Dietary and other Lifestyle Strategies for Active Aging Insights from Okinawa and Hawaii

The Secrets of Long Life

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First... some aging pupus (appetizers)...
or helpful facts about aging
The World`s Oldest Person...EVER!

Jeanne-Louise Calment of France  1875-1997

Age 20 years

Age 116 years
Projected Increases in Global Population by Age

Increase in Centenarians in Okinawa 1975-2010

Centenarian Population (922 persons or 64/100,000 and 87% women)

Okinawa Prefecture: Dept of Health and Welfare 1975-2010
Measuring Heel Bone Density in Nakamura-san from Okinawa aged 100 years old
Age-related Disability & Disease and Lifelong Accumulation of Cellular Damage through Genetic, Environment & Intrinsic Effects

Random Molecular Damage

Healthy Lifestyle

Inflammation

Stress

Environment

Poor Nutrition

Anti-Inflammatory

Healthy Nutrition

Accumulation of Cellular Defects

Conserved Nutrient Signaling Pathways Regulating Longevity

Reduction in calorie intake by restriction of nutrients (glucose, fat, proteins, amino acids)

Nutrients promote growth or growth factors either directly (yeast) or by activating a cell membrane receptor in a variety of cells.

Inhibition of nutrient-sensing pathways (colored dashed lines):
- TOR signaling pathway (green)
- RAS-AC-PKA (purple)
- Insulin/Igf-like signaling (blue)

In the presence of nutrients, these conserved biochemical signaling pathways are activated.

Yeast
- Dietary restriction
- Glucose, amino acids
- TOR is a protein kinase that is part of the TOR signaling pathway.
- RIM15 (PKA)
- Sch9 (SKK)
- GIS1, MSN2/4, HIF-1, DAF-16, and FOXO are anti-aging transcription factors that are activated by dietary restriction and regulate the expression of enzymes and proteins involved in protective and metabolic activities that increase life span (solid red arrows).

Worms
- Dietary restriction
- Ins/IGF-1-like
- DAF-2
- AGE-1 (PI3K)
- RSK-1 (SKK)
- AKT

Flies
- Dietary restriction
- Ins/IGF-1-like
- DAF-2
- AKT

Mammals
- Dietary restriction
- IGF-1
- GH

Cell membrane

Cytosol

Nuclear membrane

DNA

Antioxidant enzyme SOD, catalase (except flies), HSPs (except mammals), autophagy, translation, ER stress, other?

Yeast is a simple and unicellular organism with a short life span, facilitating the study of aging mechanisms. Several pro-aging genes identified in yeast promote aging in mammals (SKK, AC, PKA).

In worms, the role of genes in different cell types in aging and age-dependent loss of function can be investigated. The pro-aging insulin/IGF-1-like genes were first identified in worms.

Studies of flies have begun to reveal how different genes, cell types, and factors affect life span. Mutants help to determine the tissue-specific effects of particular genes on aging.

Reduced activity of the pro-aging genes identified in yeast, worms, and flies seems to mediate some of the anti-aging effects of dietary restriction in mammals. Incidence of chronic diseases is lowered.

Fontana L et al. Science 2010
Caloric Restriction: Most Powerful Anti-Aging Intervention

Calorie Restriction (CR) Reduces CVD & Cancer Mortality by 50% in Non-human Primates

Colman et al. 2009 Science 325;5937:201-204
Introduction

- The oldest old are the fastest growing population in the world.
- Utilization of health care and clinical resources is skewed toward this group.
- Identification of factors that contribute toward healthy survival is important.
- In 1987, Rowe and Kahn introduced a phenotype they described as “successful” aging. It included three factors:
  
  Avoidance of disease/disability <> Maintenance of cognitive capacity <> Active engagement in life

CHALLENGES: lack of quantifiable definition of “successful” aging so it is difficult to study, retrospective studies of aging are more open to bias, but few studies have prospectively collected data for the study of aging (e.g. less than 5% of 500 studies in using Rowe/Khan criteria (Depp and Jeste, 2006).

Questions we have focused on in our work:

- What is “healthy aging” from a biomedical and clinical perspective (i.e. how do we measure the Rowe and Khan phenotype)?
- What is the prevalence at older ages?
- What are the modifiable risk/protective factors and implications for healthy aging?
Hypotheses

- *Healthy aging* can be better quantified for use in biomedical studies
- Protective environmental (non-genetic) and genetic factors exist that have major effects for our odds of aging in a healthy way
- These factors may be more prevalent and easily identified in populations with large numbers of “healthy agers” (e.g. Okinawa, Hawaii, etc.)
- Such factors facilitate decreased mortality from major age-related diseases and enhance resilience to functional loss (physical/cognitive disability)
- The factors may be useful in clinical settings for *enhancing odds* of healthy aging
General Methods

- We have taken a clinical epidemiological approach using mainly cross-sectional “discovery” studies and cohort-based “replication” studies.

- Our main “discovery” population is located in the longest-lived prefecture (state) of the longest-lived country (Okinawa, Japan), we utilize national and prefectural datasets and we collect our own data in the field from centenarians and younger-old “controls.”

- We have several cohort studies but our principal “replication” population is the Honolulu Heart Program cohort study (HHP), we validate putative risk/protective factors in a comprehensive longitudinal dataset with five decades of epidemiological data (includes demographic, biological, behavioral/lifestyle, psychological, social data).

**Strengths:** large number of centenarians in our discovery population, large replication cohort (n>8,000) with a large number of biomedical variables, prospectively collected dataset, fairly homogenous populations, excellent follow-up over 40 years.

**Limitations:** our main replication cohort is men only and has only 2 ethnicities (Japanese and Okinawan) which limits generalizability, mainly observational studies (limits inference of cause and effect relationships).
<table>
<thead>
<tr>
<th>Rank</th>
<th>Location</th>
<th>LE</th>
<th>CHD</th>
<th>Cancer</th>
<th>Stroke</th>
<th>All-Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Okinawa</td>
<td>81.2</td>
<td>18</td>
<td>97</td>
<td>35</td>
<td>335</td>
</tr>
<tr>
<td>2</td>
<td>Japan</td>
<td>79.9</td>
<td>22</td>
<td>106</td>
<td>45</td>
<td>364</td>
</tr>
<tr>
<td>3</td>
<td>Hong Kong</td>
<td>79.1</td>
<td>40</td>
<td>126</td>
<td>40</td>
<td>393</td>
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<tr>
<td>4</td>
<td>Sweden</td>
<td>79.0</td>
<td>102</td>
<td>108</td>
<td>38</td>
<td>435</td>
</tr>
<tr>
<td>8</td>
<td>Italy</td>
<td>78.3</td>
<td>55</td>
<td>135</td>
<td>49</td>
<td>459</td>
</tr>
<tr>
<td>10</td>
<td>Greece</td>
<td>78.1</td>
<td>55</td>
<td>109</td>
<td>70</td>
<td>449</td>
</tr>
<tr>
<td>18</td>
<td>USA</td>
<td>76.8</td>
<td>100</td>
<td>132</td>
<td>28</td>
<td>520</td>
</tr>
</tbody>
</table>

Suzuki et al. Asia Pac J Clin Nutr 2001
Who are among the healthiest agers?

Discovery Population – Okinawa Centenarian Study

- Population-based study (1000+ cases 1975-current)
- Mostly cross-sectional and case-control, some longitudinal studies
- Age validation
- Geriatric exam: past medical history, life history, family history of disease and longevity, health habits, anthropometry, ECG
- Family pedigree
- ADLs, IADLs, psychosocial/cognitive tests
- Blood and saliva
Interesting “Longevity” Phenotype in Older Okinawans—genetic or environmental?

- Less chronic disease
- Higher physical/cognitive function
- Shorter stature
- Lower BMI
- Lower blood sugar
- Lower % T2DM
- Higher HDL
- Low cancer

(Willcox et al. Ann NY Acad Sci 2007)
Discovery Studies (hypothesis generating):
What do the Okinawans do to stay so healthy for so long? What behavioral (diet, smoking, alcohol), psychosocial and other factors might be important and testable?

- Bitter Melon with Tofu
- Nigana Greens
- Mozuku Seaweed
- Tofu with Fish
- Se-Fan: Rice with Vegetables
- Okinawan Sweet Potatoes
Key Features of Traditional Okinawa Diet

1) Low Caloric Density (plant-based, low fat, moderate protein from soy, fish, lean meats)

2) High Nutrient Density (Vitamins A, C, E, potassium, magnesium, folate, and healthy oils)

3) Phyto-nutrient Rich (anti-oxidants, polyphenols, flavonoids, carotenoids mostly from green leafy and yellow root vegetables)

4) Low in Glycemic Load (high quality carbohydrates from staple sweet potato)

5) Anti-inflammatory (CR, antioxidants, polyphenols, flavonoids, omega 3 fatty acids, curcumins)

Centenarian Health Habits:

Few Major Smokers
Centenarian Health Habits

Few Major Drinkers

- No major drinkers among centenarians.
- Majority are never drinkers.
- Fewer men than women are major drinkers.
Replication Cohort

The Hawaii Lifespan Studies I and II
Defining the Healthy Aging Phenotype (I) NIAR01AG027060 and Genotype (II) 2NIAR01AG027060

POPULATION
• 8,006 middle-aged American men of Japanese ancestry from the Honolulu Heart Program, followed since 1965
• > now over 1200 nonagenarians and centenarians

Hawaii LIFESPAN Study I AIMS
• Improve “healthy aging” phenotypes (better quantify)
• Examine (1) environmental and (2) genetic correlates of healthy aging and longevity using mainly regression analyses
• Focus on insulin-signaling pathway genes

Hawaii LIFESPAN Study II AIMS
• Sequence the FOXO3 gene to find “the” variant
• Understand how the gene reduces mortality
• Better understand the “longevity mechanism”
The “Disablement” Process
(a simplified biomedical path toward “unhealthy” aging)

Risk Factors
- e.g. health habits (diet, smoking, physical activity), psychological, social factors

Disease
- e.g. cardiovascular diseases, diabetes, chronic lung diseases

Disability
- e.g. physical and/or cognitive disability
OUTCOME GROUPS

1. Healthy Survivors ("successful" agers)*:
   - survival free of major chronic diseases and physical/ cognitive impairment

2. Survivors:
   - survival with a chronic disease or physical or cognitive disability

3. Non-Survivors:
   - those who did not survive

*Note: Rowe and Khan criteria were operationized as incidence of ANY of six major age-related chronic diseases (coronary artery disease, stroke, cancer, chronic lung disease, Parkinson's disease, diabetes) AND/OR

   Physical and/or Cognitive Disability: physical (can’t walk half-mile), scored <74 on Cognitive Abilities Screening Instrument (Willcox et al, JAMA, 2006)
## Empiric Evidence for Risk Factors that May Alter the Healthy Aging Process over a Four Decade Period

*Willcox et al., JAMA 2006.*

### Aging Phenotype in Late Life (age 85 y in 2005)

<table>
<thead>
<tr>
<th>Characteristics in Mid-life (mean age = 54 y at baseline exam in 1965)</th>
<th>Healthy* (n=655)</th>
<th>Diseased (n=758)</th>
<th>Disabled (n=1038)</th>
<th>Dead (n=3369)</th>
<th>(P) Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight in youth (%)</td>
<td>5.4</td>
<td>6.4</td>
<td>7.5</td>
<td>9.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Grip strength, kg</td>
<td>39.5</td>
<td>39.2</td>
<td>38.8</td>
<td>38.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Blood pressure, mm Hg (Systolic)</td>
<td>127.1</td>
<td>132.3</td>
<td>132.4</td>
<td>136.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>High triglycerides (&gt;150 mg/dl) (%)</td>
<td>56.8</td>
<td>63.5</td>
<td>66.2</td>
<td>67.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Ever smoker (%)</td>
<td>56.4</td>
<td>62.4</td>
<td>62.8</td>
<td>76.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Low education (%) (&lt;12 y)</td>
<td>39.8</td>
<td>48.3</td>
<td>53.5</td>
<td>52.0</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

* Met operationalized Rowe and Khan criteria

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**Willcox et al., JAMA 2006.**
Avoiding Mid-Life Risk Factors Substantially Increases the Probability of Healthy Survival

Note: All participants are Japanese/Okinawan-American men followed from baseline (1965-1968) to the end of 2005.

10 Major Risk factors =

Adapted from Willcox BJ et al., JAMA, 2006.
It’s Never too Late. Late-Life Risk Factors Still Affect Survival (and Healthy Survival)*

*Number of Risk Factors Present in Late Life (mean age 75 years) strongly affects survival.
### FOXO3 Genotype & Longevity

Genetic Factors may also be Important for Healthy Aging

<table>
<thead>
<tr>
<th></th>
<th>*Control Phenotype (n=402)</th>
<th>Longevity Phenotype (n=213)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at Death (y)</td>
<td>78.5</td>
<td>97.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Baseline age (y)</td>
<td>74.6</td>
<td>85.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Waist/Hip Ratio</td>
<td>0.95</td>
<td>0.93</td>
<td>0.0008</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>117.8</td>
<td>109.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin (mIU/L)</td>
<td>25.5</td>
<td>13.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Log Insulin</td>
<td>2.7</td>
<td>2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FOXO3 MAF** [prevalence]</td>
<td>0.26 [44%]</td>
<td>0.37 [62%]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Control phenotype consisted of men in the cohort with average lifespans

**protective allele

Note: No significant association for BMI, Total cholesterol, HDL, Triglycerides

*(Willcox et al. PNAS, 2008)*
Even in *Very Late Life* (Nonagenarians) Survival is Longest in those with Healthy Diet *and* Good Genes (Honolulu Heart Program)

**Diagram:**
- **HDI+/FOXO3+**
- **HDI+/FOXO3-**
- **HDI-/FOXO3+**
- **HDI-/FOXO3-**

**Legend:**
- **HDI** = Healthy Diet Index (ate healthy diet)
- **FOXO3+** indicates prevalence of protective allele
Testing Hypotheses Regarding Diet and Healthy Aging with an Intervention Study in Americans

Q: Does the Traditional Okinawan Diet improve Risk Factors for Healthy Aging?
Vacuum Packed Bento
RESULT:
Okinawa Diet Intervention Achieves “DASH*-like” Blood Pressure Reductions in Americans

1. SBP reduced 2.6 mm Hg (95% CI -4.3, -1.2)
2. DBP reduced 2.1mmHg (95%CI -3.1 -1.0) and 0.3mmHg (95%CI -2.1 0.6).
3. 24h-urinary sodium and body weight reduced (between-group differences ranged from p=0.032 to 0.0002).

*Dietary Approaches to Stop Hypertension (DASH:
Most common physician prescribed diet to lower high blood pressure in the U.S. Todoriki et al J Hypertension 2008
Conclusions

- The Rowe and Khan definition (at least the “avoidance of disease” component) of “successful” aging can be quantified from a biomedical perspective.

- However, in a healthy (at baseline) cohort of middle-aged men, only 11% met the Rowe and Khan criteria by age 85 years, highlighting the odds that eventually most of us will not be “successful” by these criteria.

- Common, potentially modifiable risk/protective factors affect risk for healthy aging over six-fold, which could have important clinical implications.

- Interventions show some of the risk factors for “unhealthy aging” (e.g. blood pressure) were modifiable by dietary intervention. More interventional studies are needed to infer cause-effect relations.

- More study of risk/protective factors and biomarkers is needed in order to better understand biomedical mechanisms for healthier aging.

- An interdisciplinary approach is needed in order to better characterize healthy aging and its public health and societal implications.

- Components other than “avoiding disease” (such as adaptation) will become more important for redefining “successful aging” among the oldest old.
Ushi-san 102 Years Young and Still *Diggin’ Life*

Mahalo!
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