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Translational Article

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Cancer and Longevity—Is There a Trade-off? A Study of Cooccurrence in Danish Twin Pairs Born 1900–1918

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Background. Animal models and a few human studies have suggested a complex interaction between cancer risk and longevity indicating a trade-off where low cancer risk is associated with accelerating aging phenotypes and, vice versa, that longevity potential comes with the cost of increased cancer risk. This hypothesis predicts that longevity in one twin is associated with increased cancer risk in the cotwin.

Methods. A total of 4,354 twin pairs born 1900–1918 in Denmark were followed for mortality in the Danish Civil Registration System through 2008 and for cancer incidence in the period 1943–2008 through the Danish Cancer Registry.

Results. The 8,139 twins who provided risk time for cancer occurrence entered the study between ages 24 and 43 (mean 33 years), and each participant was followed up to death, emigration, or at least 90 years of age. The total follow-up time was 353,410 person-years and, 2,524 cancers were diagnosed. A negative association between age at death of a twin and cancer incidence in the cotwin was found in the overall analyses as well as in the subanalysis stratified on sex, zygosity, and random selection of one twin from each twin pair.

Conclusions. This study did not find evidence of a cancer–longevity trade-off in humans. On the contrary, it suggested that longevity in one twin is associated with lower cancer incidence in the cotwin, indicating familial factors associated with both low cancer occurrence and longevity.

Key Words: Cancer—Longevity—Trade-off—Twins—Mortality.

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ANIMAL models have supported the idea that apoptosis and senescence, which are important cellular tumor suppressing mechanisms (1–5), could be antagonistically pleiotropic, that is, these mechanisms protect organisms from early life cancer, but in late life, they accelerate the aging phenotypes and the development of a host of age-related diseases. The role of p53 in activating cell cycle checkpoints and apoptosis has been suggested as a specific mechanism for serving as guardian and suppressor of longevity (6). In particular, p53 mutant mice with augmented p53 activity that display early aging sign and at the same time enhance the resistance to spontaneous tumors compared with wild types (7) have promoted the "better cancer protection–accelerated aging" hypothesis. However, an undefined 20 kb region upstream of the p53 gene was also deleted in the p53 mutant mice, and other mice strains do not confirm this association (3,4).

An area that has received particular attention is telomeres and telomerase in cancer and aging. K5-mTert transgenic mice overexpress telomerase in a wide spectrum of tissues, which results in higher incidence of both induced and spontaneous tumors and, accordingly, increased mortality during the first year of life (8). However, despite this elevated

tumor incidence and initial lower survival, the K5-mTert mice show a substantial extension of the maximum life span corresponding to a 10% increase in mean life span compared with wild types. This suggests that telomerase overexpression extends both the maximum life span and the cancer risk in mice (8). Notably, telomerase is a key element in most human cancers as well as central in the aging mechanisms in an interplay with p53 and mitochondrial dysfunctioning (9). The data for humans are rather sparse and conflicting; Van Heemst and colleagues (10) performed a meta-analysis of the published literature in 2005, showing that carriers of the TP53 codon 72 Pro/Pro have an increased cancer risk compared with Arg/Arg carriers, but at the same time, a significantly increased survival at the highest age, suggesting that human p53 protects against cancer but at the cost of longevity.

Although it is expected that long-lived individuals have a lower cancer incidence (as cancer reduces the chances of exceptional longevity; 11), the family (co)occurrence of cancer and longevity is the optimal design for studying the cancer–longevity trade-offs. A study of 106 families with 295 offspring of centenarians in the New England Centenarian Study (12) compared with a similar-sized control group suggested that the offspring of centenarians had lower all-cause, cardiovascular, and cancer mortality compared with the control offspring. This was a small study, and the risk of socioeconomic confounding was considerable. A more powerful study (13) investigated individuals born from 1830 to 1963 using the Utah-population Database Cohort. The study focused on the effect of familial longevity and familial mortality for 10 of the leading causes of death. It was found that families with greater longevity did not die from causes distinct from other members of the cohort; they died from the same causes at reduced rate. Individuals of longer-lived families had lower mortality rate for most age-related diseases including heart disease, stroke, and diabetes but not from cancer. The study has the drawback of being conducted in a special population (Mormons) and only using cause of death data and not cancer incidence data.

In this study, the closest possible relative of long-lived individuals, namely the cotwin of monozygotic (and dizygotic) twins, is used to study the potential cancer–longevity trade-off. The hypothesis is that longevity is positively associated with cancer risk in zero (monozygotic cotwin) and first-degree (dizygotic twins) relatives.

Methods

The present study is based on linkable Danish health registers:

"The Danish Twin Registry" was established in 1954 with ascertainment of twins born 1870–1910. Currently, more than 85,000 twin pairs from birth cohorts 1870–2008 are included in the Registry. Ascertainment has been population based and independent of the traits studied. In the older cohorts, until 1930, both twins had to survive until the age of 6 years to be included (14,15). Vital status was assessed annually through 1979 with information from "the Cause of Death Register." Since 1979 vital status has been updated regularly by linkage to the "Civil Registration System," which includes all persons living in Denmark since April 2, 1968. Based on four questions on the similarity of the two twins, the zygosity of same-sexed twin pairs was assessed. This method classifies 95% of the twin pairs with correct zygosity compared with zygosity assessment by genetic markers (16).

"The Danish Cancer Registry" was founded in 1942 and holds information on cancers diagnosed in Denmark since January 1, 1943 (17). Cancer diagnoses were coded according to a modified International Classification of Diseases (ICD)-7 classification until 2004. Topography and morphology were also coded according to ICD-O-1 classification from 1978 to 2003. Since 2004, cancer diagnoses are registered with ICD-10 codes and topography and morphology coded according to the ICD-O-3 classification. As part of the modernization of the Cancer Registry, cancer diagnoses from 1978 to 2003 were converted to ICD-10, and topography and morphology were converted to ICD-O-3 (18).

In the present study, cancer diagnoses were grouped into 40 entities as defined by the NORDCAN project (19) in order to make diagnoses comparable over the whole period of cancer registration. Data on age-, sex-, and calendar time–specific Danish cancer incidence of all cancers except nonmelanoma skin cancer were obtained from the NORDCAN database.

Study Population

The study population was restricted to Danish same-sexed twin pairs born 1900–1918 for two reasons: First, if a twin was alive at the end of follow-up on December 31, 2008, he/she could still be classified in the group "age at death 90+." Second, the twins were all younger than 44 years at entry into the study, which means that very few cancers had occurred before the follow-up time began.

The Danish Twin Registry comprises a total of 4,356 same-sexed complete twin pairs from the Danish birth cohort of 1900–1918 in which at least one twin was alive on January 1, 1943. Of these, two twin pairs had a twin who emigrated prior to January 1, 1943, making these two pairs uninformative. This resulted in a study population of 4,354 twin pairs or 8,708 twins, of whom 4,064 (46.67%) were men. The distribution on zygosity was 2,724 (31.3%) monozygotic twins, 5,344 (61.4%) dizygotic twins, and 640 (7.3%) twins of unknown zygosity.

Of the 4,354 twin pairs, both twins in 3,785 pairs (87%) had known age at death, and both twins were alive on January 1, 1943, so each twin in these pairs contributed both with risk time and cancer information (outcome) as well as with age at death ("exposure" for cotwin). Of the remaining 569 twin pairs, 147 had one twin who was censored (eg, emigrated) before age 90, so that their cotwin lacked exposure information, and hence, for these pairs, each twin contributed either

with risk time and cancer information or with exposure information but not with both. Similarly, 433 twin pairs had one twin who died before January 1, 1943, so that only their cotwin was included in the cancer risk population, and they only contributed with exposure information (age at death). There was an overlap between these two criteria in that 11 pairs had one twin censored before age 90, whereas the other twin died before 1943. Therefore, a total of 8,139 twins from the 4,354 twin pairs provided risk time and/or cancer occurrence information.

Statistical Analysis

The aim of the statistical analysis was to estimate the association between age at death in one twin (exposure) and cancer occurrence (outcome) in the cotwin. The cancer occurrence in the cotwin was estimated as standardized incidence rate ratios (SIRs), that is, observed cancers divided by expected number of cancers. The expected values were calculated based on the observation time and the age-, sex-, and calendar time–specific cancer incidence data available from the NORDCAN (19) database for the period 1943–2008. SIRs estimation was based on a Poisson regression model treating the cancer incidence rates in the general population as known (ie, without sampling error). The rates were stratified by sex, 5-year age bands, and 5-year calendar periods starting in 1943. Inference for the SIRs was made using a quadratic approximation to the Poisson likelihood. The main exposure variable was the age of the cotwin at death categorized in six groups of ages 0–49, 50–59, 60–69, 70–79, 80–89, and 90+ at death. Tests for trend were made treating this exposure variable as a continuous variable with values 1, 2, 3, 4, 5, and 6 to the six exposure groups in increasing order corresponding to increasing cotwin age at death.

Estimation of SIRs was made for the total sample so that each twin in a pair contributed with information on cancer incidence as well as with exposure information on his/her cotwin for those twin pairs, where both twins had known age at death and both twins entered the risk population. These estimations were supplemented with the two subpopulations where exactly one twin in a twin pair was chosen at random to be included in the risk population and where the other twin in the pair only contributed with his/her age at death as exposure variable. The random selection was made by simulating a sample of independent values from a uniform distribution on (0; 1) and allocating one value to each of the 8,708 twins of the study population. The twin within each pair with the largest value of the simulated value from the uniform distribution was then considered twin 1 and the other twin in the pair twin 2.

In the analyses where both twins in a pair were included, robust estimates of standard errors were used to adjust for twin dependency. SIRs were stratified on sex and zygosity (monozygotic and dizygotic).

Data were analyzed using Stata 11.

Results

The 8,139 twins who provided risk time for cancer occurrence entered the study between ages 24 and 43, with an average age at entry of 32.7 years. At the end of follow-up on December 31, 2008, each participant had been followed until censoring (death or emigration) or to at least 90 years of age, and the total follow-up time was 353,307 person-years with an average of 43.4 follow-up years per participant (range 0.01 –66.0 years). The average age at exit from study was 76.1 (range 24.5–105.4). A total of 2,524 cancers were diagnosed during the study period. Of these, 2,180 individuals had one cancer diagnosis, whereas 163 participants were diagnosed with two cancers, and six participants were diagnosed with three cancers. The overall SIR was 0.94 (95% confidence interval [CI]: 0.90–0.98), and the estimates for men and women were 0.95 (95% CI: 0.89–1.00) and 0.94 (95% CI: 0.89–0.99), respectively. Consequently, for both men and women, the twins in the Registry had a slightly lower cancer incidence than the general population. Stratified on zygosity, the estimated SIRs were .90 (95% CI: 0.84–0.97) for monozygotic (MZ) twins and .97 (95% CI: 0.92–1.02) for dizygotic (DZ) twins.

Both in the overall analyses (Table 1) and the random twin approach (Table 2), as well as the results stratified for

Table 1. Cancer Incidence in Danish Same-Sex Twins Born in 1900–1918 and Stratified for Age at Death of Cotwin

Gender	Lifespan of Cotwin	Observed Number of Cancers	Expected Number of Cancers*	SIR† (obs/exp)	95% CI
Males	0–49 y	132	111.4	1.18	1.01–1.39
	50–59 y	76	71.7	1.06	0.85–1.32
	60–69 y	208	184.0	1.13	0.98–1.30
	70–79 y	348	382.1	0.91	0.82–1.01
	80–89 y	318	363.2	0.88	0.78–0.98
	90+ y	100	137.8	0.73	0.59–0.89
	Total	1,182	1,250.3	0.95	0.89–1.00
Females	0–49 y	114	117.8	0.97	0.81–1.16
	50–59 y	87	71.5	1.22	0.96–1.54
	60–69 y	151	137.0	1.10	0.93–1.31
	70–79 y	281	298.9	0.94	0.83–1.06
	80–89 y	453	508.8	0.89	0.81–0.98
	90+ y	256	297.2	0.86	0.76–0.98
	Total	1,342	1,431.1	0.94	0.89–0.99
Males + females	0–49 y	246	229.2	1.07	0.95–1.21
	50–59 y	163	143.1	1.14	0.97–1.34
	60–69 y	359	321.0	1.12	1.00–1.25
	70–79 y	629	681.0	0.92	0.85–1.00
	80–89 y	771	872.1	0.88	0.82–0.95
	90+ y	356	435.1	0.82	0.73–0.91
	Total	2,524	2,681.4	0.94	0.90–0.98

Notes: CI = confidence interval; SIR = standardized incidence rate ratio. Test for trend in SIRs associated with age of cotwin at death resulted in a statistically significant decline in SIRs with p values of .000007 for men, .013 for women, and .000002 for the combined group.

*Based on age-, sex-, and calendar time–specific cancer incidence in the general population.

†Standardized incidence rate ratio.

Table 2. Cancer Incidence in Danish Same-Sex Twins Born in 1900–1918 and Stratified for Age at Death of Cotwin; Analyses of Subpopulations of One Randomly Selected Twin From Each Twin Pair

Gender	Lifespan of Cotwin	Observed Number of Cancers	Expected Number of Cancers*	SIR† (obs/exp)	95% CI	Observed Number of Cancers	Expected Number of Cancers*	SIR† (obs/exp)	95% CI
		Random twin 1				Random twin 2			
Males	0–49 y	64	55.3	1.16	0.91–1.48	68	56.1	1.21	0.95–1.54
	50–59 y	38	34.1	1.11	0.81–1.53	38	37.6	1.01	0.74–1.39
	60–69 y	106	91.6	1.16	0.96–1.40	102	92.4	1.10	0.91–1.34
	70–79 y	198	216.1	0.92	0.80–1.05	150	166.0	0.90	0.77–1.06
	80–89 y	149	173.4	0.86	0.73–1.01	169	189.8	0.89	0.77–1.04
	90+ y	51	65.1	0.78	0.60–1.03	49	72.7	0.67	0.51–0.89
	Total	606	635.7	0.95	0.88–1.03	576	614.6	0.94	0.86–1.02
Females	0–49 y	59	57.0	1.04	0.80–1.34	55	60.8	0.90	0.69–1.18
	50–59 y	42	35.5	1.18	0.87–1.60	45	36.0	1.25	0.93–1.68
	60–69 y	68	68.5	0.99	0.78–1.26	83	68.4	1.21	0.98–1.50
	70–79 y	121	153.2	0.79	0.66–0.94	160	145.7	1.10	0.94–1.28
	80–89 y	216	245.4	0.88	0.77–1.01	237	263.5	0.90	0.79–1.02
	90+ y	125	154.5	0.81	0.68–0.96	131	142.7	0.92	0.77–1.09
	Total	631	714.1	0.88	0.82–0.96	711	717.0	0.99	0.92–1.07
Males + females	0–49 y	123	112.2	1.10	0.92–1.31	123	116.9	1.05	0.88–1.26
	50–59 y	80	69.6	1.15	0.92–1.43	83	73.5	1.13	0.91–1.40
	60–69 y	174	160.2	1.09	0.94–1.26	185	160.8	1.15	1.00–1.33
	70–79 y	319	369.3	0.86	0.77–0.96	310	311.7	0.99	0.89–1.11
	80–89 y	365	418.8	0.87	0.79–0.97	406	453.3	0.90	0.81–0.99
	90+ y	176	219.6	0.80	0.69–0.93	180	215.4	0.84	0.72–0.97
	Total	1,237	1,349.8	0.92	0.87–0.97	1,287	1,331.6	0.97	0.92–1.02

Notes: CI = confidence interval; SIR = standardized incidence rate ratio. Test for trend in SIRs associated with age of cotwin at death resulted in a statistically significant decline in SIRs in all groups except for the random twin 2 women where the decline was less steep and only marginally statistically significant. The *p* values were .002, .031, .0001, .001, .103, and .001, respectively, for random twin 1 men, women, men + women, and random twin 2 men, women, and men + women.

*Based on age-, sex-, and calendar time–specific cancer incidence in the general population.

†Standardized incidence rate ratio.

Table 3. Cancer Incidence in Danish Same-Sex Twins With Known Zygosity Born 1900–1918 Stratified for Age at Death of Cotwin

Lifespan of Cotwin	Observed Number of Cancers	Expected Number of Cancers*	SIR† (obs/exp)	95% CI
MZ				
0–49 y	59	61.1	0.97	0.76–1.22
50–59 y	39	40.0	0.97	0.69–1.38
60–69 y	115	91.6	1.26	1.04–1.52
70–79 y	195	216.8	0.90	0.78–1.04
80–89 y	269	309.1	0.87	0.77–0.98
90+ y	120	167.1	0.72	0.59–0.87
Total	797	885.7	0.90	0.84–0.97
DZ				
0–49 y	158	142.9	1.11	0.95–1.29
50–59 y	119	96.8	1.23	1.02–1.48
60–69 y	223	208.3	1.07	0.93–1.23
70–79 y	396	418.8	0.95	0.86–1.04
80–89 y	468	520.7	0.90	0.82–0.99
90+ y	229	259.0	0.88	0.77–1.01
Total	1,593	1,646.6	0.97	0.92–1.02

Notes: CI = confidence interval; DZ = dizygotic; MZ = monozygotic; SIR = standardized incidence rate ratio. Test for trend in SIRs associated with age of cotwin at death resulted in a statistically significant decline in SIRs in both groups. The *p* values were .003 for MZ twins and .001 for DZ twins.

*Based on age-, sex-, and calendar time–specific cancer incidence in the general population.

†Standardized incidence rate ratio.

sex (Tables 1 and 2) and zygosity (Table 3), the trend of the association between age at death of the twin and cancer incidence in the cotwin was similar: The SIR tended to be larger among the twins whose cotwin died at a relatively young age, whereas the SIRs were relatively low among the twins whose cotwin died at an older age. The association is slightly less pronounced among the monozygotic twins. In Table 2, the association between cotwin age at death and the SIRs is studied by randomly selecting one twin in each pair as belonging to the risk population and by using the cotwin only in supplying information on exposure, that is, his/her age at death. On the basis of this design, it seems reasonable to assume independence between observations used for the estimation of SIRs. The associations in Table 2 are similar to those found in Table 1, with a tendency of SIR to decline with increasing cotwin age at death. For all tables, tests for trend showed a downward tendency associated with increasing cotwin age at death. The tendency was statistically significant in all cases except for women in the "twin 2 random sample" population. Across the strata of Tables 1, 2, and 3, the estimated rate between SIRs associated with an increase by one category of cotwin age at death varied between .90 and .96. Also, for each of these strata, the log-linear association between cotwin age at death and SIR was found to be a

satisfactory fit to the table (as assessed by a likelihood ratio test) except among MZ twins, where the linearity was not sufficient to capture the pattern of SIRs in the six categories of cotwin age at death ($p = .04$). In all analyses where both twins in a pair were included in the risk population, robust standard errors were used in the CI calculations to adjust for intratwin pair dependency.

Discussion

The present study was undertaken to test the hypothesis that longevity is positively associated with cancer risk in zero (monozygotic cotwins) and first-degree (dizygotic cotwins) relatives. The hypothesis could not be confirmed. On the contrary, it was found that longevity in one twin is associated with lower cancer incidence in the cotwin. The basis for this familial aggregation of cancer and mortality is likely to be both of genetic and environmental origin including behavioral risk factors and socioeconomic conditions.

A modest heritability is found for most cancers with prostate, colorectal, and breast cancer among the common cancer types with the highest heritability (20,21). This, together with the strong effect of cancer on mortality, can contribute to the cancer–mortality association within families. Shared (familial) environmental factors are also likely to contribute to this association: Socioeconomic status correlates within families, and low socioeconomic status is associated with higher mortality as well as most common cancers except breast cancer (22).

As pointed out in the introduction section, there are a number of animal models suggesting that cellular tumor suppressing mechanisms protect organisms from early life cancer, but in late life, they accelerate the aging phenotypes and the development of age-related diseases. However, other animal models do not confirm this association (1–5). Also from an evolutionary perspective, the antagonist pleiotropy theory has been questioned (23). Although telomerase overexpression extends both the maximum life span and the cancer risk in mice and thus indicates a cancer–longevity trade-off (8), a recent study of leukocyte telomere length in humans showed a statistically significant inverse association between telomere length and both cancer incidence and cancer mortality (24), suggesting that increased aging rate (measured as shorter leukocyte telomere length) is associated with higher cancer risk. A possible molecular mechanism could be growth hormone resistance or deficiency, which in animal models has been associated with longevity, whereas in humans, Laron dwarfism, which is characterized by growth hormone receptor deficiency, is associated with a very low cancer and diabetes rate (25).

The strength of the present study is the very large and fairly nonselected sample with thorough cancer registration dating back to 1943 (17). This enables a study where the participants enter into the study in young adulthood and are followed up to death, emigration, or at least 90 years of age, providing a nearly noncensored study population in terms of cancer incidence and longevity. Furthermore, the zygosity information available to the Danish Twin Registry enables the separate analysis for monozygotic and dizygotic twins. It is reassuring that both the overall and all the subanalyses provide the same general pattern with an inverse relationship between age at death in one twin and cancer occurrence in the cotwin, including stratification on sex and zygosity as well as random selection of one twin from each pair.

A limitation of the present study is that 7.3% of the twins have unknown zygosity. Zygosity information has been obtained by questionnaires, and the collection of this information is obtained either through the twins themselves or through close relatives. The zygosity classification for these cohorts was made from the early 1950s, and early death could be one of the reasons for no information on zygosity. Similarly, in the identification of twins in the Danish Twin Registry, which is based on parish records, early death including death from cancers may be a reason for the small proportion of twins not identified through civil registration systems. Early death can also be the reason for the slightly lower overall cancer occurrence in the twin population under study, which is not found in more recent cohorts of the twin register. However, the most statistically significant results are obtained in the groups where the cotwin died after ages 80 and 90, and these are the groups least vulnerable to this potential selection as one member of the twin pair has been alive up to recently and hence been available for providing information on the cotwin. This means that potential nonidentification of early cancer deaths is less likely in the groups where the cotwin died after ages 80 and 90. Accordingly, the inverse association between longevity and cancer incidence may be underestimated.

In principle, the zygosity information should provide information on whether the observed familial aggregation of cancer and mortality is due to shared environmental factors or shared genetic factors. If genetic factors are the main responsible, the inverse association between cancer incidence and cotwin age at death should be stronger in monozygotic twins than in dizygotic twins. If, on the other hand, familial (shared) environmental factors are mainly responsible for the association, there should be little or no differences between the two trends (26). However, even with the large sample size and the long follow-up time, the present study does not have the power to discriminate between these two scenarios, although the results for the 90+ group (Table 3) suggest the influence of genetic factors as the association is stronger in monozygotic twins compared with dizygotic twins.

Obviously, the study is also time and cohort specific, that is, the results might not be generally valid for other time periods and countries, for example, early death in the studied cohorts is to a large extent due to infectious diseases, which are currently, in the Western world, of much smaller importance (27). In order to address some of these limitations, we plan to extend the current study to include twin and cancer

registries in more of the Nordic countries and to study cancer occurrence in exceptionally long-lived families. The latter is possible through the Long Life Family Study (28), which includes nearly 5,000 Danish and U.S. individuals consisting of long-lived siblings, their spouses as well as their children and their spouses. Similarly, we intend to include participants from the GEHA study (GEnetics of Healthy Aging; 29), which comprises long-lived siblings (90+ years) as well as children of these participants. This, combined with the Danish Cancer Registry dating back to 1943, will enable us to test whether the cancer–longevity association within families observed in the present twin study can be confirmed across generations in these long-lived families. Based on the present twin results, we will expect lower cancer incidence in the children of the long-lived siblings, both compared with their spouses and to the background population.

Conclusions

Some animal models and a few observational epidemiological human studies suggest a cancer–longevity trade-off, and plausible biological mechanisms have been proposed. However, in a large sample of Danish twins followed from young adulthood to age 90+ regarding mortality and cancer incidence, no evidence of a cancer–longevity trade-off in humans was found. On the contrary, longevity in one twin was associated with lower cancer incidence in the cotwin, indicating familial factors associated with both low cancer incidence and longevity.

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