Number of life-years lost at the time of diagnosis and several years post-diagnosis in patients with solid malignancies: a population-based study in the Netherlands, 1989–2019

Carolien C. H. M. Maas,[a,b,*] David van Klaveren,[a] Otto Visser,[c] Matthias A. W. Merkx,[d,e] Hester F. Lingsma,[a] Valery E. P. P. Lemmens,[a,b] and Avinash G. Dinmohamed[a,b]

[a]Department of Public Health, Erasmus University Medical Centre, Rotterdam, the Netherlands
[b]Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands
[c]Department of Registration, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands
[d]Department of Oral and Maxillofacial Surgery and IQ Healthcare, Radboud University Medical Centre, Nijmegen, the Netherlands
[e]Netherlands Comprehensive Cancer Organization, Utrecht, the Netherlands

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Summary

Background Loss of life expectancy (LOLE) may provide more intuitive information on the impact of cancer than relative survival over a fixed time horizon (e.g., 5-year relative survival). We aimed to assess the evolution of the LOLE using a nationwide, population-based cohort including patients diagnosed with one of 17 most frequent solid malignancies.

Methods From the Netherlands Cancer Registry, we selected adult patients diagnosed with one of the 17 most frequent solid malignancies in the Netherlands during 1989–2019, with survival follow-up until 2022. We used flexible parametric survival models to estimate the LOLE at diagnosis and the LOLE after surviving several years post-diagnosis (conditional LOLE; CLOLE) by cancer type, calendar year, age, sex, and disease stage.

Findings For all cancers combined, the LOLE consistently decreased from 1989 to 2019. This decrease was most pronounced for males with prostate cancer (e.g., from 6.9 [95% confidence interval [CI], 6.7–7.1] to 2.7 [95% CI, 2.5–3.0] for 65-year-olds) and females with breast cancer (e.g., from 6.6 [95% CI, 6.4–6.7] to 1.9 [95% CI, 1.8–2.0] for 65-year-olds). The LOLE among patients with cancers of the head and neck or the central nervous system remained constant over time. Overall, the CLOLE showed that the life years lost among patients with cancer decreased with each additional year survived post-diagnosis. For example, the LOLE at diagnosis for 65-year-old females diagnosed with breast cancer in 2019 was 1.9 [95% CI, 1.8–2.0] compared with 1.7 [95% CI, 1.6–1.8], 1.0 [95% CI, 0.9–1.1], and 0.5 [95% CI, 0.5–0.6] when surviving one, five, and ten years post-diagnosis, respectively. Estimates for other combinations of patient and tumour characteristics are available in a publicly available web-based application.

Interpretation Our findings suggested that the evolution of LOLE substantially varies across cancer type, age, and disease stage. LOLE estimates help patients better understand the impact of their specific cancer diagnosis on their life expectancy.

Funding None.

Keywords: Oncology; Population-based registry; Loss of life expectancy; Flexible parametric survival model

Introduction

The impact of cancer on population-level survival is frequently quantified using relative survival, which estimates cancer patient survival by accounting for the expected mortality from the general population.[1] Relative survival rates reflect excess mortality related to a

Abbreviations: CI, Confidence interval; CLOLE, Conditional loss of life expectancy; IQR, Interquartile range; LOLE, Loss of life expectancy; NCR, Netherlands Cancer Registry; PCLOLE, Proportional conditional loss of life expectancy; PLOLE, Proportional loss of life expectancy

*Corresponding author. Department of Public Health, Erasmus University Medical Centre, Doctor Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands.
E-mail address: c.h.m.maas@erasmusmc.nl (C.C.H.M. Maas).

Research in context

Evidence before this study

Using the search terms ("cancer" AND "flexible parametric survival model" AND "population-based" AND "loss of life expectancy"), we searched PubMed up to January 12, 2022. We retrieved eight studies of which only two comprehensively assessed temporal trends in LOLE for many malignancies. These two studies illustrated that the increase in the life expectancy of Australian patients with cancer was larger than that of the general population for patients diagnosed with leading malignancies over the past decades across all age groups and disease stages, except for those diagnosed with advanced cancers. However, since patients with cancer live longer in contemporary clinical practice, the LOLE of patients surviving several years post-diagnosis may be more informative (i.e., the conditional LOLE) but was lacking in the prior two studies.

Added value of this study

Compared to relative survival, LOLE estimates more intuitively describe the impact of a cancer diagnosis on life expectancy. In this nationwide, population-based study among 1,948,575 adult (≥18 years) patients diagnosed with one of the 17 leading solid malignancies in the Netherlands between 1989 and 2019, we are the first to report (i) the LOLE for each age separately instead of broad age groups and (ii) the conditional LOLE. To the best of our knowledge, this is the first application to present a wide range of life expectancy estimates in patients with cancers.

Implications of all the available evidence

The LOLE estimates allow (i) to inform patients with cancer about the impact of a cancer diagnosis on their lives at diagnosis and after each year survived post-diagnosis and (ii) to assess the effectiveness of oncological care. Overall, the decreasing LOLE in the Netherlands between 1989 and 2019 indicates a reduced impact of a cancer diagnosis on life expectancy, which can be attributed to advances in screening and treatment. Nevertheless, we also found that the LOLE was comparatively high for some malignancies, indicating the need for early detection and better treatment options, even in contemporary clinical practice, particularly in patients diagnosed with advanced cancers. The LOLE conditional on surviving several years post-diagnosis help tailor surveillance activities for survivorship care after treatment.

cancer diagnosis within a fixed period (e.g., up to five years post-diagnosis). Overall, 5-year relative survival increased between the 1990s and 2010s for most cancer types in most countries, although the magnitude of this increase differed across countries, cancer types, and age groups.[2–4]

An inherent drawback of relative survival is that it does not quantify patients' survival over the complete lifespan. Since the early 2010s, measures that can quantify life expectancy have been applied in population-based cancer research due to methodological developments.[1] One such measure is the expected life-years lost, i.e., the loss of life expectancy (LOLE).[5–9] This measure is defined as the difference between the life expectancy of a patient with cancer and the life expectancy of an age-sex-year-matched group from the general population. The LOLE portrays the average number of life years lost after a cancer diagnosis.[5] Compared to relative survival, the LOLE more intuitively describes the impact of a cancer diagnosis on life expectancy. Besides, the LOLE can provide insights into the overall progress in the effectiveness of oncological care. Therefore, it can complement relative survival to monitor advances in cancer management and identify areas for improvement in oncological care (i.e., for cancer types for which the prognosis remained poor).

As of the early 2020s, two Australian population-based studies comprehensively analysed trends in the LOLE due to a cancer diagnosis.[6,7] These studies only assessed the LOLE at the time of cancer diagnosis. However, due to survival improvements in most cancer types, trends in the LOLE for patients who survived several years post-diagnosis (i.e., the conditional LOLE; CLOLE) provide additional information on longevity for cancer survivors. Therefore, this nationwide, population-based survival study aimed to quantify the LOLE and the CLOLE and to assess temporal trends in these measures for patients diagnosed with solid malignancies in the Netherlands between 1989 and 2019.

Methods

Data sources and study population

Data for this nationwide, population-based survival study was extracted from the Netherlands Cancer Registry (NCR), covering all newly diagnosed malignancies in the Netherlands since 1989.[10] The Netherlands Comprehensive Cancer Organisation (IKNL) manages and hosts the NCR. The NCR relies on case ascertainment via the Nationwide Histopathology and Cytopathology Data Network and Archive. Cancer diagnoses not established through histo- and cytopathological analysis were notified to the NCR via the National Registry of Hospital Discharges containing inpatient and outpatient discharges. After case notification to the NCR, trained registrars of the NCR routinely collect a basic dataset consisting of information on sex, birth and diagnosis dates, and disease stage, topography, and morphology via retrospective medical records review. Information on each patient's vital status (i.e., alive, dead, or emigrated) was retrieved annually by linking

the NCR to the Nationwide Population Registries Network, which holds information on the vital status of all residents in the Netherlands. When the data were extracted for this study, the vital status was available until January 1, 2022.

We selected adult (≥18 years) patients diagnosed with solid invasive cancer between January 1, 1989 and December 31, 2019, from the NCR (Figure S1). For patients with multiple cancers, only the first cancer was included in the analyses. Malignancies diagnosed at autopsy were excluded. All patients were followed-up for survival from the date of diagnosis to death, emigration, or end of follow-up (January 1, 2022), whichever occurred first. Collectively, this study focused on the 17 most common solid malignancies in the Netherlands. Solid cancers were defined according to their anatomical localisation (topography) and morphology, according to the International Classification of Diseases for Oncology (ICD-O; Table S1). The supplement provides more information on the editions of ICD-O used over time and the coding of the stage of disease.

According to the Central Committee on Research involving Human Subjects (CCMO), observational, non-interventional studies do not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the NCR approved the use of anonymous data for this study.

Statistical analysis

LOLE was defined as the difference between the life expectancy of patients with cancer and the general population. The life expectancy of the general population was obtained from Dutch population cohort life tables that were stratified by age, sex, and calendar year. The life expectancy of patients with cancer was estimated using the flexible parametric survival model using age, sex, and calendar year at diagnosis and their 2-way interactions.[5] The model includes restricted cubic splines to model the baseline hazard to account for the non-linearity of continuous variables (i.e., age and calendar year at diagnosis) and time-dependent effects. The interaction terms of the continuous variables are modelled non-linearly, but year at diagnosis is modelled linearly in the interaction with age at diagnosis to make the model more robust. The degrees of freedom for the models for each cancer type were determined based on the best Bayesian Information Criterion (BIC), which is explained in detail in the Supplemental Information. We assumed that the excess mortality remained constant after ten years. Separate models were fitted to estimate the life expectancy stratified by disease stage. These models included interaction terms between disease stage and age, sex, and calendar year at diagnosis. The flexible parametric survival models were fitted with the stpm2 command in Stata/SE version 17.0 (StataCorp, TX, USA). The script used for the calculations was made available on Github.[11]

Besides the LOLE, we estimated other related measures using the same models as described above. First, the proportional LOLE (PLOLE) was estimated to compare groups with varying population life expectancy, because the LOLE can vary markedly across age and sex.[1] The PLOLE was calculated by dividing the LOLE by the life expectancy of an age-sex-year-matched group from the general population. Second, the LOLE of patients conditional on surviving several years post-diagnosis was estimated (conditional LOLE; CLOLE). The CLOLE was estimated for patients who survived each additional year post-diagnosis up to ten years post-diagnosis. The CLOLE can also be expressed as a proportion of life lost after surviving several years post-diagnosis (proportional CLOLE; PCLOLE). The PCLOLE was calculated by dividing the CLOLE by the conditional life expectancy of an age-sex-year-matched group from the general population. For example, the PCLOLE of a 65-year-old female cancer patient diagnosed in 2000 conditional on surviving five years after diagnosis is calculated by dividing the LOLE of a 65-year-old female diagnosed in 2000 surviving five years post-diagnosis by the life expectancy of a 65-year-old female conditional on surviving five years after 2000.

The life expectancy, LOLE, and PLOLE were presented according to cancer type, by sex and calendar year of diagnosis, and stratified for three ages at diagnosis (i.e., 45, 65, and 75 years). In addition, we produced a summary of absolute change in PLOLE over time (expressed in percentages) between 1989 and 2019 together with the prognosis in 2019. This summary resulted in three clusters of cancer types with different prognoses in 2019 (i.e., good: PLOLE $\leq$ 25%, intermediate: 25 < PLOLE $\leq$ 50%, and poor: PLOLE > 50%). These estimates were presented for each cancer type, stratified by sex and three ages at diagnosis (i.e., 45, 65, and 75 years). When stratifying by cancer stage we excluded patients with unknown disease stage and the PLOLE was only presented for patients aged 65 years at diagnosis. Finally, the PCLOLE was presented for patients aged 65 years at diagnosis who survived up to ten years post-diagnosis according to three calendar years: 1989, 2005, and 2019.

Role of the funding source

There was no funding source for this study. CCHMM, OV, and AGD had full access to all the data in the study. The corresponding author had the final responsibility for the decision to submit to the publication.

Results

Patient characteristics

Our analytical cohort included 1,948,575 adults (≥18 years) diagnosed with a solid invasive (behaviour code 3 in ICD-O) cancer in the Netherlands between 1989 and 2019 (Fig. 1). Cancers of the breast (18%), colorectum

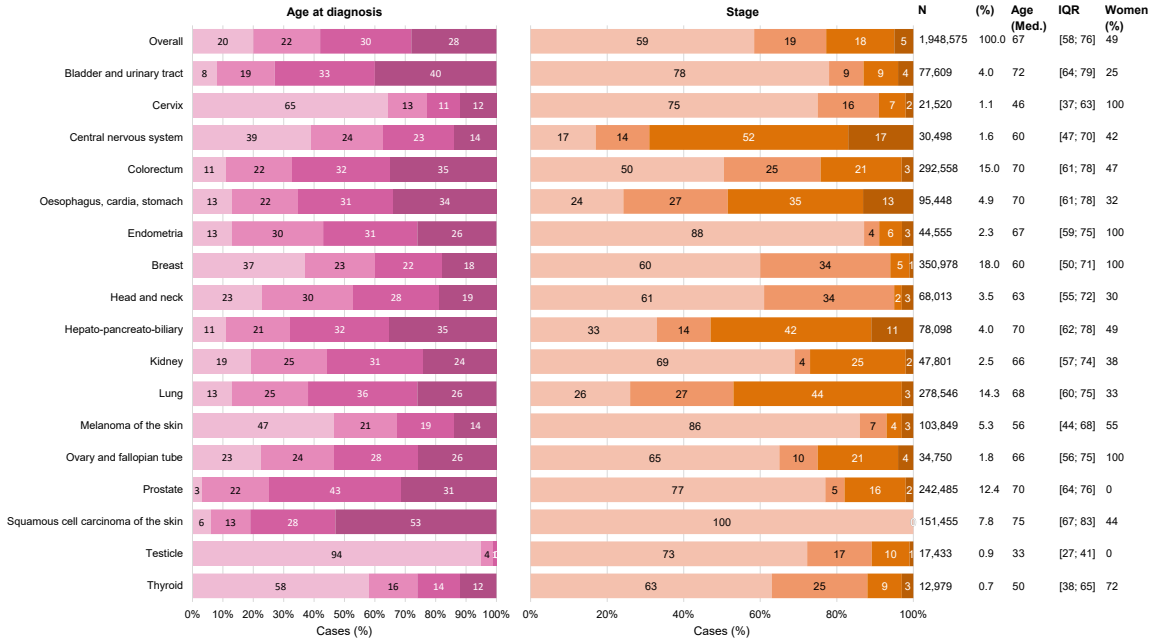

Fig. 1: **Age, stage, and sex distributions of patients diagnosed with a first, primary, solid malignancy in the Netherlands between 1989 and 2019.** The age categories (18–54, 55–64, 65–74, and ≥75 years) are represented by four shades of red (dark to light pink), and stage categories (localised, regional, distant, and unknown) are represented by four shades of green (dark to light orange). Of note, the disease stage for central nervous system (CNS) cancers are defined as follows: (i) localised corresponds with grades one and two, (ii) regional with grade three, and (iii) distant with grade four. Abbreviations: Med, median; and IQR, Interquartile range.

(15%), and lung (14%) were the three most commonly diagnosed malignancies in our cohort. The three most rare malignancies in our cohort were cancers of the cervix (1.1%), testis (0.9%), and thyroid (0.7%). The median age at diagnosis for the overall cohort was 67 years (interquartile range [IQR], 58–76), with notable differences across the cancer types, ranging from 33 years (IQR, 27–41) in testicular cancer to 75 years (IQR, 67–83) in squamous cell carcinoma of the skin. Furthermore, our study cohort had a slight male predominance (51%), with different sex distributions across the non-sex-specific cancer types. For example, bladder cancer was more observed in males (75%), whereas the incidence of thyroid cancer was higher in women (72%). Lastly, there was variation across the cancer types in the stage distribution: squamous cell carcinoma of the skin was diagnosed mainly in the localised stage (99.7%), while cancers of the central nervous system were diagnosed mainly in the advanced stage (52%).

Patterns for all cancers combined

The life expectancy of patients with all cancers combined increased between 1989 and 2019, irrespective of age and sex (Fig. 2). This increase followed a gradual pattern, although the increase in absolute terms was more significant for younger individuals. For example, 45-year-old females diagnosed in 1989 and 2019 would, on average, have 18.8 [95% confidence interval [CI], 18.6–19.0] and 26.9 [95% CI, 26.7–27.2] life years remaining, respectively. On the other hand, the corresponding estimates for 75-year-old females were 5.6 [95% CI, 5.6–5.7] and 8.4 [95% CI, 8.3–8.4], respectively.

The life expectancy of patients with all cancers combined increased more noticeably than the life expectancy of the general population (Fig. 2). As a result, the LOLE for all cancers combined decreased between 1989 and 2019 (Fig. 3). Nevertheless, the magnitude of this decrease varied across ages. The reduction in the LOLE was most pronounced for 45-year-olds, while it was less pronounced for 75-year-olds. For example, 45-year-old females diagnosed in 1989 and 2019 have a reduced LOLE of 19.6 [95% CI, 19.4–19.8] and 12.1 [95% CI, 11.8–12.3] years, respectively. The corresponding estimates for 75-year-old females were 6.0 [95% CI, 6.0–6.1] and 4.4 [95% CI, 4.3–4.4] years, respectively. This age-related difference in the LOLE is explained partly due to younger individuals having more life years remaining than older individuals.

The proportion of expected life lost (i.e., PLOLE) considers this varying population life expectancy across age at diagnosis. Our analysis revealed varying trends in PLOLE across different cancer types. While younger female patients with all cancer types combined tended to lose a smaller proportion of their lives after diagnosis than older female patients, this was not the case

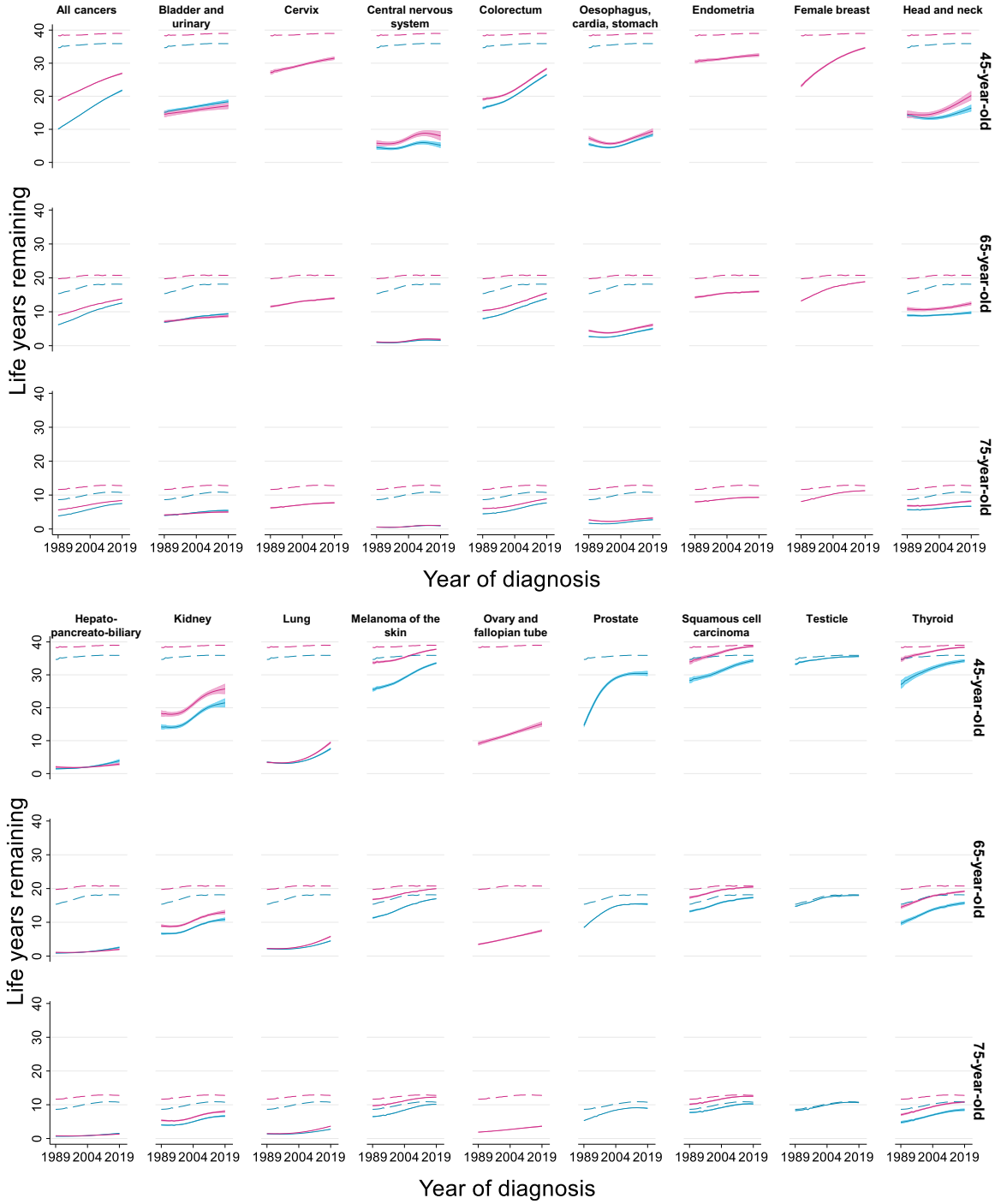

Fig. 2: **Life expectancy of the general population (dashed line) and cancer patients (solid line) with a 95% confidence interval (shaded area) for males (blue) and females (pink).**

for certain cancers, such as those affecting the oesophagus and stomach, head and neck, lung, and breast (Fig. 4). For the overall cohort, in 2019, the PLOLE for females aged 45 years was 30.9% [95% CI, 30.3%–31.6%], while for those aged 75 years, it was 34.3% [95% CI, 33.8%–34.7%], resulting in a 7.7-year difference in LOLE. On the other hand, for all cancer types combined, younger male patients lost a higher proportion of their lives after a cancer diagnosis compared to older male patients, which was primarily

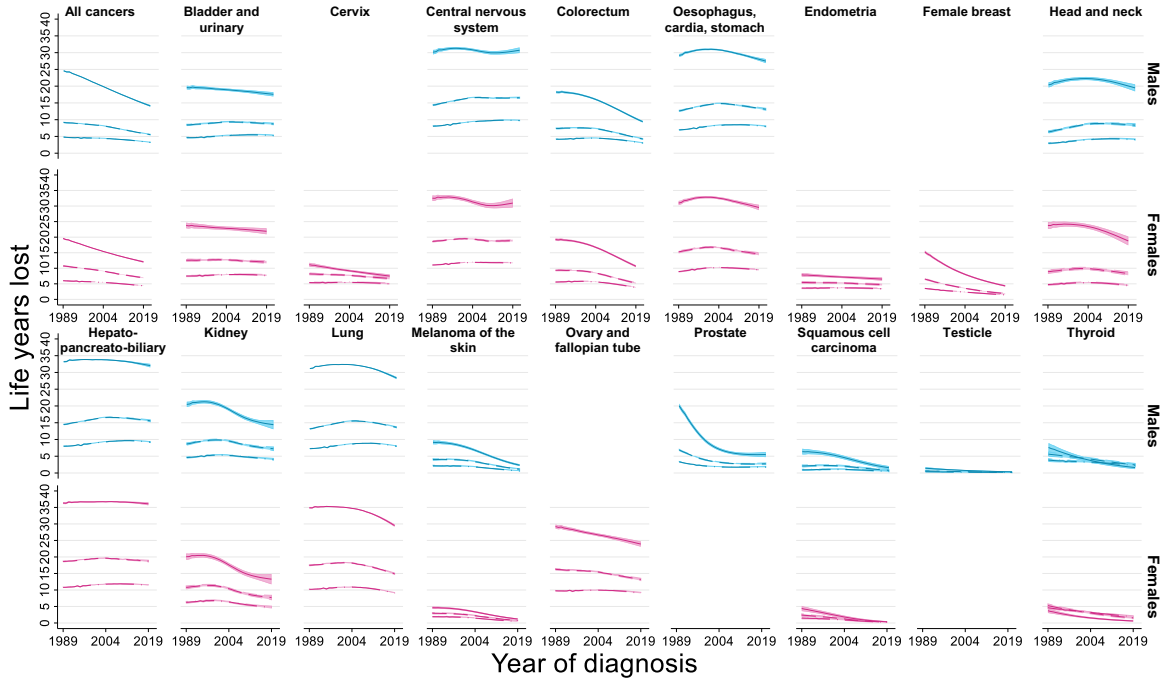

Fig. 3: Loss of life expectancy for 45-year-old (solid line), 65-year-old (dashed line), and 75-year-old (long dashed dotted line) male (blue) and female (pink) patients diagnosed between 1989 and 2019.

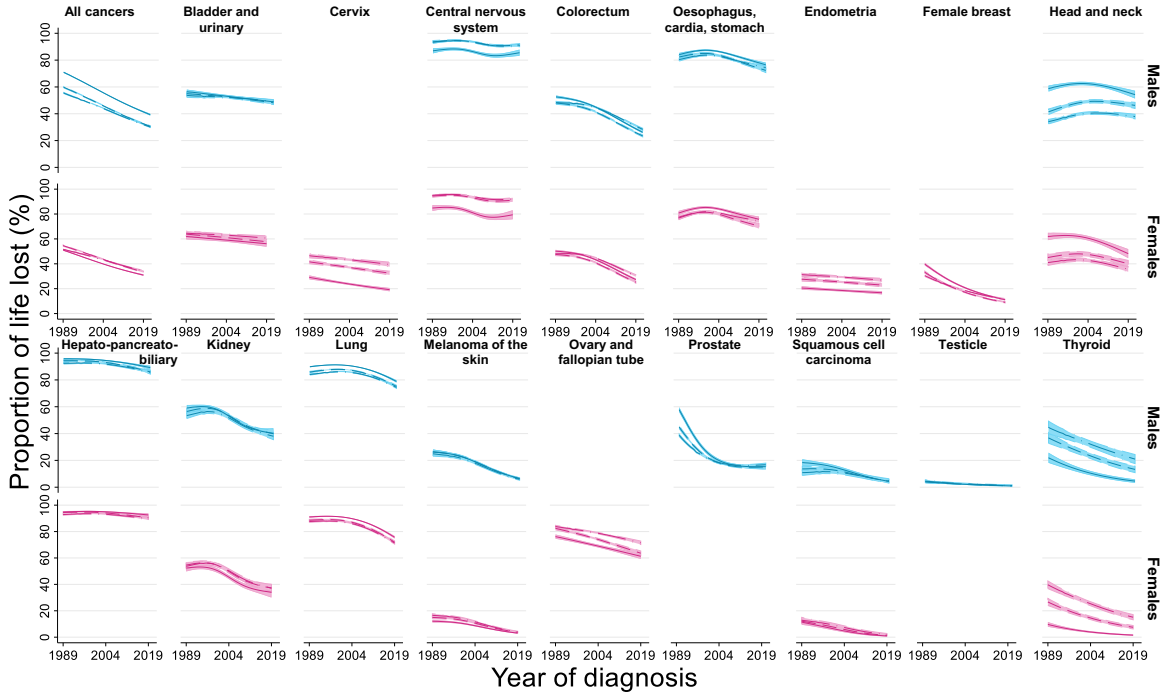

Fig. 4: Proportional loss of life expectancy for 45-year-old (solid line), 65-year-old (dashed line), and 75-year-old (long dashed dot line) male (blue) and female (pink) patients diagnosed between 1989 and 2019.

driven by cancers of the oesophagus and stomach, head and neck, and lung that were more prevalent in males (Figs. 1 and 4).

For all cancers combined, patients diagnosed in 1989 lost a more significant proportion of their lives after a cancer diagnosis than those diagnosed in 2019. For example, the PLOLE of females aged 65 years decreased from 54.6% [95% CI, 54.1%–55.1%] to 33.5% [95% CI, 32.9%–34.0%] between 1989 and 2019, corresponding to a decrease in the LOLE of 3.8 years (Figs. 4 and 5). Collectively, the PLOLE provides a greater understanding of the impact of a cancer diagnosis on the LOLE across ages, sex, and calendar year. In the remainder of this manuscript, we will report on cancer-specific patterns using PLOLE.

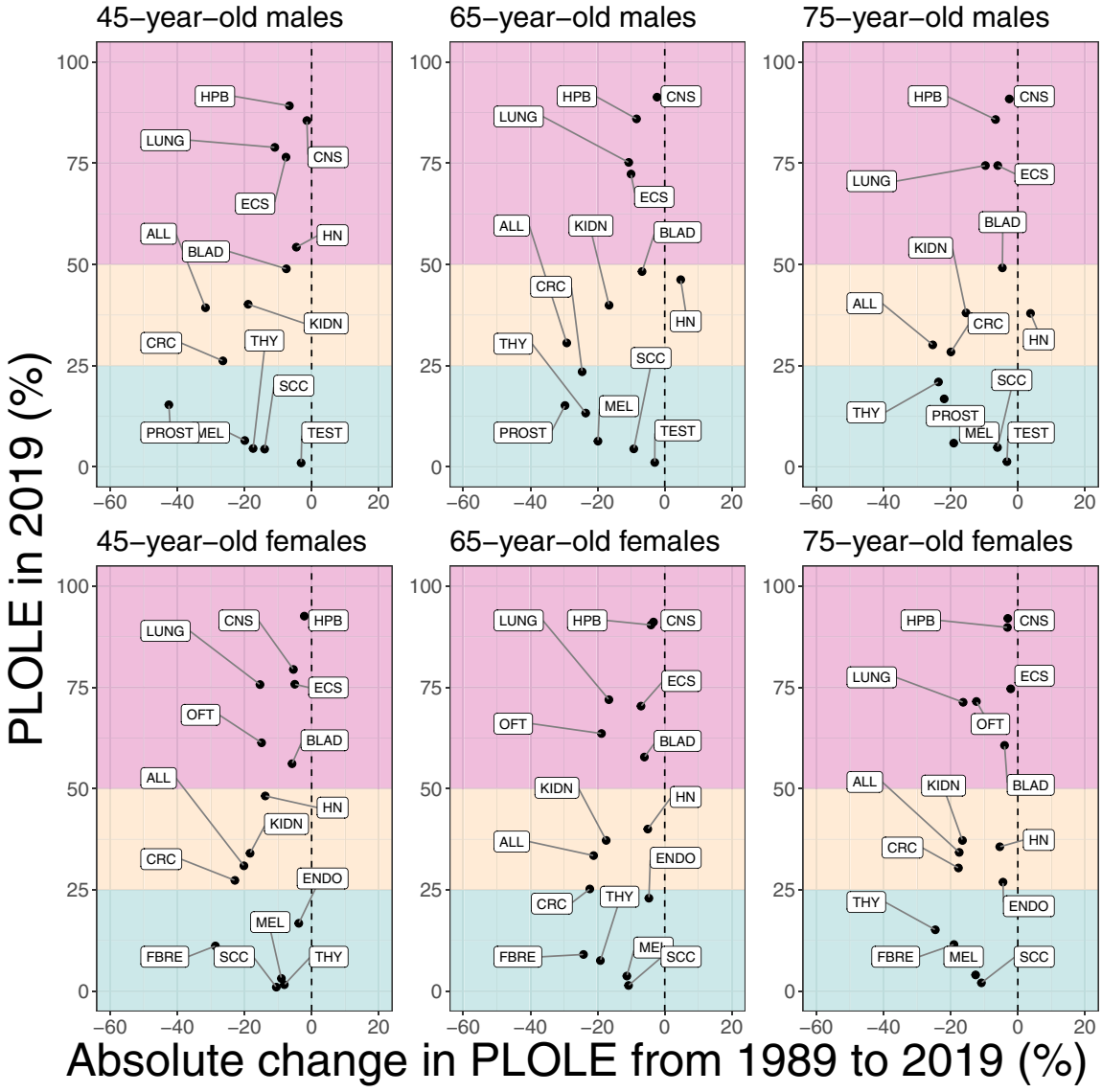

Fig. 5: **Proportional loss of life expectancy (PLOLE) in 2019 versus the absolute difference in PLOLE from 1989 to 2019 for 45-year-old, 65-year-old, and 75-year-old patients, clustered in terms of good, intermediate, and bad prognosis in 2019.** We created clusters in terms of good (PLOLE < 25%, green), intermediate (25% < PLOLE < 50%, orange), and bad (PLOLE > 50%, pink) prognosis in 2019. Abbreviations: proportional loss of life expectancy (PLOLE); all cancers combined (ALL); bladder and urinary tract (BLAD); cervix (CERV); central nervous system (CNS); colorectum (CRC); oesophagus, cardia, stomach (ECS); endometria (ENDO); breast (FBRE); head and neck (HN); hepato-pancreato-biliary (HPB); kidney (KIDN); melanoma of the skin (MEL); ovary, fallopian tube (OFT); prostate (PROST); squamous cell carcinoma of the skin (SCC); testicle (TEST); thyroid (THY).

Cancer-specific patterns

The PLOLE varied substantially across different cancer types (Fig. 5). The first cluster identified for 65-year-old patients consists of cancers with a high PLOLE in 2019 (i.e., poor prognosis with a PLOLE > 50%; pink shaded part), including cancers of the hepato-pancreato-biliary tract, lung, central nervous system, oesophagus and stomach, and ovaries and fallopian tube. The PLOLE of most of the cancers in this cluster barely decreased over time, i.e., the absolute decrease in PLOLE was no more than 10%. However, the PLOLE of females with lung, and ovary and fallopian tube cancer decreased notably over time.

The second cluster defined by intermediate PLOLE in 2019 (i.e., intermediate prognosis; 25% < PLOLE ≤ 50%; orange shaded part) comprises of 65-year-old patients with cancer of the kidney, and head and neck. The PLOLE of kidney cancer has decreased notably since 1989 (i.e., more than 10%). Of note, the PLOLE of 65-year-old patients with head and neck cancer was intermediate in 2019 but slightly increased for males since 1989 (i.e., the prognosis for these patients became slightly worse over time). The third cluster for 65-year-old patients consists of cancers with a low PLOLE in 2019 (i.e., good prognosis; PLOLE ≤ 25%; green shaded part). The PLOLE of most of these cancers (i.e., melanoma of the skin, thyroid, prostate, and breast cancer) decreased notably between 1989 and 2019 (i.e., more than 10%). For patients with squamous cell carcinoma of the skin, testicle, and endometrial cancer, the PLOLE remained virtually unchanged between 1989 and 2019.

Stratified by stage

The PLOLE varied substantially across different disease stages (Fig. 6; Figure S2). The PLOLE of most cancer types diagnosed in localised stages was low in 2019 (i.e., good prognosis; PLOLE ≤ 25%; green shaded part of Fig. 6). The PLOLE of most of these cancers decreased since 1989, i.e., for melanoma of the skin, squamous cell carcinoma of the skin, and cancers of the kidney, colorectum, thyroid, prostate, cervix, breast, and endometrium. The PLOLE of localised cancers of the lung, central nervous system, oesophagus and stomach, and bladder with an intermediate PLOLE in 2019 (i.e., intermediate prognosis; 25% < PLOLE ≤ 50%; orange shaded part) decreased substantially between 1989 and 2019. Localised cancers of the hepato-pancreato-biliary tract, and ovaries and fallopian tubes had a high PLOLE in 2019 (i.e., poor prognosis; PLOLE > 50%; pink shaded part). Nevertheless, their PLOLE decreased over time.

The PLOLE was generally higher for cancers diagnosed in regional than localised stages (Fig. 6; Figure S2). The PLOLE of some regional cancers with a high PLOLE (i.e., poor prognosis; PLOLE > 50%; Fig. 6) did not decrease noticeably over time, i.e., cancers of the bladder, hepato-pancreato-biliary tract, and oesophagus and stomach. However, the PLOLE of other cancers in regional stages with a high PLOLE decreased over time, i.e., cancers of the central nervous system, lung, kidney, head and neck, endometrium, and ovaries and fallopian tube. The PLOLE of most regional cancers with a good and intermediate PLOLE (i.e., PLOLE ≤ 50%) also decreased between 1989 and 2019, including melanoma of the skin, and cancers of the colorectum, thyroid, breast, cervix, and prostate. The PLOLE of testicle cancer in regional stages stayed low between 1989 and 2019.

Virtually all cancers diagnosed in distant stages had a poor prognosis in 2019 (Fig. 6; Figure S2). The only exception was testicle cancer, with a good prognosis in 2019 and decreasing PLOLE between 1989 and 2019 (Fig. 6). The PLOLE of most cancers diagnosed in distant stages only slightly decreased between 1989 and 2019, but the PLOLE of melanoma of the skin, cancers of the thyroid, prostate, and ovaries and fallopian tubes decreased notably over time.

Life expectancy several years after diagnosis

For most cancer types, the decrease in proportional conditional LOLE (PCLOLE) levelled off somewhat after five years post-diagnosis (Fig. 7). For example, for all cancers, a 65-year-old female diagnosed in 2019 lost 33.5% of her life [95% CI, 32.9%–34.0%]. This proportion reduced to 7.8% [95% CI, 7.2%–8.4%] and 4.5% [95% CI, 4.1%–4.9%] when she survived five and ten years post-diagnosis, respectively. The PCLOLE remained steady over time for squamous cell carcinoma of the skin and testicle cancer.

The PCLOLE was substantially higher for all cancers diagnosed in 1989 than in 2019 (Fig. 7). For example, a 65-year-old female diagnosed in 1989 who survived five years post-diagnosis was expected to lose 20.7% of her life [95% CI, 20.0%–21.4%], whereas a 65-year-old female diagnosed in 2019 who survived five years post-diagnosis was expected to lose 7.8% of her life [95% CI, 7.2%–8.4%], corresponding to a 2.0-year decrease in LOLE.

Web-application

In a publicly available web-based application, we displayed the outcomes for each combination of cancer type, age (18–90), sex, year at diagnosis (1989–2019), conditional on surviving 0 up to 10 years post-diagnosis, for each disease stage.[12]

Discussion

Our findings suggested that for all of the most frequent solid invasive malignancies combined, the life expectancy of adult patients with cancer increased in the Netherlands between 1989 and 2019. This increase was greater than the increase in the life expectancy of the general population, resulting in a decrease in LOLE between these years. This encouraging trend is due to

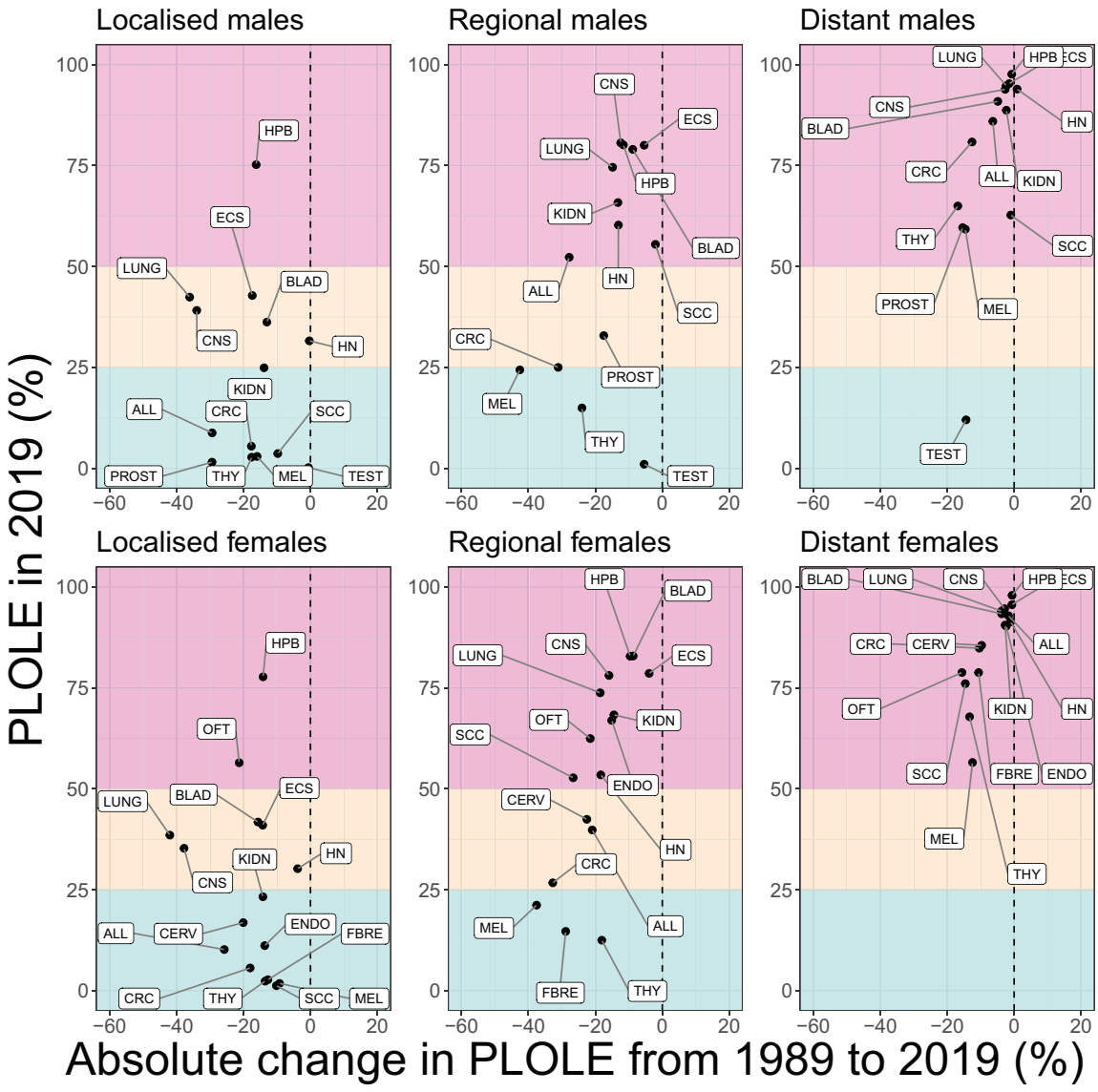

Fig. 6: **Proportional loss of life expectancy (PLOLE) in 2019 versus the absolute difference in PLOLE from 1989 to 2019 for 65-year-old patients with cancer in localised, regional, and distant stage, clustered in terms of good, intermediate, and bad prognosis in 2019.** We created clusters in terms of good (PLOLE < 25%, blue), intermediate (25% < PLOLE < 50%, orange), and bad (PLOLE > 50%, pink) prognosis in 2019. This Figure is based on patients for which cancer stage is known. Abbreviations: proportional loss of life expectancy (PLOLE); all cancers combined (ALL); bladder and urinary tract (BLAD); cervix (CERV), central nervous system (CNS); colorectum (CRC); oesophagus, cardia, stomach (ECS), endometria (ENDO); breast (FBRE); head and neck (HN); hepato-pancreato-biliary (HPB); kidney (KIDN); melanoma of the skin (MEL); ovary, fallopian tube (OFT); prostate (PROST); squamous cell carcinoma of the skin (SCC); testicle (TEST); thyroid (THY).

advances in cancer diagnosis and management, which provides optimism for patients diagnosed with cancer. Nevertheless, differences persisted across cancer types.

The decrease in LOLE over time in patients with cancer is consistent with the increasing relative survival estimates.[2–4] Also, our findings are in line with two previous studies that studied the evolution of the LOLE over time in the Australian population.[6,7] More importantly, our study complements and extends these studies by providing LOLE estimates for each age between 18 and 90 in an online calculator instead of only presenting the average LOLE for broad age groups.[12] Furthermore, we estimated measures of life expectancy according to disease stage and conditional on being alive up to ten years post-diagnosis (i.e., conditional LOLE; CLOLE). In the prior two studies, data on disease stage were not available across the entire cohort and the conditional LOLE was not estimated.

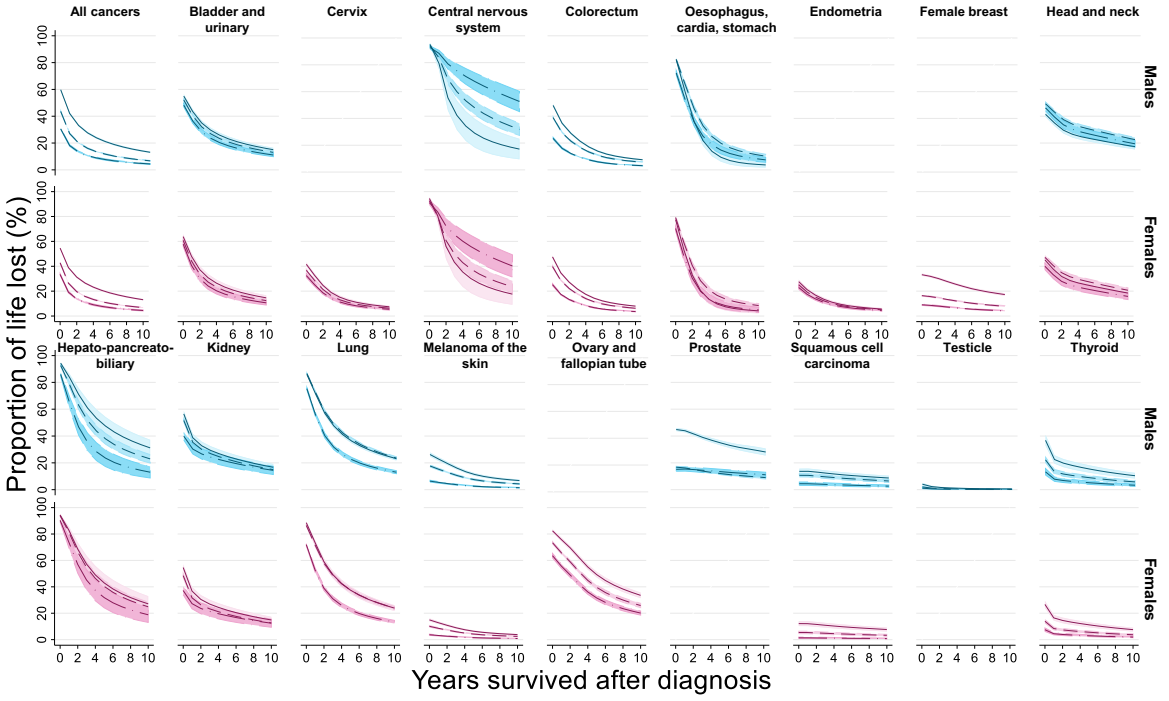

Fig. 7: **The proportional loss of life expectancy and conditional proportional loss of life expectancy from one up to ten years after diagnosis for 1989 (solid line), 2005 (dashed line), and 2019 (long dashed dotted line) for 65-year-old male (blue) and female (pink) patients.**

Treatment developments can explain the decreased impact of cancer for specific cancers over time. In brief, examples of advances in cancer treatment are the introduction of total mesorectal excision for colorectal cancer,[13] increasing use of neoadjuvant and endocrine therapies for breast cancer,[14] the use of androgen-ablation therapy for prostate cancer,[15] extended lymphadenectomy in early-stage tumours, and improved chemotherapy regimens for advanced stage stomach and oesophagus cancer.[16]

The decreased impact of cancer can also be explained by earlier cancer detection since we found that the LOLE increased with advancing disease stage. In the Netherlands, national population screening programs have been implemented for cervical, breast, and colorectal cancer since the early 1970s,[17] 1987,[18] and 2014,[19] respectively. These screening programs can reduce the impact of cancer due to a timely cancer diagnosis in apparently healthy, asymptomatic individuals. This allows for early treatment of early-stage cancer, which can lead to better outcomes for individuals diagnosed through screening programs. On the other hand, one could argue that the LOLE estimates can be influenced by overdiagnosis, i.e., a cancer diagnosis that would never cause excess mortality to patients if they remained undetected. A prime example of a potential overdiagnosis can be found in early-stage prostate cancer due to widespread prostate-specific antigen (PSA) screening.[20–22] When patients with early-stage cancer with LOLE estimates close to zero are included in the overall cancer cohort, these patients can decrease the LOLE estimates for the overall cohort. Moreover, the LOLE could be artificially decreased due to lead-time bias; that is, the period between disease detection through screening and when a diagnosis would have been made without screening (i.e., due to symptoms).[23] Therefore, estimates for cancers that might be influenced by lead-time bias should be interpreted with caution.

Our study highlighted that diagnosis with some cancer types gave poor prognosis during the entire period of 1989–2019, particularly in patients diagnosed with metastasised disease. This finding shows that advances in early detection and treatment of malignancies in advanced stage are important. Also, we found for some cancer types that the proportional LOLE (PLOLE) was higher for older than younger patients. This may be explained by the decreased comorbidity burden of younger patients because they are more likely to tolerate the adverse effects of anti-neoplastic treatments, resulting in less treatment-related morbidity and mortality.[24] Furthermore, older patients may more often opt for palliative care than younger patients, resulting in age differences in PLOLE. Therefore, life expectancy estimates in older patients with cancer should be placed in the context of quality of life because the treatment goals

may differ between younger and older patients. The broader use of quality-of-life questionnaires could extend this research to provide more insight into these age differences in PLOLE. Interestingly, for certain cancer types, we observed a higher PLOLE among younger patients, possibly due to the more aggressive nature of tumours in young adults compared to their older counterparts.[25,26] This finding highlights the need for further research to explore the relationship between age and PLOLE across different cancer types and sex.

Overall, we have shown that cancer patients live longer than before. The CLOLE estimates showed that cancer patients lost fewer life years, with each additional year surviving post-diagnosis. Furthermore, these CLOLE estimates highlighted that those who survived five years post-diagnoses had minimal excess mortality, i.e., the life expectancy of cancer patients became close to the life expectancy of the general population. As a result, the number of cancer survivors is increasing. These findings may help tailor surveillance activities for survivorship care after treatment ends.

The strengths of this study are the use of a long-running nationwide cancer registry, encompassing all cancer types, long-term survival follow-up, and information on disease stage, of which the latter was only unknown in a small number of patients (5%). Also, to make LOLE comparable between ages, we estimated the PLOLE. Further, the CLOLE provided additional information for cancer patients who survived a certain period post-diagnosis. Finally, we designed a publicly available web-based application that provides the life expectancy estimates for a combination of cancer type, age, calendar year at diagnosis, and cancer stage.[12]

Future research may focus on (i) expanding the life expectancy estimations for more specific patient groups with rarer malignancies or based on baseline characteristics that are not standardly available in the NCR (e.g., socioeconomic status), (ii) stratifying life expectancy estimations by the type of therapy, and (iii) the calculation of reference adjusted LOLE to correct for other causes of death (which are not routinely available in the NCR).[27]

The flexible parametric survival model extrapolates the observed survival curve beyond available follow-up. This can be problematic, especially for patients diagnosed in recent years. Nevertheless, it has been shown that the flexible parametric survival model accurately estimates the life expectancy for short follow-up length under the assumption that excess mortality remained constant ten years after a cancer diagnosis.[5] This assumption is likely to hold in our study cohort because the hazard of patients levelled-off and approached zero already five years after diagnosis for all cancer types investigated (Figure S3).

The life expectancy of the general population also includes cancer deaths, which might lead to an underestimation of the loss of life expectancy in this population. In a sensitivity analysis, we found that correcting for the proportion of cancer deaths changes the life expectancy of the general population negligibly (Table S3). As a result, the cancer deaths in the general population barely influenced the loss of life expectancy estimates.

In summary, LOLE estimates help patients better understand the impact of their cancer diagnosis on their life expectancy compared to when they would not have been diagnosed with cancer. The overall increasing life expectancy of cancer patients over the past three decades in the Netherlands provides optimism about the progress against cancer. Nevertheless, we show that the prognosis widely differs between cancer types, ages, and disease stages.

Contributors

C.C.H.M. Maas was responsible for conceptualisation of the manuscript, verification of the data, methodology, software, formal analysis, visualisation, writing the original draft, and reviewing and editing the manuscript. **D. van Klaveren** and **A.G. Dinmohamed** were responsible for conceptualisation of the manuscript, verification of the data, methodology, and reviewing and editing the manuscript. **O. Visser** was responsible for data curation, and reviewing and editing the manuscript. **M.A.W. Merkx, H.F. Lingsma**, and **V.E.P.P. Lemmens** were responsible for conceptualisation, reviewing and editing the manuscript.

Data sharing statement

The data that support the findings of this study are available via the Netherlands Comprehensive Cancer Organisation. These data are not publicly available, and restrictions apply to the availability of the data used for the current study. However, these data are available upon reasonable request and with permission of the Netherlands Comprehensive Cancer Organisation.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101994.

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