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Special Announcement

Due to state budget constraints, Kentucky Epidemiologic Notes & Reports will be migrating our publication to an online only format in the near future. To learn more and sign up to receive notification via e-mail when new issues are posted, please visit our new Web site at http://chfs.ky.gov/epinotes

Effect Modification
Biostatistical Research Topics

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This is the second article in our bimonthly series in *Kentucky Epidemiological Notes and Reports* discussing biostatistical and epidemiologic research topics. The series is intended to provide biostatistical reviews for readers who do not often use statistics in their everyday practice and to generate discussion about biostatistical topics as they relate to areas of interest for those who commonly use these methods. In this issue, our topic is effect modification. We will describe effect modification, give examples, and discuss how to assess for effect modification.

As you may recall, in a previous issue we discussed confounding. Confounding is the distortion of the relationship between exposure and disease by the presence of a third factor that is associated with both factors, but is not in the causal pathway between exposure and disease. A confounding factor is associated with the outcome of interest in both the exposed and unexposed group. In contrast, effect modification (also called "interaction" by biostatisticians) is present when "the degree of association between an exposure and outcome differs in different subgroups of the population" (Gregg Ed. (2002). **Field Epidemiology**. Oxford University Press, New York, p. 159). Whereas confounding is considered an artifact of the data, and is therefore relatively common, effect modification represents a true epidemiologic or biologic association and is consequently uncommon (Gregg, p. 159).

There are several ways that effect modification can manifest itself. The effect modifier may increase the effect of the exposure on the outcome, or it may decrease the effect of the exposure on the outcome. Effect modification may also be present with both continuous and dichotomous variables.

In order to assess whether effect modification exists, we evaluate whether or not the outcome would be the same, given certain levels of exposure, regardless of the presence of the third variable (the effect modifier). As an example, we know that increasing amounts of sun exposure results in skin cancer in a certain proportion of the population. However, suppose a researcher hypothesizes that this relationship is affected by smoking. In order to test the hypothesis that smoking is an effect modifier of the relationship between sun exposure and skin cancer, she graphs

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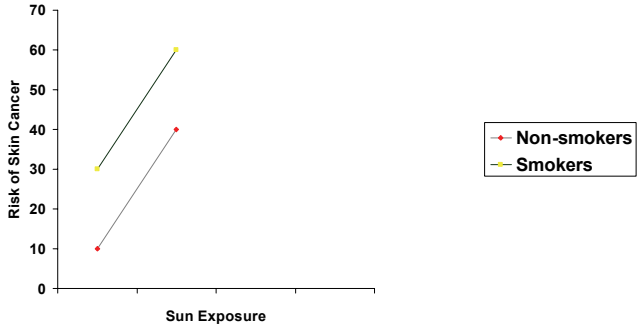
the relationship between sun exposure and skin cancer for both smokers and non-smokers. If she determines that the lines are parallel (Figure 1), meaning that for both smokers and non-smokers the relationship between sun exposure and skin cancer are equal, there is no effect modification. However, if the lines aren't parallel (Figure 2) then this means that the presence of smoking affects the relationship between sun exposure and skin cancer differently than does the absence of smoking. Therefore, smoking would be an effect modifier of the relationship between sun exposure and skin cancer.

Figure 1



It is important to note that the main effect is usually, by convention, considered to be the modifiable exposure, whereas the effect modifier is more commonly the variable which can not be modified. For example, a certain gene may modify the relationship between smoking and lung cancer. Since the presence of a gene can not be prevented, it would be considered the effect modifier, whereas smoking, which can be modified, would be the variable of interest.

Another way to think about effect modification is to evaluate the joint effect of the variable of interest and the effect modifier on the outcome. If the absolute, or relative, sum effect of the variable of interest and the effect modifier in people with both risk factors is what would be expected by adding the two independent effects together, then no effect modification is present. However, if the absolute or relative sum of the exposure and effect modifier does not equal the expected outcome, then effect modification is said to be present. For example, if the independent risk of losing an arm for farmers is 3.0 and the independent risk of losing an arm for males is 2.0 we might expect the risk of losing an arm for ***male farmers*** to be 5.0 (summing the risks). If we actually found the risk of losing an arm for male farmers to be significantly higher or lower than that, then we would conclude that effect modification was involved. Effect modification is synergistic if the sum of the exposure and effect modifier is greater than the outcome, and antagonistic if the sum of the exposure and effect modifier is less than the outcome.

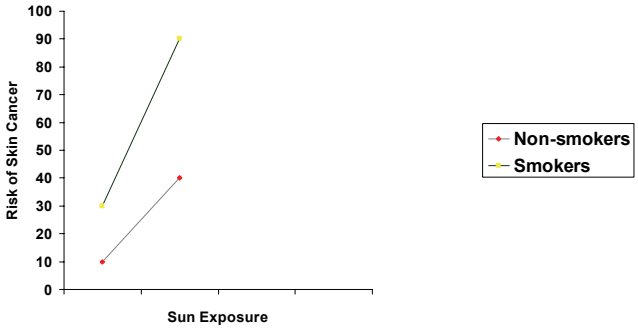
Effect modification can be considered in either an additive model, as above, or a multiplicative model, where we project that the expected combined effect to be a multiple of the independent effects. Using a multiplicative model with the above example, then, we would expect the risk for male smokers to be 6.0 (multiplying the two independent effects). Effects significantly higher or lower than 6.0 would be considered effect modification. In this article we will only illustrate using the additive model but researchers make the decision which model to use based on previous research, model complexity issues, and capabilities or logic of the mathematical model being used (for instance, linear vs. logistic regression).

One way to evaluate for effect modification is to stratify the data by the potential effect modifier. If the relative risk of male smokers compared to male nonsmokers developing lung cancer is 2.0, but the relative risk of female smokers compared to female nonsmokers developing lung cancer is 4.0, then gender can be considered an effect modifier between smoking and lung cancer. A statistical test called the Breslow-Day test can be used to evaluate for effect modification; a Breslow-Day p-value of <.20 is considered to denote effect modification. However, the researcher should not use the Breslow-Day p-value in isolation; if the relative risks are very different, effect modification may be present even in the

absence of a statistically significant p-value. Conversely, effect modification may be absent in a study with a large sample size that demonstrates a small difference in relative risk between the two strata.

The medical literature contains many examples of epidemiologic studies describing effect modification. Carmichael et al (J Nutr 2007, 139, pp 2087-2092) describe effect modification between lack of food access during pregnancy and folic acid intake on the development of tetralogy of Fallot, a cardiac birth defect. The authors found that when women took a folic acid supplement there was no association between lack of food access and tetralogy of Fallot. However, for women who did not take a folic acid supplement, there was a positive association between lack of food access and tetralogy of Fallot. Therefore, folic acid supplements are an effect modifier of the relationship between lack of food access and tetralogy of Fallot.

Figure 2



Another interesting study written by Dobre et al. (Br J Clin Pharmacol 2007, 63, pp 356-364) was designed to determine whether age was an effect modifier of the association between use of Beta blockers and mortality in patients with severe congestive heart failure. They found that in patients aged less than or equal to 75 years, treatment with Beta blockers was associated with a 71% relative risk mortality reduction, whereas for those aged greater than 75 years, Beta blocker therapy was associated with a 21% mortality reduction. Do you think age is an effect modifier in this case? The authors concluded that age was an effect modifier, and hypothesized several physiologic reasons for the effect modification of age on the relationship between Beta blockers and mortality. Again, one important reason to recognize effect modification is because it is a true association rather than an artifact. Therefore, it may lead to an additional research question which enables us to better understand the relationship between the exposure and outcome.

On the other hand, suppose a study was performed to evaluate the relationship between eating peanut M&Ms and obesity. Let us presume that having blue eyes may be an effect modifier on the exposure (M&Ms) and the outcome (obesity). After performing the study, we find that the relative risk of obesity for people who eat peanut M&Ms and have blue eyes, compared to those who don't eat peanut M&Ms, is 4.1. However, for those who eat peanut M&Ms but don't have blue eyes, the relative risk is 4.2. In this case, should blue eyes be considered an effect modifier of the relationship between eating peanut M&Ms and obesity? We would conclude that since the relative risks are very similar, having blue eyes is not likely to be an effect modifier in this example.

In conclusion, it is important to consider and evaluate effect modification when analyzing data or when reading studies, because effect modification can clue us into important epidemiologic and biological relationships that should be further investigated. Effect modification occurs when the presence or absence of a given variable differentially modifies the relationship between an exposure and outcome. It can be assessed by stratifying the data by the potential effect modifier and calculating a Breslow-Day p-value. If the p-value is <.20, many would consider effect modification to be present. However, as always, the statistical results should be judged in light of the epidemiological or biological plausibility of the data.

CDC Health Advisory

Temporary Decrease in Human Rabies Vaccine Supplies

The Centers for Disease Control and Prevention (CDC) has been notified that Novartis Vaccines, maker of RabAvert (Rabies Vaccine), will temporarily cease to provide their rabies vaccine for both pre- and post-exposure prophylaxis uses to health care providers. This includes physicians, nurse practitioners, hospitals, clinics, etc. A second company, Sanofi Pasteur, produces IMOVAX Rabies (Rabies Vaccine), and will continue to supply vaccine to health care providers for post-exposure prophylaxis (PEP). In certain circumstances, such as an allergic reaction to one company's vaccine product, the other company's vaccine product can be obtained to complete a vaccination series after consultation with state health departments and CDC, on a case-by-case basis. Overall, both manufacturers have limited supplies of rabies vaccine, necessitating the need for judicious use of these products by health care providers. (It is expected that additional RabAvert will be available on the market in July 2008. When that occurs, it is expected that the demand for pre-exposure vaccinations can be fully met with RabAvert.)

Due to temporarily limited supplies, distribution of vaccine for pre-exposure prophylaxis (PreP) will be approved by state and federal public health authorities. Priority will be given for those individuals at greatest rabies exposure risk (e.g., rabies laboratory workers, animal control officers, veterinary staff, wildlife workers) and in consideration of available rabies vaccine supplies. In lower risk rabies exposure categories (e.g., travelers, veterinary students, etc.), human rabies PreP should be delayed until vaccine supply levels are restored.

Priority use of rabies vaccine will be for post-exposure prophylaxis (PEP) following ACIP human rabies prevention recommendations (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5703a1.htm). IMOVAX rabies vaccine is available for PEP and providers should carefully review the ACIP recommendations and guidelines from their states to ensure that PEP is needed. They are also strongly encouraged to consult with local/state public health departments.

Public health authorities and health care providers are encouraged to educate the public concerning the need to take appropriate precautions to avoid rabies exposure and actions to take if an exposure occurs. Appropriate precautions include vaccination of pets, as well as livestock having close human contact, avoiding stray and wild animals, and safely capturing or detaining biting animals or obtaining owner contact information for follow up. Such practices will decrease the need for rabies PEP and thus allow for the responsible management of currently limited vaccine supplies.

CDC is working closely with both vaccine companies and state and federal public health authorities to ensure that health care providers receive up to date information on supply fluxes. Discussions among federal, state, and local public health personnel are ongoing to review additional strategies to manage the current supply of rabies vaccines. State and local health departments are working to ensure that health care providers are informed and have available consultation regarding best practices for the use of rabies vaccine.

Information about rabies, its prevention, and updates on the rabies vaccine situation can be obtained on the CDC rabies website http://www.cdc.gov/rabies/ or by calling 1-800-CDC-INFO. The rabies web site will be updated as new information becomes available.

Kentucky Quit Line
Data Collection and Evaluation

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What are Quit Lines?

Many tobacco users attempt to quit using tobacco products, but few find success on their own. "Quit lines" have been established as a cessation method that offer telephone-based support for people who want to quit using tobacco. California established the first quit line in 1992, and by 2004, a total of 38 states had followed suit. In 2004, a federal initiative was launched to establish a national network of quit lines. Quit lines offer a range of services and eliminate barriers that tobacco users encounter in traditional cessation programs. Among the services are:

- nicotine replacement therapies;
- online cessation information and programs;
- referrals to community-based cessation programs;
- elimination of the need to wait for a local tobacco cessation program to begin;
- no-cost service to callers and toll-free telephone numbers;
- services that are available at the tobacco user's convenience; and
- tobacco cessation services to smokers in rural and underserved areas.

The North American Quit Line Consortium (NAQC) was formed in 2004 as a response to the federal initiative. NAQC seeks to bring together health departments, quit line service providers, researchers, and national organizations in the United States, Canada, and Mexico to achieve the following goals: increase access use and effectiveness of quit lines; provide a unified voice to promote quit lines; and link quit line operations. Today, all states have quit lines, as well as Canada and Mexico; this further expands the widespread success of quit lines by providing all tobacco users with access. Additionally, the Clinical Practice Guideline and the Guide to Community Preventive Services have each acknowledged quit lines as an effective evidenced-based cessation method.

Kentucky's Tobacco Quit Line (1-800–QUIT–NOW)

According to the 2006 Behavioral Risk Factor Surveillance System, Kentucky continues to lead the nation in adult smoking prevalence. It was found that 28.5 percent of Kentuckians were current cigarette users and, of those, 48.3 percent had attempted to quit smoking for at least one day or longer. The Quit Line is an invaluable tool for Kentucky as it reaches out to a broad base of the population in an effort to increase comprehensive services for tobacco cessation.

Kentucky's Tobacco Quit Line has been operational since July 2005 and provides traditional counseling and support, in addition to specialized protocols for pregnant women and spit/chew tobacco users. English and Spanish language counselors are available and a TDY/TDD toll free number is available for individuals who are deaf and hard of hearing: 1-800-969-1393.

The number of callers utilizing the Quit Line has dramatically risen since the service became operational. In the latter half of 2005, the call volume of the Quit Line was 3,567. This number included incoming calls, outgoing calls, and information requests. Of the incoming calls, 208 enrolled in the proactive counseling program. 30 percent were verified as having initially quit tobacco use and 17 percent had sustained quitting after one month. By 2007 the annual call volume was 58,318, with 2,699 enrolled in proactive counseling services. 78.5 percent were verified as having initially quit, while 66.5 percent sustained quitting after one month.

Quit Line Partnerships

Despite the increased use of the Quit Line, current funding does not provide for a statewide media campaign to promote cessation services. However, the Quit Line has been promoted successfully through advocacy and partnerships with different groups.

A recent partnership with Medicaid included coverage of cessation counseling and Nicotine Replacement Therapy for that program's recipients. This pilot project alone drove a large volume of calls to the Quit Line. Approximately 89% of callers who completed the intake questionnaire enrolled in the proactive counseling program. The partnership with Medicaid began in March 2007 and officially ended in December 2007.

The Hospital-Based Tobacco Treatment Initiative is an ongoing program that relies upon partners, testing materials, and training of staff at five pilot hospital sites on a systems-based approach to cessation. Quit line materials and the fax referral system are an integral part of this initiative.

The Giving Infants & Families Tobacco Free Starts (GIFTS) is a pilot program currently partnering with nine Kentucky county health departments to target pregnant smokers through case management and family involvement. The aim of the program is to help smokers set a quit date and become tobacco free. In addition, the women are referred to the Quit Line for counseling.

Minimal Data Set

Since 2003, NAQC has worked with the Centre for Behavioral Research and Program Evaluation at the University of Waterloo to develop a standard approach for evaluating tobacco cessation quit lines. A workgroup was established in October 2003 to assess Minimal Data Set (MDS) implementation, process, and impact. They reported their results at the 2007 National Conference on Tobacco or Health.

The MDS was created as a standard approach to evaluate smoking cessation quit lines. MDS also collects consistent and comparable data across quit lines for improved analysis of the multiple variables involved in quit line services. NAQC requested that quit lines implement the MDS by October 1, 2005, but it was not mandatory.

Data captured by MDS includes:

- reasons for calling and awareness of the quit line;
- tobacco usage behaviors;
- caller demographics; and
- a seven month follow-up questionnaire about caller satisfaction and behaviors since using the quit line services.

Additionally, states can incorporate modules that obtain data beyond the MDS.

Kentucky collects data beyond MDS such as:

- years tobacco used, age started, brand of tobacco used;
- telephone number, alternate number, address, and county;
- reasons motivated to quit, how important it is to quit, family support;
- health care provider information, referral source;
- length of intake, and projected quit date;
- counseling protocols for specific populations (pregnancy or smokeless protocol); and
- number of users in household,
- tobacco use in the home and among friends and co-workers.

Conclusion

Not only can quit rates and call volumes be determined, but the opportunity also exists to examine behavioral changes so that the overall impact of quit lines can be determined. Data gathered from the Quit Line and partner projects are shared and disseminated to counties/area development districts. These data can be a powerful tool for legislative briefings and trend analysis. It is also important to note that in Kentucky, the Quit Line is the only source from which data can be gathered about attempted smoking cessation. No other program, such as Cooper-Clayton Method to Quit Smoking, one-on-one counseling initiatives, etc. collects data and/or reports it. The MDS has proven to be an invaluable resource and methodology in understanding how the Quit Line has served the needs of tobacco users by identifying gaps, and by providing insight on how to further expand the reach of quit line services.

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Tanning Bed Regulation

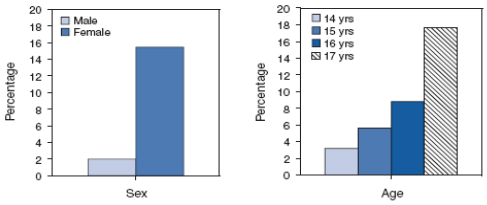
Melissa Chauvin—Food Safety Branch, Division of Public Health Protection and Safety, Kentucky DPH

To keep a summer tan through the winter, or to prepare for a vacation at the beach, many people use tanning beds to achieve a bronze color on their skin. This popular trend may be appealing to some, but has serious health disadvantages. Regulations have been implemented to protect members of the public who frequent tanning facilities, particularly young people. Local health departments throughout Kentucky are now required to monitor and oversee tanning facilities in their area.

"Exposure to ultraviolet (UV) rays—which you are exposed to in a tanning bed—is hazardous to your health and can lead to skin damage and, in some cases, skin cancer, said William Hacker, M.D., Public Health Commissioner. "Many times, people don't realize the dangers of tanning bed use and are unknowingly putting themselves at risk. The changes made to state law regulating tanning facilities were designed to protect the public and inform them about the dangers of tanning."

Tanning Bed Use in United States

- % of Teens (14-17) who used Indoor Tanning Devices during 12 months, by sex and age (United States, 2005)



- From MMWR weekly report (Oct. 13, 2006)

Cabinet for Health and Family Services

Tanning is defined as the darkening of skin in a natural physiological response stimulated by exposure to UV rays, usually by sunlight. Commercial tanning facilities use devices equipped with fluorescent lamps with phosphorus blends that emit UV radiation in a similar spectrum to that of the sun.

Exposure to UV radiation and the release of melanin (within the skin) is what gives the skin a darkened or tan look. Despite the known health risks of UV exposure, tanning beds have remained popular in Kentucky.

A large percentage of tanning bed users are minors below the age of 18 and are unaware of the dangers and harmful effects. Many tanning facilities have no system in place to track who visits their establishment or how often and how long particular patrons have been exposed to the lamps.

In 2005, a Casey County teen was diagnosed with malignant melanoma during her junior year of high school. After researching why melanoma occurs in young women, and with no real family history of cancer, she discovered that frequent trips to the tanning bed most likely contributed to the cancer. From there, state and local legislators began to examine existing controls and safeguards in Kentucky tanning bed facilities in hopes of preventing additional cases such as this.

The requirements of 902 KAR 45:075 are as follows:

- All tanning facilities in Kentucky must register with their local health department.
- All tanning facilities must pay an annual registration fee of $20.
- The law requires that people younger than 14 years old be accompanied by a parent or legal guardian when using a tanning bed.
- Teenagers older than 14 years old do not have to have a guardian present to use the tanning bed, but written parental consent is required for those older than 14 but younger than 18.
- Each facility shall maintain records for a minimum of two years.
- The facility must provide a written statement to the consumer that outlines the warnings associated with use of tanning devices. Sample forms can be found at http://chfs.ky.gov/dph/info/phps/food.

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Responsibilities for local health departments (LHDs) are as follows:

- LHDs will register facilities within their jurisdiction
- (but will not conduct routine or sanitation inspections)
- LHDs will require facilities to have proper paperwork
- (parental consent, records of use, proper warnings)
- LHDs will only investigate a facility if there is a complaint relating to a warning, a parental consent issue, or for documentation requirements.

Many states across the US have adopted and incorporated health based laws, regulations, or codes regarding the tanning industry. Since the majority of sun exposure in a person's lifetime occurs during childhood, many states, including Kentucky, are regulating the use of tanning beds. Kentucky's regulation primarily focuses on registration and documentation and *does not* include general sanitation requirements.

According to the National Conference of State Legislatures, there are 26 states and four counties which currently regulate tanning facilities for minors. Sixteen states introduced bills on this topic; four passed into law in the past year.

As Dr. Hacker elaborated, "These new measures were created to protect the public by providing adequate warnings about tanning beds and booths. The goal is to prevent overuse of tanning facilities and over-exposure to potentially dangerous UV radiation." This new tanning facility regulation is a start in preventing some factors that may contribute to an increased risk of developing melanomas in younger individuals.

For additional information or questions regarding the Tanning Bed Program and compliance, please contact:

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