Cigarette smoking and periodontitis: methodology to assess the strength of evidence in support of a causal association


Abstract – Identification of the cause of the development and progression of periodontitis has received extensive attention, with notable advances over the past decade in clinical, microbiological, immunological, biochemical, and behavioral knowledge. However, it is still largely unknown which factors lead to the conversion of non-destructive forms of periodontal disease into destructive forms and disease progression. Chronic adult periodontitis is believed to be influenced by an interaction of host defense and environmental factors. Although these variables have been studied extensively, no study has employed randomized controlled prospective human or randomized controlled community intervention designs, methodologies necessary to prove a variable to be a cause of periodontitis. Owing to the absence of literature employing rigorous experimental design, this article assesses systematically observational, cross-sectional and longitudinal studies to examine the potential causal association between cigarette smoking and periodontitis. The methodology of Sir Bradford Hill’s criteria for causation was used as the framework. Results suggest that cigarette smoking is causally associated with periodontitis. That is, cigarette smoking is consistently associated with an increased prevalence/severity of periodontitis and is suspected on theoretical grounds of playing a causal role. Hill’s criteria provide a useful methodology to better understand the pathogenesis of periodontal diseases and may be applied to study the pathogenesis of other dental diseases as well.

The prevalence of moderate adult periodontitis (4–6 mm clinical attachment loss ≥1 site) in North America is approximately 30% while advanced disease (≥6 mm clinical attachment loss ≥1 site) affects 10% of the population (1). This chronic disease is believed to be influenced by an interaction of environmental and host variables, many of which have been studied over the past decade, providing a better understanding of the cause-and-effect association between clinical, microbiological, immunological, biochemical and behavioral variables and chronic adult periodontitis (AP) (2–5).

The best means by which to study any cause-and-effect association is a randomized controlled prospective human study or a randomized controlled community intervention study. Since exposing humans to risk is unethical, the former is not feasible. Consequently, the risk assessment literature is predominated by observational, cross-sectional, case-control and, more recently, longitudinal studies, designs which may be used to investigate the strength of evidence in support of causal association (6).

Since the 19th century, there has been a historical evolution of the concept “causality”. The Henle-Koch postulates were based on early knowledge of...
Table 1. Bradford Hill’s criteria for causation

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
<th>Example</th>
<th>Critique</th>
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<tbody>
<tr>
<td>Strength</td>
<td>The larger the relative risk (RR) or odds ratio (OR), the less likely the association is spurious</td>
<td>Hill cited a 200-fold increased mortality rate from scrotal cancer among chimney sweeps compared to workers not exposed to tar and mineral oils (71)</td>
<td>Even if an association appears weak, causality should not be ruled out since observed strength may be dependent on the relative prevalence of other variables (69)</td>
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<td>Consistency</td>
<td>Repeated observation of association observed under varied study conditions</td>
<td>US Surgeon General’s report on smoking and lung cancer cited 30 studies of various populations and study designs. All found a positive, statistically significant association (17)</td>
<td>Lack of consistency does not rule out causality because some effects are produced by the agent only under specific circumstances</td>
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<td>Specificity</td>
<td>A cause is specific to an effect if the introduction of the exposure is followed by the effect and if removal results in resolution of the effect</td>
<td>Nifedipine-associated gingival overgrowth appears shortly after start of therapy and decreases upon withdrawal of the drug (72) suggesting specificity. However, specificity is not confirmed since overgrowth occurs in only 15% of those exposed to nifedipine</td>
<td>Specificity should be used as evidence for causality, but since it suggests single-factor causation, lack of evidence for specificity should not be used to refute cause</td>
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<td>Temporality</td>
<td>A causal relationship requires that the exposure believed to cause a disease must precede the disease</td>
<td>Plaque allowed to accumulate for 21 days in periodontally healthy individuals induces gingivitis (73)</td>
<td>Temporal sequence is thought to be a <em>sine qua non</em> for causation; however, temporality is difficult to ensure in chronic diseases where onset is insidious, progress continuous, of long duration and modulated by the host (69)</td>
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<td>Biologic gradient</td>
<td>A dose-response curve is observed when an increase or decrease in exposure corresponds to an increase or decrease in the frequency and/or severity of disease</td>
<td>A dose-response relationship was observed between the number of cigarettes smoked/day and lung cancer mortality among male British physicians, with the mortality rate being approximately 1 among nonsmokers compared to ~8 for 1–14 cigarettes/day, ~13 for 15–24 cigarettes/day, and ~25 for those smoking ≥25 cigarettes/day (65)</td>
<td>Not all associations that show a dose-response trend are causal. Confounding variables can produce the trend if the confounder itself shows a biologic gradient with the disease (69)</td>
</tr>
<tr>
<td>Biologic plausibility</td>
<td>The suspected cause should be biologically credible</td>
<td>A number of studies support the biologic credibility of a causal association between diabetes mellitus and periodontitis. Among those with diabetes, vascular changes occur in tissues of the periodontium; blood vessels thicken; degenerative vascular changes occur in gingival specimens, all credible explanations affecting delivery of nutrients/oxygen to the tissues (2, 74, 75)</td>
<td>Plausibility is based on current biological knowledge and therefore lack of biological credibility should not singularly nullify a causal hypothesis (9, 11)</td>
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Table 1. Continued

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<td>Coherence</td>
<td>The association does not conflict with what is known about the natural history of the disease</td>
<td>The propensity for tobacco extracts to cause skin cancer in mice is coherent with the theory that use of tobacco causes lung cancer in humans (76)</td>
<td>Lack of coherence is dependent on current understanding of natural history of disease so that lack of coherence should not exclude an exposure as a potential cause</td>
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<td>Analogy</td>
<td>A causal relationship becomes more believable if the exposure has been shown to have a causal effect on a related condition</td>
<td>That the causal role of thalidomide and rubella in birth defects has been demonstrated makes researchers ready to accept evidence that another drug used during pregnancy could do the same (11)</td>
<td>Caution should be exercised not to create analogies where they do not logically exist (69)</td>
</tr>
<tr>
<td>Experiment</td>
<td>The strongest support for causation is experimental evidence using randomized prospective studies</td>
<td>The etiologic role of bacterial plaque in gingivitis in human (73) and periodontitis using an animal model (77) has been confirmed</td>
<td>Beyond rare ‘natural experiments’ such as the observation that communities with naturally fluoridated water had experienced fewer dental caries than communities without fluoridated water (78), evidence for risk is seldom available from human studies</td>
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bacterial disease and formed the classic reference point for medical studies of causation (7). The postulates now have questionable validity and reliability because of their limitations in considering the asymptomatic carrier, the biologic spectrum of disease and the multifactorial nature of chronic diseases (8–10).

In 1965, the Bradford Hill criteria for causation methodology first appeared in *The environment and disease: association or causation* (11) and were subsequently outlined in Hill’s *Principles of Medical Statistics* (12). The methodology has since been cited as the chronic disease epidemiologist’s equivalent of the Henle-Koch postulates. Hill recognized that researchers must frequently depend on observational data to distinguish between association and causation. He proposed a set of nine criteria to be considered before concluding that a variable is “most likely” causal (11). The criteria are outlined and critiqued in Table 1.

Hill’s methodology has been well described in textbooks of epidemiology, and examples of its application appear in the medical literature (9, 11, 13–16). For instance, an early US Surgeon General’s *Report on Smoking and Health* reported that cigarette smoking appeared causally associated with lung cancer. The report was based on Hill’s methodology, evaluating 29 case-control studies. All studies demonstrated a positive, highly statistically significant association between smoking and lung cancer and a 9–20-fold dose-response increase in risk of lung cancer among current and heavy smokers. Since over 200 co-carcinogens were shown to exist in cigarette smoke, the cause of the association was biologically plausible. Ex-smokers were consistently found to have a lower risk of lung cancer compared to those who continued to smoke, supporting temporality and specificity (17).

Hill’s methodology has also been used to investigate whether a causal association exists between high concentrations of cholesterol and lipoproteins in blood plasma and coronary heart disease (CHD). Consistent evidence from observational, clinical, and animal studies showed a high plasma cholesterol concentration was associated with CHD; hypercholesterolemia preceded CHD; a biologic gradient with increasing levels of serum cholesterol; and a 3.4-fold increase in risk of CHD. Knowledge regarding the development of atherosclerotic plaques and thrombi was plausible and “coherent” with the results of animal and clinical experiments (18).

The current article describes Bradford Hill’s criteria for causation, and demonstrates how Hill’s methodological framework was used to assess the strength of evidence in support of a causal associa-
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Methods
A computer medline search was carried out for articles written in English that included the key words nicotine or cigarette smoking and periodontitis or periodontal disease. The search encompassed the period January 1970 to May 1998. Those references which (a) were relevant to the study question and (b) represented original research were critiqued, abstracted, and entered into Reference Manager Software database (19). All articles were evaluated using each of Bradford Hill’s nine criteria for causation.

Results
The current assessment of the literature showed that most of Hill’s criteria for causation were satisfied, albeit to varying degrees, suggesting a causal association between cigarette smoking and chronic adult periodontitis. The extent to which each of the criteria were met was as follows:

Strength of association
The strength of association between smoking and adult periodontitis has been shown to be positive and of moderate magnitude in numerous studies. About half of periodontitis diagnosed among young (≤33 years) adults is believed to be smoking related, with an odds ratio (OR) ≥14 for established periodontitis (two sites with ≥6 mm attachment loss plus one site with ≥5 mm probing depth) (20) and approximately 90% of individuals with refractory periodontitis have been shown to be heavy smokers (21).

The magnitude of strength varies (OR=2.5–5.3) among other cross-sectional and case-control studies depending on study design, cut-off points for and methods of measuring and defining AP, the population studied, and whether the effects of plaque, age, and gender were controlled (22–24). An OR of 2.9 has been observed among black and 6.2 among white elders and 8.6 among those with diabetes (25). The latter group may not be representative of a healthy population. Healthy adults and young adults (35–54 years) who smoked heavily experienced a 7.28–7.33 times increased risk of AP compared to non-smokers (26, 27).

The results of a recent meta-analysis from six studies reported an OR=2.82 (95% CI 2.36–3.39), suggesting a consistent yet slightly lower magnitude of risk than those identified in the current assessment (28). However, the meta-analysis assessed risk of advanced AP. Smokers with slight to moderate periodontitis were either excluded from the meta-analysis or included as controls, which may have underestimated the magnitude of association.

Consistency
The literature is consistent in reporting a positive association between smoking and AP, regardless of population studied, methods of measuring and defining AP, or study design. Cross-sectional studies which measure exposure to smoking and AP currently have reported the association (25, 26, 29, 30, 31–39). Cross-sectional studies, however, are generally unable to establish that exposure preceded outcome. Interestingly, most studies show a lower prevalence of gingivitis among smokers, even though smokers often have greater levels of plaque (23, 33, 37–42). Smoking may mask the clinical signs of inflammation.

Several case-control studies have reported that smoking was significantly more prevalent among those with AP than those with a healthy periodontium, even after controlling for plaque (22, 24, 27). Case-control studies cannot easily establish temporality, particularly for chronic diseases.

Recently, a number of longitudinal studies have investigated the association between cigarette smoking and AP. A 3-year incidence study showed that cigarette smokers were at increased risk of progressive attachment loss although smoking did not increase risk of initiating periodontitis (43). A 6-year longitudinal study showed that when compared to non-smokers, smokers responded significantly worse to initial, surgical and supportive therapy, experiencing residual probing depth and progressive attachment loss (44). Cigarette smoking was associated with a reduced healing response following guided tissue regeneration, even after controlling for higher levels of plaque among smokers (45). Both smokers and non-smokers with moderate to advanced AP responded favorably, 2 months following initial therapy. However, smokers responded significantly less favorably, i.e., smaller reductions in probing depths than non-smokers despite the fact that therapy was equally effective in reducing periopathogens (46). These recent longitudinal studies provide an additional important perspective on the question of causality; however, such studies are often unable to control for known and potential confounding variables.
Both original studies and meta-analysis of studies consistently report a positive association between cigarette smoking and AP regardless of study design or definition used for periodontitis. Consideration should, however, be given to the potential for publication bias whereby authors and journal editors may have a predilection for publishing positive findings over negative findings. Such a bias could overestimate the association.

**Specificity**
Specificity is weakly suggested in a 10-year study which showed radiographic evidence of periodontal disease progression nearly twice as rapid in smokers as in non-smokers and significantly retarded bone loss among those who quit smoking compared to those who continued to smoke (47). Although smoking cessation resulted in a favorable periodontal effect, the study did not control for certain potential confounding variables such as the influence of smoking on impaired host response in the periodontium, defects in peripheral blood polymorphonuclear leukocyte function and the presence of periopathogens. These variables could have partially or fully explained the differences in outcome observed between those who quit and those who continued to smoke. The importance of specificity is questionable today, particularly for chronic diseases such as periodontitis which are believed to have multifactorial etiology.

**Temporality**
Several longitudinal studies provide evidence of a compromised healing response among smokers compared to non-smokers following periodontal therapy (43, 44, 46) and halted alveolar bone loss among individuals with AP who stopped smoking compared to those continuing to smoke (47). These studies did not, however, control for certain known confounding variables.

**Biologic gradient**
There is evidence of a dose-response or biologic gradient when periodontal status among current smokers is compared to that of previous smokers and never-smokers, or when light and heavy smokers are compared to never-smokers. Current smokers have the highest prevalence of AP (34) and those who smoke heavily have a higher (OR=7.28–7.33) prevalence/severity of disease than those who smoke less (OR=3.15–3.25) compared to non-smokers (26, 27, 38, 39). The results of a national US survey showed no gradient effect between cigarette smoking and AP (36). This inconsistency could be due to differing definitions of AP, recall/social desirability bias, or variations in study design.

**Biologic plausibility/coherence**
The biologic plausibility of explanations of the relationship between cigarette smoking and AP is strong and supported by a number of studies.

Longitudinal studies have demonstrated that nicotine disturbs the alignment of gingival fibroblasts to glass and to human root surfaces in vitro (48); however, the generalizability of these findings in vivo is unknown. Nicotine has been shown to coat root surfaces of periodontally diseased teeth in smokers and may interfere with healing/reattachment (49).

Nicotine has been shown to produce a severe reduction in intra-arterial blood-flow rates in a rabbit model (50) and humans (51, 52). Nicotine may cause ischemia of the periodontal tissues, particularly since vessels which deliver blood to gingiva are end-arterioles giving no collateral circulation to the papillae (50). The pharmacological effect of tobacco smoke on circulation may be vasoconstriction (50), resulting in decreased oxygen and nutrients to tissues. Smokers frequently exhibit a lower prevalence/severity of gingivitis than non-smokers (39, 41, 52, 53).

Another mechanism of action was suggested in a 3-day quasi-experimental prospective study which showed that smoking one cigarette immediately before cell collection resulted in significant decrease of oral polymorphonuclear leukocyte (PMN) vitality and ability to phagocytize (54). The study, however, failed to control for potential differences in plaque level between smokers and non-smokers. Another study demonstrated that one cigarette produces a sufficient amount of toxic material in the oral cavity to inhibit completely the function of exposed oral leukocytes (55). Recent studies also show that cigarette smoking affects leukocyte function (21). An immunosuppressant effect may be caused by combustion products of tobacco, measured by salivary immunoglobulin A and IgG2 levels (56). These results are supported by other similar studies (57–59). However, a study of young, periodontally healthy individuals failed to show an impaired response of PMNs to nicotine (60); in fact, Totti et al. (61) showed that nicotine is a chemoattractant for PMNs and that it enhances responsiveness. This inconsistency among studies could be due to differences in subjects’ age, levels of...
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plaque, severity of disease and study methodologies.

A longitudinal cohort study found bone mineral content among smokers to be 10–30% lower compared to non-smokers (62). The authors speculated that constituents of tobacco smoke may disturb the metabolism of vitamin D or influence hormonal states. The relevance of these findings to alveolar bone loss is unknown.

A cross-sectional study among 145 patients with severe periodontitis showed no difference between smokers and non-smokers regarding presence of certain periodontopathogens, namely, Actinobacillus actinomycetemcomitans, Bacteroides gingivalis (now classified as Porphyromonas gingivalis) and Bacteroides intermedius (now classified as Prevotella intermedia and Prevotella nigrescens) (63). However, the laboratory tests had only poor to moderate (0.2–0.6) reliability due inherently to sampling/culturing techniques. Alternative or unknown periodontopathogens may eventually be shown to have a key role in the initiation/progression of periodontitis among smokers, as it has been reported that smoking results in increased proportions of gram-negative bacteria (21, 64).

The studies reviewed strongly support the biological plausibility of a local and/or systemic effect of cigarette smoking on AP. There is coherence within studies based on the current understanding of the natural history of periodontitis.

Analogy

The adverse effects of smoking on general health have been well documented and are analogous to the mechanisms of action that have been proposed for periodontal disease. Smoking has been shown to increase the risk of lung cancer and cancer of the oral cavity, esophagus and larynx, and to increase the prevalence of hypertension and cardiovascular diseases (36, 65, 66) as well as the prevalence of osteitis following oral surgery (67). Healing following periodontal treatment is compromised among smokers (44–46, 68).

Experiment

No randomized controlled prospective human studies or randomized intervention studies were found to investigate the effect on periodontal health when individuals were exposed to cigarette smoking. Longitudinal studies consistently showed that smoking was associated with greater progression of disease (26), healing response to periodontal therapy was compromised (44–46) and smoking cessation resulted in retarded bone loss (47). However, these longitudinal studies were not randomized and were unable to control for confounding variables.

Discussion

Bradford Hill's criteria for causation constituted the theoretical framework employed to assess the strengths and weaknesses of the scientific evidence in support of a causal association between cigarette smoking and AP. The methodology contributes to a better understanding of the pathogenesis of periodontal diseases.

When applied to the literature, this systematic methodology suggests a causal relationship between cigarette smoking and periodontitis. The scientific evidence for this association comes primarily from cross-sectional, case-control studies and several recent longitudinal studies. These studies, regardless of the cut-off points or means used to define periodontitis, were consistent in finding a positive association between smoking and periodontitis. Cross-sectional and case-control studies are not able to prove causality because exposure and outcome are generally assessed concurrently, making it difficult to ensure that exposure preceded outcome. In addition, cross-sectional studies consider prevalent cases, therefore reflecting determinants of survival as well as etiology. The cause of AP may only be confirmed through prospective randomized controlled studies as this design is able to control for extraneous and temporal variables (9, 69). Such studies, however, are often lengthy and require a large number of subjects because of the latency period between an exposure such as smoking and an outcome such as AP. Moreover, imposing risk exposure on humans is not ethical.

The only true experiments critiqued in the current assessment either were in vitro or employed animal models, with uncertain generalizability to humans. Lack of rigorous experimental evidence explains why it has been difficult to confirm that cigarette smoking is a cause of AP.

The case-control studies reviewed proceeded from effect (AP) to cause (cigarette smoking), attempting to establish that antecedent smoking behavior led to disease. This design is based on the selection of subjects with a condition (cases) and a comparison group(s) of individuals in whom the condition is absent (controls). Cases are then compared to controls in terms of their exposure to
smoking, producing an odds ratio for risk assessment. This study design has been utilized widely to study the effect of smoking on AP because it poses no risk to subjects, is expedient, and allows other explanatory variables to be controlled simultaneously. A number of case-control studies failed to control for certain extraneous and confounding variables and all may have been affected by recall and social desirability bias (22, 24). These issues considered, the reported magnitude of association between smoking and periodontitis, although of moderate strength, has likely been underestimated. Hill cautioned researchers not to dismiss a cause-and-effect hypothesis merely on the grounds that the strength of association appears slight since exposure to an agent does not always result in disease for everyone (11). AP is believed to have multiple causative agents and therefore testing one variable at a time, as several studies did, may give an incomplete picture of causality. More recent studies utilizing statistical regression models have investigated the unique and combined role of multiple variables (70). Future studies investigating diseases believed to have multifactorial etiology should employ these more sophisticated statistical analyses.

The degree to which each of Hill’s criteria must be satisfied in order to suggest a causal relationship was not addressed specifically by Hill although he gave most weight to the experiment criterion, as it provides the strongest support for the causation hypothesis. Certainly, the magnitude of association should be strong, but Hill held that one should not dismiss a cause-and-effect relationship because the association appears slight or because specificity cannot be demonstrated. Hill’s methodology could be criticized for its subjectivity; however, it may be more useful to view the criteria in their entirety. How fully the criteria are met depends heavily on the current knowledge of the disease.

Although randomized controlled human prospective studies or community intervention studies will be necessary to prove that cigarette smoking causes AP, researchers and clinicians must not discount existing literature that suggests a causal association. Individuals designing programs of dental public health promotion, as well as private practitioners, should incorporate smoking prevention, cessation, and reduction into their prevention and treatment strategies (5). As Bradford Hill (11) cautioned, “All scientific work is incomplete, whether it be observational or experimental. This does not confer upon us a freedom to ignore the knowledge we already have or to postpone the action that it appears to demand at a given time.”

References

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64. Zambon JJ, Grossi SG, Machtte EE, Ho AW, Dunford R,


