

ReFlections

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FROM THE EDITORS

Another year has passed and we welcome you to the January 2017 edition of ReFlections – RGA's global medical newsletter. It has truly been our pleasure to see so many of you recently at various conferences and client events.

With this edition of ReFlections we introduce two new authors as well as a new feature – the *Brief Report* – in which the author prepares a short article on a focused topic.

Dr. Lisa Duckett, Vice President and Medical Director, provides a detailed update on Alzheimer's disease and mild cognitive impairment with a focus on early diagnosis and use of biomarkers, as well as discussing new treatment strategies.

Kyle Nobbe, Assistant Actuary, Global Research and Development, introduces us to his original research into the observations and correlations of seasonal mortality variations. His conclusions are insightful and practical for all insurers.

Dr. Sharylee Barnes, Vice President and Medical Director, inaugurates our *Brief Report* feature with an excellent summary of recent updates from various endocrine societies on the interpretation of thyroid sonogram imaging results. Given the frequency of these reports in attending physician statements, this is essential reading.

ReCite continues to bring our readers recent and relevant highlights from the medical literature, and the Longer Life Foundation report heralds two substantial milestones achieved over the past year – the foundation's 100th peer-reviewed article and 100th grant.

We hope you enjoy this edition of ReFlections and wish all of our readers well in the New Year.

Thank you,

Phil, Dan, and Neil

ALZHEIMER'S: AN UPDATE ON AN OLD DISEASE

Abstract

Alzheimer's disease (AD) was first described more than 100 years ago. It was and still is characterized by the presence of amyloid plaques and neurofibrillary tangles (NFTs). These pathologic and histologic changes continue to define the disease and are the focus for current research. The brain changes can be correlated with biomarkers, imaging, and cognitive testing. Mild cognitive impairment (MCI) may represent an important step toward the development of dementia but may also represent a nonpathologic state. The long prodromal period before clinically detectable declines in cognition offer opportunities for intervention on multiple levels. The goal of future therapies is to decrease the accumulation of toxic proteins in the brain and prevent decline in cognitive function.

Given the pace at which the world's population is aging, this complex and heterogeneous disease may well be the next worldwide epidemic. Alzheimer's disease and MCI present serious challenges to the insurance industry. Knowledge of progression factors creates opportunities for risk stratification. A full understanding of potential future epidemiologic and treatment trends should form the basis for insurer actuarial modeling and product development planning.

Introduction

Although Alzheimer's disease (AD) was first described more than a century ago, its complexity and heterogeneity have made early diagnosis and treatment elusive, and its pathogenesis remains uncertain. Research-based understanding of the disease, specifically the interplay between beta-amyloid, phosphorylated tau, and small vessel disease of the brain, biomarkers and imaging techniques that aid in diagnosis of dementia, and MCI definition and risk factors for disease will all be discussed. In addition, potential areas for disease modification through medications will be covered.

Aging Population Worldwide Translates Into Potential Dementia Epidemic

AD is the most common form of dementia, and epidemiologists predict it will be "the" epidemic of the 21st century. For asymptomatic individuals, the lifetime risk of developing AD at age 65 is 10.5%¹. The world's population is expanding in such a way that the highest risk cohort for developing the disease is also going to be the fastest-growing segment of the world's population over the next 30 years. By 2050, the U.S. Census Bureau is predicting there will be 88 million Americans over age 65. The world's over-65 population is projected to swell to 1.6 billion by then, as well. Additionally, Asian and South American countries will all experience a quadrupling of individuals over 80 years of age².

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AD's Long Preclinical Course

Alois Alzheimer, M.D., described the clinical symptoms and histologic changes in the brain of a woman with presenile dementia in 1906. The histologic features Dr. Alzheimer identified in the autopsy – amyloid plaques and neurofibrillary tangles – remain the defining features of the disease and the focus of AD research³.

The specific protein responsible for the formation of amyloid plaques was identified 30 years ago⁴ and is the product of the cleavage of the amyloid precursor protein (APP), which is tethered to the cell membrane for reasons still not clear. Once APP is cleaved into discrete fragments by secretases, the beta amyloid protein is cut at both ends of the molecule and is released to the space outside the neuron. It then begins to aggregate with other beta-amyloid fragments, forming oligomers, which are believed to be the core components of the amyloid plaques. Over time, other proteins are added to the misfolded oligomers and conglomerate to form insoluble plaques⁴. Accumulation of amyloid plaques may precede clinical symptoms by 20 years⁵.

The second histologic feature, the neurofibrillary tangle, is composed of tau protein and is a component of the microtubular system in neurons. The function of tau protein is to provide structural stability for axons and transport nutrients and neurotransmitter-containing vesicles, from the neuronal cell body to the axon⁴. The disruption of this microtubular system begins a destructive process that is characterized by accumulation of hyper-phosphorylated tau and the aggregation of tau fibrils, which eventually forms tangles within the cell that lead to synaptic dysfunction. Synaptic dysfunction and loss are the findings most closely associated with cognitive decline in brains of those with dementia^{6, 7}. This stage of the disease is characterized by progressive cognitive decline that correlates with a clinical diagnosis of MCI transitioning to dementia⁷.

**Epidemiologists
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Diagnosis of MCI

In 2011, the National Institute on Aging and the Alzheimer's Association convened a working group to revise diagnostic criteria for MCI due to AD. The working group examined clinical, cognitive, and functional criteria to improve the accuracy of the diagnosis and project the risk of future AD. Using MCI clinical criteria along with cognitive screening tools, biomarkers, and imaging studies made it easier to identify the points of transition from AD's asymptomatic to symptomatic phase.

Early recognition of the pre-dementia state is relevant for therapeutic intervention and to benchmark disease progression⁸. MCI is characterized by a change in cognition noted by the patient or other reliable source and is diagnosed by a measureable decline from prior function in one or more cognitive domains. The most important of these is memory loss, as loss of episodic memory correlates with risk for progression to AD⁸.

Cognitive assessment is vital to the diagnosis of MCI. Tests that detect deficits in the ability to acquire new information as well as retention are able to detect decrement in episodic memory include: word list learning test, Logical Memory I and II, the Wechsler Memory Scale, and the Visual Reproduction subsets of the Wechsler Memory Scale I and II. Additional assessment of all cognitive domains is important, since not all MCI patients have decrements in episodic memory⁸. MCI patients will typically score 1 to 1.5 standard deviations below their age- and education-matched peers⁸. To fulfill the diagnosis of MCI, other causes for the cognitive impairment must also be sought, which can include vascular, traumatic, and toxic causes. These causes must be evaluated with the goal of determining the likelihood of neurodegenerative disease with characteristics consistent with AD.



Assessing the Risk for Progression of MCI Via Biomarkers

Dementia may have a very long prodromal stage with normal cognition. Researchers hypothesize that amyloid is deposited in the brain during AD's asymptomatic period⁵. Detecting this process early in the prodromal period may be an opportunity for future therapeutic intervention as well as differentiating risks for insurance products.

As MCI develops, pathologic changes in the brain are characterized by the deposits of tau protein, concomitant loss of synaptic function, and degenerating neurons with abundant NFTs⁵. Over time, the loss of neuronal integrity leads to progressive cognitive decline.

Key findings indicating AD's progression include: predominance of amnesic or episodic memory impairment on cognitive screening tests paired with lower overall memory scores, abnormal imaging studies, positive biomarkers, and testing positive for the gene variant ApoE₄. Some or all of these variables could form the basis for a risk scoring system predicting low to high likelihood that MCI might progress to AD.

Fluid biomarkers in current use include cerebrospinal fluid beta-amyloid 42 (CSF₄₂), which reflects the deposition of amyloid in the brain, and CSF tau/ phosphorylated tau, which reflects neuronal injury following amyloid deposition. Positive results on tests for both biomarkers confers the greatest likelihood that MCI changes are due to AD. One but not both markers positive confers an intermediate likelihood, and low likelihood of progression to AD would encompass discrepant and/or ambiguous results. Negative biomarker results have a negative predictive value, which may be useful as well⁸.

Imaging studies may substantiate the risk further if they are concordant with the fluid biomarker results. Imaging studies assess amyloid deposition in the brain and quantify the extent of atrophy present in the brain. PET scans that use one of the recently approved amyloid binding agents – florbetapir F-18 (AMYVID), flutemetamol F-18 (Vizamyl), or florbetaben F-18 (Neuraceq) – detect brain amyloid deposition. A volumetric MRI can quantify volume declines in the hippocampus and related regions, making this test a good marker for AD¹³. The results of MCI brains studied demonstrate substantial

volume loss in the hippocampal region: approximately 50% reduction in volume compared to control subjects without known MCI¹³.

The detection of decreased glucose uptake during FDG-PET scanning is another method for detecting the presence of significant neuronal loss. The characteristic areas of the brain that are the most affected are the temporal and parietal lobes. A March 2016 article reported a sensitivity of 94% and a specificity of 73%. This test can also correctly predict a progressive course of dementia with 91% sensitivity and a non-progressive course with 75% specificity^{14,15}. Combining biomarker results with imaging scans, cognitive testing, and clinical course of symptoms may very accurately predict the possible development of AD⁸.



Biomarker Limitations

Many studies have used biomarkers to predict progression of MCI to AD. However, due to the newness of the technology, there are limitations to the use of biomarkers. It is important to note that there is a lack of standardization between labs and thresholds for significance. Controversy exists on how to use the biomarkers and who to evaluate with them. The tests are expensive and may be inconsistent or misleading. Comparisons for accuracy have not been evaluated in multivariate studies. Limited studies have looked at combinations of biomarkers and interpretation of results for multiple biomarkers – particularly if there are discrepant findings. Furthermore, the biomarkers are not necessarily specific for AD and can be present in other neurodegenerative diseases⁸.

Small Vessel Disease Substrate for Neuronal Degeneration and Cognitive Impairment

Inadequate clearance of amyloid plaques from the brain might be one of the reasons beta-amyloid is found in abundance in neurodegenerative diseases. Researchers are studying the association between vascular pathology and the development of cognitive decline. Atherosclerosis and amyloid angiopathy are the leading causes of small vessel disease in the brain⁹. Lacunae and white matter lesions are ischemic events that are commonly visualized on neuroimaging; however, less commonly seen are hemorrhagic lesions of blood vessels manifested by cranial microbleeds. Such microbleeds may explain why cardiac risk factors as well as amyloid deposition are important in the development of chronic degenerative brain diseases⁹. The atherosclerotic changes that occur in blood vessels with ischemic events are associated with cardiac risk factors: hypertension, smoking, and diabetes. The pathogenesis of hemorrhagic events that occurs in small vessel is related to beta-amyloid accumulation in the vessel wall, vascular dysfunction, with resultant inflammation and vessel wall weakness to produce hemorrhages⁹. Both vascular changes, ischemic and hemorrhagic, appear to be related to decreased clearance of toxic amyloid protein, local ischemia, and ultimately cognitive decline.



To test the hypothesis that there may be a relationship between the number of microbleeds and cognitive dysfunction, the Rotterdam study, a longitudinal prospective population-based study, evaluated individuals for both parenchymal and cognitive changes over time. The study

concluded that a high microbleed count of >4 is associated with cognitive decline on serial testing and increases the risk of dementia. The authors of the study remarked that the mechanisms by which microbleeds can influence cognitive function remain speculative; however, it appears that microbleeds may be a biomarker for advanced vascular and neurodegenerative damage that then leads to progressive cognitive decline. Whether this is related to vascular disease that causes local ischemic damage to brain tissue or hypertensive disease that causes decreased clearance of amyloid is uncertain⁹.

Genetics of AD

Presence of genetic mutations in both the amyloid precursor protein (APP) and the presenilin 1 and 2 mutations may develop early-onset disease at 65 years of age or younger with a variable time course from MCI to dementia. ApoE₄ allele homozygotes also are at risk for development of late-onset dementia and the genetic phenotype has been used to stratify risk for the development of AD when MCI is present¹⁰.

Therapeutic Interventions for Disease Modification

Drug development to modify the course of AD has been slow. The last FDA-approved drug for moderate to severe AD, memantine, was released in 2003¹¹. At present, there are no drugs approved for treatment of MCI, and none of the approved medications for AD offers any clear mortality benefit.

Researchers are developing medications aimed at modifying steps in amyloid processing to eliminate the production and deposition of amyloid. Phase 3 trials are in progress to test the efficacy of inhibition of beta secretase (BACE), which cleaves amyloid into the smaller molecules with potential to become oligomers of amyloid. Another medication currently in clinical trials that is designed to reduce amyloid production is solanezumab, a monoclonal antibody. This medication binds amyloid protein to reduce the formation of plaques and assists with clearance of amyloid protein. Some encouraging results in mild AD have prompted further studies¹².

Reducing tau production is another potential method for disease modification. The AADvac1 vaccine, also currently

in clinical trials, targets the abnormal tau protein that destabilizes microtubules. Another anti-tau medication in clinical trials, Epothilone D, is designed to stabilize the microtubules in the neurons to decrease the propensity for the formation of neurofibrillary tangles in animal models.

A novel anti-inflammatory drug, CSP-1103, acts to reduce inflammation in the brain associated with the deposition of amyloid protein. The anti-inflammatory activity of this drug, currently in clinical trials as well, is directed against the microglial cells in the brain.

Additional trials are under way to determine the effect of neuroprotective agents such as insulin. Insulin activity is reduced in the brains of individuals with AD, and restoration of normal insulin levels seems to stabilize and improve cognition in those with amnesic mild cognitive impairment (aMCI) and those with mild to moderate AD. Nasally-administered insulin is used here because it is quickly absorbed into the central nervous system and may not affect serum glucose or insulin levels¹³. Results of the trials are encouraging; however, they are in the very early stage of research¹².

Summary

Dementia is likely to increase tremendously worldwide over the next 30 years due to the globe's rapidly aging population. Understanding of the disease is growing, and it is apparent it has a long preclinical stage before cognitive decline actually occurs.

Abnormal accumulations of amyloid and tau proteins interact to cause AD. Research has advanced the diagnostic accuracy of MCI and identified risk factors for disease progression.

Vascular pathology is also important in neurocognitive disease development and substantiates the importance of vascular health in disease prevention. Vascular risk factor modification, particularly treatment of hypertension and smoking cessation, appears to play an important role for initiation of neurodegenerative processes that occur in blood vessels to include ischemic and hemorrhagic changes.

Medications have been slow to develop and few are in trials to determine efficacy. Some have shown progress, but the last time the FDA approved a drug for AD was in 2003 and no drugs are currently available for MCI. Multiple areas of intervention are plausible for reduction of amyloid and tau proteins in the brain and are being studied, but few medications in the more immediate production pipeline are promising.

Insurers will need to remain vigilant and informed with regard to the epidemiology, pathophysiology, and impact of potential treatment trends for neurocognitive risks. Hopefully, with improved predictive and diagnostic testing, risk stratification and claims experience can be refined over time. 

**Medications have
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RGa MEDICAL TEAM UPDATE

RGa welcomes the following doctors to our global network of medical officers:

- Dr. Adela Osman, MBBCH, Chief Medical Research Officer of South Africa (General Practice), Johannesburg, South Africa
- Dr. Shivani Sarwal, Executive Director, Underwriting (Insurance Medicine), Kuala Lumpur, Malaysia
- Dr. Elyssa Del Valle, Vice President and Medical Director (Internal Medicine), St. Louis, Missouri (U.S.)

SEASONALITY OF MORTALITY

Abstract

The first few months of 2015 exhibited exceptionally high mortality experience in several countries, including the U.S., Japan, and the U.K. This experience was noted by insurance investment analysts, and research was carried out during the first half of 2015 to further develop an understanding of the underlying causes. The new research built on the 2012 seasonality research conducted by RGA¹. The 2012 study had highlighted how a variety of demographic, socioeconomic, and geographic factors influence the degree and direction of seasonal mortality. The 2015 research focused on global seasonality, and how flu and pneumonia (F&P) mortality correlates with other causes of death. These findings were used to monitor the 2016 season, which turned out to be less severe than the 2014-15 season, when flu vaccine effectiveness was especially poor. This article focuses on understanding how seasonality varies by country and region, and how F&P mortality correlates with other causes of death.

Introduction

Seasonality refers to a trend pattern that repeats every 12 months. In insurance, knowledge of seasonality's impact on mortality is not new. Life insurers sometimes experience poor financial results stemming from large fluctuations of claims in colder months. The ability to understand the main drivers of seasonal mortality, and therefore why certain years have higher seasonal mortality than expected, can be vital for insurer reporting and planning.

Although higher mortality is expected in winter months, the magnitude of seasonality can vary by year and is unpredictable. One method of assessing the degree of seasonality by year is via the winter-to-summer ratio. This ratio is defined as shown below.

$$\text{Winter-to-Summer Ratio} = \frac{\text{Total \# of deaths Dec, Jan, \& Feb}}{\text{Total \# of deaths Jun, Jul, \& Aug}}$$

where December deaths are from the prior year.

Note that the ratio's values would be inverted for southern hemisphere countries (i.e., the winter months would be defined as June, July and August, and the summer months as December, January and February).

While all years demonstrate increased seasonal mortality, Figure 1 also shows that some years have had exceptionally high seasonal mortality.

ABOUT THE AUTHOR

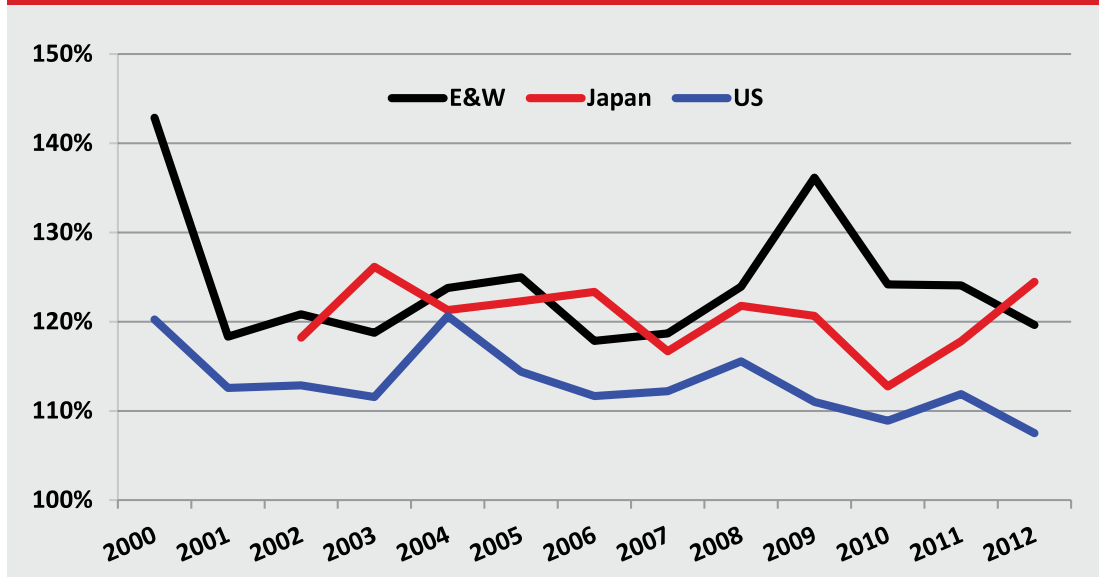


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Kyle Nobbe is a Fellow of the Society of Actuaries (FSA) and an assistant actuary in RGA's Global Research and Development department. He works on various research initiatives around the globe ranging from life and morbidity studies to future data solutions for the insurance industry.

Figure 1: 2000-2012 Winter-to-Summer Death Ratios for the U.S., Japan, England & Wales



Source: Centers for Disease Control (U.S.), Japan Government Statistics, E&W, ONS, RGA

Global Seasonality

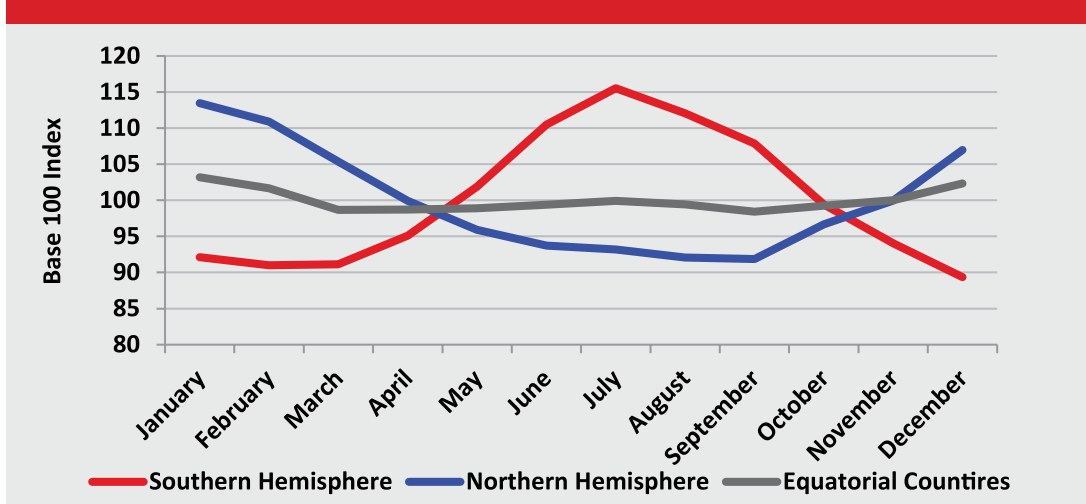
Geographic location is one of the most important drivers of the degree and direction of seasonal mortality. A company's distribution of business by location could have a significant impact on their exposure to seasonality.

In Figure 2, monthly mortality data from the United Nations² was used to create a Base 100 Index. The index's purpose was to examine the differences in seasonal mortality among countries in the northern hemisphere, the southern hemisphere, and near the equator. (For this chart, the equatorial region was defined as limited to countries located within latitudes 20 degrees north and south of the equator.)

Not surprisingly the southern hemisphere's seasonality curve mirrors that of the northern hemisphere. The seasonality curve is less dramatic for equatorial countries, as climate differences by season in this region are far less pronounced.

A company's
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exposure to seasonality.

Figure 2: 2000-2012 Base 100 Index by Hemispheric Region

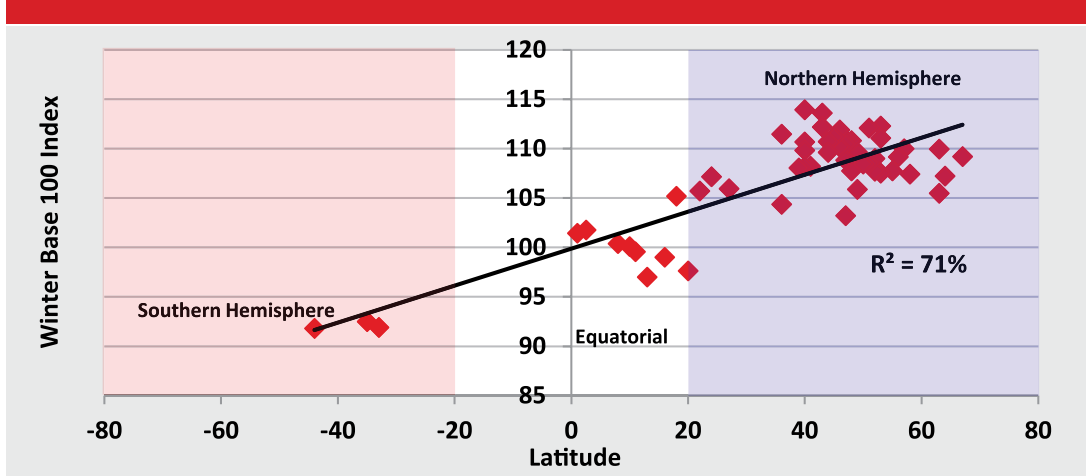


Source: United Nations, RGA

The Base 100 Index explains positive and negative variances of death counts across years relative to a trending average. Months with an index of 110, for example, have 10% higher mortality than the monthly average for that time period, whereas months with an index of 90 would have mortality that is 10% lower than the average trend.

An additional assessment of seasonal variation by location explores the impact of distance from the equator. Figure 3 compares the average Base 100 Index for the northern hemisphere's winter months of more than 50 of the world's most populated countries to their median geographic latitude. Plotting the winter Base 100 Index against latitude yields the strong correlation shown below. If the southern hemisphere's winter months were used for the chart, the same correlation would hold but with a negative sloping trend line. (Note that extreme northern countries, defined as those with latitudes around 70 degrees, appear to experience less seasonality relative to most countries at latitudes between 40 and 50 degrees.)

Figure 3: 2000-2012 Northern Hemisphere Winter Base 100 Index for Countries by Latitude

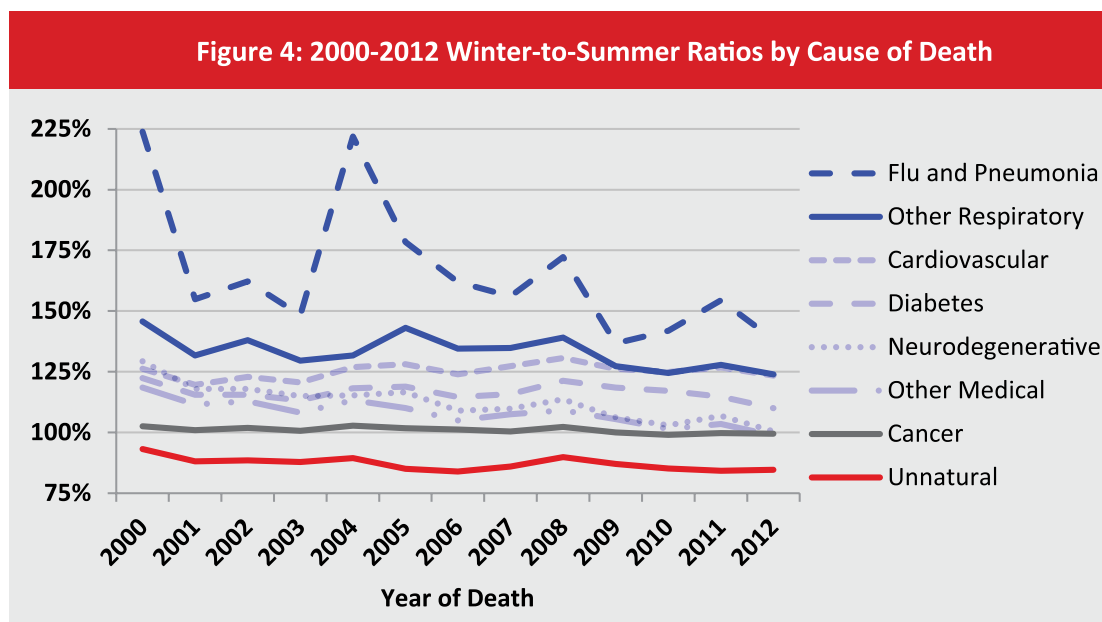


Source: United Nations, RGA

Flu and Pneumonia Seasonal Mortality and Other Causes of Death

Flu and pneumonia (F&P) mortality is the most winter-specific seasonal cause of death, followed by all other respiratory causes. Unnatural deaths such as suicide, accidents, and homicides are summer seasonal; i.e., these deaths tend to trend higher in the summer. The medical causes of death that are grouped broadly in Figure 4 are also winter seasonal, albeit not as significant as respiratory causes, with the exception of cancer.

Figure 4 demonstrates this by charting the winter-to-summer ratios for different causes of death in the U.S.



Source: Centers for Disease Control (U.S.), RGA

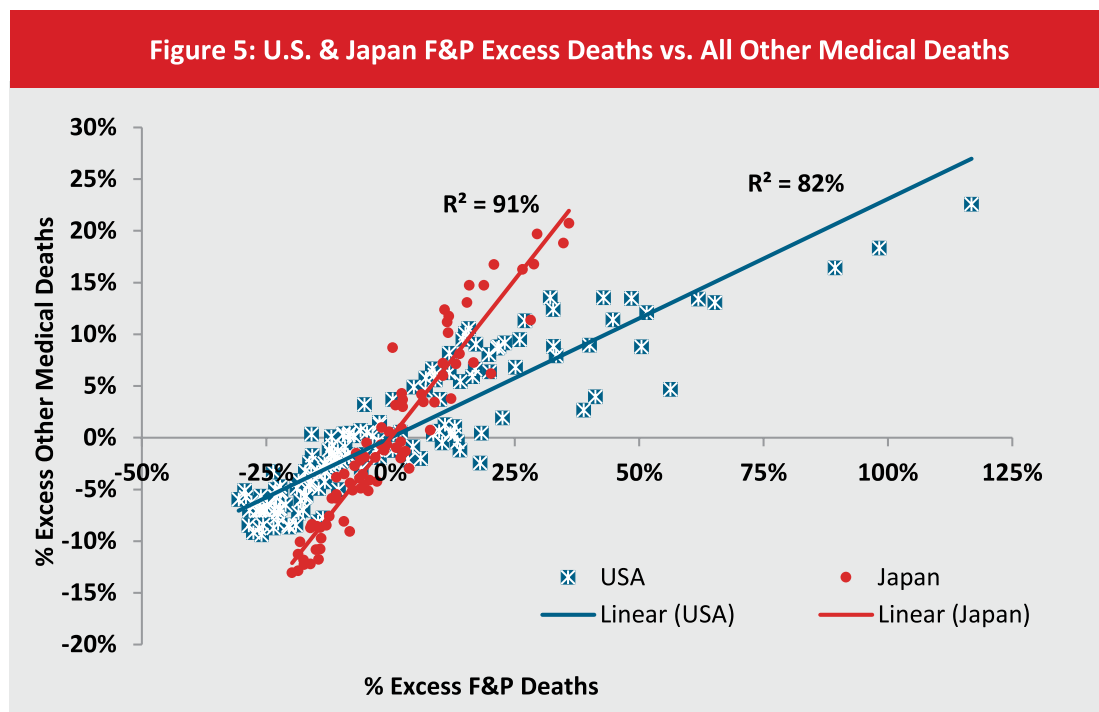
Figure 4 also sets the stage for identifying correlations and causations. The data suggests that flu and pneumonia are the most seasonal causes of mortality. Thus it would be expected that in years with higher than normal F&P incidence, or where in the case of influenza there was poor vaccine match with circulating strain (as was seen in the 2014-2015 season), exceptionally high seasonal mortality could be experienced. Additionally, F&P involves a pro-inflammatory process, and inflammation is a driver in many other diseases, so this may explain seasonal mortality for causes of deaths other than respiratory. This observation is supported by Centers for Disease Control and Prevention (CDC)³ position on individuals at high risk for flu-related complications. The CDC lists asthma, neurological conditions, lung disease, heart disease, diabetes, kidney, liver, blood, and metabolic disorders, obesity, and weakened immune systems (e.g. HIV/AIDs and cancer) as conditions that heighten the risk for flu complications.

The only inconsistency between our data analysis and the CDC's opinion is the conclusion with regard to cancer. Cancer patients, especially the terminally ill, tend not to exhibit seasonal mortality for a number of reasons, such as: more aggressive medical treatment; better nutrition; a strong support system; and increased sensitivity to factors that may prolong survival, such as immunizations and avoidance of crowds in winter⁴.

Figure 5 shows the correlations, or possible causal connections, between F&P mortality and overall winter seasonality for the U.S. and Japan. Using a scatterplot graph, it plots influenza and pneumonia deaths against all other medical deaths and compares the percentage of excess deaths that occur each month. (The percentage of excess deaths for a given month is defined as the additional number of deaths in a month relative to the trending average.)

Figure 5 demonstrates the positive relationship between increasing F&P deaths in the U.S. and increasing all other medical deaths. When fitting a linear trend line to the graph, the goodness-of-fit (i.e., the extent to which observed data match the trend line) is about 82%, signifying a strong correlation. The graph's trend line also shows that all other medical deaths increase by about 20% to 25% of the increase of F&P deaths. For example, if F&P deaths exceed the norm by 40%, then all other medical deaths would exceed their norms by about 16% to 20%.

Figure 5 also shows data for Japan using the same methodology. Results look very similar, except the trend line's goodness-of-fit is much stronger, at 91%. The trend line also implies that all other medical excess deaths increase by about 60% of what the F&P deaths increase. This is a much higher proportion than the U.S., and could be due either to the population density or other demographic characteristics. Lastly, Japan's F&P excess deaths never exceed 35% while the U.S. exceeds 100%, which could mean that Japan's F&P mortality is more controlled. (England and Wales data is not shown on this graph due to the differences in data availability.)



Source: Centers for Disease Control (U.S.), Japan Government Statistics, RGA

Unfortunately, identifying whether F&P mortality is not just correlated with seasonal mortality, but actually causes it, is very difficult to distinguish. Given, however, how significant the correlation is at the different deep-dives of the analysis, some level of causation might exist.

Implications for Insurers

The relationship between F&P mortality and seasonality has potential direct implications for insurance companies. As flu season predictions continue to evolve and improve, insurance companies may eventually be able to better prepare for seasonal as well as potentially adverse experience and financial results. This greater knowledge could also result in an enhanced understanding of how each individual company's seasonality differs, based on their policyholders' exposure to the complications of infectious diseases.

It is also important to understand the relationship between the seasonality of a general population and that of insured lives. For insured lives, the latter is typically much less significant than the former for a variety of reasons, including: 1) age demographics that skew younger for insured lives; 2) the generally higher socioeconomic status of policyholders and their better access to health care; 3) volatility of claim size; and 4) lags in claim reporting¹.

An understanding of seasonality can also be quite valuable when interpreting partial year claims experience analyses. Results are often skewed by external stimuli such as seasonality. Underwriters or medical directors who utilize an experience study to make decisions need to bear such factors in mind.



An understanding of seasonality can be quite valuable when interpreting partial year claims experience analyses.

The most interesting aspect of the implications of seasonality for insurance companies is that there is still much to learn. Currently, forecasting and predicting F&P seasonality are still in their infancy. When forecasts become more accurate, insurance companies will have a new tool to monitor and analyze seasonal claims experience. Eventually there might even be new ways for companies to mitigate seasonal risk to their earnings. This is an area of great interest to insurers, and will undoubtedly receive more attention and research in the future. 

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UPDATE ON THYROID NODULE IMAGING GUIDELINES

In May 2016, The American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE), and the Associazione Medici Endocrinologi (AME) issued the latest update of their Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules¹.

One of the goals of this update was to stratify the risk represented by different ultrasound images of thyroid nodules. Older guidelines did not have the same emphasis on ultrasound patterns, which underwriters are seeing more frequently in attending physician statements^{2, 3, 4}.

The update includes fine needle aspiration (FNA) recommendations as well as five histologic classifications and comprehensive treatment recommendations. The latter two will not be addressed in this brief report. The new update also addresses both the American and British Thyroid Associations ultrasound thyroid nodule classification schemes.

Prevalence of Thyroid Nodules

Large nodules exist in 5% to 8% of the healthy adult population^{6, 8} whereas small nodules (< 10 mm) exist in 50% to 60%^{1, 5}. Only about 2.5% of all thyroid nodules are malignant^{6, 7}.

Patient Characteristics

The presence of any historical or clinical findings can impact the interpretation of the guidelines from the AACE/ACE/AME. Adverse history can include personal or family history of thyroid cancer, multiple endocrine neoplasia (MEN), or personal history of neck irradiation. Clinical findings such as dysphonia, dysphagia, dyspnea, anterior neck pain, nodule enlarging on exam, lymphadenopathy, and presence of hypo- or hyperthyroidism add additional risk consideration^{6, 8}. Age under 14 years or over 70 also increases malignancy potential, as does being male¹.

Guidelines: Malignancy Risk and Recommended FNA Based on Ultrasound Findings^{1, 6, 7, 4, 9}

Thyroid ultrasound results can be divided into favorable and unfavorable features. As the number of unfavorable features increases, so does the risk of malignancy^{1, 6, 9, 10}.

These guidelines are for individuals without adverse histories and clinical features described above in "Patient Characteristics" unless otherwise noted.

Any nodule <5 mm should be monitored and should not be biopsied with FNA regardless of the ultrasound characteristics. Even with the adverse features FNA is not recommended if scintigraphy shows normal function.

Patients with multinodular goiter have the same risk stratification guidelines for their nodules as would a patient with a solitary nodule¹. For multinodular goiter, each nodule is classified and the nodules with the most adverse features should be biopsied. The guidelines support performing FNA on no more than two nodules¹.

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Class 1 Lesion: Low-Risk Malignancy - ~1%

- cysts with fluid component >80%
- isoechoic spongiform nodules, either confluent or with regular halo
- FNA if >20 mm and with adverse patient history features present (described on previous page) or enlarging nodule

Class 2 Lesion: Intermediate Risk Malignancy - ~ 5% to 15%

- not a definite benign appearance
- cystic and some solid components
- slightly hypoechoic, isoechoic, or indeterminate hyperechoic spots
- ovoid to round shape
- margins may be smooth or ill-defined
- intranodular vascularization
- continuous calcified rim
- elevated stiffness at elastography
- FNA if >20 mm

Class 3 Lesion: High-Risk Malignancy - ~50% to 90%

Has at least **one** of the following suspicious features:

- markedly hypoechoic
- spiculated or microlobulated margins
- microcalcifications
- height greater than width
- disruption of a calcified rim
- capsular abutment
- pathologic lymphadenopathy
- FNA if:
 - Nodule >10 mm
 - extension beyond the thyroid
 - pathologic lymph nodes
 - vascular features or mass effect on the jugular vein by the lymph nodes
 - consider FNA if nodule is 5 mm to 10 mm, depending on clinical setting

Managing Ultrasound Results

The principal goal of a thyroid ultrasound is to find or rule out cancer^{1, 8, 5}. If a nodule is found, appropriate clinical follow-up must acknowledge the dangers of over-investigation^{1, 11, 12}, which can include excess radiation, bleeding, surgical complications, anxiety, anesthesia risk, hospital-acquired infections, and scarring. Surgical complications can include vocal cord paralysis (due to nerve damage), hypothyroidism and hypoparathyroidism^{7, 11, 12}.

Underwriting Considerations

Understanding the natural history of lesions found during thyroid imaging and whether or not they are meaningful to prognosis or represent increased mortality or morbidity risk is essential to underwriting.

Thyroid ultrasound reports are frequently encountered in attending physician statements. It is essential for risk assessors to understand the risk associated with findings even if not clearly stated in the report, and from there determine if appropriate follow-up testing has been scheduled or performed. The historical and clinical features of the proposed insured must also be considered in order to interpret ultrasound findings properly. Taking all of this information into consideration should assist in reaching an appropriate underwriting decision. **Rf**



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Longer Life Foundation

An RGA/Washington University Partnership

The Longer Life Foundation partnership between RGA and Washington University in St. Louis is approaching its 20th anniversary of granting seed money to researchers investigating the enhancement of disease prognostication accuracy and the improvement of quantity and quality of life.

Over the years, LLF has provided several benefits to the global life insurance industry. These include access to Washington University's world-class academics engaged in cutting-edge research on human health and topical webcasts by top insurance industry chief medical officers to sponsorship of events and lectures on topics of immediate and long-term interest such as aging, obesity, cancer, cardiovascular disease, infection risk, longevity, and comorbidity. The results of this research ultimately filter to the insurance industry, strengthening product development

Since late 2015, LLF has achieved several important milestones: the publication of the 100th peer-reviewed article generated from LLF-funded research, the disbursement of the 100th research grant, and the complete redesign of our www.longerlife.org website, supported by a dedicated Twitter feed. With peer-reviewed articles now numbering 106, LLF is increasingly being recognized as both recognizing and supporting research that produces medical advances benefiting human health. 

2016 ARTICLES

- 1. High-Protein Intake During Weight Loss Therapy Eliminates the Weight Loss-Induced Improvement in Insulin Action in Obese Menopausal Women**
Smith GI, Yoshino J, Kelly SC, Reeds DN, Okunade A, Patterson BW, Klein S (LLF grantee), Mittendorfer B. (LLF grantee)
Cell Reports, Oct. 11, 2016
[http://www.cell.com/cell-reports/abstract/S2211-1247\(16\)31286-4?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2211124716312864%3Fshowall%3Dtrue](http://www.cell.com/cell-reports/abstract/S2211-1247(16)31286-4?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2211124716312864%3Fshowall%3Dtrue)
- 2. Predicting All-Cause Mortality From Basic Physiology in the Framingham Heart Study**
Zhang WB, Pincus Z (LLF grantee)
Aging Cell, Feb. 15, 2016
<https://www.ncbi.nlm.nih.gov/pubmed/26446764>
- 3. Effects of Moderate and Subsequent Progressive Weight Loss on Metabolic Function and Adipose Tissue Biology in Humans with Obesity**
Magkos F, Fraterrigo G, Yoshino J, Luecking C, Kirbach K, Kelly SC, de Las Fuentes L, He S, Okunade AL, Patterson BW, Klein S (LLF grantee)
Cell Metabolism, Feb. 22, 2016
<https://www.ncbi.nlm.nih.gov/pubmed/26916363>
- 4. Probiotic Gut Bacteria Enhance Cancer Immunotherapy in a Mouse Model of Melanoma**
Dey N, Ciorba MA (LLF grantee)
Gastroenterology, May 26, 2016
<https://www.ncbi.nlm.nih.gov/pubmed/27238844>
- 5. Long-Term Administration of Nicotinamide Mononucleotide Mitigates Age-Associated Physiological Decline in Mice**
Mills KF, Yoshida KF, Stein LR, Grozio A, Shunsuke K, Sasaki Y, Redpath P, Migaud ME, Apte RS, Uchida K, Yoshino J, Imai SI (LLF grantee)
Cell Metabolism, October 27, 2016

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Intensive vs. Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >75 Years: A Randomized Clinical Trial

Williamson J, et al. JAMA 2016 Jun 28;315(24):2673-82. Doi:10.1001/jama.2016.7050

<https://www.ncbi.nlm.nih.gov/pubmed/27195814>

This study was designed to evaluate the impact of intensive (<120 mm Hg) compared with standard (<140 mmHg) systolic blood pressure treatment targets in persons aged 75 years and older with hypertension without diabetes. Among the 2,636 participants who were followed for a mean period of 3.14 years there was a significantly lower (HR 0.66) risk of cardiovascular events and lower all-cause mortality (HR 0.67) in the intensive treatment group compared with the standard treatment group. Serious adverse events were comparable in both groups. While few insurance applicants are currently greater than 75 years of age, that number may increase in the coming years. From an older-age underwriting point of view, the results of this study demonstrate better outcomes in those with more aggressive blood pressure control.

Atrial Fibrillation and Risks of Cardiovascular Disease, Renal Disease, and Death: Systematic Review and Meta-analysis

Odutayo A, et al. BMJ 2016;354:i4482. Doi: 10.1136/bmj.i4482

<http://www.bmj.com/content/354/bmj.i4482>

The authors performed a meta-analysis of 109 eligible studies incorporating more than 9.5 million subjects. The authors were able to confirm that atrial fibrillation (AF) was associated with increased overall all-cause mortality (RR 1.46) and stroke (RR 2.42). However, the risk did not stop there. They also demonstrated increase relative risk for cardiovascular (CV) mortality (RR 2.03), CV events (RR 1.96), ischemic heart disease (RR 1.61), sudden cardiac death (RR 1.88), heart failure (RR 4.99), chronic kidney disease (RR 1.64), and peripheral arterial disease (RR 1.31). Given that the risks of some of these are near or greater than the risk of stroke the authors concluded that greater efforts are needed to reduce the risk of non-stroke CV outcomes in adults with AF. Insurers should consider all of these complications in detail especially when developing living benefits products which might be offered to individuals with a history of AF.

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

Cardoso F, et al. N Engl J Med 2016 Aug 25;375:717-29. doi: 10.1056/NEJMoa1602253

<http://www.nejm.org/doi/full/10.1056/NEJMoa1602253>

This was a randomized Phase 3 study of women with early stage breast cancer deemed to be at high clinical risk and low genomic risk and vice versa, based upon MammaPrint, the 70-gene signature genomic test. The groups were divided into chemotherapy recipients and those who did not receive chemotherapy. Those with high clinical risk and low genomic risk who did not receive chemotherapy only had a 1.5% lower five-year survival rate without distant metastasis compared with those receiving chemotherapy. Those with low clinical and high genomic risk had no statistically significant outcome difference regardless of whether or not chemotherapy was used. If a 1.5% lower survival rate is acceptable, the authors conclude that for women with high risk clinical disease and low risk MammaPrint results, a 46.2% reduction in the use of chemotherapy in that group could be realized. From an insurance point of view, there would likely be little difference in mortality outcomes, yet potentially significantly less morbidity and health care costs if chemotherapy is not utilized.



Association Between *Helicobacter pylori* Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis

Lee YC, et al. Gastroenterology 2016 May;150:1113-24.doi: 10.1053/j.gastro.2016.01.028.

<https://www.ncbi.nlm.nih.gov/pubmed/26836587>

*A systematic review and meta-analysis were performed to investigate the effects of *Helicobacter pylori* (*H pylori*) eradication on the incidence of gastric cancer. Twenty-four studies were selected, incorporating 48,064 individuals and 340,255 person-years of follow up. After adjusting for baseline cancer incidence, those receiving *H pylori* eradication therapy had a pooled incidence rate ratio of gastric cancer of 0.53 compared with those not receiving this therapy. The authors also reported their data demonstrated that eliminating *H pylori* when atrophic gastritis and intestinal metaplasia had already developed still contributed to a reduction in the gastric cancer incidence. Underwriting *H pylori* and gastric cancer risk does vary somewhat geographically globally. Nonetheless, this paper would suggest that potentially more favorable underwriting action can be taken when it is known or documented that *H pylori* has been eradicated.* 

RECENT WEBCAST



Latest Developments in Polycythemia Vera

Presenter: Stephen T. Oh, M.D. Ph.D.

Assistant Professor, Medicine, Division of Hematology, Washington University School of Medicine in St. Louis

Polycythemia vera (PV) is a chronic stem cell disorder that can cause severe complications and premature death. Dr. Oh, whose research into phenotypes of PV is currently being funded by The Longer Life Foundation, discusses the current state of knowledge of PV.

To arrange to view this webcast and others, please contact jchurchill@rgare.com.



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