

VA Summer Epidemiology Session

Developing Scientific Research Proposals (Grant Writing)

Session 8 (Readings)

Abstract Essentials

Example 1 - Cohort Study of Dietary Supplements and Cancer Risk

Neither chemoprevention trials nor observational studies have established the benefits or risks of vitamin and mineral supplement use. The aim of this proposal is to investigate the association of intake of supplemental vitamin C, vitamin E, calcium and multivitamins with total cancer incidence.

To meet this aim, a cohort will be recruited within the 13 counties of western Washington State, and followed for a mean of 2 ¼ years. A mailing will be sent to 225,000 men and women age 50-74 using names obtained from a commercial mailing list, which will include a recruitment letter targeting supplement users and a questionnaire. The recruitment procedures have been tested, and should yield 35,000 male respondents and 40,000 female respondents with 75% of respondents having used at least one dietary supplement in the prior 10 years. The questionnaire solicits detailed information on supplement use over the last 10 years, and information on covariates that may be associated with supplement use and with future risk of cancer (e.g., medical history, cancer risk factors, cancer screening, reasons for supplement use). The questionnaire also incorporates a food frequency questionnaire, with additional items on supplemented foods. A second mailing to respondents 2-4 months later will supply a tape measure for anthropometric measures and brushes for collection of DNA from cheek cells. Studies to quantify the relative validity of our primary exposure measures will be conducted.

Endpoint information will be efficiently and accurately collected by linking participant identifiers to the western Washington SEER cancer registry and the Washington State death tapes. Out-migration from the catchment areas of these files will be monitored by linkage to the National Change of Address tape.

Longer term follow-up of this cohort will allow the investigation of the association of supplements with specific cancers (lung, prostate, breast and large bowel) and with total mortality, and will allow investigation of gene-supplement interactions. If supplements are harmful or of no use, this information would be important for the large number of Americans taking supplements. If a beneficial effect is found, it could be translated into effective cancer control measures.

Example 2 - Epidemiology of Barretts Esophagus

DESCRIPTION: Barrett's esophagus is a metaplastic condition that develops in an estimated 10-20% of persons with long-standing gastroesophageal reflux disease (GERD). Patients with this condition are at high risk, estimated at 1-2% per year, of developing esophageal adenocarcinoma, a rapidly fatal cancer that, for unknown reasons, has risen sharply in incidence since the mid-1970s. Although much research has been directed toward identifying predictors of progression in patients with Barrett's esophagus, there is little information about the causes of the conditions itself. The first Specific Aim of this case-control study is to compare cases with newly diagnosed Barrett's esophagus (N=335) to controls from the general population (N=335) to test the hypothesis that specific environmental exposures and host factors increase risk of Barrett's metaplasia, and to estimate the fraction of cases attributable to them. Also to be examined will be the role of obesity, diet high in fat and low in fruits and vegetables, low serum vitamin C, vitamin E, carotenoids and selenium, tobacco use, alcohol consumption, use of medications that promote reflux and family history. The second Specific Aim is to identify determinant of Barrett's esophagus among individuals with severe and persistent GERD, by comparing cases to patients undergoing upper endoscopy for reflux symptoms, but who are biopsy-proven negative for Barrett's esophagus (N=335). Specifically, the hypothesis to be tested is that among patients with GERD: 1) cigarette smoking, alcohol consumption and dietary intake of nitrosamines are associated with increased risk of Barrett's esophagus, and that higher dietary intake and serum levels of antioxidants are associated with decreased risk; and 2) duodenogastric reflux (measured as the concentration of bile in fasting gastric juice) is associated with an increased risk of metaplasia. The prevalence of short-segment Barrett's will be estimated among patients undergoing endoscopy for GERD, using the largest sample of endoscoped patients, to date, all biopsied according to a standard protocol. Given that 95% of persons with Barrett's esophagus remain undiagnosed and that esophageal adenocarcinoma survival rates are dismal, the most direct means of reducing esophageal adenocarcinoma incidence by preventing metaplasia, rather than by the surveillance and treatment of patients already diagnosed with the condition.

Example 3 - Alternative Therapies for Menopause: A Randomized Trial

Hormone replacement therapy (HRT: estrogen and progestin) remains the treatment of choice for women with vasomotor symptoms, and long-term HRT has been recommended for prevention purposes. The demand for alternatives to HRT, and the availability and use of over-the-counter products including dietary phytoestrogen supplements, and naturopathic medicines has grown dramatically. Few of these products have faced the rigors of randomized trials and none have been tested to evaluate their effects on long-term outcomes.

The purpose of this 4-year, randomized controlled trial is to evaluate the efficacy and safety of three alternative approaches utilizing phytoestrogens to treat vasomotor symptoms in peri- and postmenopausal women. The treatments were chosen because of the scientific evidence supporting a possible benefit, the availability of products with adequate quality control, their frequency of use in

naturopathic medicine, and our ability to blind participants to the intervention. The 5 proposed treatment arms are: 1) esterified estrogen and micronized progesterone; 2) a single herbal product, black cohosh; 3) a multibotanical preparation; 4) a combination regimen that includes the same multibotanical preparation plus soy diet counseling; and 5) placebo. Our primary aim is to compare the effects of three alternative treatments, HRT and placebo on the frequency and intensity of vasomotor symptoms measured by The Wiklund Menopause Symptom Checklist and a daily Vasomotor Symptom Diary. Our secondary aims are to compare the effects of three alternative treatments, HRT and placebo on: 1) vaginal cytology (vaginal maturation index); 2) serum lipids (total cholesterol, HDL and LDL cholesterol, triglycerides); 3) bone mineral density (hip and spine dual energy x-ray absorptiometry scan); 4) glucose metabolism (insulin, fasting blood glucose); and 5) coagulation factors (fibrinogen, PAI-1).

Our hypotheses are that compared to placebo, the three alternative treatments tested in this proposal will; reduce frequency of hot flashes and night sweats, improve vaginal maturation and decrease vagina atrophy as measured by maturation index, lower total cholesterol and LDL with no effect on HDL, reduce the rate of decline in bone mineral density (BMD), and have no effect on glucose metabolism or clotting factors.

To accomplish our specific aims we will: 1) recruit and randomize 400 peri- and post-women to one of 5 treatment arms for one year; 2) collect measurements of primary and secondary outcomes at baseline, 3, 6, and 12 months; and 3) compare changes in outcomes in the groups taking alternative treatments to those in the HRT and placebo groups.

Example 4 - Selection Bias by Elderly Medicare Beneficiaries with Diabetes

The purpose of this study is to examine the effect of Medicare HMO enrollment on the mortality and cost of care for Medicare beneficiaries with diabetes between 1994 and 1998. There are two major public policy concerns regarding individuals with chronic conditions that enroll in Medicare HMOs: Does Medicare contain costs by encouraging people with chronic diseases, such as people with diabetes, to join TEFRA-risk HMOs? and Are the quality of care and health outcomes provided to these enrollees comparable to those in the fee-for-service sector? This study will provide insight into both of these questions using Medicare administrative data from 1992 to 1998.

This proposal will extend recent work by Dowd, et al., (1998) and Maciejewski, et al. (2001) looking at biased selection of the general Medicare population into TEFRA-risk HMOs. It will use a unique dataset (the National Medicare Diabetes Cohort), which contains 2.5 million elderly Medicare beneficiaries with diagnosed diabetes mellitus in fee-for-service plans in 1994. The following specific research questions will be addressed:

- 1) Do healthier beneficiaries with diabetes systematically enroll in Medicare HMOs
- 2) Do HMO enrollees with diabetes have different five-year survival rates than Medicare beneficiaries with diabetes who remain in the fee-for-service (FFS) sector
- 3) Do unhealthier beneficiaries with diabetes systematically disenroll from Medicare HMOs?

4) Do HMO disenrollees with diabetes have different FFS costs than Medicare beneficiaries who remain in the FFS sector?

The first research question will be analyzed as a logit mortality equation. The second research question will be analyzed as a Cox proportional hazards model, controlling for selection bias into HMOs using the HMO enrollment equation. The third research question will compare the number of months in an HMO between HMO enrollees and disenrollees, and post-disenrollment expenditures in the FFS sector for HMO disenrollees and continuing FFS beneficiaries. The fourth research question will generate predicted FFS expenditures from an OLS equation from the third research question for Medicare beneficiaries that remain in an HMO.

No previous study has examined the issue of mortality or biased selection for a Medicare population with chronic illnesses. Compelling arguments can be made either that the healthiest or that the most severely ill beneficiaries with diabetes enroll in HMOs. The cost-conscious environment of an HMO may appeal to relatively healthy, low cost beneficiaries with diabetes. Alternatively, a beneficiary with advanced diabetes may gain a distinct financial benefit by joining an HMO, since many HMOs cover the cost of prescription drugs. This proposal will provide the first evidence of the direction of selection bias of Medicare beneficiaries with diabetes by exploring the determinants of HMO enrollment and disenrollment in a chronic population, and will provide an indication of the relationship between HMO enrollment and mortality.

Example 5 - Abstract of a Research Plan

The primary objective of this study is to compare the effectiveness of two "alternative" therapies (traditional Chinese acupuncture and therapeutic massage) for chronic low back pain with each other and with the use of relatively inexpensive self-care educational materials. Three hundred enrollees of a large health maintenance organization (HMO) in Washington State will be randomized to receive either acupuncture (n=100), massage (n=100) or a book and videotape emphasizing self-management strategies for chronic back pain (n=100). HMO enrollees with low back pain that has persisted at least 6 weeks (with or without sciatica) and who are between 20 and 70 years of age will be eligible. Exclusion criteria include: heart pacemakers, clotting disorders or on anticoagulant therapy, evidence of severe or progressive neurologic deficits, recent history of vertebral fractures, serious comorbid conditions, inability to speak or read English, and acupuncture or massage treatment for low back pain within the past year. Back pain treatment protocols recently developed by national acupuncture and massage therapy associations will be used. The treatments will be provided by licensed acupuncturists and massage therapists nominated by the Acupuncture Association of Washington and the Washington chapter of the American Massage Therapy Association, respectively. The number of treatments will be limited to a maximum of 12 to be provided over a maximum of 6 weeks. The primary outcome measures are: symptom relief, improved function, decreased disability and use of health services for back pain. Patient satisfaction and adverse reactions to treatment will also be measured. Outcomes will be

measured 3, 6, 12 and 52 weeks after randomization. Unlike previous studies of alternative therapies for back pain, this study will evaluate the outcomes of greatest concern to patients (pain and function) and to health care systems (satisfaction and costs) in a real world setting. The findings of this study will provide guidance to health care providers, insurers and patients who want to know about the relative benefits and costs of alternative treatments for common problems such as back pain.

STUDENT EXAMPLES OF SPECIFIC AIMS

COX-2 Inhibitors and Squamous Cell Carcinoma Risk

Cumulative evidence from in vitro and animal studies suggests that the enzyme cyclooxygenase-2 (COX-2) is important in the development and progression of cutaneous squamous cell carcinomas (SCCs). However, no epidemiological studies have examined the association between non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit COX-2, and SCCs. One of the problems with studying NSAID exposure is the difficulty in ascertaining exposure from over-the-counter formulations. The goal of this project is to examine the association between use of NSAIDs and the development of cutaneous SCCs. Over-the-counter and prescription NSAID use will be determined by a self-administered questionnaire. The validity of the questionnaire will be compared to pharmacy records for prescription NSAIDs. The epidemiologic studies will use two population-based study designs. The first is a series of two retrospective case-control studies using the electronic databases from the Seattle VA Puget Sound and Group Health Cooperative in Washington State. One-hundred and eighty five cases with histologically confirmed SCCs and 185 age- and gender-matched controls will complete a questionnaire on over-the-counter and prescription NSAID use, as well as potential confounding factors including history of previous skin cancer, smoking history, and skin type. The second study involves data analysis from an ongoing population-based cohort study that has enrolled 77,624 individuals and contains detailed medication histories, including over-the-counter uses. These individuals will be followed over a five-year period for incident SCCs. The data from these two studies will be used to test the validity of self-report of NSAID use (using pharmacy records of prescription NSAID use as the gold standard). And to examine whether NSAID use protects against the development of cutaneous SCCs. The results of these studies will provide important data to direct future chemopreventative trials.

Specific Aim 1: To develop and validate a self-administered questionnaire-based method for ascertaining NSAID exposure including over-the-counter formulations.

Hypothesis 1.1: The NSAID questionnaire data will demonstrate reliability when comparing prescription NSAID use to the pharmacy database.

Hypothesis 1.2: The NSAID questionnaire data will have poor correlation with pharmacy records for total NSAID use because of failure of pharmacy records to capture over-the-counter NSAID use.

Specific Aim 2: To examine the association between NSAID use and the incidence of cutaneous SCCs and assess how patterns of use, such as duration, dose, and type of NSAIDs affect incidence of SCCs.

Hypothesis 2.1: High-dose NSAIDs will be associated with greater reduction in incidence of SCCs than low-dose NSAIDs.

Hypothesis 2.2: Longer duration of NSAID exposure will be associated with greater reduction in incidence of SCCs.

Hypothesis 2.3: NSAIDs that are the most potent COX-2 inhibitors, will be associated with the greatest reduction in SCC risk.

Web-Based Instruction for Counselor Training

The primary aim of the proposed study is to explore the feasibility of using Instructional Design and Technology (Dempsey & Reiser, 2002) to provide community-based drug abuse counselors with engaging, case-based, online training regarding empirically supported treatments for Substance Use Disorders. For this developmental project, we propose to translate the content from the NIDA therapy manual "A Cognitive-Behavioral Approach: Treating Cocaine Addiction" (Carroll, 1998) into a series of interactive, media-rich, web-based modules for clinician training. Working in collaboration with a panel of community treatment providers, we propose to transform each of the topics from this NIDA treatment manual (e.g. "Problem-solving", "Coping with Craving" and "Refusal Skills") into a set of problem-focused modules or "tools" designed to provide counselors with the knowledge, skills and abilities required to successfully implement each component of the skills-training approach in their daily clinical practice. Each module will employ a variety of vignettes, video role-plays, graphics and interactive animated sequences to promote active engagement with the material. Completed modules will be accessible to clinicians through a web-based "Online Clinical Toolbox" (see Appendix B or visit www.nidatoolbox.org to view a prototype). Phase III of this project consists of a randomized trial that will evaluate: (1) the degree to which clinicians choose to engage with the Web-Based Training (WBT) material, (2) whether learner satisfaction is higher for participants in a WBT condition relative to participants in a face-to-face workshop condition or a minimal training condition, and (3) whether participants in the WBT condition demonstrate improved transfer of knowledge regarding Cognitive Behavioral Therapy techniques, relative to participants in the other two conditions. This proposal is offered in response to NIDA PA 03-066 "Behavior Therapies Development Program". In it, we propose to conduct study wherein we develop and evaluate an innovative procedure to teach therapists and counselors how to administer an empirically-supported, manual-based therapy. Conceptually, this research is analogous to Stage I research in the sense that a new behavioral intervention is under development. In this case, however, the new behavioral intervention is not a behavioral therapy, but a procedure or technique to help therapists administer new therapies (NIDA, 2003). To our knowledge, the proposed study will be the first to evaluate the effectiveness of using the principles, processes and tools of Instructional Design and Technology (IDT) to break down treatment manual content into digestible modules and deliver it in an engaging, interactive

format via technology that can be accessed anywhere, anytime. Another noteworthy strength of this proposal is that our WBT intervention can easily be expanded to include additional modules that cover important elements of other empirically supported treatments for Substance Use Disorders. For example, future versions of this product might also include such tools as "12-step Participation" or "Relationships in Recovery" drawn from the Individual Drug Counseling (IDC) manual used in the NIDA Collaborative Cocaine Study (Mercer & Woody, 1999).