NON-CIGARETTE TOBACCO USE - WHAT IS THE RISK?

Vera F. Dolan, MSPH, FALU
Research Associate
Clinical Reference Laboratory
Lenexa, KS

Robert L. Stout, PhD
President
Clinical Reference Laboratory
Lenexa, KS

Michael Fulks, MD
Consulting Medical Director
Clinical Reference Laboratory
Lenexa, KS

Dolan

Stout

Fulks

Executive Summary: An 8 to 10 year (mean 8.8 years) follow-up study of mortality among 2,193,014 insurance applicants who disclosed their cigarette smoking and other tobacco use status found that "nonsmokers" and "non-cigarette tobacco users" who were positive for cotinine (=> 200 ng/mL) had mortality that was substantially elevated. Non-cigarette tobacco users who were negative for cotinine had mortality that was not significantly different than the mortality seen among cotinine-negative nonsmokers. The presence of cotinine in the urine is the key factor in determining mortality risk rather than how nicotine is consumed.

Introduction

Unlike cigarette use, the mortality risk associated with non-cigarette tobacco use is unclear. Various insurers may treat this group like cigarette smokers, as an intermediate risk or (in some cases) like nonsmokers. To better quantify the risk, insurers may ask applicants about how much or how often they use non-cigarette tobacco. Insurers may also turn to thiocyanate testing, which can provide evidence of inhaling burned tobacco in order to differentiate between types of nicotine-associated risk.

Tobacco studies from the general population have usually found that non-cigarette tobacco use has an intermediate mortality risk between that of smokers and nonsmokers. However, these studies do not generally include data on cotinine levels, nor do they suffer from misclassification problems resulting from cigarette smokers claiming non-cigarette tobacco use or nonsmoking status. Most excess mortality associated with tobacco comes from increased cardiovascular disease largely related to nicotine and, to a lesser extent, cancers related to tars and other substances present in tobacco but not in nicotine gum and patches.

To help define the risk in non-cigarette tobacco users and the role of cotinine testing, we performed an 8 to 10 year (mean 8.8 years) follow-up study of mortality in insurance applicants, looking at both their admitted tobacco use status and cotinine levels.

How the Study Was Done

Clinical Reference Laboratory (CRL) performs testing on a substantial proportion of U.S. life insurance applicants. Most adult applicants are tested for urine cotinine, a highly sensitive and specific marker of nicotine use. A cotinine threshold of 200 ng/mL (0.2 ug/mL) was used in this study to indicate nicotine use. Increasingly, this is a typical cut-off used by insurers although a cut-off of 500 ng/mL is in common use as well. The lower cut-off improves sensitivity but reduces specificity in the absence of a confirmatory step, as discussed in a previous study by CRL published in *ON THE RISK*.[1]

Since confirmatory gas chromatography/mass spectroscopy (GC/MS) tests were not done for this study, this means that a few nonsmokers may be classified as nicotine users, potentially reducing the mortality differences between nonsmokers and cigarette/other tobacco users. Using the higher cotinine cut-off of 500 ng/mL would create the same limitation by adding nicotine users to the nonsmokers.

This study included 2,193,014 applicants age 20 to 94 years (mean 43 years) who were tested for cotinine between 1998 and 2000; 37,995 deaths occurred among those applicants. Questions about cigarette smoking and tobacco use were asked at the time of test authorization; only applicants who answered these questions were included in this study.

The question on CRL's authorization forms in 1998 through 2000 that asked about cigarette smoking was: "Do you smoke cigarettes?" Answer boxes were provided for the applicant to check either "Yes" or "No." The question that asked about tobacco use was: "Do you use any tobacco products?" Answer boxes were provided for the applicant to check either "Yes" or "No." Applicants who did not answer these questions were excluded from this study. Individuals who admitted using tobacco but not cigarettes were identified by separating admitted cigarette smokers from those who only admitted tobacco use.

The Social Security Administration keeps a database (the Death Master File) that lists the deaths of U.S. citizens, and allows this to be used for research purposes. This database was accessed in June 2008 by CRL to determine who in our study had died. The mean duration of follow-up was 8.8 years with a range of 8 to 10 years.

To reduce the impact of mortality attributable to different age and sex characteristics in the use of cigarettes and other forms of tobacco, our analysis splits the study population by sex and age group (20 to 59 years, 60+ years). To compare mortality results within the different age/sex groups that were further distinguished by admitted tobacco use status and cotinine result, we calculated mortality rates for each subgroup based on the number of people who died (numerator) and the total number of people in that subgroup (denominator).

From these rates we then calculated mortality ratios and their 95% confidence intervals.[2] Our mortality ratios compared the mortality rate of a subgroup of interest divided by the rate of the reference group: the admitted nonsmokers who were negative for cotinine. No outside reference group was needed because the study population itself provided sufficiently large numbers of cotinine-negative nonsmokers to provide stable and representative benchmarks for comparison. Subgroups were selected only by admitted tobacco use status and cotinine result.

The number of deaths among males was sufficiently high to provide narrow 95% confidence intervals. Fewer deaths were available among females because of fewer applicants and a lower likelihood of tobacco use, resulting in wider 95% confidence intervals.

What the Study Found

Table 1 shows the mortality ratios for females and Table 2 shows the mortality ratios for males, subdivided by age, admitted tobacco use status and cotinine result. Figure 1 is a graphic representation of these mortality ratio results for each of the four age/sex groups.

In all four age/sex groups, when compared against admitted nonsmokers who were negative for cotinine, those who admitted to smoking cigarettes had 205% to 320% relative mortality, similar to the difference seen in insured lives. The relative mortality for non-cigarette tobacco users who were cotinine negative ranged from 88 to 144% in females (with wide 95% confidence intervals), but was only 82 to 90% for males where, because of more deaths, the 95% confidence intervals were much narrower. Mortality among cotinine-negative non-cigarette tobacco users was not significantly different from mortality among cotinine-negative nonsmokers.

In the cotinine-positive non-cigarette tobacco groups, the relative mortality ranged from 135% to 278% with females experiencing higher relative mortality than males. Mortality for cotinine-positive non-cigarette tobacco users was distinctly higher than mortality for those groups that were negative for cotinine.

What Do the Study Results Contribute to Risk Assessment?

In this large study limited to an otherwise unselected group of insurance applicants, cotinine results were a far better predictor of mortality than stated tobacco use. Both nonsmokers and non-cigarette tobacco users who were positive for cotinine experienced relative mortality that was markedly elevated. Non-cigarette tobacco users who were negative for cotinine had low mortality that was not significantly different than the mortality of nonsmokers who were negative for cotinine. Although the mortality ratios in each age/sex group varied, the pattern of mortality is very similar within all groups.

The key is the cotinine status, the most objective marker available as to extent and recency of tobacco or other nicotine use. An accurate history on the nature and frequency of non-cigarette tobacco use may be difficult to obtain, and is unlikely to change the relative risk to any great degree once the cotinine status is known. The role of additional testing in an attempt to separate inhaled tobacco vs. oral and other nicotine use is unclear, since the mortality implications of the difference is unknown and may be limited once the cotinine status is known.

Consideration of admitted non-cigarette tobacco use with negative cotinine for more favorable risk categories may be appropriate. Cotinine-positive applicants have a much higher mortality risk regardless of admitted tobacco use status.

References

1. Stout RL, Magee M, and Dolan VF. "Improvements in cotinine testing of insurance applicants" *ON THE RISK* 2006;22:58-61
2. Kleinbaum DG, Sullivan KM and Barker ND. ActivEPI Companion Textbook. New York City, NY: Springer; 2003, pp 350-1

Table 1. Mortality Rates and Ratios for Females by Age Group, Cotinine Results, and Admitted Tobacco Use Status

	Deaths	Total Applicants	Mortality Rate	Mortality Ratio (%)	95% CI†
Ages 20 to 59, negative cotinine*					
Nonsmokers (reference)	3,660	667,302	.00548	100	
Non-cigarette tobacco users	7	887	.00789	144	69-301
Ages 20 to 59, positive cotinine**					
Nonsmokers	285	16,430	.01735	316	282-355
Non-cigarette tobacco users	10	690	.01449	264	143-489
Ages 20 to 59, cigarette smokers	1,126	64,184	.01754	320	302-339
Ages 60+, negative cotinine					
Nonsmokers (reference)	5,328	68,194	.07813	100	
Non-cigarette tobacco users	5	73	.06849	88	38-204
Ages 60+, positive cotinine					
Nonsmokers	285	1,894	.15048	193	173-214
Non-cigarette tobacco users	25	115	.21739	278	197-394
Ages 60+, cigarette smokers	706	4,403	.16035	205	192-220

* Urine cotinine <200 ng/mL

** Urine cotinine =>200 ng/mL

† See Reference 2

Table 2. Mortality Rates and Ratios for Males by Age Group, Cotinine Results, and Admitted Tobacco Use Status

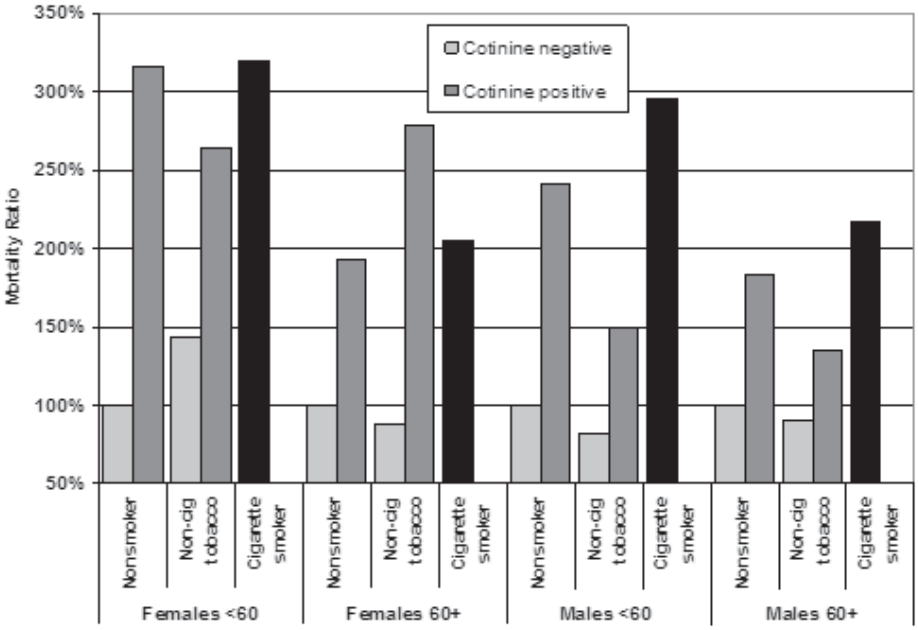
	Deaths	Total Applicants	Mortality Rate	Mortality Ratio (%)	95% CI†
Ages 20 to 59, negative cotinine*					
Nonsmokers (reference)	9,213	1,010,815	.00911	100	
Non-cigarette tobacco users	227	30,222	.00751	82	72-94
Ages 20 to 59, positive cotinine**					
Nonsmokers	981	44,688	.02195	241	226-256
Non-cigarette tobacco users	454	33,194	.01368	150	137-164
Ages 20 to 59, cigarette smokers	3,297	122,436	.02693	295	286-306
Ages 60+, negative cotinine					
Nonsmokers (reference)	9,848	111,822	.08807	100	
Non-cigarette tobacco users	123	1,544	.07966	90	76-107
Ages 60+, positive cotinine					
Nonsmokers	629	3,900	.16128	183	170-197
Non-cigarette tobacco users	275	2,309	.11910	135	121-151
Ages 60+, cigarette smokers	1,511	7,912	.19098	217	207-227

* Urine cotinine <200 ng/mL

** Urine cotinine =>200 ng/mL

† See Reference 2

Figure 1. Mortality Ratios by Age Group, Sex, Admitted Tobacco Use Status, and Cotinine Results



About the Authors

Vera F. Dolan, MSPH, FALU, Research Associate at Clinical Reference Laboratory, is a consultant specializing in underwriting research and product development. At CRL Vera assists with the analysis and publication of CRL's mortality study data. In her consulting practice, Vera develops risk assessment tools for underwriters, including underwriting manuals, as automated risk assessment systems and underwriter training. Vera provides litigation support for misrepresentation and other underwriting issues, as well as life expectancy calculations for use during litigation.

Vera has a BA in Public Health from the Johns Hopkins University, and a master's in Public Health in Epidemiology from the University of North Carolina at Chapel Hill. Vera was employed as an underwriting researcher at Lincoln Re and Transamerica Occidental Life before starting her consultancy in 1989. Vera is an Associate Editor of *ON THE RISK*, and regularly speaks to actuaries and underwriters on risk assessment topics.

Robert L. Stout, PhD, is President and Director of the Clinical Reference Laboratory based in Lenexa, Kansas. He completed undergraduate studies at California State University (Fullerton) and obtained a Ph.D. in Biological Chemistry from UCLA School of Medicine. Since 1978 he has been directly responsible for introducing many of the new tests and procedures used in risk assessment such as urine and saliva HIV. Dr. Stout has produced nine patents over the last decade.

Dr. Stout has published numerous articles in the *Journal of Insurance Medicine* and *ON THE RISK*. He has made presentations to the Institute of Home Office Underwriters, the ACLI Medical Section, AAIM, the Home Office Life Underwriter's Association, the Canadian Institute of Underwriters, the International Underwriting Congress, ICLAM, the Impaired Risk Group and numerous regional underwriters associations. Dr. Bob is grandfather of three and an avid golfer, fisherman and gardener.

Michael Fulks, MD, Consulting Medical Director, analyzes, interprets and writes up CRL's mortality study results. Dr. Fulks is a graduate of the University of California at Davis, completing his residency at the University of Wisconsin and practicing for eight years before joining Allmerica in 1987. He became VP & Medical Director of Phoenix Life in 1989, working with its direct and reinsurance areas, group health and disability. Moving to Merrill Lynch in 1997, he developed an underwriting approach for its older age clientele. In 2001, he joined MassMutual creating its first electronic underwriting manual and updating its requirements, preferred programs and ratings. He moved home to northern California in 2005 and now mixes ranch work with consulting, including ongoing research work for CRL.

Mike has contributed to articles in the *Journal of Insurance Medicine* and *ON THE RISK* on laboratory testing. He regularly speaks to medical directors and underwriters on various topics including predictive value of testing and patterns of mortality in general and in relation to specific impairments ranging from coronary disease to hepatitis. Mike is board-certified in Insurance and Internal Medicine.