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Original article

Low tobacco-related cancer incidence in offspring of long-lived siblings: a comparison with Danish national cancer registry data

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ABSTRACT

Purpose: Familial clustering of longevity is well documented and includes both genetic and other familial factors, but the specific underlying mechanisms are largely unknown. We examined whether low incidence of specific cancers is a mechanism for familial clustering of longevity.
Methods: The study population of individuals from longevity-enriched families consisted of 3267 offspring from 610 Danish long-lived families defined by two siblings attaining an age of 90 years or more. The offspring of the long-lived siblings were followed from 1968 to 2009. Using high-quality registry data, observed numbers of cancers were compared with expected numbers based on gender-, calendar period-, and age-specific incidence rates in the general population.
Results: During the 41-year-follow-up period, a total of 423 cancers occurred in 397 individuals. The standardized incidence ratios (95% confidence interval) for offspring of long-lived individuals were 0.78 (0.70–0.86) for overall cancer; 0.66 (0.56–0.77) for tobacco-related cancer; 0.34 (0.22–0.51) for lung cancer; 0.88 (0.71–1.10) for breast cancer; 0.91 (0.62–1.34) for colon cancer.
Conclusions: The low incidence of tobacco-related cancers in long-lived families compared with non–tobacco-related cancers suggests that health behavior plays a central role in lower early cancer incidence in offspring of long-lived siblings in Denmark.

Introduction

Familial clustering of longevity has been demonstrated in a number of studies in different populations. It has been shown that relatives of individuals or sib pairs attaining high ages have a better survival than comparison groups [1–3]; that the oldest proportion

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of a population is more closely related than would be expected by chance [4]; and that the association between long-lived probands and survival in their relatives is stronger the closer they are related [4,5]. Several studies of Scandinavian twins found that life span is moderately heritable [6–8], and that the heritability is likely to increase at the highest ages [9]. Less is known about the mechanisms behind the familial clustering of longevity, but both genetic and environmental factors contribute to longevity. In cross-sectional studies, evidence has been provided for better health status in longevity-enriched families compared with control groups not enriched for longevity in terms of lower prevalence of myocardial infarction, hypertension, diabetes, cardiovascular disease, and pulmonary disease [10–13]. Interestingly, in a U.S. and a Danish nationwide study [10,12], no association was found between familial longevity enrichment and cancer prevalence, and in a Dutch study [14], no association between number of cancer-associated risk alleles and longevity-enriched families was found. Studies involving other measures of health such as self-rated health and physical measures [12] and measures of tasks requiring attention, working memory, and semantic processing [15] found favorable outcomes in offspring of longevity-enriched families when compared with individuals without a family history of exceptional survival.

To better understand the mechanisms that lead to these states of good health in long-lived families and to longevity itself, longitudinal studies are needed that follow members of these families over time. Some such studies exist and have found lower cause-specific mortality and delayed onset of disease for several leading causes of death [16–19], but only one [18] found lower cancer mortality. The previously mentioned literature provides mixed evidence for a lower cancer occurrence as a mechanism for clustering of longevity in families. Although some animal studies indicate a trade-off mechanism between aging and the risk of cancer [20–24], two more recent studies suggest that familial longevity enrichment is associated with lower cancer incidence [25,26]. In the following, we take advantage of Danish population registers, and the screening of long-lived families in three nationwide studies to shed light on possible mechanisms by comparing incidence of all cancers except nonmelanoma skin cancer, as well as incidence of specific common cancer types, breast cancer, colon cancer, prostate cancer, lung cancer, and tobacco-related cancer, in the long-lived families, with population-based cancer incidence rates stratified for gender, age, and calendar period. The offspring generation of long-lived families is thus compared to the entire Danish population using the population-based rates. Based on the Danish twin study [25], we expect to find lower cancer incidence among offspring, indicating that lower cancer occurrence is contributing to familial longevity. Also, incidence of specific cancers may provide further information about the mechanism.

Methods

Study population

For a more detailed description of the procedure for identifying and including offspring from long-lived families, see Appendix. Here, follows a brief outline of the inclusion procedure: The identification of offspring from long-lived families was undertaken in three nationwide, consecutive studies in Denmark, for which recruitment ran sequentially during the years 2004 to 2009, a pilot study—Danish Oldest Siblings (DOS) pilot study, the Genetics of Healthy Aging (GeHA) study [27], and the Long Life Family Study (LLFS) [28].

Initially, all individuals born before April 2, 1918, and alive in 2004 were identified in the Danish Civil Registration System (DCRS), which covers all persons alive and living in Denmark on or after April 2, 1968 [29]. Identification of long-lived sib pairs from the DCRS and church records is described in the Appendix. In all, 1511 siblings from 659 families were enrolled in either DOS, GeHA, or LLFS, with 246 siblings from 114 families in DOS, 1000 siblings from 469 families in GeHA, and 265 siblings from 76 families in LLFS. To further ensure reliable family information and that the families in this study were strongly enriched for longevity, we restricted our study population to the offspring of those siblings who (1) participated in an interview in either DOS, GEHA or LLFS, (2) survived to the age of 90 years or more before July 1, 2010, and (3) had at least another participating sibling surviving to the age of 90 years or more before July 1, 2010. This means that the population under study consisted of the offspring of those sets of siblings who survived to the age of 90 years or more and participated in an interview (DOS, GEHA, or LLFS). A total of 1405 siblings from 628 families (99 families in the DOS, 454 families in the GeHA study, and 75 families in the LLFS) fulfilled these criteria. Of the 1405 siblings, 264 had no offspring, so of the remaining 1141 siblings from 611 families, 3297 offspring were identified. Of these offspring, six had unknown vital status in the DCRS, further 17 had a status as emigrants at the end of study in 2009 but with an unknown date of emigration, and one with emigration status had emigrated before April 2, 1968; four offspring had died at an unknown date, and two had died before April 2, 1968. The remaining 3267 offspring from 610 families comprise our study population.

Cancer incidence

To study cancer incidence in the long-lived families, we used the personal identification number to link the study population to the Danish Cancer Registry (DCR) [30]. This registry is population-based and contains records of all incidences of malignant neoplasms in the Danish population from 1943 onward. The register is considered almost complete: in a comparison with independent and redundant data from the Hospital Discharge Registry system, death certificates, and a pathology register, the validity and completeness of the DCR was found to be 95% to 98% [30–32]. Moreover, with a proportion of 89% of all tumors having been morphologically verified, it has a high degree of validity.

The classification of cancer in the DCR before 1977 was based on the modified *International Classification of Diseases* (ICD) seventh revision classification, between 1978 and 2003 cancer was also classified according to the ICD-Oncology-1 (ICD-O-1) classification, and from 2004 onward, the ICD-10 and ICD-O-3 classifications have both been used. Furthermore, for the period 1978 to 2003, the classification was converted from modified ICD-7 to ICD-10 and from ICD-O-1 to ICD-O-3 [30]. To allow for comparison of cancer incidence across periods of different classification systems, cancer diagnoses were grouped into 41 entities of specific cancers following the methodology in the trans-Nordic cancer study collaboration (NORDCAN) [33,34]. We studied overall incidence as well as breast, colon, prostate, lung, and combined tobacco-related cancer. In the study of all cancers, we excluded nonmelanoma skin cancer, and in the study of overall as well as tobacco-related cancer, we permitted an individual to have several primary cancers while adhering to the International Agency for Research on Cancer or the International Association of Cancer Registries rules of counting multiple cancers in the same site as one primary cancer only [35]. Consequently, prevalent cases do not contribute with new cancers to the cancer site for which they are prevalent, nor do they contribute with risk time for the cancer incidence of that specific site. The category of tobacco-related cancers consisted of the pooling of the following 18 NORDCAN cancer sites (using NORDCAN terminology): lip, tongue, mouth, salivary glands, pharynx,