

## Increased Mortality Associated with Elevated Carcinoembryonic Antigen in Insurance Applicants

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**Objective.**—Determine the relationship between the carcinoembryonic antigen (CEA) value and all-cause mortality in life insurance applicants aged 50 years and over.

**Method.**—By use of the Social Security Master Death Index, mortality was examined in 115,590 insurance applicants aged 50 and up for whom blood samples for CEA were submitted to the Clinical Reference Laboratory. Results were stratified by CEA value (<5 ng/mL, 5 to 9.9 ng/mL, 10+ ng/mL), smoking status, and age groups (50–59 years, 60–69 years, and 70 years and up).

**Results.**—Relative mortality is increased at CEA values between 5 and 9.9 ng/mL and further increased at 10+ ng/mL for all age groups, with the most dramatic increase at the youngest ages. Excess mortality appears to last at least 3 to 4 years after the elevated result. Five-year all-cause mortality in applicants with CEA values of 10+ ng/mL is 25.2% with a mortality ratio relative to those with a CEA <5 ng/mL of 1156%.

**Conclusion.**—This study shows that CEA can detect the risk of early excess mortality in life insurance applicants; CEA levels of 5 ng/mL and over may be of concern. CEA testing beginning at age 50 years for life insurance applicants could capture 4.6% of early mortality if the threshold for further evaluation was set at 10 ng/mL. Only 0.4% of all applicants aged 50 and over have CEA values at or above this threshold.

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### INTRODUCTION

Carcinoembryonic antigen (CEA) is a cell-surface glycoprotein that normally circulates in the blood at low levels. Its normal range is higher in smokers than non-smokers, but the upper limit for normal values is below 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.<sup>1</sup> Preoperative CEA levels are clinically useful when determining the

prognosis of suspected tumors, including tumors of the colon,<sup>2-7</sup> stomach,<sup>8-10</sup> pancreas,<sup>11-12</sup> lung,<sup>13-15</sup> and breast<sup>16</sup> while post-operative levels may be useful to look for tumor recurrence.

CEA is not recommended as a screen for the general population because its sensitivity and specificity for malignancy is relatively low; hence, in a low prevalence situation, the positive predictive value is limited.<sup>3,17</sup> Another consideration against using CEA as a screen for the general population is that CEA elevations do not often appear until the malignancy is advanced, and the likely outcome is poor and unchanged by detection.

When screening people buying life insurance, however, the ability to treat any cancer discovered by screening is not of primary concern. The sensitivity of the CEA test is also of less importance, since detecting even some of the otherwise unknown advanced malignancies would be of great value to insurers, if not the applicants themselves. However, sufficient test specificity is of critical importance, since a positive CEA result will arouse applicant concern. A positive CEA test may initiate a round of testing which, if negative, would still not produce a definitive answer.

There have been few opportunities to assess the relationship of CEA levels with mortality in a large, presumably healthy, adult population. Fewer yet have sufficient data and participants to stratify by age and a range of CEA values. The all-cause mortality impact of different CEA values for insurance applicants or those issued coverage also is not well studied. Both the point where mortality begins to increase and the amount of increase at various values and ages have been debated. Attempts to ascertain the mortality impact of elevated CEA in insured lives have been hampered by the lack of sufficient industry data, and in selecting a matched reference group.

Life insurance applicants provide a useful, if not perfect, surrogate for insured lives.

Applicants for life insurance are a self-selected group of relatively healthy adults, typically employed or retired with access to health care. They are representative of that portion of the general adult population seen regularly for preventive care screening, providing insights for this group as well.

## METHODS

A blood sample is usually obtained as part of the life insurance application process, except for those at younger ages and lower amounts of insurance. This sample is then sent by overnight mail to one of a small number of laboratories serving the life insurance industry, including Clinical Reference Laboratory (CRL). All of the authors are either employees of CRL or have a consulting relationship with CRL.

CEA testing was performed on 115,590 life insurance applicants aged 50 and over who had blood samples tested at CRL between 2001 and 2005. All applicants for life insurance at participating insurers meeting age and policy face amount criteria were tested for CEA levels.

Follow-up of applicants for mortality was done through February 2007 utilizing the Social Security Administration Master Death Index service. This allowed identification of reported deaths through the end of 2006. The study is independent of the insurers that ordered CEA tests, and any action they may have taken on the test results. Identification information for each applicant in the study was removed before analysis was conducted.

Median follow-up for the entire study population was 3 years; life table and survival analyses were calculated for 5 years of follow-up.<sup>18-20</sup> Analyses were performed with SPSS for Windows, release 11.5.1 (SPSS, Inc).

## ANALYSIS

Mortality was calculated using life table analysis shown in Table 2 for all ages and

**Table 1.** Percent of Males, Mean Age, Percent of Smokers in Population and Deaths, by Age Group and CEA Band

Age Group (years)	CEA (ng/mL)	Population At Risk	Male (%)	Mean Age (years)	Percent of Smokers <sup>1</sup> in Population (%)	Percent of Smokers <sup>1</sup> in Deaths (%)
50 to 59	<5 (reference)	72,576	64.1	54.3	11.0	30.6
	5 to 9.9	2080	67.3	54.4	49.8	52.0
	10+	247	67.2	54.5	60.4	42.1
	Total	74,903	64.2	54.3	12.3	32.5
60 to 69	<5 (reference)	29,915	66.1	63.5	8.8	20.1
	5 to 9.9	1069	67.5	63.8	40.2	54.8
	10+	134	61.9	63.3	44.4	40.0
	Total	31,118	66.1	63.5	10.0	24.1
70+	<5 (reference)	9052	61.8	74.3	5.8	10.1
	5 to 9.9	443	55.3	75.2	21.0	16.0
	10+	74	48.6	74.5	20.5	20.0
	Total	9569	61.4	74.4	6.6	10.9

<sup>1</sup> Urine cotinine  $\geq 200$  ng/mL

smoking status combined. Reference mortality was taken from the CEA band that represented the lowest risks for malignancy (<5 ng/mL). This reference group includes 96.5% of the population at risk in this study. Using this internal group as a reference population avoids unknown bias and assumptions that would have to be made if an external population group was selected. Unfortunately, the small numbers of individuals observed in the elevated CEA bands (when distributed by years of duration) can result in mortality ratios dependent on few deaths; this ruled out further subdivision of the life table by age and smoking status.

Another approach shown in Tables 3 and 4 is to simply divide the number of deaths within each age and CEA band by the person-years of exposure in that group. This produces the mortality rate of deaths per person-year. These mortality rates can then be compared between age groups and CEA bands in a ratio that is analogous to the traditional mortality ratio that reflects the entire 5-year study period rather than each year of the study. This allows further division by age band and smoking status. Excess deaths over the 5-year study period also are presented in Tables 3 and 4.

## RESULTS

CEA ranges of <5 ng/mL, 5 to 9.9 ng/mL, and 10+ ng/mL were chosen based on observed mortality and on clinical practice. CEA values of 5 ng/mL and over are generally considered clinically abnormal, and values of 10 ng/mL and over are generally considered to be very abnormal when following patients with a history of cancer.

The median CEA value for non-smokers in the study (urine cotinine <200 ng/mL) was 1.40 ng/mL and the median value for smokers was 2.40 ng/mL. The distributions by gender, median age, and smoking status within the population at risk and within deaths for each group are shown in Table 1. Proportions of males and mean age are fairly consistent across CEA bands for the younger age groups; the proportion of males drops with increasing CEA in the oldest age group. A roughly 4-fold increase in the proportion of smokers is found for those with increased CEA within each age group. However, among the deaths, about half of this increase disappears. This suggests that the excess of smokers in higher CEA bands is due to both the direct impact of smoking on CEA levels and increased malignancy risk.

**Table 2.** Life Table Analysis for All Ages, by CEA Band and Duration

Duration (years)	Population At Risk	Deaths	Censored Lives	Interval q	Interval p	Cumulative p	Interval Mortality Ratio <sup>1</sup>	Cumulative Mortality Ratio <sup>1</sup>
<b>CEA &lt;5 ng/mL (reference)</b>								
0-1	111,543	363	29,863	0.0038	0.9962	0.9962		
1-2	81,317	267	23,461	0.0038	0.9962	0.9924		
2-3	57,589	183	28,690	0.0042	0.9958	0.9882		
3-4	28,716	102	21,994	0.0058	0.9942	0.9825		
4-5	6620	22	6598	0.0066	0.9934	0.9760		
<b>CEA 5-9.9 ng/mL</b>								
0-1	3592	45	1480	0.0158	0.9842	0.9842	420%	420%
1-2	2067	21	1129	0.0140	0.9860	0.9705	364%	392%
2-3	917	12	416	0.0169	0.9831	0.9540	400%	395%
3-4	489	3	370	0.0099	0.9901	0.9446	171%	322%
4-5	116	1	115	0.0171	0.9829	0.9285	258%	304%
<b>CEA 10+ ng/mL</b>								
0-1	455	27	170	0.0730	0.9270	0.9270	1942%	1942%
1-2	258	16	146	0.0865	0.9135	0.8469	2254%	2100%
2-3	96	4	43	0.0537	0.9463	0.8014	1269%	1802%
3-4	49	2	38	0.0667	0.9333	0.7480	1158%	1591%
4-5	9	0	9	0.0000	1.0000	0.7480	0%	1156%

<sup>1</sup> Mortality ratios (interval and cumulative) based on CEA <5 ng/mL as reference.

The prevalence of an elevated CEA between 5 and 9.9 ng/mL is 2.8% among ages 50 to 59 years, 3.4% among ages 60 to 69 years, and 4.6% among ages 70 years and over. The prevalence of an elevated CEA of 10+ ng/mL is 0.3% among ages 50 to 59 years, 0.4% among ages 60 to 69 years, and 0.8% among ages 70 years and over.

Table 2 shows a life table analysis for the reference group (CEA <5 ng/mL), as well as life tables for each of the higher CEA bands. For CEA results of 5 to 9.9 ng/mL, the all-cause mortality after 5 years is 7.2%, and for CEA results of 10+ ng/mL, the all-cause mortality after 5 years is 25.2%. Relative mortality for those with elevated levels of CEA is very high and stable during the first 3 to 4 years, and then drops. Due to insufficient data, the authors cannot comment on mortality risk associated with CEA level beyond a 5-year time frame.

Table 3 combines all durations of follow-up within age groups and CEA bands for nonsmokers only, and Table 4 presents sim-

ilar data for smokers only. Urine cotinine results were available for 99.2% of the population at risk, and for 98.6% of the total deaths. Urine cotinine levels that indicate positive smoking status are 200 ng/mL and higher. Among nonsmokers, elevated CEA levels are associated with increased mortality for all ages for CEA results above 5 ng/mL. Among smokers, the relative increase is smaller; because of smaller total numbers, the confidence intervals overlap.

#### OTHER LABORATORY STUDIES IN APPLICANTS WITH HIGH CEA RESULTS

Since other laboratory tests were performed on these life insurance applicants, including blood chemistries, urinalysis, and (if male, and aged 50 or over) a PSA, the question arises as to the independent value of CEA in predicting early mortality, otherwise known as the "attribution rate" for CEA. To answer that, 48 applicants were reviewed who died in the first 5 years of this

**Table 3.** Nonsmokers<sup>1</sup> Only: Deaths Per Person-Year and Ratios for All Durations Combined, by Age Group<sup>2</sup>

Age Group (years)	CEA (ng/mL)	Deaths	Population At Risk	Person-Years	Deaths/Person-Years	Ratio <sup>3</sup> (%)	95% CI <sup>4</sup> (%)	Excess Deaths <sup>5</sup>
50 to 59	<5	234	64,094	165,326	0.0014	100	83–120	
	5 to 9.9	12	1039	1954	0.0061	434	243–775	9.2
	10+	11	97	186	0.0591	4178	2282–7649	10.7
60 to 69	<5	254	27,088	68,098	0.0037	100	84–119	
	5 to 9.9	14	635	1170	0.0120	321	187–549	9.6
	10+	12	74	125	0.0960	2574	1442–4592	11.5
70+	<5	241	8435	19,653	0.0123	100	84–120	
	5 to 9.9	21	349	644	0.0326	266	170–415	13.1
	10+	8	58	110	0.0727	593	293–1200	6.7

<sup>1</sup> Urine cotinine <200 ng/mL<sup>2</sup> Rounding of numbers may cause some calculations to appear erroneous.<sup>3</sup> Ratio as a percentage is the deaths per person-year in the target band divided by the deaths per person-year in the <5 ng/mL band, multiplied by 100.<sup>4</sup> See references 19 and 20.<sup>5</sup> Derived by multiplying deaths/person-year for the reference group by the person-years in each higher CEA band, and then subtracting these “expected” deaths from actual deaths observed in each higher CEA band.

study, had complete laboratory results available, and had a CEA of 10 ng/mL or higher.

The following testing thresholds were used to identify applicants whose lab results might have led to an adverse action on a life insurance application in the absence of CEA testing or other adverse information: GGT

>100 U/L, ALT or AST >70 U/L, alkaline phosphatase >160 U/L, albumin <3.4 g/dL, PSA 10 ng/mL or higher, total cholesterol <140 mg/dL.

Six of the 48 deaths had 1 additional abnormal laboratory result besides elevated CEA, and 6 more had 2 or 3 abnormal

**Table 4.** Smokers<sup>1</sup> Only: Deaths Per Person-Year and Ratios for All Durations Combined, by Age Group<sup>2</sup>

Age Group (years)	CEA (ng/mL)	Deaths	Population At Risk	Person-Years	Deaths/Person-Years	Ratio <sup>3</sup> (%)	95% CI <sup>4</sup> (%)	Excess Deaths <sup>5</sup>
50 to 59	<5	103	7954	22,257	0.0046	100	76–131	
	5 to 9.9	13	1032	2334	0.0056	120	68–214	2.2
	10+	8	148	299	0.0268	578	282–1187	6.6
60 to 69	<5	64	2598	6850	0.0093	100	71–141	
	5 to 9.9	17	426	863	0.0197	211	124–360	8.9
	10+	8	59	104	0.0769	823	395–1717	7.0
70+	<5	27	518	1328	0.0203	100	59–170	
	5 to 9.9	4	93	180	0.0222	109	38–312	0.3
	10+	2	15	36	0.0556	273	65–1149	1.3

<sup>1</sup> Urine cotinine ≥200 ng/mL<sup>2</sup> Rounding of numbers may cause some calculations to appear erroneous.<sup>3</sup> Ratio as a percentage is the deaths per person-year in the target band divided by the deaths per person-year in the <5 ng/mL band, multiplied by 100.<sup>4</sup> See references 19 and 20.<sup>5</sup> Derived by multiplying deaths/person-year for the reference group by the person-years in each higher CEA band, and then subtracting these “expected” deaths from actual deaths observed in each higher CEA band.

laboratory results. This means that out of 48 applicants with CEA results of 10 ng/mL or above, 12 (25%) were possibly identifiable as having an elevated risk of mortality from a test other than CEA. GGT was the test that was most frequently elevated in this group.

## DISCUSSION

CRL's life insurance clients have reported a disproportionate number of early cancer deaths relative to early deaths (or benefit claims in the case of critical illness insurance) from cardiovascular causes. This can be expected as malignancy has been more difficult to detect than cardiovascular disease by the underwriting process at the time of application.

Our results from this self-selected population applying for life insurance demonstrate that applicants with elevated CEA results carry a high mortality risk relative to those with CEA <5 ng/mL; the absolute risk increases with age though the relative risk decreases. The mortality for applicants with CEA results of 10+ ng/mL and over is very high when compared to mortality for CEA results below 5 ng/mL; almost all of the excess deaths are likely related to cancer.

The downside of using the more predictive CEA threshold of 10 ng/mL as compared to 5 ng/mL is that we will miss about half of all excess deaths associated with the CEA results above 5 ng/mL. CEA values of 10+ ng/mL are much more predictive, but values between 5 and 9.9 ng/mL are more common.

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 from this study. What we can do is observe from Tables 3 and 4 that in the 50–59 age group, identifying insurance applicants with CEA 10+ ng/mL could have avoided 5.0% of early deaths; in the 60–69 age group, 5.3% of early deaths; and in the 70+ age group, 3.2% of early deaths. Using 10 ng/mL as a cut-off would have excluded only 0.4% of all

applicants from further consideration of an offer of insurance. From an insurance perspective (and increasingly from a clinical one), the important question is not who has cancer but rather, who will die from it. For life insurers, predicting the likelihood of early mortality is the primary purpose of laboratory testing of applicants.

Based on the thresholds for abnormal results that we assigned to other laboratory tests, 25% of the deaths associated with a CEA of 10 ng/mL or higher would have been identified without the test for CEA. Since one half of the elevations of these other laboratory tests were isolated, and many test results were near the cut-off values (data not shown), this estimate of the efficacy of other testing may be generous. No medical history was available for the applicants in this study, so it is unknown if any of the deaths in the elevated CEA result groups would have been identified through their medical records or other sources of information. The authors believe that few persons with a documented history of high risk cancer apply for life insurance. If such a history was present, the pretest likelihood for cancer would be higher, and a lower cut-off value for CEA might be appropriate. High proportions of smokers were found within the elevated CEA bands, but smoking status alone is insufficient to identify individuals at risk.

Smokers are overrepresented at higher CEA levels. This appears to be caused in equal amounts by a direct effect of smoking on CEA levels which is reversible, and because there is more malignancy in smokers. Because mortality rates are higher in smokers even at low CEA levels and because smoking increases CEA directly, the ratios between mortality in the lowest CEA group vs higher CEA groups among smokers are reduced relative to nonsmokers.

If CEA were to be used as a screen for life insurance applicants and the threshold for adverse underwriting action on the application were to be set higher than 5 ng/mL (where we have documented increased

relative mortality), a question arises as to the handling of those with CEA results between 5 ng/mL and that new threshold. Insurance companies already have their own policies regarding notification of applicants regarding laboratory values that fall outside the statistical "normal range," but are not considered to be of sufficient concern for an adverse underwriting action based on that test result alone.

The difference here is the more obvious association with cancer, potentially leading to additional applicant concern and clinical evaluation. Since there is no evidence from clinical studies that such knowledge or further evaluation is of value to the applicant, insurers may wish to use their usual notification practice or develop special notification. An alternative is to have results below the action cut-off reported as a qualitative result instead of a number. However, there is potential value from CEA results between 5 and 9.9 ng/mL to the insurer, in prompting focused review of the application.

Our approach has certain limitations. Only mortality rather than actual presence or absence of disease could be ascertained. In addition, the Social Security Master Death Index does not immediately capture all deaths. Few deaths among those receiving Social Security benefits are missed, though inclusion in the database may be delayed. Reporting of other deaths (younger persons) is voluntary but is encouraged and becoming more complete. Fortunately, incomplete reporting should impact all CEA bands equally. Because of this, the deaths per person-year may be understated (especially in the 50- to 59-year-old age group) but the ratios between CEA bands and proportion of excess deaths should be close to the true value for the population.

## CONCLUSIONS

This all-cause mortality study provides the information needed for objective decision-

making on the part of a life insurer regarding the possible use of CEA as a screening tool. It also provides a reference for evaluating CEA results from other sources.

CEA levels of 10+ ng/mL in this population of life insurance applicants were associated with high absolute and relative mortality over the first 4 years after testing. CEA testing beginning at age 50 years for life insurance applicants would prevent 4.6% of early mortality at this threshold. Other laboratory tests miss at least 75% of this early mortality. CEA test results in a range of 5 to 9.9 ng/mL are associated with lower relative mortality.

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