Cardiovascular Disease Delay in Centenarian Offspring

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Background. Previously, the authors have shown that an important component of the ability to survive to exceptionally old age is family health history. This study assessed the age at onset of age-related diseases in centenarian offspring.

Methods. The health histories of 177 offspring of centenarians enrolled in the nationwide New England Centenarian Study, and 166 controls were assessed from 1997 to 2000. Controls were the offspring of parents born in the same years as the centenarians but at least one of whom died at average life expectancy. Ages at onset of heart disease, hypertension, diabetes, cancer, osteoporosis, cataracts, glaucoma, macular degeneration, depression, thyroid disease, and stroke were compared in the two groups.

Results. The median ages of onset for coronary heart disease (p < .001), hypertension (p < .001), diabetes (p = .002), and stroke (p = .017) were significantly delayed in the centenarian offspring by 5.0, 2.0, 8.5, and 8.5 years, respectively, compared with the age-matched controls. Adjusted hazard ratios were 0.388 (p = .0004), 0.39 (p < .0001), 0.302 (p = .008), and 0.328 (p = .06). No differences were found in the ages of onset for the other diseases investigated.

Conclusions. The offspring of centenarians show a marked delay in the age of onset for cardiovascular disease, diabetes, hypertension, and stroke but not for other age-related diseases such as cancer, osteoporosis, and thyroid disease. These results suggest that the children of centenarians may be following in their parents’ footsteps, markedly delaying the onset of lethal diseases that commonly affect older persons.

At the turn of the century in the United States, approximately 1 person per 100,000 in the general American population was 100 years or older. The current prevalence is 10 times greater. This dramatic increase is due to relatively recent public health measures that have allowed persons who would have otherwise died as a result of preventable or treatable diseases to survive to much older age and to much improved medical care of older persons, thus allowing them to live to even older age (1,2). One of the concerns of having more persons achieve exceptional longevity could be that these persons, by living to older age, would also experience longer periods of poor health and disability. Alternatively, the compression of morbidity hypothesis suggests that with healthy lifestyles and preventive measures that would result in longer lives, disability and poor health would be reduced to a shorter period nearer the end of life (3–5). Consistent with this hypothesis, Perls and colleagues (6) have found that among their sample of centenarians, 90% were functionally independent at the age of 92 years. When examining the most lethal diseases of the elderly population, heart disease, non–skin cancer, and stroke, Evert and colleagues (7) found that 87% of male and 83% of female centenarians delayed beyond the age of 80 years or altogether escaped these diseases.

The siblings of centenarians have been found to maintain one half the mortality risk of their average birth cohort from young adulthood into extreme old age, resulting in high relative probabilities that these siblings would themselves survive to age 100 years (8). Thus, we suspected that the offspring of centenarians, who are, on average, in their mid-70s, also have an increased propensity to delay or escape age-related diseases, particularly those associated with increased mortality risk. When compared with birth cohort-matched controls whose parents died at average life expectancy, the children of centenarians, at an average age of 71 years, have 56%, 66%, and 59% reduced relative prevalences of heart disease, hypertension, and diabetes, respectively. These prevalence estimates were adjusted for major confounding factors (9). In the current study, we extended these findings by considering the age at onset of age-related diseases in the offspring of centenarians and birth cohort controls to evaluate our hypothesis that the delay of onset of age-related diseases is at least familial and perhaps heritable.

Methods

The criteria for eligibility, recruitment, and the main study outcomes have been published elsewhere (9). Briefly, we compared the offspring of centenarians (n = 177, mean age = 71 years) with the offspring of persons whose parents were born in the same years as the centenarians but at least one of whom died at age 73 years, the average life expectancy for the centenarian birth cohort (n = 166, mean age = 70 years). The ages of the other parent for both groups were statistically the same (mean age = 77 years). Study participants were sent packets that included questions about demographics, medical history, medications, alcohol and tobacco use, and exercise.
Statistical Analyses

Survival analytic methods were used to estimate the differences in age of onset for 11 disorders, including heart disease (any of the following: coronary artery disease, myocardial infarction, congestive heart failure, arrhythmia), hypertension, diabetes mellitus, cancer, stroke, osteoporosis, cataracts, glaucoma, macular degeneration, depression, and thyroid conditions. Persons not diagnosed with a disorder were censored at the age of last observation for the disorder.

Kaplan-Meier product-limit estimates of the age of onset distribution within each group were computed, and tests of the equality of the survival functions across groups were conducted using SAS version 8.2 (SAS Institute, Cary, NC). Graphs of the survival (onset) distributions for the disorders were produced using S-Plus (version 6.0; Insightful Corp., Seattle, WA). SAS was also used for proportional hazards modeling to estimate the crude and adjusted hazard ratios for onset of each of the diseases. Adjustment factors considered in each model were sex, marital status, income, education, alcohol consumption, smoking, exercise, and age. Age was the only continuous variable among the covariates; all others were represented by sets of indicator variables.

RESULTS

A complete accounting for all potential participants for both groups and a complete description of all enrolled participants have been published elsewhere (9). Briefly, 55% of the centenarian offspring and 20% of the controls agreed to participate in the study. Based on family pedigree information and Social Security Death Index data, 41% of the controls and 17% of the centenarian offspring died in the years before the study (9).

Both groups were similar with respect to age, ethnicity, marital status, income, exercise, and alcohol use. More controls were current smokers: 13% versus 7% of centenarian offspring (p < .05), although the proportion of persons who reported ever smoking was the same for both groups. Centenarian offspring had more years of education: 36% versus 22% of the controls (p < .05) reported more than 16 years of education. Centenarian off-

Table 1. Median Age at Onset and Prevalence

<table>
<thead>
<tr>
<th>Disease</th>
<th>Offspring</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>60 (26)</td>
<td>58 (54)</td>
</tr>
<tr>
<td>Coronary heart</td>
<td>69 (12)</td>
<td>64 (28)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>69 (5)</td>
<td>60 (11)</td>
</tr>
<tr>
<td>Cancer</td>
<td>65 (15)</td>
<td>65 (17)</td>
</tr>
<tr>
<td>Cataract</td>
<td>69 (30)</td>
<td>70 (22)</td>
</tr>
<tr>
<td>Depression</td>
<td>49 (7)</td>
<td>45 (7)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>66 (6)</td>
<td>70 (5)</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>72 (6)</td>
<td>68 (2)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>65 (13)</td>
<td>65 (15)</td>
</tr>
<tr>
<td>Stroke</td>
<td>72 (2)</td>
<td>63 (5)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>54 (11)</td>
<td>60 (11)</td>
</tr>
</tbody>
</table>

Table 2. Crude and Adjusted Hazard Ratios

<table>
<thead>
<tr>
<th>Disease</th>
<th>Crude</th>
<th>Adjusted</th>
<th>CI for Adjusted</th>
<th>p Value</th>
<th>Adjusted</th>
<th>Adjustment Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.37</td>
<td>0.39</td>
<td>0.27–0.56</td>
<td>&lt;.0001</td>
<td></td>
<td>Martial status</td>
</tr>
<tr>
<td>Coronary heart</td>
<td>0.33</td>
<td>0.39</td>
<td>0.23–0.65</td>
<td>&lt;.0004</td>
<td>Age, gender</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.33</td>
<td>0.30</td>
<td>0.12–0.73</td>
<td>&lt;.008</td>
<td>Age, alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>Stroke*</td>
<td>0.33</td>
<td>NA*</td>
<td>0.10–1.07</td>
<td>&lt;.060</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: *The small number of strokes in the sample (n = 13: 9 controls and 4 offspring) and several missing values for covariates resulted in empty cells precluding an adjusted model.

CI = confidence interval; NA = not applicable.

spring were more functional as assessed by the IADL questionnaire (p < .003) (9).

Table 1 shows the median ages of onset, prevalence, and the Wilcoxon probability value for the test of equality of the onset distributions. The Wilcoxon test was used because differences in the distributions early on carry more weight. Median ages of onset for coronary heart disease (p < .001), hypertension (p < .001), diabetes (p = .002), and stroke (p = .017) were delayed in the offspring of centenarians by 5.0, 2.0, 8.5, and 8.5 years, respectively. No significant differences in the onset distributions were found in the age of onset for cancer, osteoporosis, glaucoma, depression, cataracts, macular degeneration, and thyroid disease. The distributions for osteoporosis and thyroid disease were not proportional to one another, so the Wilcoxon test may not be an accurate reflection of the differences in the distributions.

Table 2 shows the crude and adjusted hazard ratios for age of onset of each of the diseases for which the product-limit estimates were different by group. The crude and adjusted hazard ratios for hypertension, heart disease, and diabetes ranged from 0.30 to 0.40 and were significantly lower than the null hypothesis of 1. The crude hazard ratio for stroke was 0.33 (p = .06). Only 13 study participants experienced stroke. The small number of events and two missing covariate values resulted in a probability value of .06 for the crude hazard ratio and prevented an accurate adjustment for covariates.

Figure 1 shows the onset distributions for heart disease, hypertension, stroke, diabetes, and cancer. Significant differences are noted in the onset of heart disease, hypertension, stroke, and diabetes but not of cancer.

DISCUSSION

Our findings suggest that centenarian offspring significantly delay the onset of cardiovascular disease and its associated risk factors of hypertension and diabetes when compared with controls who had both parents on average die at approximately the age of average life expectancy. The median ages of onset of several other age-related diseases were not statistically different. This suggests that perhaps it is specifically the delay in cardiovascular disease and its risk factors that account for a substantial component of the longevity in centenarians and their offspring rather than a universal delay of all age-related diseases. This is supported by the lack of difference in the median ages at
onset and prevalence of cancer, osteoporosis, thyroid diseases, depression, and eye diseases.

Our study is potentially subject to ascertainment bias. These are extensively numerated in our previous publication (9). Because of 30-year-old obituary information, we had difficulty locating 51% of the controls. Missing participants may have been lost to death and disease or, alternatively, they may have been healthier and moved to another location for retirement. The relatively low control participation rate raises the concern about a selection bias in favor of healthier participants. By using family pedigree information and Social Security Death Index listings, we tried to determine whether participants were alive but not interested in participating, were too ill to participate, or had died. Data about nonparticipants were collected and segregated by health-related reasons (2% and 4% of nonparticipation for the centenarian offspring and controls, respectively) and nonhealth-related reasons (54% of the centenarian offspring

Figure 1. Onset of heart disease, hypertension, stroke, cancer, and diabetes.
and 21% of the controls, respectively), such as lack of interest or time to participate in a scientific study. If participating controls were, in fact, healthier than centenarian offspring, this would bias our findings toward the null (9).

Our previous research has shown a decreased prevalence of age-related diseases, particularly cardiovascular disease and its risk factors, in the offspring of centenarians (9). In this study, the centenarian offspring had a later age of onset of cardiovascular disease, hypertension, diabetes, and stroke, suggesting that the offspring of centenarians may fit the compression of morbidity model, in which their ability to achieve older age entails a delay of age-associated diseases (3). What remains to be seen is the effect of such compression on longevity and the environmental and genetic characteristics these offspring share with each other and with their parents that could explain such a remarkable difference in cardiovascular disease-free survival.

We have previously noted that the siblings of centenarians experience half the mortality risk of their birth cohort-matched peers from age 20 years through extreme old age (8). During young adulthood, much of this survival advantage may be due to environmental and behavior-related factors (e.g., fighting in a war, automobile accidents, suicide, tobacco use), but at older ages, genetic factors may be playing an increasingly greater discriminating role (e.g., lacking genetic variations that predispose to premature cardiovascular disease, Alzheimer’s disease, or other lethal age-related diseases) (8). A similar interplay of environmental and genetic determinants might be present among the children of centenarians.

The delay in the onset of potentially lethal age-related diseases bodes well for the offspring of centenarians, but what are the implications for those whose parents are not long-lived? Although we cannot control the set of genes we inherit, we can modify behaviors that may contribute to a delay in age-related diseases. Fraser and Shavlak (10) found that choices in diet, exercise, cigarette smoking, and body weight altered life expectancy by several years in a survey of the Adventist Health Study cohort. Among those surviving to at least age 30 years, the Seventh Day Adventists exceeded their birth cohort’s average life expectancy by 7.3 years for men and 4.4 years for women (10). This increased life expectancy and evidence indicating delayed disability at older ages (3,6,11) suggest that, with the right preventive measures and healthy lifestyle, we can live not only longer but also, in the process, healthier (5). Furthermore, if the secret to longevity is related to a delay in cardiovascular disease specifically, rather than a general avoidance of age-related diseases, then preventive measures such as maintaining a healthy weight (12), increasing physical activity (13), smoking cessation (14–16), lowering serum cholesterol (17,18), and maintaining a normal blood pressure (19,20) may be of benefit not only for avoiding cardiovascular disease but also for living significantly longer in good health.

Conclusions

Similar to many of their centenarian parents, the offspring of centenarians have a significantly delayed age of onset for cardiovascular disease, hypertension, stroke, and diabetes. These findings are consistent with the compression of morbidity model, in which the ability to achieve older age entails a delay of age-associated diseases (3). What remains to be seen is how this compression of morbidity influences longevity.

Unlike their parents, the offspring of centenarians, who are in their 70s and 80s, are generally not near the end of their lives and may better reflect phenotypic characteristics conducive to achieving exceptional longevity. As such, they offer a unique opportunity to learn more about the genetic and environmental correlates of healthy aging. Future genetic studies will help to untangle environmental and genetic characteristics these offspring share with each other and with their parents and their effect on longevity and the development of age-related diseases.

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