Cancer-Related Reductions in Survival: Extent and Duration Evaluated Using a Large Cohort Study of Twins, 1943–2011

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ABSTRACT

Background: The time during which there is an increased risk of death for cancer survivors was evaluated in a large twin study, which allows for matching on shared components such as age, genes, and socioeconomic factors in childhood.

Methods: By use of data from Danish registers, time to death from initial cancer was studied prospectively in twins in two different settings. The twins were diagnosed with at least one cancer in the period 1943 to 2011. Setting I included 5,680 same-sex twin pairs aged 6 and over, while Setting II included 3,218 twin individuals from age 70 and over. The study provides comparisons within twin pairs and across birth cohorts, age at diagnoses, and time at diagnosis.

Results: In 2001 to 2011, the 5-year mortality risk for a twin surviving cancer after the age of 70 was twofold that of the co-twin, regardless of sex and zygosity, and it was 1.5-fold if the twin survived the initial 9 months. After 5 to 6 years, the mortality risk corresponded to that of the co-twin. In previous decades, the excess hazard risk was considerably higher for both older and younger cohorts. There were no indications of change in relative survival across old birth cohorts.

Conclusions: This large twin study suggested that for a cancer-treatment survivor diagnosed at age 70 or later, the additional mortality risk was largely absent 5 years later, by which time the survival relative to the co-twin was 60%.

Impact: Elevated mortality risk after cancer is offset after 5 to 6 years.

Introduction

Cancer is associated with an increased risk of death, but it is unclear how long the increased risk lasts after the initial diagnosis. Surviving several years after diagnosis may eliminate an elevated risk of death relative to peers who did not get cancer. As the risk of death is no longer elevated, the surviving patients may, from a statistical perspective (1), be viewed as having recovered even though the possibility of later cancer recurrence cannot be ruled out. It is of interest to examine how long it takes for the elevated mortality risk to fall away among cancer survivors. A common approach is to consider age-standardized relative survival rates, where patients with cancer are matched to representative individuals in the general population, and where it is an underlying assumption that cancer deaths are a negligible proportion of all deaths in the general population. However, relative survival can lead to misestimates (1). An alternative is to use a matched cohort design that actively uses the matched structure and where controls are matched to patients at the time of exposure (2). In the current study, such a matched cohort study was performed on Danish twins.

By examining matched twins, one reduces genetic predisposition; socioeconomic, childhood background factors; and lifestyle differences that may introduce problems in the traditional relative survival approach. Noteworthy, cancer incidence for twins is comparable with that of the background population (3), twins are not at a different risk of specific cancers when compared with non-twins (4), and mortality after the age of 6 for Danish twins corresponds to that of the background population (5). In addition, no substantial or systematic difference in survival after infancy has been found between monozygotic and dizygotic twins (6). However, a difference in infant mortality with higher mortality among twins than in the general population has been uncovered (7).

The predominant risk factor for developing cancer is age, and in the increasing ageing populations an elevated incidence of cancer is expected in the coming years with predictions of an increase of 45% from 2010 to 2030 in the United States and of 32% in Denmark towards 2030 (8, 9). Age-specific incidence rates of cancer generally peak around the age of 80 followed by a decline after the age of 85. Explanations for the reduced risk of cancer for older adults include biological mechanisms (10) as well as an abated diagnostic activity at high age (11). Positive advances in overall and cancer-specific survival have occurred in recent decades (12) with more prominent results for younger than for older persons (9, 11, 13). Compared with the general population, there is a long-term increased risk of cardiovascular mortality for adolescent and young adult cancer survivors (14, 15). Cancer survivors also have an increased risk of several other diseases such as diabetes, asthma, and liver diseases (16). Regarding older patients with cancer, an additional mortality risk is expected because of the cancer itself and many late effects such as lung and heart problems (17).

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Using data from the Danish Twin Register, which was linked to several other registries including the Danish Cancer Register, the overall aim of the current study was to investigate long-term survival reductions associated with cancer and cancer treatment with a focus on cancer diagnosed in old age. The survival reduction was also studied for patients who survived a presumed initial treatment period of 9 months. In addition, it was investigated whether there were modifications across long-lived birth cohorts with respect to the force of mortality. Two distinct analyses were applied. First, time since diagnosis as well as age were used as time scales in a matched cohort setting of same-sex twin pairs from which cumulative excess hazards (CEH) and period effects could be quantified. Second, cohort effects were studied by use of one timescale only (time since diagnosis) in a cohort of twins in old age of any zygosity. In summary, the study considers comparisons within twin pairs as well as across birth cohorts, age at diagnosis, and time at diagnosis.

Materials and Methods

The Danish Twin Register

Twins were identified via the population-based Danish Twin Register, which dates back to 1954 (18). The register covers twins and multiple births from as early as 1870. The identification of twins has been carried out via church records for the early birth cohorts, the Danish Civil Registration System for births after April 1968, and the Medical Birth Register from 1973 (18, 19). The register is considered almost complete from birth cohort 1960 (18). The zygosity misclassification of twins of the same sex is below 5% (20); however, the zygosity of some same-sex twins is undetermined due to the ascertainment method, most often in the birth cohorts from 1870 to 1960 for twin pairs with early mortality (18). For this reason, the mortality of twins registered with unknown zygosity is likely to be higher than for twins with known zygosity (6).

The Danish Cancer Register

All individuals were followed in the Danish Cancer Register, which was initiated in 1943, for cancer diagnoses of type C00–C97, with the exception of C44 (nonmelanoma skin cancer), of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (21). The register classified incident tumors via a modified version of the 7th revision for the period 1943 to 1977 (22).

Setting and study population

A prospective cohort study was performed on Danish-born twins between 1870 and 2009, for whom one or more cancer diagnoses were registered in the corresponding pair of twins. The Lexis diagram in **Fig. 1** illustrates registered onset cancer among Danish twins between the 1870s and the end of 2011. In total, about 12% of the twins had been diagnosed with cancer (corresponding to 12,020 individuals) between 1943 and 2011 with the frequency of cancer diagnoses generally increasing with age. In 2009, the Danish Twin Register had records of 151,091 individuals from 78,756 multiple births of which 99% were Danish (excluding Greenland). Non-domestic born twins, triplets and quadruplets, incomplete twin pairs, and non-survivors until the age of 6 were excluded, leaving 124,838 Danish born twins from complete twin pairs. Of these, 18,436 twins came from pairs with an unambiguous date of the first cancer. The analyses were limited to pairs of twins, where both twins were alive at

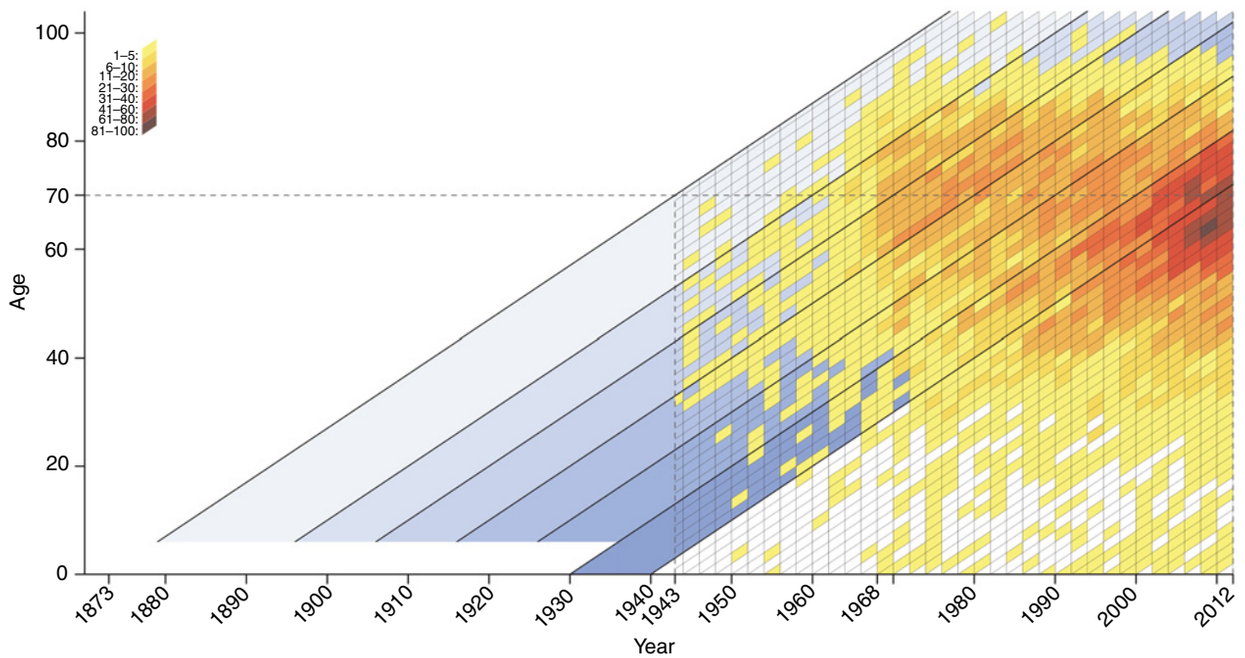

Figure 1.

A Lexis diagram illustrating the number of initial cancers in Danish born twins recorded in the Danish Twin Register. Birth cohorts, which move along diagonal lines between calendar time on the horizontal axis and age on the vertical axis, were recorded in the Danish Cancer Register for cancer diagnosis from 1943 onwards (to the right of the vertical dotted line). The 1873-birth cohort reaches age 70 in 1943 while the birth cohorts from 1942 onwards do not reach age 70 during follow-up. Birth cohorts (shaded) for which cancer was recordable after the age of 70 (above the horizontal dotted line) are considered in Setting II. For the calendar years 1870–1930, twins that died or emigrated before the age of 6 were not followed up in the twin register. All birth cohorts are considered in Setting I from the age of 6.

the first cancer diagnosis, leaving 15,980 twins, corresponding to 7,990 complete twin pairs. Two subsamples were derived: Setting I for the main analyses, which included 5,680 same-sex twin pairs with a first cancer in the pair diagnosed after the age of 6, and Setting II for sensitivity analyses on older twins, which consisted of 3,218 twin individuals from twin pairs born after April 1, 1898, with both members surviving to adulthood 70. The flow chart in Supplementary Fig. S1 summarizes the exclusions.

Statistical analyses

Analyses were twofold: (i) With a matched cohort design actively using the matched structure, the exposed twins (that is, the first diagnosed twin in a pair) were compared with their co-twins. The twins were followed from the date of diagnosis of the first cancer in the twin pair to the date of death or censoring due to emigration or end of follow-up; (ii) using a Cox proportional hazard model, time to death after cancer diagnosis for 70-year-old or older twins was examined, comparing the group of twins who got cancer first to their co-twins.

In Setting I, the excess mortality risk of cancer was estimated by a proportional excess risk model, which matches exposed and unexposed individuals on the age at exposure, where the hazard for the exposed twins was represented as a sum of a population baseline hazard and a proportional excess hazard (2). The method, which removes individual effects on background mortality related to matching, assumes that the risk of mortality for a cancer survivor is the sum of a co-twin–specific background risk, defined on the age timescale, and an excess term for the exposed twins, defined on the timescale starting at the time of exposure. The chosen model captures the structure of the matched design to provide the fairest comparison

Table 1. Baseline characteristics of the study population.

Setting I: Danish born, same-sex twin pairs with one or more cancer diagnoses in the pair at age 6 or later and both members alive at first cancer in the pair.

	Pairs	%	Pairs alive 9 months after first cancer in the pair	%
Total	5,680		4,000	
Year for FCIP				
1943–April 1, 1968	295	5.2	286	7.2
April 2, 1968–1990	1,035	18.2	663	16.6
1981–1990	1,038	18.3	697	17.4
1991–2000	1,379	24.3	952	23.8
2001–2011	1,933	34.0	1,402	35.1
Age at FCIP				
6–39	587	10.3	533	13.3
40–69	3,649	64.2	2,671	66.8
70+	1,444	25.4	796	19.9
Sex				
Male	2,568	45.2	1,663	41.6
Female	3,112	54.8	2,337	58.4
Zygosity				
Monozygotic	1,764	31.1	1,300	32.5
Same-sex dizygotic	3,421	60.2	2,376	59.4
Unknown	495	8.7	324	8.1

Setting II: Danish born twin individuals with one or more cancer diagnoses in the pair at the age of 70 years or later, both members alive at the first diagnosis, and born from April 2, 1898 to December 31, 1941.

	All	Born 1898–1910	Born 1911–1920	Born 1921–1930	Born 1931–1941
Total, no. (%)	3,218	812 (25%)	728 (23%)	790 (25%)	888 (28%)
Age at follow-up, median (IQR)	79.7 (75.5–85.1)	83.2 (77.5–88.5)	83.1 (77.5–89.3)	82.2 (77.4–87.9)	75.7 (73.3–78.4)
Dead during follow-up, no. (%)	2,335 (69.5)	810 (99.8)	671 (92.2)	499 (63.2)	255 (28.7)
Age at FCIP, median (IQR)	74.6 (72.1–78.1)	75.8 (72.6–80.3)	75.9 (73.0–79.4)	75.5 (72.7–79.1)	72.5 (71.2–74.9)
Cancer, no. (%)					
No	1,365 (42.4)	331 (40.8)	298 (40.9)	329 (41.6)	407 (45.8)
Yes, but not cancer first	244 (7.6)	75 (9.2)	66 (9.1)	66 (8.4)	37 (4.2)
Cancer first	1,609 (50.0)	406 (50.0)	364 (50.0)	395 (50.0)	444 (50.0)
Sex, no. (%)					
Male	1,552 (48.2%)	374 (46.1)	324 (44.5)	372 (47.1)	482 (54.3)
Female	1,666 (51.8%)	438 (53.9)	404 (55.5)	418 (52.9)	406 (45.7)
Zygosity, no. (%)					
Monozygotic	822 (25.5)	190 (23.4)	224 (30.8)	258 (32.7)	150 (16.9)
Dizygotic	2,250 (69.9)	584 (71.9)	474 (65.1)	494 (62.5)	698 (78.6)
Unknown	146 (4.5)	38 (4.7)	30 (4.1)	38 (4.8)	40 (4.5)

Abbreviation: FCIP, first cancer in pair.

within the pair, providing the excess hazard function with control for non-shared covariates (2). The model was stratified into three intervals (6–39, 40–69, and 70+) based on age at first cancer in the pair and adjusted for period of year of diagnosis, which was a covariate observed in the exposed individuals. The analysis was repeated on subsets for each combination of sex and zygosity. The procedures were replicated for pairs who were conditioned to be alive 9 months after the first cancer in the pair. The assumptions of proportional hazards were verified by a graphical approach. Analyses were performed using the R-package matchsurv (23), which provides an implementation of the proportional excess risk model by Boschini and colleagues (2).

In Setting II, two groups were considered. The group of exposed twins aged 70 years or older and the corresponding group of co-twins were compared using Kaplan–Meier survival curves and Cox regression models with cluster-robust standard errors. Cancer diagnoses were collected from April 2, 1968 to the end of follow-up on December 31, 2011. Four groups of birth cohorts, each spanning about a decade, were defined by, 1898 to 1910, 1911 to 1920, 1921 to 1930, and 1931 to 1941. For each birth cohort, Kaplan–Meier survival curves for the exposed and unexposed groups were graphed after applying a multiplicative distortion, for anonymity reasons, of a Gaussian distributed random error with mean 1 and SD 0.05. Three age groups for age in years at first diagnosis in the pair were defined by the intervals 70 to 74, 75 to 79, and 80+. The possible time-varying impact on mortality after cancer was assessed by Aalen's additive model from which a functional form (f) was introduced to encapsulate the time-varying effect by fitting a first order regression on the complimentary log-log scale for the corresponding cumulative effect for the exposed group. The time dependent function found was f: $t \to exp(-\sqrt{t})$. The hazard for the exposed group relative to the unexposed group was then estimated via Cox proportional hazard model adjusted for sex, zygosity, birth cohort, age group, and interactions with f. The assumptions of proportional hazards were verified via Schoenfeld residual tests. Analyses were performed using Stata version 16.0 (StataCorp).

Compliance with ethical standards

According to Danish law, ethical approval is not required for register-based studies.

Availability of data

The data behind this work is subject to national data protection laws and restrictions. Access to the data requires an application to the Danish authorities.

Results

Characteristics of twin pairs in Setting I and of twins in Setting II are listed in **Table 1**. For Setting I, the matched analyses were completed on 5,680 same-sex twin pairs with one or more cancer diagnoses, and on the subset of 4,000 pairs that met the condition of being alive 9 months later. The age at onset of cancer was 70 years or more for 1,444 pairs, of whom 55% were alive 9 months later. In Setting II, the age at the end of follow-up and at the first cancer in the pair was lower for the later-born cohorts due to censoring at the end of study (December 31, 2011). There were slightly more females (52%) than males and close to 3 times as many dizygotic as monozygotic twins. Less than 5% of the twins were registered with unknown zygosity.

Results based on Setting I

The estimated periodic effect from the individually matched analysis is summarized with **Table 2**, which shows excess hazard ratios (EHR). A twofold excess hazard [EHR = 1.98; 95% confidence interval (CI), 1.75–2.23] was found among patients with cancer diagnosed in the 70s (1968–1980) when compared with patients with cancer diagnosed in the 2000s (2001–2011), while for the 80s and 90s there was an excess hazard of 70% (EHR = 1.71; 95% CI, 1.51–1.93) and 30% (EHR = 1.32; 95% CI, 1.17–1.49). There was a 40% reduced excess hazard when comparing the period 1943 to 1968 (HR = 0.56; 95% CI, 0.40–0.78) to 2001–2011. Conditioned on 9 months initial survival, the excess instantaneous mortality rate decreased by 10% to 15% (**Table 2**). There was no indication of violating of the proportional hazard assumption between the periods.

Table 2. Multivariable excess hazard models where twins with cancer first are matched to their co-twins. The excess hazard is modelled on the time scale of time since FCIP.

When the pairs are alive at FCIPs		
Year of FCIP	**EHR**	**95% CI**
2001–2011	Ref.	
1991–2000	1.32	1.17–1.49
1981–1990	1.71	1.51–1.93
1968–1980	1.98	1.75–2.23
1943–1968	0.56	0.40–0.78
Given that the pairs are also alive 9 months after FCIPs		
Year of FCIP	**EHR**	**95% CI**
2001–2011	Ref.	
1991–2000	1.10	0.90–1.34
1981–1990	1.54	1.27–1.86
1968–1980	1.77	1.46–2.14
1943–1968	0.68	0.47–0.99

Abbreviation: FCIP, first cancer in pair.

Baseline (i.e., cancer diagnosed in 2001–2011) cumulative curves for excess hazards of death after initial cancer diagnosis with 95% pointwise CIs are shown in **Fig. 2**. For specific timepoints, estimates are given in **Table 3**. For the age group 70+, the cumulative estimates reach an equilibrium 5 to 6 years after onset cancer, which is reflected in **Fig. 2** by a flattening of the upper curve/band and in **Table 3** by the cumulative estimates with CIs reaching a limit. The equilibrium after 5 to 6 years for the age group 70+ corresponded to a relative survival of about 45%, which can be seen from the corresponding survival curves relative to the co-twins (**Fig. 3**). When stratifying by sex and zygosity, it was found that the baseline CEHs from the proportional excess risk models showed almost no difference across sex and zygosity for the age group 70+ (Supplementary Fig. S2). However, curves were more similar for monozygotic than for dizygotic twins in younger age groups. For the age groups 6 to 39 and 40 to 69, the CEH was markedly lower than for the age group 70+, though with no indication of reaching an asymptote within the first 10 years. Conditioned on being alive 9 months after the first cancer diagnosis at the age of 70 or later, the baseline CEH (Supplementary Fig. S3A) reaches an asymptote after the same duration as in the unconditioned analyses, after 5 to 6 years, but at lower CEH. The corresponding survival relative to the co-twin was about 60% (Supplementary Fig. S3B). For specific timepoints, estimates are given in Supplementary Table S1. For the age group 6–39, the CEH was again considerably lower than for the age group 70+; however, compared with the age group 40 to 69, the baseline CEH for the age group 70+ was only slightly increased at most timepoints. The baseline cumulative hazards after stratifying by sex and zygosity are illustrated in Supplementary Fig. S4 for the pairs who survived the initial 9 months.

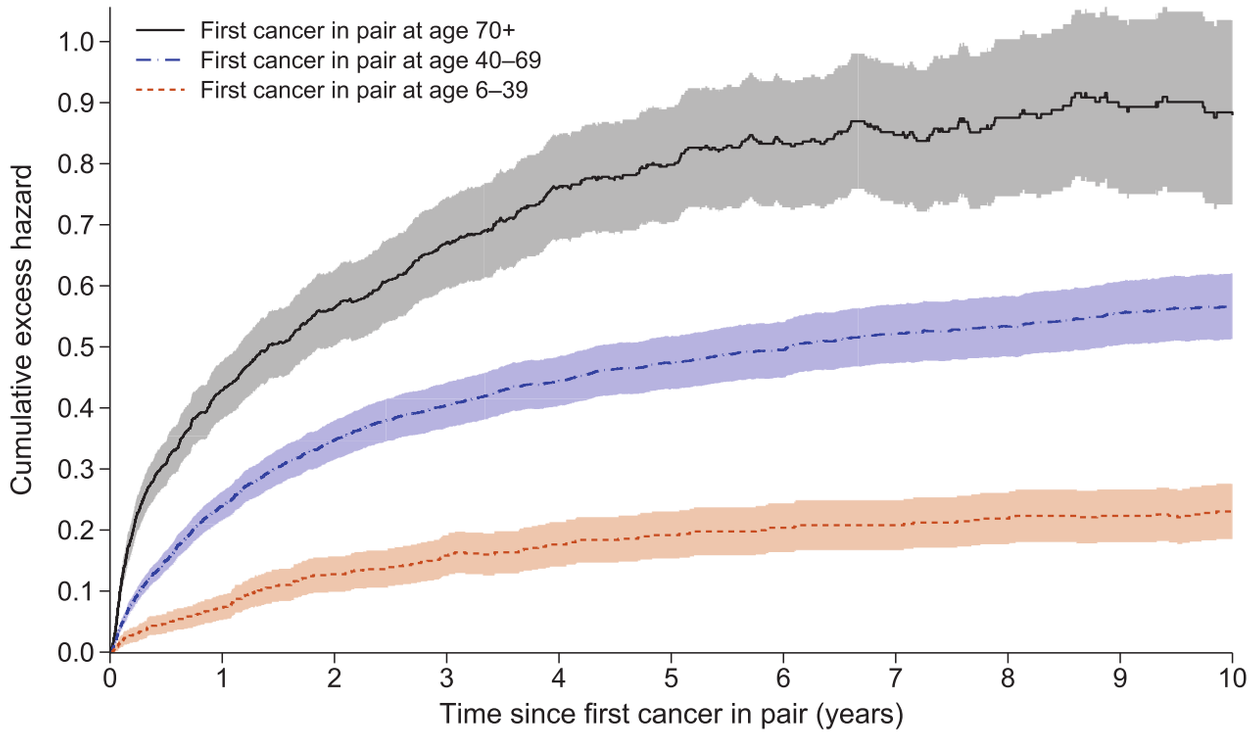

Figure 2.
Cumulative curves for excess hazards of death after initial cancer diagnosis with 95% pointwise confidence bands when year of initial cancer in the twin pair spans over the period 2001–2011. The excess risk model was adjusted for year of initial cancer in the pair and stratified by the age groups 6–39, 40–69, and 70+ years.

Results based on Setting II

For the exposed twins when referenced to the co-twins, the HRs decreased across the four birth cohorts from HR = 0.91 (95% CI, 0.82–1.01) for 1911 to 1920 to HR = 0.59 (95% CI, 0.50–0.69) for 1930 to 1941 when compared with 1898 to 1910; however, no effect modification on getting cancer first was found ($P = 0.89$). While the instantaneous mortality rate for females was less than that for males (at 5 years after onset: HR = 0.67; 95% CI, 0.60–0.75), the impact of getting cancer first was unchanged across sex ($P = 0.40$). There was also no interaction between zygosity and the effect of getting cancer first ($P = 0.55$). The instantaneous mortality rate among dizygotic twins (HR = 1.13; 95% CI, 1.03–1.25) and twins with unknown zygosity (HR = 1.37; 95% CI, 1.10–1.72) was increased when compared with that among monozygotic twins. Supplementary Table S2 lists HRs at specific timepoints for exposed twins referenced to the co-twins. For example, at age 70 to 74 years, there was an eightfold force of mortality (HR = 8.32; 95% CI, 6.90–10.0) 1 year after onset, a fourfold (HR = 4.24; 95% CI, 3.67–4.90) after 2 years, and a twofold after 5 years (HR = 2.03; 95% CI, 1.76–2.34). By the age of 80 or older, these ratios were reduced by a factor of about two. Among the exposed twins, the instantaneous mortality rate was slightly related to the age at cancer onset. If the twins were exposed at 70 to 74 years of age, it was at 80%

Table 3. Estimated baseline CEHs at specific timepoints. Baseline corresponds to year of FCIP in 2001–2011.

Time in years since FCIP	Age 6–39 at FCIP CEH (95% CI)	Age 40–69 at FCIP CEH (95% CI)	Age 70+ at FCIP CEH (95% CI)
1/4	0.031 (0.018–0.044)	0.096 (0.085–0.11)	0.23 (0.20–0.26)
1/2	0.047 (0.031–0.063)	0.15 (0.13–0.17)	0.31 (0.27–0.35)
3/4	0.061 (0.043–0.080)	0.20 (0.18–0.22)	0.38 (0.34–0.43)
1	0.074 (0.054–0.095)	0.24 (0.22–0.26)	0.43 (0.38–0.48)
2	0.13 (0.10–0.16)	0.35 (0.32–0.38)	0.56 (0.50–0.62)
3	0.16 (0.13–0.19)	0.40 (0.37–0.44)	0.67 (0.60–0.74)
4	0.18 (0.14–0.21)	0.44 (0.40–0.48)	0.76 (0.68–0.85)
5	0.19 (0.16–0.23)	0.47 (0.43–0.52)	0.80 (0.71–0.90)
6	0.21 (0.17–0.25)	0.50 (0.45–0.54)	0.83 (0.73–0.94)
7	0.21 (0.17–0.25)	0.52 (0.47–0.57)	0.85 (0.73–0.96)
8	0.22 (0.18–0.26)	0.53 (0.48–0.58)	0.88 (0.75–1.05)
9	0.23 (0.18–0.27)	0.56 (0.50–0.61)	0.89 (0.75–1.03)
10	0.23 (0.19–0.28)	0.57 (0.51–0.62)	0.88 (0.73–1.03)

Abbreviation: FCIP, first cancer in pair.

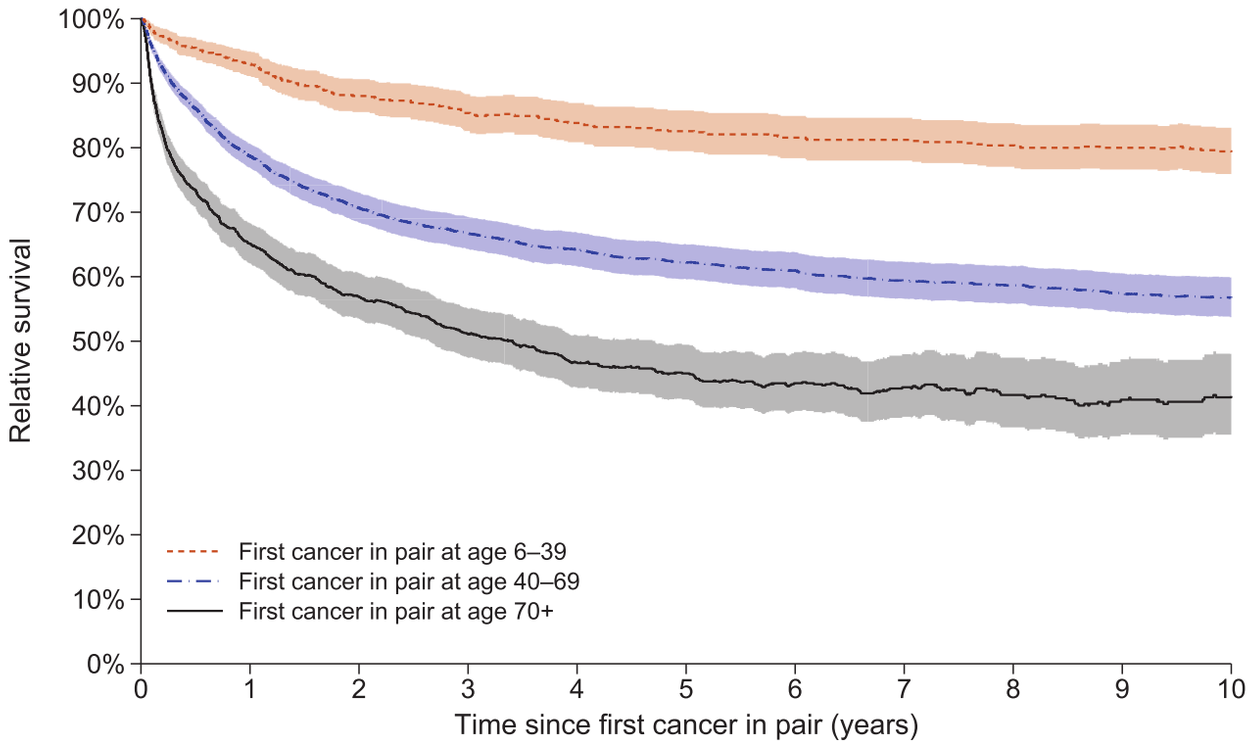

Figure 3.
Survival curves for twins with initial cancer relative to their co-twins with 95% pointwise confidence bands when year of initial cancer in the pair spans over the period 2001–2011. The excess risk model was adjusted for year of initial cancer in the pair and stratified by the age groups 6–39, 40–69, and 70+ years.

(HR = 0.81; 95% CI, 0.69–0.94) of that for twins exposed at age 80 or later. In contrast, the hazard was at about 40% (HR = 0.42; 95% CI, 0.35–0.50) when comparing co-twins in the age group 70 to 74 to co-twins aged 80+. Because time-varying covariates were included in the model, the assumption of proportional hazards was not violated ($P = 0.85$). An overview of estimates is displayed with Supplementary Table S3. Kaplan–Meier survival curves for the four birth cohorts, which are shown in Supplementary Fig. S5A, showed an illusory improvement in median survival across increasing birth cohorts. However, median survival was not comparable across the cohorts due to censored observations. When limiting the age at first cancer diagnosis to the age range 70 to 80 the relative median survival after first cancer in the pair showed little improvement across the four cohorts. The corresponding Kaplan–Meier survival curves are shown in Supplementary Fig. S5B.

Discussion

In this large Danish twin study, which included complete pairs of twins with at least one cancer diagnosis, a levelled CEH was found at 5 to 6 years after initial cancer in late adulthood (age 70+). Statistically, the additional mortality risk for cancer survivors in old age was therefore offset after approximately 5 to 6 years, after which the survival relative to the co-twins was about 45% when the onset cancer was in the 2000s. Given 9 months initial survival, it increased to 60%. These observations were regardless of sex and zygosity. In contrast, there were indications of familial influence in terms of (cancer) genetic effects (24) in the younger age groups for the CEH of mortality. For the age groups 6 to 39 and 40 to 69, the survival relative to the co-twins were at 80% and 60% after 5 years; however, with no indication of being statistically cured within a decade. The comparison by design to the undiagnosed co-twin in the population-based cohort qualifies as the best achievable approach to the scenario "what would happen if the cancer had not arisen". The comparison, which is constructed by considering familial influences, is novel to the authors' knowledge as it adjusts for familial influences and allows for the occurrence of all non-cancer diseases that may affect mortality.

Consistent with previous studies (9, 11, 13, 25), cancer mortality was found to decline over decades, most likely reflecting earlier cancer diagnoses and improvement of cancer treatment over time. The elevated mortality risk after cancer was found to be lessened in more recent decades with a substantial difference between the period before and after 1990. Going from 1991–2000 to 2001–2011, the elevated mortality risk during the initial months after diagnosis declined, while it was largely unchanged when conditioned on 9-month initial survival.

When considering the old birth cohorts in the Danish Twin Register, no indication of HR-change across birth cohorts was found when comparing twins with cancer first with their co-twins. The instantaneous mortality rate when comparing twins with cancer first to their co-twins was found to be eightfold, fourfold, and twofold at 1, 2, and 5 years, respectively, if the first cancer was diagnosed at the age of 70 to 74 years. These ratios decreased with age at cancer onset; if the first cancer was diagnosed at 80 years or later, the HR was instead 4, 2, and not present, respectively. These findings emphasize the need to focus on improving the cancer treatment of older people, although there are many challenges before reaching optimal treatment in this age group (9).

With the introduction of the Danish Civil Registration System, it became possible, with few exceptions, to identify all Danish citizens alive at the beginning of its initialization and onwards. As reflected in the Lexis diagram, April 1, 1968 is a date after which an increase in recorded cancer incidences for twins is expected. The approach used in Setting I adjusts for the unknown incidence of unregistered cancers among twins from 1943 to 1968. Due to the severity of a cancer diagnosis, the underrepresentation in the Danish Twin Register of twins born in 1943 to 1968 leads to seemingly considerably better survival estimates for this period compared with later periods (many early deaths for twins after getting cancer in 1943 to 1968 may never have followed a cancer registration). In Setting II, the selection approach for both age and date of the first cancer in the pair bypasses the issue of April 1, 1968; however, some loss of accuracy is introduced, demonstrated by a wide CI immediately after the onset of the cancer for the effect of getting cancer first.

A notable strength of the study was the large, nonselected sample of Danish twin pairs born from 1870 to 2009 in combination with thorough cancer registration starting in 1943 (22), which gave a study population with few censored observations in relation to cancer incidence and survival for early cohorts. In contrast to other studies, absolute estimates of the impact of cancer were presented, using an individual-matched twin design. It should be noted that matching on co-twin partly resolves problems with alternative approaches like age-standardized relative survival. Matching on co-twin does not control for socioeconomic and lifestyle/behavioral differences in adulthood, which could have associations with both cancer risk and mortality unrelated to cancer. A limitation of nonparametric comparison across birth cohorts was the upper limit of 81 years for detecting cancer for the cohort 1931 to 1941, whereas cancer was detectable at higher ages in the earlier cohorts. Therefore, because life expectancy is highly affected by the age at diagnosis, the change in survival across the four cohorts may be confounded due to selection bias from age at diagnosis. It can be argued that a clearer insight into survival after cancer would be obtained by analyzing twin pairs, where only one twin was diagnosed with cancer during their lifetime and the co-twin was never diagnosed with cancer. However, excluding co-twins with a later cancer would lead to bias in the survival difference between the twin with cancer, who can die from any cause, and the co-twin with no cancer, who can only die of non-cancer–related causes.

The finding of a 5-to-6-year retrieval period from the time of cancer diagnosis in terms of mortality is of validity for the population. On the basis of the current study, general population prognostics of importance for cancer prevention, treatment improvement, geriatric regimes, and related may therefore potentially be improved. Inferred from the matched design, the relative survival was found to increase over the last decades but with no indications of the presence of a cohort effect. Likely explanations for the increase are improved treatment and earlier cancer detection, which are non-shared within the twin pairs, while the rise seems unattributed to improvement in living conditions over recent decades. The findings are for a general cancer diagnosis and may vary considerably according to site-specific cancers or groups of related cancer. As a perspective with the present design, reductions in cancer-specific mortality can be further investigated to reveal the impact from early detection, treatment, and subsequent care on for instance tobacco-related cancers and hormone related cancers that may have different catch-up periods.

In conclusion, for cancer survivors with cancer diagnosed in old age in the 2000s, the excess instantaneous mortality rate was less than for earlier decades, and the mortality risk was comparable with that of healthy individuals after 5 to 6 years, by which time the increased mortality risk was slightly more than twofold.

Authors' Disclosures

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Authors' Contributions

M.D. Villumsen: Conceptualization, data curation, formal analysis, supervision, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **L.J. Ahrenfeldt:** Supervision, visualization, writing–review and editing. **K. Christensen:** Conceptualization, resources, data curation, supervision, funding acquisition, methodology, project administration. **M. Ewertz:** Conceptualization, supervision, methodology, writing–review and editing. **J.B. Hjelmborg:** Conceptualization, resources, supervision, methodology, writing–review and editing.

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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