UNDERWRITING IMPLICATIONS OF ELEVATED CARCINOEMBRYONIC ANTIGEN

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Executive Summary: This seven-year follow-up study shows that CEA can detect early excess mortality risk in insurance applicants who are age 50 years and over. CEA levels of 10 ng/mL and over correlate with high excess mortality, and CEA levels 5 ng/mL and over are of sufficient concern that focused review is indicated. The addition of CEA testing beginning at age 50 for life insurance applicants could reduce early mortality by 3.2% if the threshold for requiring further evaluation were set at 10 ng/mL.

Introduction

Carcinoembryonic antigen (CEA) is a cell-surface glycoprotein that normally circulates in the blood at low levels. Levels are higher in smokers than non-smokers but the upper limit for normal values for all is less than 5 ng/mL. CEA is present in a variety of tissues, including the gastrointestinal tract, liver, pancreas, lung, kidney, bladder, prostate, breast, ovary and thyroid. Blood levels of CEA may be elevated by malignancy involving tissues producing CEA, but are also elevated by benign tumors and inflammation including hepatitis and inflammatory bowel disease.

CEA can be used as a tumor marker to follow known malignancy, but it is not commonly used as a screening test for the general population because its sensitivity and specificity for malignancy are insufficient at typical cut-off values. In addition, when CEA is elevated due to a malignancy, the disease is typically advanced, and the outcome is generally poor and unchanged by detection.

For individuals buying life insurance, however, the treatability of cancer discovered by screening is not of primary concern. The limited sensitivity of the CEA test is also of less importance, since detecting even a few applicants with otherwise unknown malignancies would be of great value to insurers, if not the applicant. Sufficient test specificity remains critically important, since a positive CEA result will arouse applicant concern and may initiate expensive and uncomfortable testing which, if negative, may still not produce a definitive answer.

How the Study Was Done

An earlier study on CEA results obtained from 2001 to 2005 with a median of three years of follow-up mortality has been published in the *Journal of Insurance Medicine*.[1] This updated and expanded study of CEA testing was performed on 245,089 insurance applicants age 50 and over who had blood samples tested at Clinical Reference Laboratory (CRL) between 2001 and 2007. All applicants for life insurance at participating insurers meeting age and face amount criteria were tested for CEA levels.

Mortality follow-up of applicants was done in June 2008, utilizing the Social Security Administration Death Master File–we found 2,456 deaths (over twice as many as in the earlier study) within our study population after seven years of follow-up. To reduce the impact of mortality attributable to different age and sex characteristics in the onset of malignancy, in our analysis we split the study population by sex and age group (50 to 59 years, 60 to 69 years, and 70+ years). We also compared mortality results within the different age groups by cotinine result, with a positive cotinine considered to be 200 ng/ml (0.2 ug/ml) or higher. Cotinine indicates current exposure to nicotine, which is both a significant risk factor for developing cancer and a direct cause of increased CEA levels.

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: those who had CEA levels <5 ng/mL. No outside reference group was needed because the study population itself provided sufficiently large numbers of <5 ng/mL CEA cases to provide stable and representative benchmarks for comparison.

In our analysis, CEA ranges of <5 ng/mL, 5 to 9.9 ng/mL, and 10+ ng/mL were used. In clinical medicine, CEA values of 5 ng/mL and over are considered abnormal, and values of 10 ng/mL and over are considered to be highly abnormal.

Median follow-up for the entire group was 2.7 years (range 0 to 7 years). Although the median follow-up period was short, there were enough lives so that life table analyses could be calculated to seven years of follow-up. Compared to mortality rates in the reference group with CEA <5 ng/mL, the mortality ratios (MRs) for the CEA groups 5 to 9.9 ng/mL and 10+ ng/mL by age and sex are listed in Table 1. Mortality ratios by age and cotinine status are listed in Table 2, with the MRs graphically shown in Figure 1. Table 3 shows the annual life table mortality for the first seven years after CEA testing for all applicants combined.

What the Study Found

Our results demonstrate that an elevated CEA in individual life insurance applicants carries a high mortality risk relative to those with CEA values <5 ng/mL. Mortality ratios for men and women with elevated CEA are similar. However, MRs for smokers with elevated CEA are lower than MRs for non-smokers, at least in part because smokers have a higher baseline mortality rate and higher mean values of CEA. Mortality ratios in the CEA 10+ ng/mL group decline over time, as shown in Table 3 (the life table), but remain substantially elevated throughout the seven years of observation. Mortality ratios in the CEA 5 to 9.9 ng/mL group are lower relative to the CEA 10+ ng/mL group, but have a smaller decline over time, suggesting that some of the extra risk is related to less extensive malignancies and/or non-malignant conditions.

At a CEA of 10+ ng/mL, the cumulative mortality at seven years is 6.9% (50 to 59 years), 11.7% (60 to 69 years), and 15.1% (70+ years). The percentage of applicants with CEA values this high is 0.4% for all ages, with the prevalence of an elevated CEA of 10+ ng/mL ranging from 0.3% at ages 50-59 to 0.7% at ages 70+ years. The early mortality for applicants with CEA results of 10+ ng/mL is very high when compared to the mortality for those with CEA results below 10 ng/mL. Almost all of the excess deaths for those with CEA levels of 10+ ng/mL are likely to be related to cancer.

The mortality risk is increased for the CEA 5 to 9.9 ng/mL group, but the cumulative mortality at seven years for this group is only 1.8% (50 to 59 years), 3.1% (60 to 69 years) and 5.4% (70+ years). The prevalence of an elevated CEA between 5 and 9.9 ng/mL ranges from 2.7% at ages 50 to 59 to 4.5% at ages 70+. Although these CEA values are associated with excess early mortality, underwriting action beyond a carefully focused review of all age and face amount requirements would result in large number of applications being at least temporarily delayed, and could result in a high number of concerned applicants. Assuming that most of those who had an elevated CEA from an advanced malignancy died during the observation period, it is clear the large majority of elevations in this lower range had other conditions or less advanced disease not associated with early mortality.

If underwriting actions were limited to those with CEA values 10+ ng/mL, there would be far fewer cases with unnecessarily raised concerns. However, the downside of using the more predictive CEA cut-off at 10 ng/mL as compared to a cut-off at 5 ng/mL is that we would miss 60% of the excess early deaths associated with CEA results 5+ ng/mL. One possible underwriting action at whatever cut-off value is chosen may be to postpone the case for 3 to 6 months and then retest the applicant. CEA values that go down or remain the same could then be viewed favorably by the underwriter.

Since we lack knowledge of who did or did not have cancer in this population, the sensitivities and specificities of the CEA test for cancer cannot be calculated. What we can do is observe from Table 1 that by testing and removing applicants with CEA >10 ng/mL, 3.2% of all deaths in this population would have been avoided. This value is obtained by subtracting expected deaths based on the mortality rate in the CEA <5 groups from actual deaths in the CEA 10+ ng/mL groups. In our earlier CEA study, it was observed that 75% of those who had a CEA of 10+ ng/mL and who died had no other laboratory abnormalities of note.[1]

One question that has been raised concerns the mortality and prevalence of CEA levels that are substantially higher than 10 ng/mL. When all applicants with CEA values above 10 ng/mL are split into 10 to 19 ng/mL and 20+ ng/mL groups, those with values of 10 to 19 ng/mL have an MR of 649% (95% CI 489-862%) and prevalence of 0.3%; those with values of 20+ ng/mL have a MR of 2,967% (95% CI 2,318-3,798%) and a prevalence of 0.07%. Because CEA values of 10 to 19

ng/mL already have a substantially increased mortality risk and CEA values 20+ ng/mL are uncommon, splitting this high CEA value range (though interesting) may not have additional underwriting value.

What Do the Study Results Contribute to Risk Assessment?

This study provides information needed for objective decision-making on the part of the underwriter for the evaluation of CEA results reported from an industry reference laboratory or present in an APS. The addition of CEA testing beginning at age 50 for life insurance applicants could reduce early mortality by an average of 3.2% over a period of seven years if the threshold were set at 10 ng/mL. Underwriters should carefully review applications with elevated CEA values.

References

1. Stout RL, Fulks M, Dolan VF, et al. "Increased Mortality Associated with Elevated Carcinoembryonic Antigen in Insurance Applicants" *J. Insurance Medicine*, 2007;39:251-8
2. Kleinbaum DG, Sullivan KM and Barker ND *ActivEPI Companion Textbook*. New York City, NY: Springer; 2003, pp 364-7

Table 1. CEA Mortality Rates and Ratios by Age Group and Sex

Age Group (years)	CEA (ng/mL)	Deaths	Total Applicants	Mortality Rate	Mortality Ratio (%)	95% CI† (%)
Females						
50 to 59	<5 (reference)	201	49,418	.00407	100	
	5 to 9.9	16	1,327	.01206	296	182-482
	10+	10	180	.05556	1,366	748-2,495
60 to 69	<5 (reference)	193	18,915	.01020	100	
	5 to 9.9	20	692	.02890	283	184-436
	10+	9	102	.08824	865	463-1,614
70+	<5 (reference)	212	9,599	.02209	100	
	5 to 9.9	29	515	.05631	255	179-363
	10+	12	90	.13333	604	357-1,022
Males						
50 to 59	<5 (reference)	555	101,629	.00546	100	
	5 to 9.9	62	2,942	.02107	386	302-494
	10+	24	312	.07692	1,409	959-2,069
60 to 69	<5 (reference)	563	41,586	.01354	100	
	5 to 9.9	47	1,505	.03123	231	174-306
	10+	22	164	.13415	991	672-1,462
70+	<5 (reference)	433	15,369	.02817	100	
	5 to 9.9	34	662	.05136	182	131-253
	10+	14	82	.17073	606	376-976

† See Reference 2

Table 2. CEA Mortality Rates and Ratios by Age Group and Cotinine Level

Age Group (years)	CEA (ng/mL)	Deaths	Total Applicants	Mortality Rate	Mortality Ratio (%)	95% CI† (%)
Cotinine negative*						
50 to 59	<5 (reference)	525	126,981	.00413	100	
	5 to 9.9	27	2,065	.01308	316	217-460
	10+	18	189	.09524	2,304	1,484-3,575
60 to 69	<5 (reference)	573	50,999	.01124	100	
	5 to 9.9	34	1,230	.02764	246	177-343
	10+	20	138	.14493	1,290	860-1,934
70+	<5 (reference)	569	21,792	.02611	100	
	5 to 9.9	47	877	.05359	205	155-271
	10+	18	128	.14063	539	351-826
Cotinine positive*						
50 to 59	<5 (reference)	199	15,134	.01315	100	
	5 to 9.9	48	1,999	.02401	183	138-241
	10+	15	280	.05357	407	249-667
60 to 69	<5 (reference)	151	5,095	.02964	100	
	5 to 9.9	32	820	.03902	132	94-185
	10+	10	109	.09174	310	171-559
70+	<5 (reference)	63	1,286	.04899	100	
	5 to 9.9	15	226	.06637	135	83-221
	10+	7	33	.21212	433	224-836

* Urine cotinine <200 ng/mL for negative and =>200 ng/mL for positive

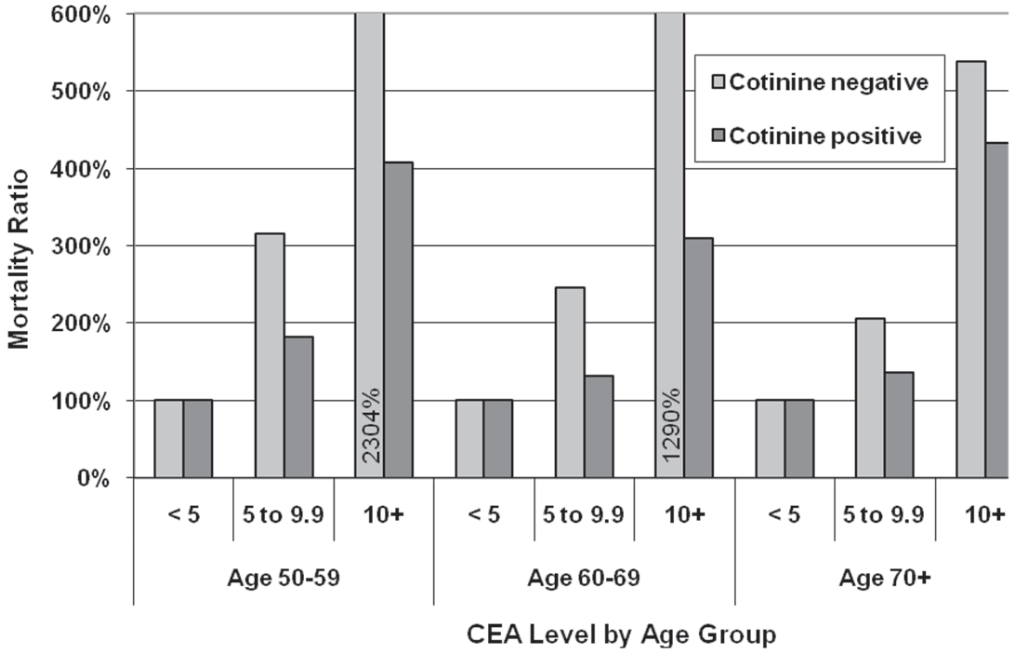
† See Reference 2

Table 3. Life Table for CEA Test Results for All Applicants

CEA ng/mL	Duration (years)	Population At Risk	Censored Lives	Deaths	Interval q	Interval p	Cumulative p	Interval Mortality Ratio*	Cumulative Mortality Ratio*
<5 (reference)	0 to 1	221,239	35,616	163	0.00080	0.99920	0.99920		
	1 to 2	185,460	35,447	386	0.00230	0.99770	0.99690		
	2 to 3	149,627	37,374	429	0.00328	0.99672	0.99363		
	3 to 4	111,824	33,223	405	0.00425	0.99575	0.98941		
	4 to 5	78,196	22,402	320	0.00478	0.99522	0.98468		
	5 to 6	55,474	27,621	215	0.00516	0.99484	0.97960		
	6 to 7	27,638	27,524	114	0.00822	0.99178	0.97155		
5 to 9.9	0 to 1	7,214	1,081	27	0.00405	0.99595	0.99595	505%	505%
	1 to 2	6,106	1,164	58	0.01050	0.98950	0.98550	456%	469%
	2 to 3	4,884	1,348	39	0.00926	0.99074	0.97637	283%	373%
	3 to 4	3,497	1,524	41	0.01499	0.98501	0.96173	352%	365%
	4 to 5	1,932	1,069	22	0.01574	0.98426	0.94659	330%	354%
	5 to 6	841	376	8	0.01225	0.98775	0.93499	237%	325%
	6 to 7	457	452	5	0.02165	0.97835	0.91476	263%	307%
10+	0 to 1	874	121	19	0.02336	0.97664	0.97664	2915%	2915%
	1 to 2	734	148	23	0.03485	0.96515	0.94261	1514%	1876%
	2 to 3	563	145	28	0.05708	0.94292	0.88880	1742%	1807%
	3 to 4	390	158	10	0.03215	0.96785	0.86022	756%	1387%
	4 to 5	222	135	4	0.02589	0.97411	0.83795	542%	1125%
	5 to 6	83	39	1	0.01575	0.98425	0.82476	305%	919%
	6 to 7	43	43	0	0.00000	1.00000	0.82476	0%	657%

* Mortality ratios (interval and cumulative) based on CEA <5 ng/mL as a reference

Figure 1. 7-Year Relative Mortality for CEA Results by Age Group and Cotinine Level



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.

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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.