Morbidity Profiles of Centenarians: Survivors, Delayers, and Escapers

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Background. The compression of morbidity hypothesis predicts that, in order to achieve their extreme old age, centenarians markedly delay or even escape diseases that would otherwise be lethal at younger ages. Phenotypic studies have not adequately characterized the prevalence and timing of age-related illnesses among those who achieve exceptional old age. Thus, we conducted a retrospective cohort study of centenarians to explore the timing of such diseases among centenarians.

Methods. Health history questionnaires were completed by 424 centenarians (aged 97–119 years) or their proxies. Lifetime (to-date) diagnoses of 10 major lethal illnesses (hypertension, heart disease, diabetes, stroke, nonskin cancer, skin cancer, osteoporosis, thyroid condition, Parkinson’s disease, and chronic obstructive pulmonary disease) and one ocular disease (cataracts) that befall the elderly population, approximate age of diagnosis, level of alcohol and tobacco use, and presence or absence of cognitive impairment were assessed. Because of the retrospective nature of the study, the typically imprecise age of onset of cognitive impairment negated the ability to include age of onset of cognitive impairment in this aspect of the analyses.

Results. Examining the ages of onset for the 10 age-associated diseases and excluding cognitive impairment, we found that the centenarians fit into three morbidity profiles—Survivors, Delayers, and Escapers. 24% of male subjects and 43% of female subjects fit the Survivor profile, or those who had a diagnosis of an age-associated illness prior to the age of 80. Delayers were individuals who delayed the onset of age-associated illness until at least the age of 80, and 44% of male and 42% of female subjects fit this profile. Escapers were individuals who attained their 100th year of life without the diagnosis of common age-associated illnesses, and 32% of male and 15% of female subjects fit the Escaper profile. When examining only the most lethal diseases of the elderly population, heart disease, nonskin cancer, and stroke, we found that 87% of male and 83% of female subjects delayed or escaped these diseases. Subjects with and without cognitive impairment did not differ in terms of the profile to which they belonged.

Conclusions. These results suggest there may be multiple routes to achieving exceptional longevity and that there are sex differences according to which route is taken. These routes represent different phenotypes and thus likely different genotypes of centenarians. The identification of three types of centenarians, Survivors, Delayers, and Escapers, provides direction for future study into the factors that determine exceptional longevity.

We have hypothesized that centenarians either markedly delay or escape age-associated morbidity such as heart disease, stroke, diabetes, cancer, and Alzheimer’s disease (1). Consistent with this hypothesis is James Fries’ proposition, known as the compression of morbidity hypothesis, that individuals who reach the limits of the human life span compress the onset and duration of illnesses toward the end of life (2,3). Although numerous studies have characterized the centenarian phenotype according to metabolic (4,5), endocrine (6), immune (7,8), physical (9), and cognitive functions (10–12), little work has emerged that describes the health histories associated with exceptional longevity. We previously noted that 88% of centenarians reported being functionally independent at an average age of 92 years (9). Functional independence, however, does not necessarily indicate that these individuals were living to very advanced age without clinically significant illnesses. The presentation and impact of illnesses is heterogeneous among the elderly population because of comorbidities, variations in how older people adapt or react to such illnesses, and the variation in functional reserve or the ability to withstand a disease before it becomes clinically evident (3). Thus, we set out to better understand the life histories of age-associated diseases among the centenarian subjects enrolled in our study through a nationwide recruitment effort, with the supposition that the results could help further delineate different patterns of survivorship to extreme old age.

Methods

Study Population

Since 1998, the New England Centenarian Study (NECS) has been recruiting and enrolling centenarians and their siblings living throughout the United States and Canada. All subjects recruited through the year 2001 were included in this study. These participants were born in the years 1880–1903. Details of the study design and recruitment have been
previously described (13). All centenarians (and/or their proxies) enrolled in the NECS were sent health history questionnaires. Biologically related individuals were excluded. In the case of two eligible biologically related persons, the male relative (men are greatly underrepresented among centenarians) was selected for inclusion. In the event that the relatives were female, the oldest female relative was included for study. Of the individuals completing the health history questionnaires, 146 were excluded because of age ineligibility or relatedness. For the health history questionnaires, 90% were completed by proxies, and 10% were completed by independently living centenarians. The study protocol was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations and the Boston University Medical Center Investigational Review Board.

Data Collection

Participants (or their proxies) reported to-date diagnoses of 14 age-associated morbidities, as well as alcohol and tobacco usage. Subjects also reported the approximate age of diagnosis for any applicable disease states. Subjects were asked about any history or the presence of the following: hypertension, congestive heart failure, heart attack, cardiac arrhythmia, diabetes, stroke, nonskin cancer, skin cancer, osteoporosis, thyroid condition, Parkinson’s disease, dementia, chronic obstructive pulmonary disease (COPD), and cataracts. Diagnoses made before the age of 25 years were not included in the analyses.

Several of the diagnoses required further delineation. A history or presence of COPD was defined as a diagnosis of emphysema or bronchitis and a positive report of cigarette smoking for ≥2 pack-years. The presence of osteoporosis was defined by a physician’s diagnosis of osteoporosis or a history of a nontraumatic hip, wrist, or spinal fracture after the age of 50. Heart disease was defined by a positive diagnosis of one or more of the following: heart attack, cardiac arrhythmia, or congestive heart failure.

A subset of 315 subjects completed the Blessed Roth Memory-Concentration (BRMC) test (14). The BRMC became a part of the study protocol later in the study, and thus a smaller number of subjects were screened for cognitive impairment with this test. A diagnosis of cognitive impairment was noted if the BRMC score was less than 34 out of 37, even if the presence of dementia was not reported. Individuals who were not administered the BRMC test were excluded from the prevalence analysis for cognitive impairment. Because of the insidious onset characteristic of cognitive impairment, the retrospective nature of this study prevented us from accurately assessing the age of onset of cognitive impairment among those who had it on the basis of the BRMC test or a physician’s diagnosis.

Descriptive statistical analyses were used and chi-squared tests were performed on selected measures.

Morbidity Profiles

A crude analysis of the data revealed that the study participants generally fell into three age-defined categories of when age-associated diseases became clinically evident. Those classified as Survivors had an age of onset of less than 80 years for at least one of the diseases. Those categorized as Delayers had an age of onset between the age of 80 and 100 years. Those noted to be Escapers had an age of onset of 100 years or had not yet been diagnosed with a disease. In addition, subjects were also grouped into these categories according to the age of onset for one of the three most lethal diseases among the elderly population, which are heart disease, stroke, and nonskin cancer. The distributions of Survivors, Delayers, and Escapers were compared according to gender, and differences were tested for by using the chi-squared test.

Categories of morbidity onset according to gender were stratified by cigarette smoking history, daily alcohol consumption history, and whether or not the subject was cognitively intact (BRMC > 33). We examined possible effect modification by these variables before computing summary Mantel-Haenzel odds ratios (with 95% confidence intervals, or CIs) to provide adjusted measures of association of group assignment and gender. We then compared these adjusted measures to the crude odds ratios (ORs) in order to assess confounding by smoking, daily drinking, or dementia. The sponsors of this study did not in any way influence the study design or the collection, analysis, and interpretation of data.

RESULTS

The sample consisted of 469 unrelated centenarians; 424 questionnaires were received (90% response rate). Fifteen percent of the subjects were deceased when the health history questionnaires were completed by their proxy, usually an offspring. The mean age of female participants (n = 322) was 102 ± 2.6 years. The mean age of male participants (n = 102) was 102 ± 3.0 years. Social characteristics are noted in Table 1.

Lifetime prevalences and mean ages of onset of age-related diseases for male and female subjects are noted in Table 2. Cataracts were the most prevalent (past or present) morbidity. Other than cataracts, the most common diseases (past or present) were osteoporosis among women (56%) and heart disease among men (42%). The mean age of diagnosis was significantly lower in women than in men for skin cancer (82 vs. 87 years, p = .04), hypertension (77 vs. 86 years, p = .02), and osteoporosis (87 vs. 92 years,
The prevalences of hypertension (35% vs. 19%, \( p = .003 \)), osteoporosis (56% vs. 29%, \( p < .0001 \)), and thyroid disease (17% vs. 8%, \( p = .03 \)) were significantly greater in female centenarians. With the exclusion of cataracts, the average age of onset of initial disease for men was 85.3 years (95% CI 81.8, 88.8), and for women it was 79.6 years (95% CI 77.8, 81.4; \( p = .004 \)).

Examining heart disease, nonskin cancer, skin cancer, hypertension, stroke, COPD, Parkinson’s disease, diabetes, osteoporosis, and thyroid disorders, we found that men and women significantly differed in their number of comorbidities (\( p = .005 \)). Male subjects had an average of 1.9 comorbidities (95% CI 1.63, 2.13), whereas female subjects had an average of 2.3 comorbidities (95% CI 2.15, 2.42).

Two hundred, forty-nine (79%) of the 315 subjects tested with the BRMC test demonstrated some degree of cognitive impairment, as indicated by a score of 33 or less out of a total possible 37 points. Of the 315 participants, 66 (21%) scored at least 34 points, meeting the test’s criteria for “no dementia.” Of the 238 female subjects, 81% demonstrated some degree of cognitive impairment, compared with 75% of the 77 male subjects (\( p = .31 \)). In this subsample, cognitive impairment (as well as tobacco or alcohol use) did not statistically affect which age of disease onset category the subjects belonged to (\( p > .05 \), Breslow-Day test).

Regarding the age of onset for age-related illnesses among the centenarian subjects and excluding cognitive impairment and cataracts because of the difficulty in ascertaining their age of onset, we found that three categories emerged: Survivors (age of onset < 80 years), Delayers (age of onset 80–99 years), and Escapers (no history of any of the diseases prior to age 100). Table 3 indicates the frequency of male and female centenarians that fall into each of these categories when heart disease, nonskin cancer, stroke, skin cancer, hypertension, Parkinson’s disease, COPD, diabetes, thyroid disorders, and osteoporosis are considered. Women were 2.53 times as likely as men to be Survivors (95% CI 1.49, 4.27, \( p = .0004 \)). Men were 2.71 times as likely as women to be Escapers (95% CI 1.60, 4.60, \( p = .0001 \)). Removing from the analysis the two diseases known to be particularly more frequent among elderly women versus men, osteoporosis and thyroid disorders, we found that women were 2.28 times as likely as men to be Survivors (95% CI 1.26, 4.11 \( p = .005 \)) and men were no longer statistically different from women in terms of the Escaper category (OR = 1.34, 95% CI, 0.83, 2.15). Finally, when considering only the three major lethal illnesses among elderly, people, that is, heart disease, stroke, and nonskin cancer, women were not statistically different from men in terms of all three morbidity profiles.

**Table 2. Lifetime Disease Prevalence and Ages of Diagnoses**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosis Prevalence (%)</td>
<td>Diagnosis Age Range (y)</td>
</tr>
<tr>
<td>Stroke</td>
<td>14</td>
<td>68–102</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>42</td>
<td>55–109</td>
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<tr>
<td>Cardiac arr.</td>
<td>25</td>
<td></td>
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<tr>
<td>Myocard. Inf.</td>
<td>13</td>
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</tr>
<tr>
<td>CHF</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Nonskin cancer</td>
<td>20</td>
<td>45–110</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19</td>
<td>38–102</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>29</td>
<td>50–107</td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>8</td>
<td>40–100</td>
</tr>
<tr>
<td>Parkinson’s dis.</td>
<td>3</td>
<td>75–102</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>14</td>
<td>80–100</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>90–98</td>
</tr>
<tr>
<td>COPD</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>Cataracts</td>
<td>82</td>
<td>50–109</td>
</tr>
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*Notes: CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.*

**DISCUSSION**

Three morbidity profiles emerged from the analysis of health history data: 38% were Survivors, those subjects diagnosed with an age-associated disease before the age of 80; 43% in the sample were Delayers, subjects who were diagnosed with age-associated disease at or after the age of 80, beyond the average life expectancy for their birth cohort; the third morbidity profile, the Escapers, who made up 19% of the centenarian sample, attained their 100th birthday without the diagnosis of the 10 common age-associated diseases investigated. These results suggest there may be multiple routes to achieving exceptional longevity. We began our studies of centenarians with the hypothesis that centenarians achieve their ages by markedly delaying or escaping age-associated diseases. However, these results suggest that a significant portion of centenarians might not fit this profile but rather have the means to cope with diseases that would otherwise cause “premature” mortality. The Survivor, Delayer, and Escaper routes represent different centenarian phenotypes and thus likely different genotypes as well. The categorization of centenarians into these and other groups (e.g., cognitively intact or smokers) should prove to be useful in the study of factors that determine exceptional longevity (15).

According to the Danish Centenarian Study, only one of the over two hundred 100-year-old subjects that were studied were disease free (16). Among our sample of centenarians aged 100–119 years, 19% were disease free at age...
100. Their inclusion of osteoarthritis as one of the diseases, which is nearly ubiquitous among the very old, negated the ability for virtually any subject to be an Escaper in the Danish study. Prevalences of specific diseases also varied significantly from those reported in the study, with some being higher (e.g., 72% had cardiovascular disease compared with ~40% in our sample) and some being lower (e.g., 52% had dementia compared with the 79% we noted to have at least mild cognitive impairment). The variation between the two studies most likely relates to the different disease definitions, the diseases included in profiling the centenarians, and the fact that hands-on examinations are more sensitive for the detection of diseases than the interview- and questionnaire-based methods utilized in the New England study. The Danish study did not address the age of onset for diseases occurring prior to the age of 100. Despite these differences, both studies concluded that a minority of centenarians exist that continue to be cognitively intact and well-functioning beyond their 100th birthdays.

When only heart disease, stroke, and nonskin cancer are examined, which are three common causes of mortality in elderly persons, approximately 50% of male and female centenarians reached their 100th year of life without these diseases (17). Approximately one third of male and female centenarians delayed the onset of the commonly fatal illnesses until at or after the age of 80. Thus, 87% of male and 83% of female centenarians markedly delayed or escaped the most severe of the diseases examined, presumably allowing them to reach exceptional longevity. However, it is of interest that approximately 16% of centenarians experienced heart disease, stroke, or nonskin cancer before the age of 80 and thus survived 20 or more years with a current or past diagnosis of a disease that is otherwise associated with a significant mortality risk in the general elderly population. For this birth cohort of Survivors, born no later than 1900, these diseases became clinically evident before 1980. To better understand how Survivors were able to live such a long part of their lives with the history or presence of one or more of these lethal diseases, and during the most vulnerable period of their adult lives, more detailed medical histories and an understanding of any medical and surgical interventions is warranted.

Specifically regarding cancer, 20% of centenarians had a lifetime history of nonskin cancer. In his review of 1990 U.S. vital statistics and census data, Smith noted that although cancer deaths accounted for nearly 40% of all deaths occurring in adults between the ages of 50 and 69 years, only 4% of all deaths were due to cancer among centenarians (18). Miyaishi and colleagues reviewed Japanese autopsy records between 1991 and 1996. Previous reviews of these data indicated that cancer incidence peaked in the sixth decade and multiple cases peaked in the eighth decade. The Japanese study reported that, compared with 90- to 94-year-olds, centenarians had a 75% reduced prevalence of metastases and a 66% reduced rate of mortality caused by cancer (19). The reduced rates of cancer deaths and metastases among centenarians are compelling. We are currently assembling a series of centenarian subjects who have undergone postmortem autopsies to further investigate the rate of occult malignancies or premalignant lesions. A further study of centenarians might be helpful in discerning the genetic and environmental factors that imparts resistance to cancer and its ability to metastasize.

Female subjects were significantly more likely than male subjects to develop illness before the age of 80. Male centenarians also had significantly fewer comorbidities than female centenarians. For the 10 diseases reviewed, 32% of male centenarians were escapers compared with 15% of females (Table 3). Even though far fewer men make it to the centenarian mark (generally 85% of centenarians are women), these findings suggest that male centenarians have considerably fewer diseases and have greater compression of morbidity toward the end of their lives compared with female centenarians. Franceschi and colleagues also found male centenarians to be healthier than their female counterparts (20). Whereas older women appear to be better able to cope and live with age-associated diseases, older men appear to be more likely than women to die from potentially lethal illnesses (21). Thus, it is likely that the men who are able to achieve very old age must be especially fit and delay or escape potentially lethal illnesses practically until their centenarian years. This exceptional survival prowess is illustrated by our previous observation that the survival curve of brothers of centenarians occurs to the right of female subjects from the general population belonging to the same birth cohort (13). The substantially higher probability of survival to very old age for the brothers of centenarians is consistent with the hypothesis that, relative to women, men require a greater “dosage” of the factors that lead to the ability to achieve extreme age (22).

It must be kept in mind that the lifetime prevalence rates and age-defined morbidity profiles reported here did not include dementia or cognitive impairment. Although the estimate of cognitive impairment prevalence among a subgroup of the sample (79%) agreed with previous dementia prevalence studies of centenarians, the retrospective nature of the study, which was based on the lifetime prevalence of dementia at the age of 100, the lifetime prevalence of dementia at the age of 85 is warranted.
of this study negated our ability to accurately determine the age of onset of dementia (11,23). We did note, however, that the presence or lack of cognitive impairment at age 100 or older did not affect which morbidity profile the subjects fell into. As some individuals in various population-based longitudinal studies are now approaching extreme old age, researchers will be able to include illnesses such as Alzheimer’s disease in this morbidity profile approach (24–27).

There are several important limitations to this study. First, the age of diagnosis of disease does not necessarily correlate to the age of onset of disease. Rather, the age of diagnosis should be used as a proxy for the age of onset of disease in comparisons between the sexes. Self-report of disease prevalence has inherent limitations. Previous studies have shown that recall of diagnosis is accurate for well-defined chronic conditions and that neither sex, race, nor education have a major effect on the accuracy of self-report (28–30). Other studies have indicated that under-reporting of some life-threatening diseases can occur as a result of denial (30). In this study, approximately 90% of subjects were represented by a proxy, most often their child. The use of a proxy could counter some of the potential denial or inaccuracy that might otherwise occur. Thus, these results should be regarded as estimates constrained by the practical considerations of studying a dispersed group of centenarians. Any underestimation or overestimation of disease prevalence would presumably be similar in men and women, making comparisons of the two groups relatively sound.

Demographic selection would dictate that centenarians are more similar to one another than younger elderly people. They likely have important genetic and environmental factors in common that facilitate the ability to achieve exceptional old age (3,13,31). However, the results presented here indicate that centenarians can still be heterogeneous enough to warrant careful phenotyping for the purposes of discovering different potential genetic and environmental correlates of exceptional longevity. In addition, there may be distinctive genetic and environmental interactions involved in the exceptional longevity of men versus women. The creation of morbidity profiles provides a framework for further investigation into the genetic and environmental factors underlying exceptional longevity. The results presented here justify future study not only into the ability of centenarians to delay or escape disease, but also into their ability to survive with illness for a very long time.

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