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The cancer burden in the oldest-old: Increasing numbers and disparities—A nationwide study in the Netherlands, 1990 to 2019

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Abstract

Adults aged ≥80 years (the oldest-old) comprise the fastest growing age group in Western populations. Yet little is known about their cancer burden. In this nationwide study, we assessed their trends in incidence, treatment and survival over a 30-year period, and predicted their future cancer incidence. All 2 468 695 incident cancer cases during 1990 to 2019 were selected from the Netherlands Cancer Registry, of whom 386 611 were diagnosed in the oldest-old (16%). The incidence of the oldest-old was predicted until 2032. Net and overall survival (OS) were calculated. Patients were divided into four age groups (<80, 80-84, 85-89 and ≥90 years). The incidence of the oldest-old doubled between 1990 and 2019 and is expected to grow annually with 5% up to 2032. In virtually all cancers the share of oldest-old patients grew, but declined for prostate cancer (25% in 1990-1994 vs 13% in 2015-2019). The proportion of undetermined disease stage increased with age in most cancers. The application of systemic therapy increased, albeit less pronounced in the oldest-old than their younger counterparts (1990 vs 2019: 12%-34%, 3%-15%, 2%-7% and 1%-3% in <80, 80-84, 85-89 and ≥90 years old). Five-year OS of the oldest-old patients increased by 7 percentage points (to 26%) between 1990 to 1994 and 2015 to 2019 compared to 19 percentage points (to 63%) in <80 years old. The oldest-old cancer patients are a rapidly growing group who benefitted less from improvements in cancer treatment than younger patients, reflecting the multiple challenges faced in the care of the oldest-old.

KEYWORDS

cancer, epidemiology, geriatrics, incidence, oldest-old, stage distribution, survival, treatment, trends

What's new?

Adults aged ≥80 years (the oldest-old) comprise the fastest growing age group in Western populations. Yet little is known about their cancer burden. This nationwide population-based study found that the incidence of the oldest old in the Netherlands doubled between 1990 and

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; CRC, colorectal cancer; EAPC, estimated annual percentage change; ICD-O, International Classification of Diseases for Oncology; NCR, Netherlands Cancer Registry; NMSC, nonmelanoma skin cancer; OS, overall survival; pp, percentage point; py, person-years; QoL, quality of life; RCT, randomized clinical trial; SCC, squamous cell carcinoma; TNM, tumor-node-metastasis; WHO, World Health Organization.

2019 and is expected to grow annually by 5% up to 2032. The oldest-old seemed to have benefitted less from improvements in systemic therapy than younger patients, and the survival gap increased. The observed trends may serve as important indicators of the progress made in this patient population and help address future health care challenges.

1 | INTRODUCTION

Population aging is a global phenomenon, with adults aged ≥80 years being the fastest-growing group.[1] At a global level, this group—hereafter referred to as the oldest-old as per the definition of the World Health Organization (WHO) and the United Nations[2,3]—is projected to increase more than 3-fold between 2017 and 2050, approximating an absolute increase from 137 to 425 million.[1] Regions in which population aging is most pronounced include Europe, Northern America and (South-)Eastern Asia.[1,4]

Population aging affects nearly all sectors of society, including health care. Many diseases, including cancer, can be considered age-related diseases. The overall cancer risk increases with age, peaking in patients aged over 80 years.[5-7] In concert with a growing and aging population, the absolute incidence of cancer is increasing worldwide.[8,9] As life expectancy is anticipated to increase gradually in the coming decades, a further rise in cancer diagnoses among the oldest-old population is also forecasted.[1] Hence, the aging of populations will affect the demand placed on healthcare systems and providers worldwide. Not only will more older patients need cancer treatment, but advanced age is also associated with a more heterogenous patient population and a higher complexity of cancer care due to the coexistence of other medical conditions and associated disabilities.[10,11]

Although the number of older patients with cancer is increasing globally and the field of geriatric oncology is advancing, relatively little is known about the cancer burden and care, particularly among the oldest-old. Since older patients with cancer are underrepresented in clinical trials,[12-14] population-based cancer registry studies can lend support to characterize the cancer burden and its evolution over time in this specific group. At present, such registry-based studies are incredibly scarce.

Therefore, this population-based study leveraged data from the Netherlands Cancer Registry to assess trends in incidence, primary treatment and survival in the oldest-old population in the Netherlands over a 30-year period, and to predict their future cancer incidence. The observed trends and predictions may serve as important indicators of the progress made in this patient population and help address future health care challenges.

2 | MATERIALS AND METHODS

2.1 | Data source

Data for our study were obtained from the nationwide, population-based Netherlands Cancer Registry (NCR).[15] Notifications of newly diagnosed malignancies to the NCR come from (a) all Dutch pathology laboratories through the Nationwide Histopathology and Cytopathology Data Network and Archive and (b) the National Registry of Hospital Discharge Diagnosis (ie, inpatient and outpatient discharges). After case notification, specialized registration clerks of the NCR extract basic information from the medical records on patient and tumor characteristics and primary treatment.

The anatomical site and tumor morphology are coded according to the International Classification of Diseases for Oncology (ICD-O). The tumor stage is coded according to the applicable version of the Tumor-Node-Metastasis (TNM) classification. Data on vital status (ie, alive, dead or emigration) are annually updated by a linkage to the Nationwide Personal Records Database that holds the vital status of residents in the Netherlands. These data were complete until 1 January 2021 (ie, the end of follow-up).

2.2 | Study population

We selected all patients diagnosed with a malignancy in the Netherlands during 1990 to 2019 from the NCR (number of patients: 2 218 799 and number of tumors: 2 468 695). During our study period, the total population of the Netherlands grew from 14.9 in 1990 to 17.3 million in 2019.[16] We defined the oldest-old as people aged ≥80 years as per the definition by the WHO.[3] All tumors classified as invasive (ie, behavior code "/3") according to the ICD-O classification were included, except for cancers of the bladder, for which noninvasive papillary urothelial carcinoma (Ta) and urothelial carcinoma in situ (Tis) were also included.

Because of an incomplete registration in the early years of our study period and changes in the registration of nonmelanoma skin cancer (NMSC), those tumors were not included in our analyses. Only the incidences of basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) in the most recent year (2019) were reported. All other malignancies were categorized into one of the following categories: cancers of the bladder, breast (females), cervix, colon and rectum, endometrium, esophagus, gallbladder and bile ducts, head and neck, liver, lung, ovary, pancreas, prostate, kidney, stomach, thyroid, mesotheliomas, sarcomas, skin melanomas, as well as lymphomas and lymphocytic leukemia, myeloid malignancies, plasma cell malignancies and tumors of unknown origin. The remaining tumors were categorized as "other." The corresponding ICD-O codes for all categories are described in detail elsewhere.[17]

2.3 | Statistical analyses

2.3.1 | Incidence

Absolute incidence and incidence rates were calculated. To calculate the incidence rates, population numbers according to age, sex and calendar year were derived from Statistics Netherlands. Rates were expressed per 100 000 person-years (py). Person-years were calculated separately for each calendar year by averaging the number of males and females at the beginning and end of each calendar year. Annual rates were calculated as well as rates over 5-year time periods. The denominator of the incidence rates over a 5-year period was the sum of the 5-year averages of person-years.[18]

Age-specific incidence rates for the total cohort were calculated according to sex for 5-year age groups (from 0 to ≥95 years) for the first (1990-1994) and last 5 years (2015-2019) of our study period. The annual number of cancer cases and incidence rates were presented for all cancers combined and according to the tumor groupings for the total number of oldest-old persons and by age group (80-84, 85-89 and ≥90 years). Changes over time in the number of the oldest-old cancer patients was evaluated by calculating the estimated annual percentage changes (EAPCs) and their corresponding 95% confidence intervals (CIs). To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (ie, $y = ax + b$ where $y = \ln(n)$ and $x =$ calendar year, then $\text{EAPC} = 100 \times [\exp(a) - 1]$).

2.3.2 | Future projection of incidence

The Nordpred software package,[19] details of which are described elsewhere,[20] was used to calculate future estimates of incidence using an age-period-cohort model. Relevant parameters from past observations are derived and used to estimate future estimations. We based our predictions of incidence on observations over the last 20 years (2000-2019). Instead of using the standard exponential link function we used a power function (power of 5) to level off the predicted growth, as it has been shown that the model often overestimates the number of cancer cases due to its exponential growth over time.[21] Data were compiled into 5-year periods and predicted up to 2030 to 2034. The drift (general linear trend) was attenuated with 25% in the second predicted period (2025-2029) and with 50% in the third predicted period (2030-2034). The outcome represented the total number of diagnoses over a 5-year calendar period. Based on these estimates, the mean annual number of diagnoses was calculated and assigned to the middle year of that period. Both absolute numbers and incidence rates were predicted. The predicted change over time in absolute number was evaluated by estimating the predicted EAPC, confidence intervals were calculated by parametric bootstrap. Underlying the Nordpred software is a Poisson GLM estimated using maximum likelihood, hence the sampling distribution of its estimator is approximately multivariate normal. Therefore, to perform the parametric bootstrap, coefficients and the variance-covariance matrix from this model were used as parameters in a multivariate normal distribution, from which coefficients were re-drawn 999 times. New forecasts were made with each of these draws, the EAPC calculated each time and 95% confidence intervals (95% CIs) were derived using the 2.5% and 97.5% quantiles of their distribution.

2.3.3 | Share of oldest-old patients

The share of the oldest-old patients out of the total number of patients was calculated by cancer type, also for the first (1990-1994) and last (2015-2019) calendar period.

2.3.4 | Stage distribution

The stage distribution was described for the 10 most common solid malignancies during 2015 to 2019, supplemented with the sex-specific tumors in the 10 most common malignancies of either males or females. Analyses were stratified by age (<80, 80-84, 85-89 and ≥90 years).

Stage distribution was derived from the TNM-stage and converted into: localized disease (N0, M0), regional disease (N+, M0), metastatic disease (M+) or undetermined/unknown stage.

2.3.5 | Primary therapy

Primary therapy of all solid malignancies was shown by plotting the annual proportion of patients receiving a particular treatment type according to age (<80, 80-84, 85-89 and ≥90 years). Treatment categories included: surgical treatment (including *metastasectomy*), systemic treatment (excluding hormonal therapy), hormonal therapy, radiotherapy (at the primary tumor site) and no antineoplastic treatment (none of the previous described treatments). Treatment categories are nonexclusive; a patient may be counted in more than one treatment category.

2.3.6 | Survival

Overall survival (OS) was calculated for all cancers combined. The 1- and 5-year OS were presented for the first (1990-1994) and last calendar period (2015-2019), stratified by age category (<80, ≥80, 80-84, 85-89 and ≥90 years). One- and 5-year net survival was calculated for each of the most common cancer types, using the Pohar Perme estimator. Net survival assumes that the disease of interest is the only possible cause of death. The Pohar-Perme estimator accounts for the competing risks of death (death due to other causes) with increasing age by inverse probability weighting.[22] Net survival was calculated for the age categories <80 years and ≥80 years, according to three calendar periods (1990-1999, 2000-2009 and 2010-2019). Survival time was defined as the

interval from the date of diagnosis to the date of death or last follow-up (1 January 2021).

A *P*-value of <.05 was considered statistically significant. The future predictions of the incidence were analyzed in R (version 3.1.1). All other analyses were performed using STATA/SE 17.0 (StataCorp, TX).

3 | RESULTS

3.1 | Incidence

Of all 2 468 695 tumors, 386 611 (16%) were diagnosed in the oldest-old (ie, patients aged ≥80 years). The age-specific incidence rates per 100 000 py of males and females during 1990 to 1994 and 2015 to 2019 are shown in Figure 1. This figure clearly shows higher incidence rates in older age categories, especially for males. For females, the age gradient was more gradual. Incidence rates peaked in age categories in the ninth decade of life, irrespective of sex and calendar period.

3.1.1 | Time trends in incidence

The absolute number of the oldest-old cancer patients (≥80 years) increased from 8717 in 1990 to 18 706 in 2019, corresponding with an annual increase of 2.7% (95% CI: 2.6%-2.7%) (Figure 2A). In all age categories of the oldest-old, the absolute incidence has more than doubled during the past 30 years (Figure 2B). In 2032, the absolute number of the oldest-old patients is expected to increase to 32 617 (95% CI: 32 412-32 808), which is an expected annual increase of 5.0% (95% CI: 4.9%-5.1%) during 2019 to 2032.

The incidence rate of oldest-old fluctuated over the years, but overall there is an increasing trend. The incidence rate was 2016/100 000 py in 1990 vs 2308/100 000 py in 2019 (males and females together). A further increase to 2460/100 000 py (95% CI: 2440/100 000 py to 2479/100 000 py) in 2032 is expected (Figure 2C). The incidence rate of the age category ≥90 years has not increased (Figure 2D).

In Figure 1 we showed that the age-specific incidence rates of oldest-old males in 2015 to 2019 were lower than in 1990 to 1994, whereas the rates in females were higher in the most recent period for all age categories until the age of 90. A decrease in prostate cancer incidence primarily drove the decrease in incidence rates among the oldest-old males. After excluding prostate cancer, the incidence rates increased over time (data not shown).

Trends in incidence among the oldest-old patients varied by cancer type and sex (Figures S1 and S2). Large increases in incidence (both in absolute numbers and incidence rate) between 1990 and 2019 are seen for skin melanoma and liver cancer in both sexes, and for mesothelioma in males. The incidence of stomach cancer decreased considerably in the oldest-old males and females (both in absolute numbers and incidence rate). Furthermore, the number of oldest-old males and females with lung cancer increased, but the incidence rate only in females. The incidence rate of unknown primary tumors decreased, particularly in males. For prostate cancer, the trends fluctuated, with the highest incidence rate in 1994 (829/100 000 py) and the lowest in 2015 (382/100 000 py). However, the absolute incidence is highest in the most recent year (1895 newly diagnosed oldest-old prostate cancer patients in 2019).

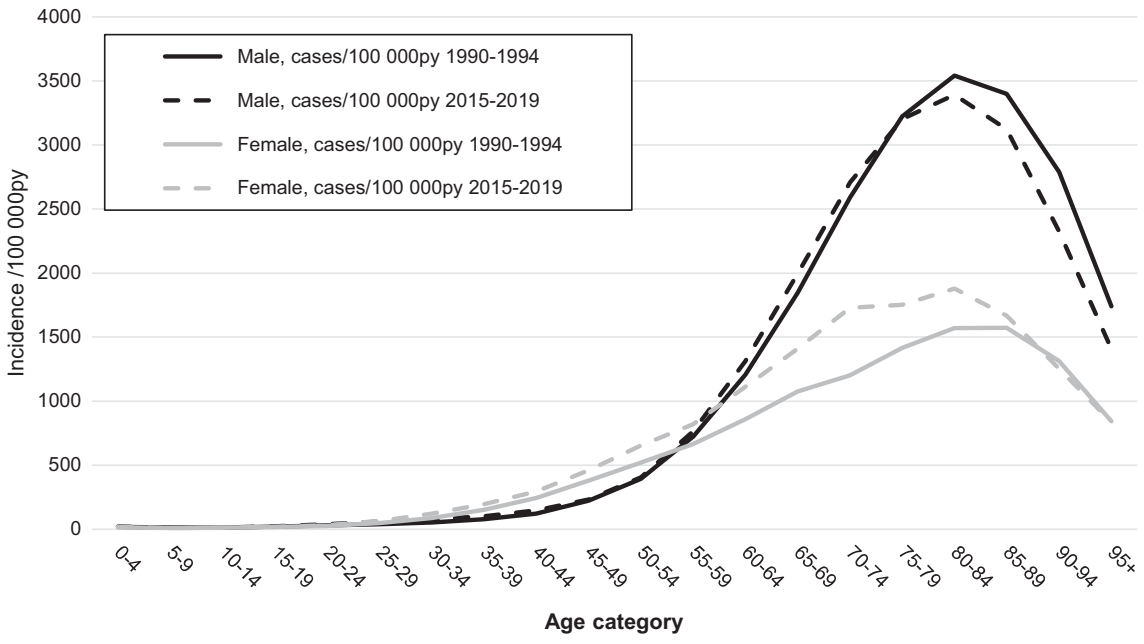

FIGURE 1 Age-specific cancer incidence rates for males and females during 1990 to 1994 and 2015 to 2019. py, person-years.

3.1.2 | Most common cancer types

The 10 most common tumor types among the oldest-old males and females diagnosed in the most recent calendar period (2015-2019) are shown in Figure 3. Prostate cancer was the most frequently diagnosed cancer among oldest-old males (17%), followed by lung (15%), bladder (15%) and colorectal cancer (CRC; 15%). In oldest-old females, breast cancer was the most frequently diagnosed cancer (21%), followed by CRC (17%) and lung cancer (10%). The 10 most commonly diagnosed tumor types together accounted for 85% and 79% of all malignancies (excluding NMSC) among the oldest-old males and females, respectively. Compared to their younger counterparts (ie, below age 80), the 10 most common cancer types are broadly comparable (see Figure S3). However, the most common cancer types among males and females (ie, prostate and breast cancer, respectively) comprise a higher proportion of all tumors in younger cancer patients.

Nationwide data on NMSC was available for patients diagnosed in 2019 In that year, SCC was the most commonly diagnosed cancer among oldest-old males (n = 6218) and females (n = 7706), followed by BCC (5024 in males and 5169 in females). These numbers are considerably higher than the number of breast cancer diagnoses among oldest-old females (n = 1782) and prostate cancer among oldest-old males (n = 1895) in 2019, which were the most common malignancies in 2019 when excluding NMSC.

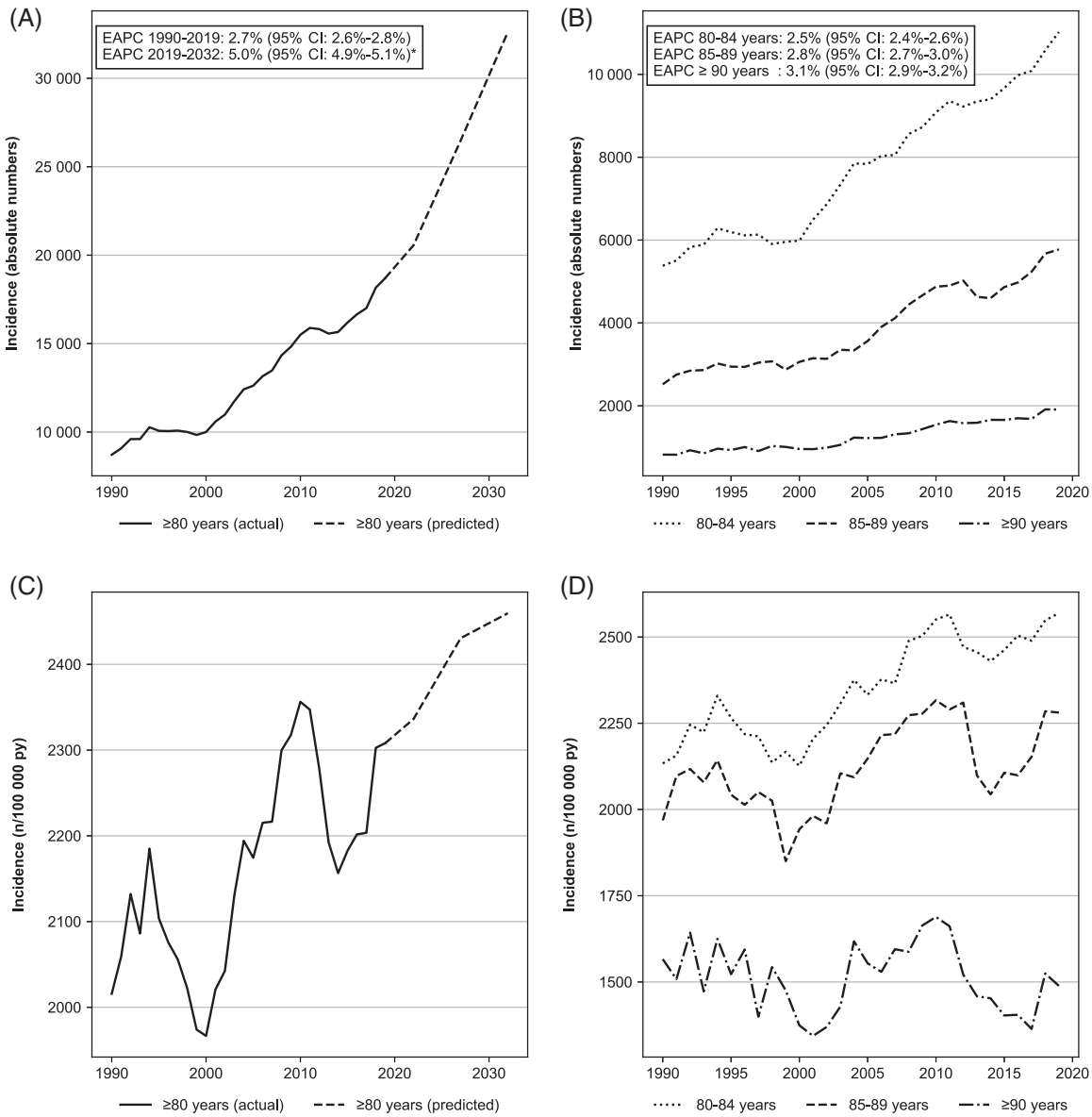

FIGURE 2 Trends in annual cancer incidence among the oldest-old showing (A) number of diagnoses including predictions (B) number of diagnoses by age group (C) cancer incidence rates including predictions (D) cancer incidence rates by age group. CI, confidence intervals; EAPC, estimated annual percentage change; py, person-years.

3.1.3 | The share of the oldest-old patients with cancer: Variation by tumor type and period of diagnosis

The share of the oldest-old patients varied enormously by cancer type and over time. In the oldest-old males, nearly all cancers showed an increase in the share of oldest-old patients over time (Figure 4A). Considerable differences were observed for mesothelioma, sarcoma, skin melanoma, lung cancer, bladder cancer and cancer of unknown primary origin. The share of the oldest-old males more than doubled between 1990 to 1994 and 2015 to 2019 for mesothelioma, sarcoma and skin melanoma. During 1990 to 1994, prostate cancer showed the highest proportion of oldest-old patients of all cancers (25%). However, it declined dramatically to 13% in 2015 to 2019.

Females showed less variation over time than males. The most substantial relative increase in the share of the oldest to old female patients over time was observed for mesothelioma (from 16% to 26% between 1990-1994 and 2015-2019), followed by lung cancer, cancer of unknown primary site and ovarian cancer (Figure 4B). The share of oldest-old females decreased for various tumor types, including thyroid, esophageal, stomach and colorectal cancer.

3.2 | Stage distribution

The stage distribution of the most common solid malignancies diagnosed during the most recent calendar period (2015-2019), including the most common sex-specific tumors, is shown in Figure 5 according to age at diagnosis. Overall, the proportion of patients with an unknown disease stage increased with advancing age. The increase was most substantial for cancer of the esophagus, endometrium and pancreas.

For prostate cancer, the proportion of metastatic disease increased strongly with age. More specifically, 15% of the patients with prostate cancer aged <80 years were diagnosed with metastatic

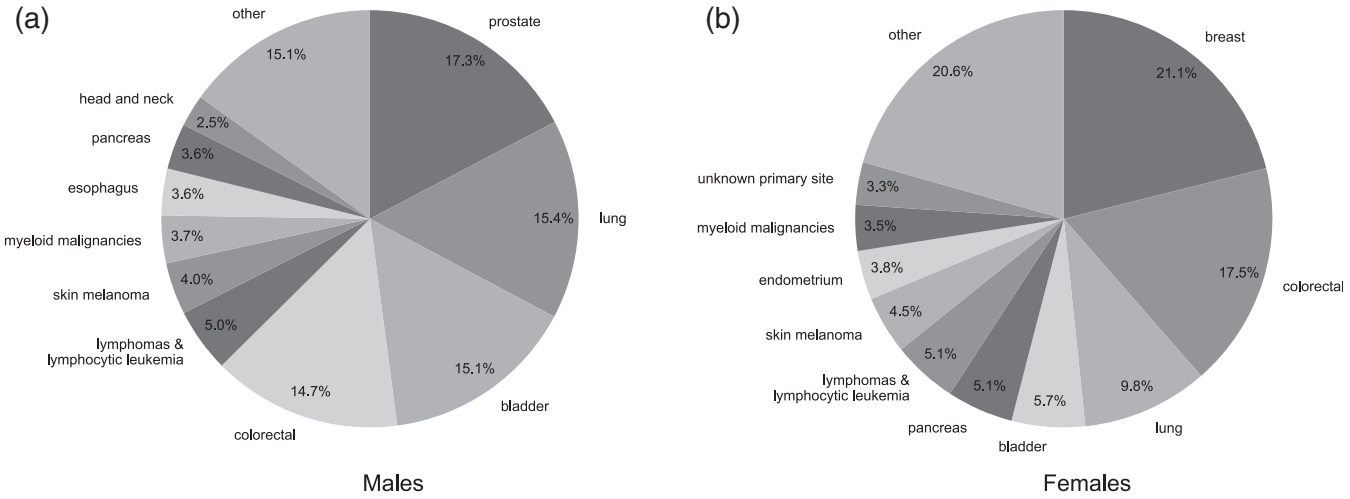

FIGURE 3 Distribution of the 10 most common cancers among the oldest-old for (A) males and (B) females during 2015 to 2019.

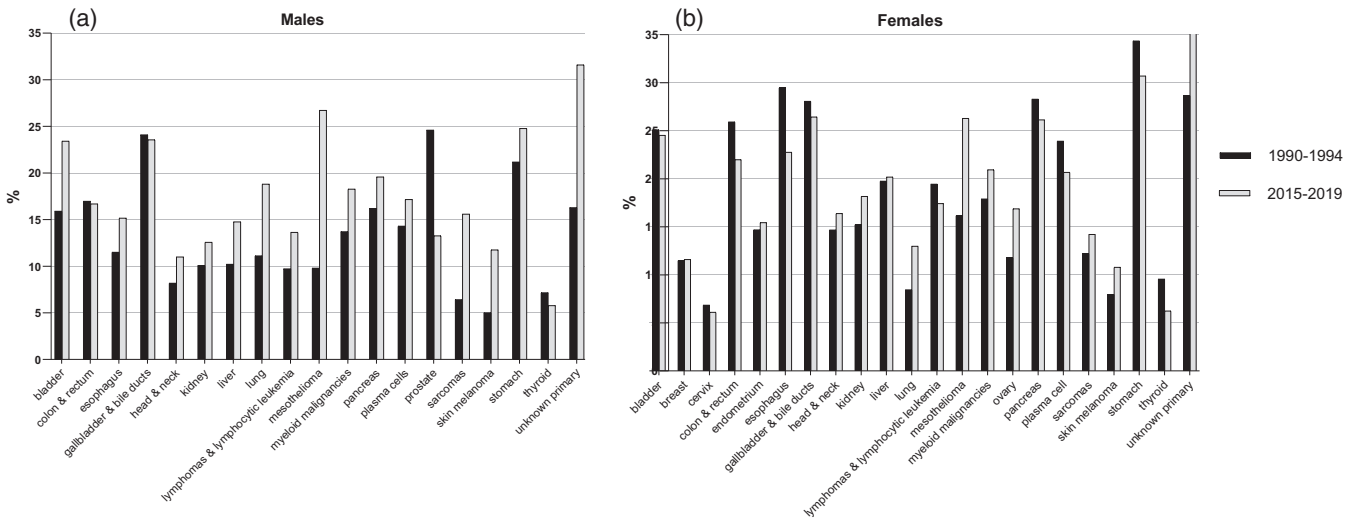

FIGURE 4 Percentage of oldest-old patients by cancer type and period of diagnosis for (A) males and (B) females.

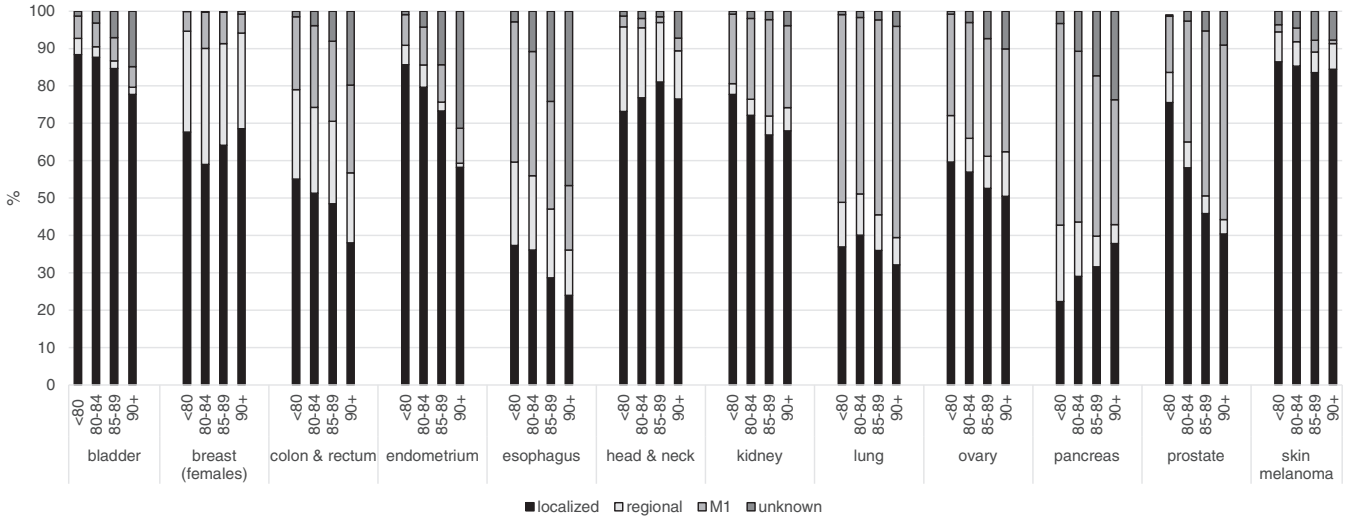

FIGURE 5 Stage distribution of the most common solid cancers by age category (2015-2019).

disease compared to 47% of the patients in the oldest age category (≥90 years). As a result, the proportion of patients diagnosed with localized and regional prostate cancer decreased. A similar pattern, albeit less pronounced, was seen in lung cancer.

For pancreatic cancer, we observed a shift from regional and metastatic disease to either localized or unknown stages with advancing age. This finding is in contrast to other cancers in which an increasing proportion of unknown stage with age is associated with a decline in localized disease.

Slight variation in stage distribution by age was objectified in skin melanoma and head and neck cancer; both showed a high proportion of local disease across all age categories.

3.3 | Trends in primary treatment

Trends in the primary treatment of solid tumors according to age at diagnosis are shown in Figure 6. For all treatment types, except hormonal therapy, we observed an apparent decrease in its application with advancing age.

Surgical treatment is the most common treatment among all age categories, ranging from over 60% for patients below age 80 to around 30% for patients aged ≥90 years (Figure 6A). Over time, the proportion of surgically-treated patients decreased slightly among those aged 85 to 89 and ≥90 years, particularly since the late 1990s.

Systemic therapy (excluding hormonal therapy) showed the largest variation in its application over time, with increasing proportions of patients receiving systemic treatment (Figure 6B,C) The most conspicuous increase was seen in patients below age 80. Consequently, the age disparity has widened over time. In the 1990s, <5% of the oldest-old received systemic treatment, increasing to 15% and 7% in 2019 among those aged 80 to 84 and 85 to 89 years and remaining below 5% for those aged ≥90 years old. In comparison, the allocation increased from 12% in 1990 to 34% in 2019 among those aged <80 years.

The use of radiotherapy also declined with age and did not show any noteworthy trend in the youngest age group, whereas minor increases were observed among the oldest-old (Figure 6D).

In contrast to other treatments, hormonal therapy was most frequently applied in the oldest age categories (Figure 6E). However, its application over time mainly increased in younger patients.

Almost half of the patients aged ≥90 years did not receive antineoplastic treatment during the past 30 years (Figure 6F). The proportion of patients aged 85 to 89 years not receiving cancer-directed treatment remained relatively stable at around 40%, whereas the proportion of untreated patients in the younger age categories (<85 years) was lower and decreased over time.

3.4 | Survival

Figure 7 shows the OS according to the calendar period of diagnosis, stratified by age at diagnosis. In 2015 to 2019, 1- and 5-year OS among the oldest-old patients was 60% and 26%. One- and 5-year OS had improved across all age groups. Notwithstanding, OS among those aged <80 increased more profoundly over time, leading to more significant age gaps in survival over time. During 1990 to 1994, there was an 18 percentage point (pp) gap in 1-year OS between patients aged <80 years and ≥80 years, which increased to 29 pp during 2015 to 2019. The gap in 5-year OS increased from 26 pp in 1990-1994 to 37 pp in 2015-2019.

The effect of age on survival differs by tumor type (Figure 8). Of the most common tumor types, the largest absolute difference in 1-year net survival between patients aged <80 and ≥80 years in 2010 to 2010 was seen for ovarian cancer (43 pp), esophageal cancer (21 pp) and lymphomas (20 pp). The smallest differences between age groups were seen among prostate cancer, breast cancer and

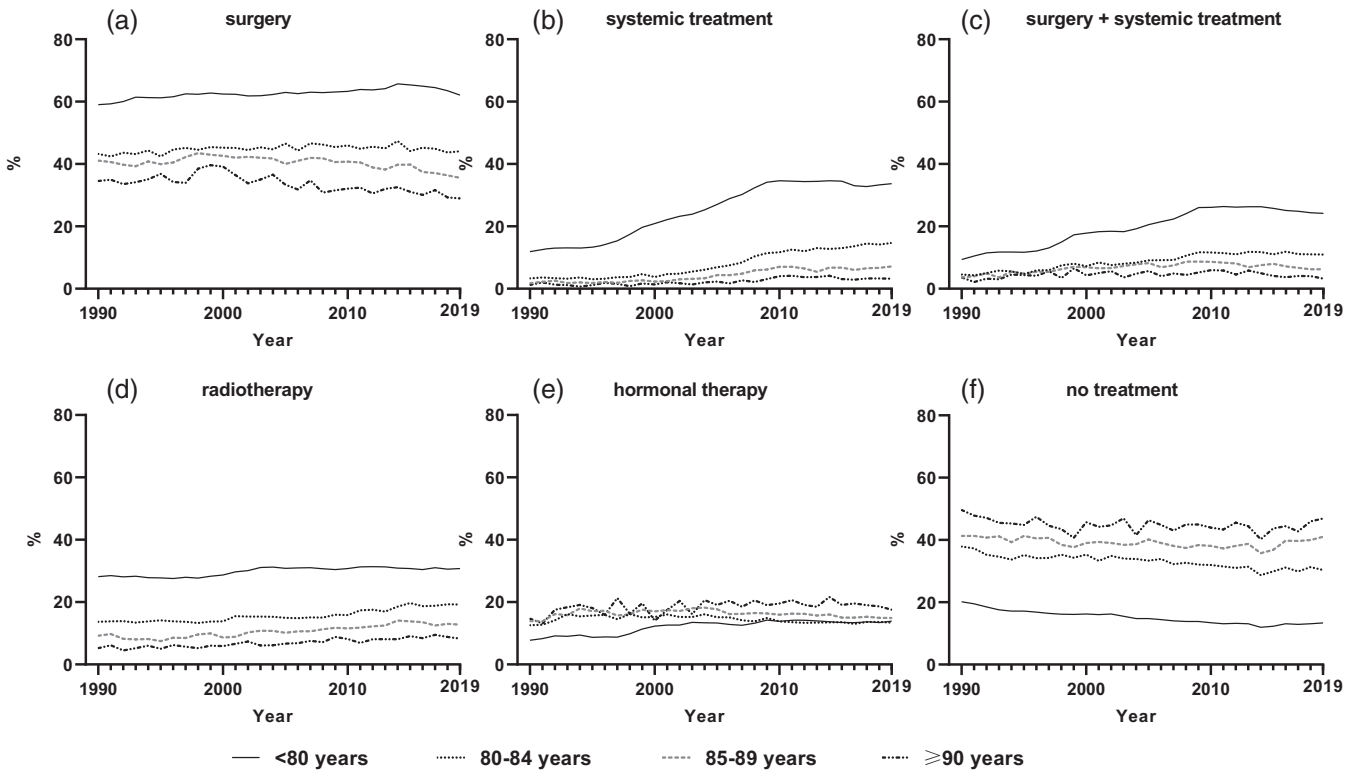

FIGURE 6 Trends in primary therapy of all solid tumors by age category (1990-2019). (A) percentage of patients treated with surgery. (B) Percentage of patients who received systemic treatment (excluding hormonal therapy). (C) Percentage of patients who received surgery plus systemic treatment (excluding hormonal therapy). (D) Percentage of patients who received radiotherapy at the primary tumor site. (E) Percentage of patients who received hormonal therapy. (F) Percentage of patients with no anti-neoplastic treatment. Treatment categories are nonexclusive; a patient may be counted in more than one treatment category.

melanoma patients. For 5-year net survival the largest absolute difference was seen in ovarian cancer (27 pp), lymphomas (27 pp) and myeloid malignancies (24 pp). Pancreatic cancer had the poorest survival of all tumor types, irrespective of age.

4 | DISCUSSION

In this nationwide, population-based study, we presented comprehensive information on cancer incidence, primary treatment and survival among the oldest-old population (ie, people aged ≥80 years) in the Netherlands over a 30-year period. At present, such comprehensive overviews are incredibly scarce. Our results showed (a) an enormous rise in incidence during the past 30 years and an even stronger forecasted rise during the next decade, (b) limited survival benefits compared to younger counterparts and (c) a large group of oldest-old who did not qualify for treatment. These findings address the urgent need for more evidence-based management of the oldest-old cancer patients.

Over the past 30 years the incidence of cancer among the oldest-old in the Netherlands has more than doubled. More than 1 out of 6 cancer diagnoses are currently in this age group. Because of the increased longevity and aging of the relatively large post-war generation the incidence is expected to rise further and will challenge our health care system.

As population aging is a global phenomenon and is even faster in many other countries than the Netherlands,[1] these challenges will be faced worldwide. Recently it has been estimated that the number of oldest-old cancer patients worldwide will triple between 2018 and 2050, corresponding with an estimated increase from 2.3 million to 6.9 million new cancer diagnoses in those aged ≥80 years. According to these estimates 21% of all cancer diagnoses will be among the oldest-old worldwide in 2050.[23] One of the few recent population-based studies showed that in Finland nearly 1 in 10 diagnoses during 2013 to 2017 was among individuals aged ≥85 years and their cancer burden has increased substantially over time.[24] The anticipated rise will lead to an increasing need for health care resources and potentially a shortage of health care providers as the demand for healthcare workers will outpace the supply.[25,26] The supply will decrease because of retirements or decreasing working hours of the older labor force, whereas the demand will increase due to increasing care needs. Generally, the higher the age, the more multifactorial and complex treatment (decision-making) becomes because the oldest-old with cancer are often frailer and exhibit more noncancer-related ailments than their younger counterparts. Therefore, the rise in very old patients will not only result in an increasing need for health care

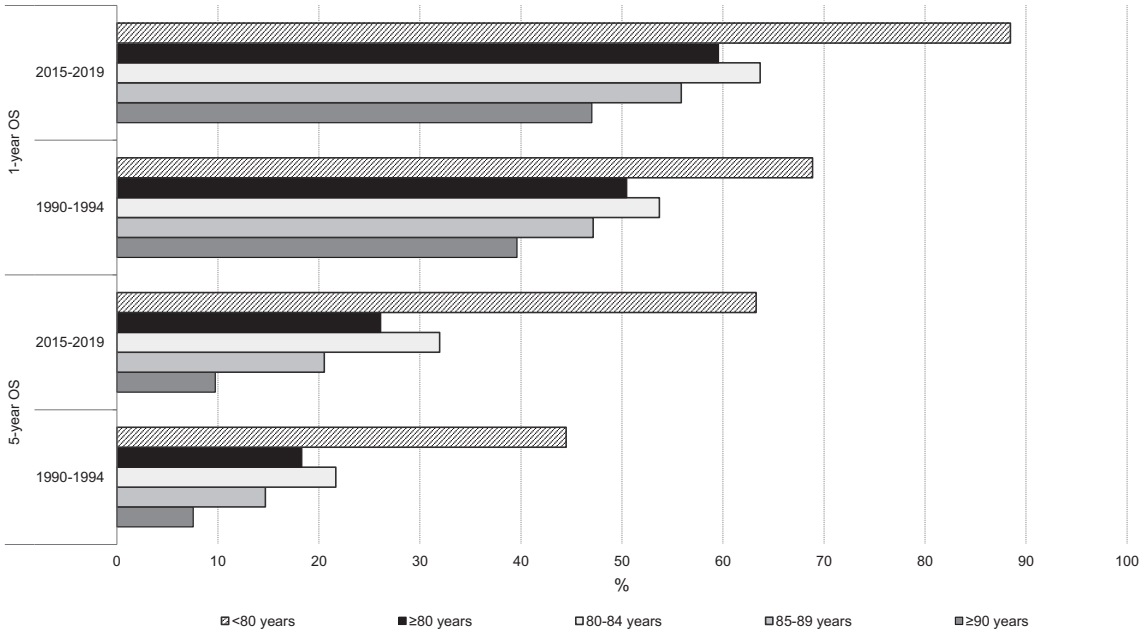

FIGURE 7 One- and 5-year overall survival (OS) by age group and period of diagnosis (1990-1994 and 2015-2019).

providers in general, but also specifically for those involved in the complex care of (very) old patients (eg, geriatric oncologists and nurses).

Over time, changes in incidence and share of the oldest-old patients were observed, reflecting changes in diagnostics and risk exposure. Whereas a slight increase in the share of the oldest-old patients could be expected due to the aging population, we observed a substantial decrease in prostate cancer. The incidence rate of prostate cancer has decreased dramatically and disproportionally among the oldest-old males since the mid-1990s, likely reflecting changes in prostate-specific antigen (PSA) testing. Currently, it is advised against asymptomatically testing males with a remaining life expectancy of <10 to 15 years, thus including the oldest old, as they are unlikely to benefit from early prostate cancer diagnosis during their remaining lifetime.[27,28] Not testing older patients causes a reduction in the age at which prevalent (often asymptomatic) prostate cancer is diagnosed and increases the share of oldest-old patients. Of note, the decreasing trend does not seem to continue in recent years, and the number of patients has increased considerably in those years.

Other cancer types, such as skin melanoma, lung cancer and mesothelioma, showed substantial increases in the proportion of the oldest-old patients over time. Changes in risk exposure might explain this finding. Skin melanoma is one of the fastest-growing cancers, particularly among older males. This trend has been previously described and thought to reflect a cohort effect of excessive sun exposure, poorer sun protection behavior (particularly among males) or overdiagnosis of thin melanomas.[29]

The growing share of the oldest-old patients with lung cancer is probably also caused by a cohort effect, as smoking was more prevalent among older generations than younger generations.

Restrictions in the application of asbestos since the 1980s and its ban in 1993, resulted in reduced asbestos exposure in younger generations, and is a likely explanation for the significant increase in the share of very oldest-old mesothelioma patients. The vast majority of mesothelioma patients are males, and unlike younger cohorts, the incidence (both in absolute and relative numbers) of the oldest-old has not yet declined.

Due to improved diagnostics, the incidence of primary unknown tumors has decreased over time. This decrease, however, is more substantial in younger patients, explaining the larger share of oldest-old patients in the most recent period.[30]

The stage distribution of the most common cancer types varied considerably between the age categories in our study. In most of these tumor types the proportion of patients with an undetermined stage increased with age, which is in line with a population-based study from the United States in which a higher proportion of unstaged patients for selected cancers were observed in the oldest-old patients defined as aged ≥85 years compared to patients aged 65 to 84 years.[7] This finding might be explained by a limited diagnostic work-up or refraining from staging in older patients because of limited therapeutic consequences. Nevertheless, the impact of age on stage varied considerably by cancer type. In breast cancer, skin melanoma and head and neck cancer, variations were minor, with small proportions of patients diagnosed with metastatic disease throughout all age groups. Prostate cancer showed the most significant variation in stage distribution, with more metastatic disease diagnosed among the oldest-old. Less opportunistic screening is a likely explanation for this,[31,32] as well as the patient delay in seeking care or a delay in referral of older males to an urologist until a higher PSA level is reached.[33]

Managing the oldest-old patients with cancer faces various challenges because of the heterogeneity of this population. More specifically, their clinical management is complicated by frailty, co-existence of other health conditions, including previous malignancies, polypharmacy and increased toxicity risks.[11,34,35] These are also reasons why

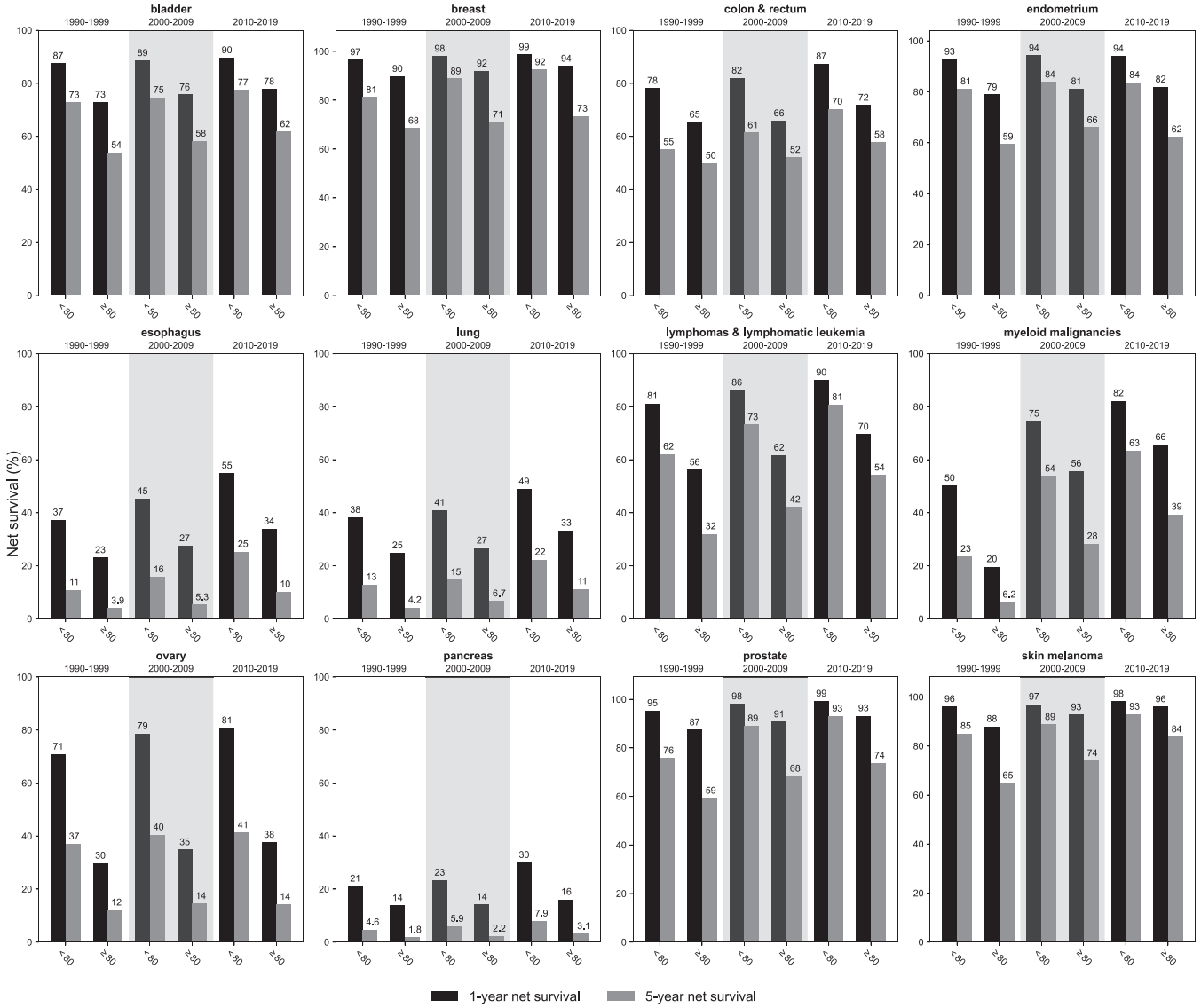

FIGURE 8 One- and 5-year net survival of the most common cancer types, by age category and period of diagnosis.

older cancer patients are underrepresented in clinical trials, which, in turn, further complicates their clinical management because of a lack of evidence to guide clinical decision-making.[36] This lack may result in considerable (unwanted) variation in treatment applications and reluctance toward particular treatments, potentially leading to poorer clinical outcomes or quality of life (QoL).

We demonstrated that the oldest-old patients less often receive antineoplastic treatment than younger patients. The share of untreated patients varied by cancer type and seemed higher for cancers with a high proportion of patients diagnosed at advanced stages and with an anticipated poor prognosis, such as lung and pancreatic cancer (data not shown). In contrast, watchful waiting or active surveillance are recommended strategies for slow-growing malignancies with favorable prognoses, such as low-stage prostate and renal cancer and indolent subtypes of B-cell non-Hodgkin lymphomas. These strategies are mainly applied to older patients to prevent overtreatment, thereby contributing to an increasing proportion of nontreated patients with advancing age. Of note, the likelihood of receiving treatment decreased with age for all treatment modalities except hormonal therapy.

Of all treatment modalities, systemic treatments have evolved most dramatically with the development of novel immuno- and targeted therapies, offering survival advantages to patients with advanced stages of cancer. These new treatment modalities and an increased application of (neo)adjuvant chemotherapy explain the increasing application of systemic treatment over time. However, with advancing age, the increase in application leveled off, particularly in patients aged ≥85 years. In the oldest-old, the benefits of (neo-)adjuvant chemotherapy may not outweigh the adverse effects, as most of them will not realize these benefits due to their limited life span. Novel therapies have specific adverse effects and potential interactions with other interventions not related to the index cancer but to another disease or malignancy. A lack of evidence on toxicity and tolerability may also result in a reluctance to treat old patients or a

slower adoption rate of new treatment among older patients, especially those with comorbidities Besides, in clinical decision-making other factors may also be highly important for particular subsets of the oldest-old; two of those factors are QoL and remaining life expectancy, which are both considered prominent factors in balancing the harms and benefits of treatment possibilities.[37] The oldest-old cancer patients are known to prioritize QoL over the length of life more often than younger patients.[38] As aging limits the remaining life expectancy of patients, it may also limit the potential benefits of treatment. Nowadays, people aged ≥80 years still have a significant life expectancy. In the Netherlands, an 80-year-old male currently has a remaining life expectancy of 8.5 years, whereas an 80-year-old female has a remaining life expectancy of 10.1 years. The corresponding estimates for 90-year-olds are 3.9 and 4.6 years, respectively.[39] It has been suggested that physicians' perceptions about life expectancy have resulted in the underutilization of treatment.[40] Although life expectancy varies significantly by individual, an accurate understanding of these estimates is important in balancing the risk and benefits of treatment, especially when cure or long-term remission or stabilization of the disease could be reached.

Over the past 30 years in the Netherlands, net survival of the oldest-old patients with cancer improved for virtually all tumor types. However, these improvements are less pronounced than their younger counterparts, resulting in an overall widening age gap in survival. As previously described, older patients with cancer may have benefitted less from treatment advances and might focus more on QoL. Besides, the proportion of the oldest-old living in solitude is increasing and is the highest among this age group.[41] Living alone and being unmarried or widowed are well-established factors associated with increased risk of metastatic disease, undertreatment and increased cancer mortality,[42,43] and may indirectly affect the survival gap since the share of the oldest-old is increasing.

The differences in stage distribution and application of primary treatment reflect the multiple challenges in the care of the older populations, which, in turn, might have contributed to poorer survival among the oldest-old patients with cancer. Relatively the survival gap between age categories was larger for tumors with a poor prognosis, corresponding to tumors for which most of the oldest-old did not receive primary treatment (eg, lung and pancreatic cancer). This finding may indicate that, among the oldest-old, an anticipated poor prognosis of the malignancy contributes to the decision not to treat and focus on QoL. In contrast, younger patients are more likely to undergo intensive treatment, which is in line with studies indicating that the preference for QoL or length of life is associated with advancing age.[38]

In conclusion, we observed large variation in stage distribution, primary treatment and survival by age, with generally the largest differences between the oldest-old and younger patients seen for cancers with a poor prognosis and requiring vigorous treatment. With the aging population, the strain on our health care system will rise enormously in the following decades. Besides, the needs of the oldest-old population differ from younger patients. Both aspects require adaptations in our health care system. More evidence is needed to optimally tailor the care of the heterogenous oldest-old population with cancer. Next to expanding the inclusion criteria of randomized clinical trials (RCTs) and providing subgroup analyses for the oldest-old patients with cancer, real word studies are needed complementary to provide insights into the oldest-old population ineligible for RCTs. Hence, population-based surveillance of the oldest-old patients with cancer remains essential since such surveillance activities can teach us how (new) treatment strategies are adopted and tolerated in this group.

AUTHOR CONTRIBUTIONS

Melinda S. Schuurman: Conceptualization, Formal Analysis, Methodology, Writing – Original Draft, Writing – Review & Editing; **Johanneke E. A. Portielje:** Conceptualization, Writing – Review & Editing; **Valery E. P. P. Lemmens:** Conceptualization, Methodology, Writing – Review & Editing; **Maaike A. van der Aa:** Conceptualization, Methodology, Writing – Review & Editing; **Otto Visser:** Conceptualization, Methodology, Writing – Review & Editing; **Avinash G. Dinmohamed:** Conceptualization, Methodology, Writing – Review & Editing. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying the findings of our study are available from the corresponding author upon reasonable request and with permission from Netherlands Comprehensive Cancer Organization.

ETHICS STATEMENT

According to the Central Committee on Research involving Human Subjects, this type of observational, noninterventional study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the NCR approved the use of anonymous data for our study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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