

Thematic Article

Implications from and for food cultures for cardiovascular disease: longevity

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A healthy cardiovascular system, with minimal arteriosclerosis, good endothelial function and well-compensated ventricular function has been observed at advanced ages, and linked to a healthy lifestyle. This has consisted of a plant-based diet, low in salt and fat, with monounsaturates as the principal fat. Other healthy lifestyle factors include regular physical activity (farming and traditional dance) and minimal tobacco use. The associated negative risk factors are low homocysteine, healthy cholesterol profile (Total:HDL ratio less than 3.5) and reasonable blood pressures throughout the life cycle. Hormone-dependent cancers including breast, ovary, prostate and colon and osteoporotic complications, such as hip fracture rates, are also less frequent compared to the west. Protective factors may include high anti-oxidant consumption, mainly flavonoids and carotenoids, through a high vegetable (e.g., onions) and soy intake. Related biological observations include low lipid peroxide, high superoxide dismutase activity and high serum hydroxyproline, a marker of bone formation. Dehydroepiandrosterone (DHEA) and its hormonal byproducts testosterone and oestrogen appear to be high in Okinawan serum compared with age-matched Americans, possibly reflecting a slower age-associated decline in the sex hormone axis in Okinawans. This may be linked to better cardiovascular and overall health. Further study is needed to delineate the reasons behind the impressive cardiovascular and overall health of the Okinawans.

Key words: cardiovascular function, homocysteine, Okinawan life style, sex hormones, superoxide dismutase activity.

Introduction

Okinawans are the longest-living population out of any country or state in the world, according to reports of WHO and Japan Ministry of Health (Koseishou). Okinawans seem to have delayed the aging process and the minimized debilitating diseases that accompany the elder years, especially coronary heart disease (CHD). The three leading killers in the west, CHD, stroke and cancer, occur in Okinawa with the lowest frequency in the world. For example, out of 100 000 inhabitants, an average of only 18 die from CHD in a typical year, compared to 20 in Japan and 100 people in the USA (Table 1).

The Okinawan lifestyle provides real, scientifically verifiable reasons why these people are so incredibly robust and healthy so far into their senior years. Below is a focus on key findings and what they mean in terms of robust health and successful aging of the Okinawans.

Physiologically young arteries and well-compensated cardiac function

In 1995, when medical researchers were just beginning to take note of homocysteine (a byproduct of methionine intake, mostly from animal protein), it was conservatively estimated to cause 10% of all coronary heart disease deaths in the west. We now recognize that Okinawans have among the lowest homocysteine levels in the world, according to Alftham *et al.* (Fig. 1).¹

Serum cholesterol levels between centenarians and septuagenarians in Okinawa have been calculated. The centenarian

level is 166.2 mg/dL of total cholesterol and is lower than the septuagenarian level. The centenarian level of low-density lipoprotein (LDL) cholesterol is 102.4 mg/dL and is also lower than the septuagenarian level (Table 2).²⁻⁵ However, the diet has recently changed greatly, to include fast fatty foods and processed foods, so that the young Okinawan's homocysteine and cholesterol levels have risen. Compared to the Japanese norm, young Okinawans now have higher than average risk for CHD, based on higher cholesterol levels, higher body mass index (BMI) and other risk factors, while older Okinawans have lower than average risk. We think of this reversal as the Okinawan paradox.

According to physical and biochemical evaluations for arteriosclerotic conditions for healthy Okinawan centenarians, pulse wave velocity data are generally in the lower range, below 10 m/s, which is considered to be a relatively young level. However, arteriosclerotic index shows generally high levels. This discrepancy may be because of the time lag of the development of arteriosclerosis. In centenarians, the development of peripheral arteriosclerosis is slower than that of arteriosclerosis of the aorta.^{4,6,7} This phenomenon suggests that the arterial changes in healthy centenarians are not

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Table 1. Average life expectancy and death rates, world rank

| Rank | Location | LE | Eating pattern | Death rates | | | All-causes |
|------|---------------|------|------------------|-------------|--------|--------|------------|
| | | | | CHD | Cancer | Stroke | |
| 1 | Okinawa | 81.2 | East-West fusion | 18 | 97 | 35 | 335 |
| 2 | Japan | 79.9 | Asian | 22 | 106 | 45 | 364 |
| 3 | Hong Kong | 79.1 | Asian | 40 | 126 | 40 | 393 |
| 4 | Sweden | 79.0 | Nordic | 102 | 108 | 38 | 435 |
| 8 | Italy | 78.3 | Mediterranean | 55 | 135 | 49 | 459 |
| 10 | Greece | 78.1 | Mediterranean | 55 | 109 | 70 | 449 |
| 18 | United States | 76.8 | American | 100 | 132 | 28 | 520 |

LE, average life expectancy world rank; CHD, coronary heart disease. Sources: World Health Organization 1995; Japan Ministry of Health 1995.

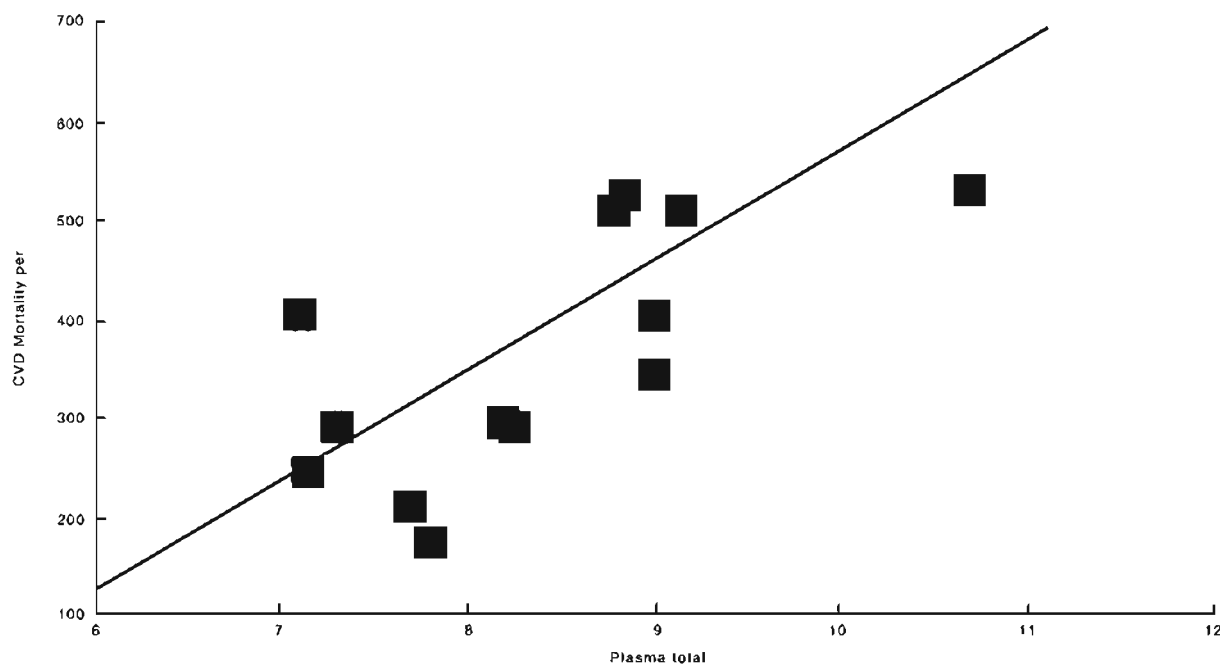


Figure 1. Correlation between plasma homocysteine level and cardiovascular mortality rate in Okinawa and European countries ($r = 0.71$, $P < 0.005$).

Table 2. Comparison of pulse wave velocity, atherosclerotic index and plasma lipid fractions between centenarians and septuagenarians

| | | PWV | AI | TC | TG | LDLC | HDLC | |
|----------------|---------------|-----|--------------------|-------------------|--------------------|--------------------|--------------------|------|
| Centenarian | total | Ave | 10.15 ⁺ | 1.91 ⁺ | 166.2 ⁺ | 108.3 | 102.4 ⁺ | 49.8 |
| | <i>n</i> = 40 | SD | 2.04 | 0.53 | 33.3 | 46.8 | 25.1 | 10.6 |
| | male | Ave | 10.88 ⁺ | 1.87 | 165.5 | 100.8 | 104.3 | 50.0 |
| | <i>n</i> = 7 | SD | 1.80 | 0.41 | 38.6 | 33.0 | 31.2 | 7.1 |
| | female | Ave | 10.02 [‡] | 1.92 ⁺ | 166.3 ⁺ | 109.6 [*] | 102.1 ⁺ | 49.7 |
| | <i>n</i> = 33 | SD | 2.05 | 0.51 | 32.3 | 48.8 | 23.9 | 11.1 |
| Septuagenarian | total | Ave | 8.45 | 2.59 | 207.6 | 129.1 | 126.0 | 52.1 |
| | <i>n</i> = 92 | SD | 1.44 | 0.88 | 36.0 | 73.7 | 30.8 | 11.2 |
| | male | Ave | 8.36 | 2.52 | 192.7 | 116.0 | 117.7 | 50.1 |
| | <i>n</i> = 45 | SD | 1.27 | 1.03 | 36.0 | 56.2 | 31.5 | 11.4 |
| | female | Ave | 8.54 | 2.66 | 221.8 | 141.5 | 133.8 | 54.1 |
| | <i>n</i> = 47 | SD | 1.56 | 0.70 | 29.7 | 85.4 | 27.9 | 10.5 |

TC, total cholesterol; TG, triglyceride; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; PWV, pulse wave velocity; AI, atherosclerotic index. ^{*} $P < 0.05$, [‡] $P < 0.001$, ⁺ $P < 0.0001$.

as a result from atheromatous change, but from physiological aging mainly based on fibrosis of arteries. This could be possibly because of higher age-related shear pressure (Table 2).^{4,7,8}

High blood pressure was recognized in only 1.5 of our apparently healthy centenarian subjects. Most never developed a taste for salt and, partly as a result of this, their heart disease and stroke rates have traditionally been much lower than the Japanese average (Table 3). Most subjects, who have segmental deviation (QS, rS patterns and ST-T) deviations in precordial leads on electrocardiogram (ECG), have rarely experienced obvious episodes of chest pain or discomfort. This phenomenon suggests that centenarians might not have developed coronary ischemia, but instead there are degenerative damages of the myocardium. As far as the pathological changes are concerned, Stemby and Ishii have reported that amyloid accumulation and deposition are recognized in the regional myocardium, in more than 50% of centenarians (Table 4).^{4,7,8}

Cardiac functional disturbances as a result of valvular regurgitation and arrhythmias, secondary to diseased myocardium and valvular calcification occur with increasing frequency with age (Fig. 2). Generally, ventricular pump

function is well compensated, but heart failure can be triggered more easily with extreme age. Much of centenarians' long life expectancy can be attributed to a minimization of cardiovascular diseases, especially through low cholesterol levels and minimal hypertension. Indeed, it would be difficult to age successfully without some degree of protection against cardiovascular diseases.^{7,8}

Low risk for hormone-dependent cancers

Okinawans have an extremely low-risk for hormone-dependent cancers, including cancer of the breast, ovary, prostate and colon. The profound differences in hormone-dependent cancer death rates can be observed between several long-lived countries. Compared to the USA, they have 90% less chance of breast cancer, 80% less chance of prostate cancer and less than 50% chance of ovarian and colon cancer.⁹ We believe this is likely due to several factors including lifelong low caloric intake, low BMI, high intake of plant foods especially green-yellow vegetables and soy products (Table 5). According to our research, caloric intakes in Okinawan centenarians are 1407 calories for men and 1096 calories for women (Table 6).¹⁰⁻¹² The most common cooking oil used by Okinawans' stir-fry cooking at home, is a canola-soy oil blend

Table 3. Blood pressure of centenarians (mmHg)

| Characteristic | nr of males (%) | nr of females (%) |
|-------------------------|-----------------|-------------------|
| Hypertension (>160/>95) | 1 (1.6) | 4 (1.4) |
| Borderline hypertension | 23 (37.1) | 101 (36.2) |
| Normotension (<139/<89) | 38 (61.3) | 174 (62.4) |
| Male | | |
| Ave | 132/71 | |
| SD | 20/12 | |
| Female | | |
| Ave | 130/73 | |
| SD | 22/11 | |

Table 4. Comparison of appearance of ECG abnormalities between centenarians and septuagenarians

| | Centenarians | % | Septuagenarians | % | Student's <i>t</i> -test (<i>P</i>) |
|-------------------------|--------------|------|-----------------|------|---------------------------------------|
| Pattern analysis | | | | | |
| Qs-rS type (V1-6) | 46 | 19.7 | 32 | 13.7 | 0.08 |
| Qs-rS type (II III aVF) | 5 | 2.1 | 0 | 0 | 0.07 |
| LVH | 13 | 5.6 | 28 | 12 | 0.02* |
| Low voltage | 57 | 24.4 | 9 | 3.8 | 0.0001**** |
| ST-T deviations | 84 | 35.9 | 57 | 24.4 | 0.007** |
| CLBBB | 3 | 1.3 | 10 | 4.2 | 0.0001**** |
| CRBBB | 16 | 6.8 | 41 | 17.5 | 0.0004**** |
| Rhythm analysis | | | | | |
| SVPC | 76 | 32.5 | 12 | 5.1 | 0.0001**** |
| PVC | 38 | 16.2 | 12 | 2.1 | 0.001*** |
| SVT | 6 | 2.6 | 1 | 0.4 | 0.1277 |
| VT | 2 | 0.9 | 0 | 0 | 0.4786 |
| af-AF | 12 | 5.1 | 4 | 1.7 | 0.075 |
| AV-B | 6 | 2.6 | 2 | 2.9 | 0.2847 |
| PM | 3 | 1.3 | 0 | 0 | 0.2467 |
| Total | 234 | 100 | 234 | 100 | |

LVH, left ventricular hypertrophy; CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; SVPC, supraventricular premature beats; PVC, ventricular premature beats; SVT, supraventricular tachycardia; VT, ventricular tachycardia; af, atrial fibrillation; AF, atrial flutter; AV-B, atrioventricular block; PM, pacemaking.

that contains mainly monounsaturated fat with a significant portion of omega-3 fatty acids. Low-calorie diets and the high intake of monounsaturated fat results in less production of cell-damaging free radicals and less exposure to mitogenic hormones.

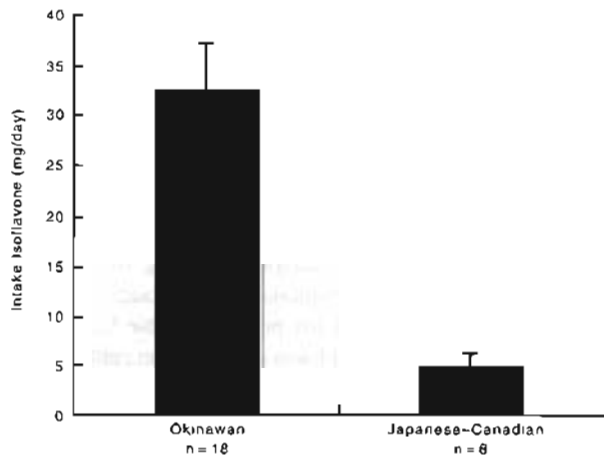


Figure 2. Comparison of daily isoflavone intakes between Okinawans and Japanese-Canadians. $P < 0.001$.

Anti-oxidants

We measured the amount of one of the main free radical byproducts, called lipid peroxide. The centenarians' level of 1.67 nmol/mL was significantly lower than the septuagenarians' level of 3.40. This is compelling evidence that they suffer less free radical-induced damage (Table 7).^{10,13}

According to our study, Okinawan centenarians' superoxide dismutase (SOD) activity is 1.41 U/mL, which is almost the same level as octogenarians.¹⁴ Other anti-oxidant defenses come from dietary anti-oxidants, such as vitamins C and E, carotenoids and flavonoids (Table 8).

Contrary to our expectations, plasma and intracellular α -tocopherol levels of centenarians are not significantly higher, compared to septuagenarian levels. This may represent a lower intake of calories or vitamin E-rich foods (Table 9).^{10,12,15}

Okinawan consumption of flavonoids is six times higher than Japanese-Canadians. The plant sterols of flavonoids taken from soy and other legumes may offer protection against arteriosclerosis and the damaging effects of hormones (Fig. 3). The carotenoid lycopene is thought to be a more powerful anti-oxidant than vitamin E. Okinawan diets have been found to have the highest lycopene content in Japan, which most probably comes from the reddish-purple pigment found in Okinawan sweet potato, but is also

Table 5. Hormone-dependent cancer death rates between Okinawans, the USA and several long-lived countries

| LE | Location | Hormone-dependent cancer risk: yearly cancer deaths (per 100 000 people) | | | |
|----|----------|---|---------|----------|-------|
| | | Breast | Ovary** | Prostate | Colon |
| 1 | Okinawa* | 4 | 6 | 3 | 7 |
| 5 | Sweden | 35 | 16 | 47 | 20 |
| 7 | Italy | 37 | 9 | 20 | 16 |
| 9 | Greece | 25 | 9 | 17 | 11 |
| 18 | USA | 34 | 13 | 25 | 20 |

LE, life expectancy world rank. Source: World Health Organization 1990-1992; *Tsugane *et al.* J. Epidemiology 1992; 2: 75-81; **American Institute for Cancer Research, 1997 (est.). Age-adjusted to world population standards.

Table 6. Intake of energy and nutrients in centenarians in Okinawa and Tokyo

| | Okinawa | | Tokyo | | National survey of nutrition in 1994 |
|------------------|---------------|---------------|--------------|--------------|---|
| | Men | Women | Men | Women | |
| Number | 11 | 28 | 12 | 22 | |
| Energy (kcal) | 1407 (70) | 1096 (54) | 1317 (65) | 1221 (60) | 2023 |
| Protein (g) | 57.1 (72) | 45.9 (58) | 50.7 (64) | 46.8 (59) | 79.7 |
| Fat (g) | 51.8 (89) | 32.5 (56) | 35.6 (61) | 34.2 (59) | 58 |
| Carbohydrate (g) | n.a. | n.a. | 180 (64) | 174 (62) | |
| Calcium (mg) | 624 (114) | 400 (73) | 465 (85) | 437 (80) | 545 |
| Iron (mg) | 20.2 (179) | 14.6 (129) | 6.7 (59) | 6.8 (60) | 11.3 |

Number indicates average intake, values in parentheses indicates percentage of intake of the result of the national survey of nutrition in 1994; n.a., not available.

Table 7. Levels of lipid peroxide in Okinawan centenarians and septuagenarians

| | Male | | Female | | Total | |
|-----------------|--------------|-----------------|--------------|-----------------|--------------|-----------------|
| | Centenarians | Septuagenarians | Centenarians | Septuagenarians | Centenarians | Septuagenarians |
| Number of cases | 30 | 11 | 109 | 18 | 139 | 29 |
| Lipid peroxide | 1.49 ± 0.51* | 3.15 ± 0.70 | 1.72 ± 1.28* | 3.56 ± 0.81 | 1.67 ± 1.16* | 3.40 ± 0.79 |

*P < 0.001, mean ± SD (nmol/mL).

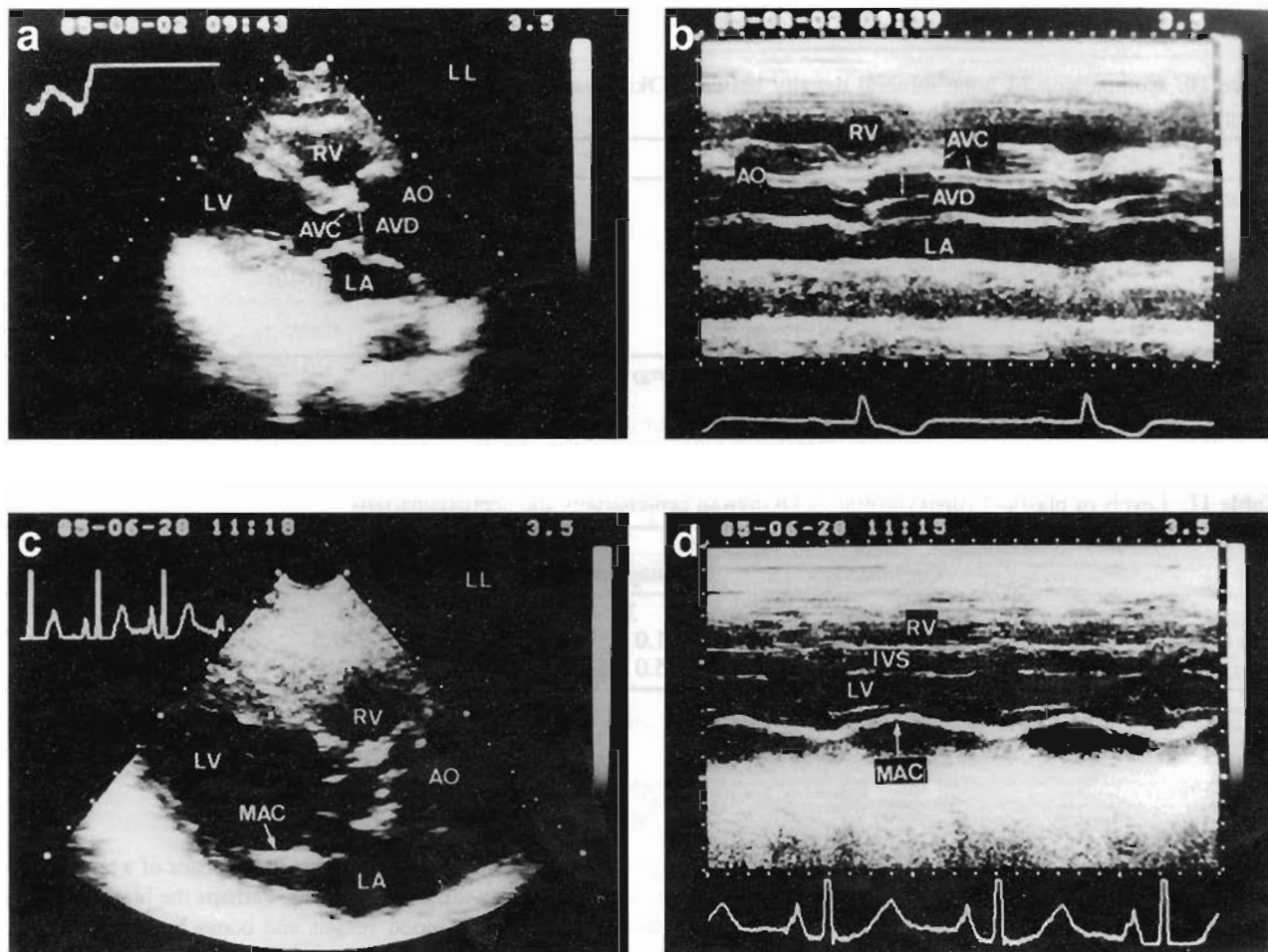


Figure 3. Echocardiogram of centenarians. Marked calcifications are recognized in (a) longitudinal view and in (b) echogram in case AT. Marked mitral annular calcifications are noted in (c) longitudinal view and in (d) echogram in case TK. RV, right ventricle; LV, left ventricle; AO, aorta; LA, left atrium; AVC, aortic valvular calcification; AVD, aortic valvular dimension; MAC, mitral annular calcification; IVS, intraventricular septum.

Table 8. Comparison of SOD activities and SOD levels between centenarians and octogenarians

| | Octogenarians | Centenarians |
|-------------------------|---------------|----------------|
| n | 9 | 11 |
| SOD activity (U/mL) | 1.49 ± 1.12 | 1.41 ± 0.68 |
| CumZn-SOD level (ng/mL) | 78.32 ± 13.74 | 71.40 ± 43.22 |
| Mn-SOD level (ng/mL) | 106.47 ± 29.4 | 105.56 ± 22.93 |

SOD, superoxide dismutase.

present in watermelon and tomatoes which Okinawans like to eat.

Okinawans have strong bone density compared with mainland Japanese. They have a 25% reduced risk of hip fracture versus other mainland Japanese and about 50% less hip fractures than in Americans. Bone mineral density was measured in 50- to 60-year-olds by using the same apparatus of single-energy X-ray absorptiometer (SXA) in Okinawa. The measurements for Okinawan men and women were 485 mg/cm²

Table 9. Levels of plasma and intracellular tocopherol in Okinawan centenarians and septuagenarians

| Sex and number of cases | Plasma | | Intracellular | |
|-------------------------|---------------|-----------------|---------------|-----------------|
| | Centenarians | Septuagenarians | Centenarians | Septuagenarians |
| Male | 8.89 ± 2.31* | 14.38 ± 8.28 | 1.80 ± 1.00* | 2.79 ± 0.30 |
| " | 31 | 17 | 31 | 17 |
| Female | 11.05 ± 3.41* | 18.24 ± 12.69 | 2.30 ± 1.22* | 2.98 ± 0.81 |
| " | 110 | 30 | 110 | 30 |
| Total | 10.58 ± 3.32* | 16.81 ± 11.32 | 2.19 ± 1.19* | 2.91 ± 0.67 |
| " | 141 | 47 | 141 | 47 |

* $P < 0.01$, $m \pm sd$ ($\mu\text{g/mL}$).

Table 10. Comparison of bone mineral density between Okinawans and mainland Japanese in 50 years old groups by using SXA

| | Male | Female |
|-----------|-------------------|-------------------|
| Okinawa | 485 ± 55 0 | 357 ± 83 (147) |
| Fukushima | | 315 ± 62 (640) |
| Tottori | 477 ± 85 (258) | |

Bone density in mg/cm^3 . Numbers tested are in parentheses. SXA, single-energy x-ray absorptiometer.

Table 11. Levels of plasma hydroxyproline in Okinawan centenarians and septuagenarians

| | Male | | Female | |
|----------------------|--------------|-----------------|--------------|-----------------|
| | Centenarians | Septuagenarians | Centenarians | Septuagenarians |
| Number of cases | 15 | 39 | 51 | 61 |
| Total hydroxyproline | 67.3 ± 13.7 | 61.0 ± 10.9 | 72.1 ± 17.5 | 58.9 ± 10.4 |
| Free hydroxyproline | 21.9 ± 10.4 | 15.0 ± 6.5 | 22.3 ± 13.3 | 13.5 ± 8.4 |

Amounts in mean ± sd (nmol/mL).

and 375 mg/cm^2 , respectively. The Okinawan measurements are higher than the age-matched adults on the mainland of Japan.¹⁶ Our study suggests that there are several factors likely to play a role including: high calcium intake from foods and natural drinking water, high flavonoid intake, high vitamin D levels from exposure to sunlight and increased physical activity, especially at older ages (Table 10). According to our comparison study of serum hydroxyproline levels between centenarians and septuagenarians, centenarian levels were 67.1 nmol/mL for men and 72.1 for women, which are remarkably high.^{10,15} Hydroxyproline is one of the important components of collagen fibers, such as arterial wall and bone matrix. It is also a key substance for recovery from wounds. High amounts of this amino acid are found in soy products (Table 11).

We studied several of the major hormones including DHEA (dehydroepiandrosterone), thyroid hormones, cortisol and the sex steroids (oestrogen and testosterone) in the Okinawan elders. What was interesting was that the sex hormones in the Okinawans may decline more slowly as they age^{14,17} (Table 12); we can speculate that the higher levels of DHEA,

testosterone and oestrogen might be evidence of a physiologically younger sex hormones axis. Perhaps the high oestrogen helps keep their blood vessels and bones healthy, while the deleterious effects of endogenous oestrogen on the initiation and promotion of breast cancer, might be reduced by strikingly high levels of flavonoids, which have been shown to block oestrogen activity in vitro. This will require further study.

Psycho-spiritual practices may be important to reduce stress-induced radical oxidant damage. However, we regret that space is too short to explore this topic in detail or to further elaborate on Okinawan health and lifestyle.

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Table 12. Sex hormones of centenarians

| | Estradiol (pg/mL) | | FSH (mIU/mL) | | Dehydroepiandrosterone (ng/mL) | |
|-----------------|-------------------|------------|--------------|-------------|--------------------------------|-------------|
| | Male | Female | Male | Female | Male | Female |
| Centenarians | 12.1 ± 10.2 | 4.2 ± 3.6 | 74.5 ± 39.2 | 99.2 ± 42.2 | 0.76 ± 0.34 | 0.62 ± 0.26 |
| Number of cases | (21) | (33) | (34) | (83) | (15) | (19) |
| Septuagenarians | 35.7 ± 14.8 | 15.5 ± 6.4 | 20.9 ± 18.9 | 69.8 ± 26.9 | 2.59 ± 0.93 | 3.03 ± 1.33 |
| Number of cases | (29) | (25) | (39) | (64) | (29) | (25) |
| Standard levels | 20.0-5.44 | 9.0-230 | 2.9-8.2 | 26.2-113.3 | 0.72-5.44 | 0.84-3.87 |

Units: Ave ± SD. **P < 0.01. FSH, follicle-stimulating hormone.

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