHANES III) of 12,367 non–diabetic individuals, it was found that there was an association of periodontal disease with body mass index (BMI). Approximately a 40% to 50% increase in the risk for periodontal disease was found in those with obesity. The mechanism likely to account for this association comes from studies which show that adipose tissue produces pro–inflammatory mediators which lead to systemic inflammation. This systemic hyper–inflammatory state likely sets the stage for greater periodontal destruction. Also, the GI flora changes with a high fat diet, leading to increased LPS–containing organisms, increased GI permeability and resulting endotoxemia, which results in a hyper–inflammatory state exaggerating the response to periodontal infection.

Possibilities for intervention with risk factors in the management of periodontal disease include diabetes control, smoking cessation and weight management/calorie restriction. These have or will become a mainstay in management of periodontal disease. They are often accomplished by all members of the treatment team including an essential role for dental hygienists.

The relationship between diabetes and periodontal disease is a two–way relationship. That is, not only does diabetes predispose to greater periodontal destruction, but periodontal disease leads to poorer glycemic control over time. This likely results, in part, from the increased level of systemic inflammation evidenced by periodontitis, which enhances insulin resistance, leading to poor glycemic control. Periodontal therapy can stabilize or restore glycemic control as shown by several studies in which HbA_{1c} levels are reduced after periodontal therapy. This is an important finding since periodontal disease is associated not only with poor glycemic control but with the increase in diabetic complications resulting from poor glycemic control. In a recent study by Saremi et al., it was shown that in Type 2 diabetics who suffer from periodontal disease, the death rate from cardiovascular disease and diabetic nephropathy increased markedly.[1]

There may also be an effect on periodontal and initiation of the diabetic state. A recent study shows that individuals free of diabetes mellitus at baseline tend to have greater development of Type 2 diabetes if they have periodontal disease. That is, periodontal disease may be related to the increased risk, not only of worsening glycemic control and more severe diabetic complications, but increased risk of development of Type 2 diabetes. The effect of periodontal disease on diabetes has only recently been revealed, and more research is needed before we fully understand this relationship. This information, in turn, will provide direction for management of periodontal disease in an effort not only to save the dentition, but also to reduce its systemic effects.

The dental team can act as an important point of contact of the patient for early diagnosis and management of dental–related systemic disease, such as screening for undiagnosed diabetes and possibly pre–diabetes. In 2007, it was estimated that 24 million people in the U.S. have diabetes and 24% of those are undiagnosed, which means there were about 5.8 million undiagnosed diabetics in the U.S. Since approximately 70% of Americans have vis-

ited a dentist in 2007, we propose that screening for diabetes mellitus in the dental office can be an effective initial step our profession can take to help mitigate the devastating effects of diabetes. The following measures are recommended:

- Administration of the "Diabetes Risk Test" (American Diabetes Association Brochure H598903)
- Administration of a home test kit for plasma glucose and A_{1c}. If plasma glucose is over 110 mg/dl, and/or hemoglobin A_{1c} level is over 6%, refer to physician for diagnosis

You would expect that per 1,000 adult dental patients, approximately 120 would have diabetes and about 40 would be undiagnosed. In addition to other good management procedures for diabetics undergoing dental procedures, this screening service may be of great value to the population.

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Translating Evidence of Oral–Systemic Relationships into Models of Interprofessional Collaboration

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For several decades there has been consistent pressure from various economic and political forces that continue to erode the boundaries of the profession of dental hygiene. Perhaps one of the most important things that must now be addressed is the revitalization of the profession, and security of its future. In addition to these critical concerns lies an unprecedented opportunity to reposition dental hygiene as a fundamental component to interprofessional health care teams. If the dental hygiene profession is committed to securing its future within the healing arts at this level of significance, the development and execution of a robust and vigorous research agenda is no longer an option – it must be done. The question becomes what area of research provides the greatest opportunity for advancement of the dental hygiene profession?

There are many areas of research that will allow for insightful discovery within our present realm of traditional dental hygiene practice. However, there are a number of paradigm shifts that cannot be overlooked in pursuit of a vibrant and secured future for dental hygiene. Taken in their totality, these paradigm shifts point out the obvious – that the greatest opportunity we have to create a compelling research agenda is in demonstrating improvement in measurable patient outcomes and health care cost savings by targeting periodontal–systemic diseases and conditions in underserved populations with co–morbidities associated with inflammatory driven, high impact diseases. The Centers for Medicare and Medicaid Services (CMS) has called for greater coordination of care for "highest impact conditions," many of which (e.g., heart disease, diabetes, rheumatoid arthritis, cancer, renal disease) are associated with systemic inflammation, potentially exacerbated by untreated periodontal disease, in an underserved population.[1] It is to this interest that we must align our research agenda.

In setting up success for the development of such a robust research agenda, there are several questions which must be addressed:

- Will the provision of periodontal treatment rendered by dental hygienists who are specialized in treating patients with multi–factorial risk reduce co–morbidities in high risk populations?
    - Of the high risk populations with multi–factorial co–morbidities, which populations provides the greatest opportunity to demonstrate a treatment effect of specialized dental hygiene care?
    - What outcomes of interest, both intermediate outcomes and long–term outcomes, as defined by CMS,[1] of periodontal intervention should be studied?
- What other disciplines should dental hygienists include in interprofessional collaboration to both cross screen and refer patients at risk for co–morbid conditions associated with periodontal disease and engage in collaborative case management?

In order to ready the profession of dental hygiene to participate in this level of coordinated, interprofessional care, it is critical that the current paradigm of dental hygiene care be expanded to include primary health assessment, intervention and the leadership of interprofessional teams in prevention and management of multi–factorial diseases related to the oral cavity (Figure 1). Within this expanded scope of practice falls an exponential number of opportunities for dental hygienists to perform primordial prevention (interventions before risk factors are acquired and health promotion), primary prevention (screen for undiagnosed systemic disease in asymptomatic patients and symptomatic patients with undiagnosed diseases) and integration of the "Common Risk Factor" approach into interprofessional continuums of care.[2]

Given the strength of evidence to support the role of periodontal disease in increasing the cumulative inflammatory burden implicated in many chronic disease states (e.g., heart disease, diabetes), health care providers from all disciplines must have an accurate and reliable means by which to identify patients who are at risk for a number of systemic diseases and conditions which are underpinned by inflammation. Development of a risk assessment tool that quantifies cumulative inflammatory burden will provide an evidence–based means by which to triage care among a team of providers from various disciplines, allowing for more aggressive treatment and interprofessional monitoring of patient outcomes. The dental hygiene profession is well positioned to take the lead in developing and testing this type of novel risk assessment tool.

Another area of investigation that provides an opportunity for dental hygienists to demonstrate a leadership role in interprofessional health care is to explore the social–ecological model of sustaining change in health behavior.[3] By piloting innovative population–level interventions that target high risk populations, we may demonstrate successful models

of change or prevention of health damaging behaviors that influence the integrity of the oral cavity and impact overall health.

For the dental hygiene profession to distinguish its role on an interprofessional health care team within a continuum of care for high risk populations, we must provide evidence (applicable to both federal funding and private insurers) of the economic benefits that accrue as the result of the provision of periodontal treatment rendered by dental hygienists in high risk populations, including the following:

- Demonstrate that expenditures made for prevention and wellness promotion (related to modifiable risk factors for periodontal disease) will translate into cost savings in the not–so–distant future. The dream case for demonstrating return on investment for prevention and wellness is tobacco–cessation services[4]
- Provide evidence that periodontal disease might increase the medical care costs for a number of high impact diseases and conditions[5]
- Provide evidence that intervention of periodontal disease will translate into cost savings on medical coverage of patients at high risk[5]

Intervention trials which have investigated the effects of periodontal treatment on diabetes, cardiovascular disease and pre–term birth (among other inflammatory driven disease states) have yielded inconclusive results. However, it is important to point out that the particular interventions prescribed in these studies may not be the specific therapies necessary to produce a treatment effect.

There are a number of ideas for strategic positioning that support this vision for a robust and rigorous research agenda for dental hygiene. It is important to acknowledge that, although the heuristic proposed in this presentation represents an extremely aggressive research agenda, it does offer the most promising future for the profession of dental hygiene. Finally, if the profession does not decisively move beyond its sole focus on the oral cavity to extend its scope into the provision of primary health practices, other disciplines are well positioned to assume this important role. Is a specialized track of training necessary to prepare dental hygienists to treat patients with multi–factorial co–morbidities within high risk populations? This is an issue which must be addressed. Nonetheless, primary health care assessment fits squarely within dental hygienists' contemporary scope of practice, and an essential component of interprofessional collaboration.

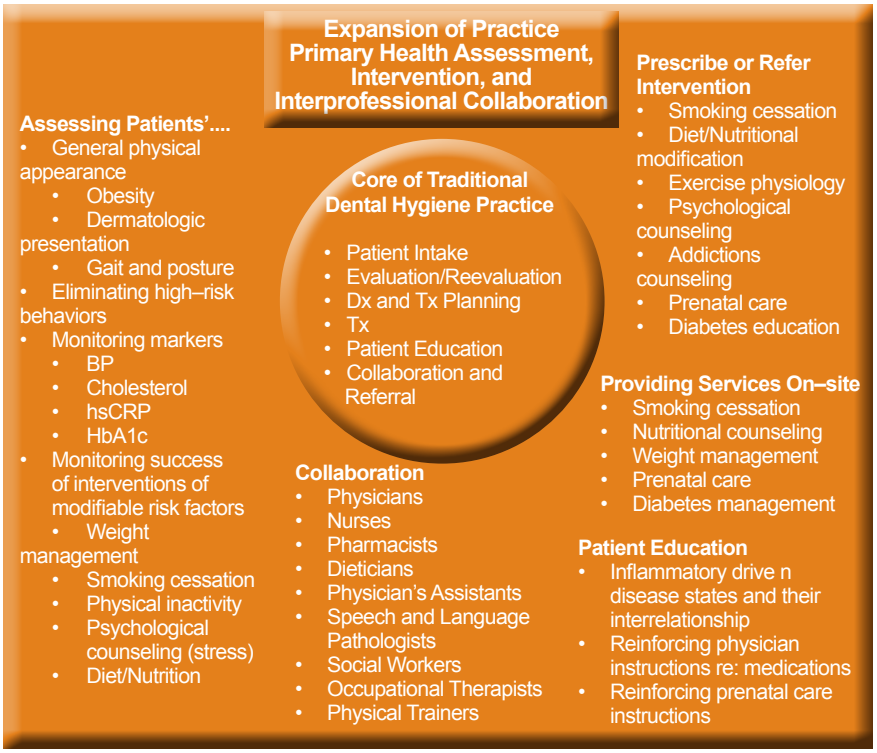

Figure 1

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Developing Research Plans and Outcome Measures for Oral–Systemic Project Assessments

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Several designs have utility for research aimed at assessing oral–systemic relationships. While experimental designs are the accepted standard for assessing effectiveness of interventions, many research questions on the oral–systemic link are not amenable to experimental designs. Observational designs are necessary for evaluating relationships between oral risk factors and serious systemic diseases such as cardiovascular disease, cancer, stroke and diabetes in a human population. Experimental studies on systemic diseases can be achieved using animal models, but results from these models may not generalize to human outcomes.

Observational designs are increasingly used to explore the natural history of dental/oral diseases, and evaluate risk factors that impact systemic disease patterns and oral health outcomes. The concept of group comparison between naturally occurring groups (in contrast to manipulated/created groups as is typical in experimental studies) is at the heart of planning observational studies. Observational research employs 3 general designs: prospective follow–up, retrospective case–control and cross–sectional designs. Each method has advantages and disadvantages but all have weaknesses with respect to demonstrating causality. In order for causality to be established between a risk factor (e.g., periodontal disease) and a systemic outcome, 5 tenets must be satisfied:

- Relationship must be biologically plausible
- Exposure to the suspected cause/risk factor must precede development of the outcome. Moreover, the period of exposure must sufficient to logically affect in the outcome
- Concomitant variation between causal/risk factor and outcome must be demonstrated (e.g., more or less exposure, higher or lower risk of outcome)
- Other possible explanations for the outcome must to be ruled out
- Findings must be replicated in multiple samples and multiple studies

While observational studies generally have 1 or more of these tenets unsatisfied, they are still important in establishing scientific evidence for or against possible relationships.

Designs

Cross–sectional studies are commonly used to describe health outcomes using a descriptive approach. A cross–sectional study typically compares the frequency and distribution of the target disease or health outcome across subgroups of the population. For example, a dental hygiene researcher is interested in examining the problem of early childhood caries (ECC) in children under the age of 5 years. Believing that ECC may be related to children's history of asthma as well as mother's educational background, the researcher collects information from mothers and children attending a pediatric clinic on the mothers' highest level of education, the children's history of having or not having asthma and examines each child for presence or absence of ECC. Comparisons are then made between children with and without asthma and across educational strata. Cross–sectional data on frequency of children falling in each strata are shown in Table 1.

An empirical view of the data suggests there may be relationships of interest to examine further. The data suggest that the child's asthma history and mother's education may be related to having ECC. However, without considering other potential confounders (dietary habits, oral hygiene behaviors, access to fluoride, parent knowledge/ attitudes and socioeconomic factors) the researcher may fail to fully explore the multi–factorial nature of ECC and make invalid conclusions about relationships.

Cross–sectional studies are advantageous as they are often cost effective, easy to accomplish in a defined period of time and have no problem with subjects dropping out. Disadvantages include response and/or participation bias and self–report bias. However, the greatest disadvantage is that, because data is collected at a single point in time (prevalence), it is not possible to determine whether exposure to the suspected risk precedes development of the outcome.

Two additional designs that produce results with higher levels of evidence are useful to consider when planning oral–systemic research. The prospective follow–up design begins with the selection of a cohort of individuals free of disease (the outcome) who are then followed over time. During that time they are observed on potential risk factors and followed until they develop or fail to develop the outcome of interest. At completion of the study, those who do and do not develop the disease are compared with respect to their exposure to specific risk factors. This strategy compared naturally formed groups (those with disease and without disease) to determine if they were differentially exposed to levels of risk for the outcome. While this strategy offers real advantages to examining potential cause and effect linkages, it can be costly, time consuming and often impractical since cohorts may

need to be followed longitudinally (sometimes for decades) to get a true picture of cause–effect associations. The second and more commonly used retrospective case–control strategy starts with the outcome of interest (comparable groups, one of which has the disease and one of which does not have the outcome) and examines the degree to which the groups differ with respect to previous exposure to factors which might be related to the disease.

Application of Designs

To illustrate these different designs, a prospective study would take a cohort of adults who are free of lung disease and who are similar with respect to age, environmental location and socioeconomic status, and follow them over a course of 20 years to examine which develop lung cancer. During the 20 years they are examined periodically to determine their exposure to potential risk factors such as smoking status and exposure to asbestos or other carcinogens. The prospective design is considered the gold standard for observational studies because they can demonstrate that exposure to the risk factor precedes development of disease outcome.

In contrast, a retrospective case–control study would compare a group of individuals with lung cancer to a group without lung cancer to determine if the groups differ with respect to exposure to a specific factor, such as smoking or asbestos retrospectively. An inherent problem with the case–control retrospective design is the difficulty in accounting for all possible confounding variables. In spite of numerous case–control studies showing a strong association between tobacco use and lung cancer, the retrospective nature of the evidence prevents legal experts from definitively stating "smoking causes lung cancer." In essence, the argument is "What other factors (variables) not accounted for in the design of the study may have an association with the development of lung cancer?" Retrospective studies have the distinct advantage of being relatively inexpensive and time efficient compared to prospective studies. In addition, they are efficient when the outcome of interest is relatively uncommon in the population.

Table 1

Mothers Education	No Asthma		Asthma		Total Kids
	No ECC	ECC	No ECC	ECC	
Less than 8th grade	236	84	156	62	462
9th through 12 grade	357	54	388	94	893
High school diploma only,	191	15	202	17	425
High school diploma plus some college.	83	2	74	6	165

Project Development and Outcome Measures

Conceptualizing a research question related to oral–systemic relationships is a necessary first step in the research planning process. The hygienist must clearly define what variables and nature of relationships will comprise the focus of the investigation. For instance, if the research question is to describe the relative frequency of particular health outcomes in a specific group or subgroups in a population, then the research design will be quite different than if the researcher wishes to explore what intrinsic or extrinsic factors (or combination thereof) influence severity or likely outcomes of disease in a target population. Irrespective of the observational design selected, the researcher must take into account that there are potentially several confounding variables that will need to be addressed. Thus, one must consider methodologically how best to either exclude these or plan for statistical control when necessary.

A central tenet in the oral–systemic link is the multi–factorial nature of disease. As a result, researchers need to consider the potential multi–factorial nature of their specific question prior to identifying outcome measures and important covariates. Covariates are those factors that may be related to the outcome measure of interest but may not be the primary predictor variables of interest.

An example may provide clarity. Let's assume a researcher is interested in determining if inflammatory burden from periodontal disease is related to Alzheimer's disease. One would first need to identify other sources of inflammatory burden that might also be common in the target population (rheumatoid arthritis, inflammatory bowel disease, genetic conditions, etc) and either rule out research subjects with those potential confounders or include these subjects, but obtain measures for statistical control in the analysis. Adequate planning in advance and fully understanding the multi–factorial nature of any given outcome is crucial to obtain meaningful results.

Lastly, selecting and operationalizing the appropriate predictor and outcome variables must be well thought out if the researcher desires meaningful results. The outcome variable is that variable thought to change as a result of influence of a potential risk factor or exposure. Using the previous example (periodontal disease as a risk factor for Alzheimer's), one would have to seriously consider how best to operationalize periodontal disease. The researcher could simply dichotomize periodontal disease (Case

Type II or less versus Case Type III or greater) or operationalize it using a severity rating based on number of periodontal probing depths >5 mm. Either would be valid, but results obtained might differ considerably. Similarly, with operationalizing Alzheimer's disease, one might opt to use the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, a self–report of dementia, a previous diagnosis of Alzheimer's or results from the Mini Mental State Exam (MMSE). Selection and operationalizing the outcome has implications for the "do–ability" of the project with respect to obtaining a sample and validity of findings.

Surrogate outcomes are frequently used as well. For instance, while the most valid measure of periodontal disease progression is tooth loss, researchers often use change in attachment level as a surrogate measure because it is more proximally available as a measure. Irrespective, selection of predictor and outcome variables with a view towards clear operational definitions should be a primary consideration in the planning process.