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ORIGINAL RESEARCH

Survival in Lung Cancer in the Nordic Countries Through A Half Century

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Objective: Lung cancer is often diagnosed at an advanced stage and survival has been poor, although long-term studies have been rare. We analyzed data on survival in lung cancer from Denmark, Finland, Norway, and Sweden over a 50-year period (1971–2020).

Methods: Relative 1- and 5-year survival data were obtained from the NORDCAN database for 1971–2020. We used generalized additive models to estimate survival trends over time and uncertainty of these estimates. We additionally calculated conditional survival from the 1st to 5th year (5/1-year), estimated annual changes in survival rates, and determined significant breaking points.

Results: In 2016–2020, 5-year survival rate for lung cancer was best for Norwegian men (26.6%) and women (33.2%). The sex difference was significant and it was found for each country. Survival improved modestly until the year 2000, after which time survival curves increased steeply and kept the linear shape to the end of follow-up, indicating consistent improvement in survival. Survival curves for 1- and 5/1-year survival were almost superimposable, indicating that deaths in the first year were approximately as many as in the subsequent 4 years, thus marking sustained long-term survival.

Conclusion: We could document a positive development in lung cancer survival with steep upward trends after the year 2000. Intensions for curative treatment have been increasing and the outcomes have been improving with the help of novel imaging methods. Pathways for facile patient access to treatment have been instituted. Close to 90% of the patients are ever smokers. National anti-smoking acts and alerting people who smoke about early symptoms may be beneficial, as metastatic lung cancer remains difficult to cure.

Keywords: smoking, lung cancer, relative survival, conditional survival, treatment, surgery

Introduction

Global incidence of lung cancer has been shaped by the cigarette smoking epidemic which started before or after World War II, depending on the country.[1,2] Lung cancer incidence rates increased with increasing consumption of cigarettes with a lag time of 20 to 40 years, and after peaking started to decline along the decreasing prevalence of smokers in the population.[3,4] Relative risk of lung cancer is 10 to 20 times higher in people with long-term smoking history compared to people who never smoked, but the relative risk depends on the cumulative smoking history and other factors; quitting smoking helps to reduce the relative risk but it may remain at 3–5 times higher compared to non-smokers, even 20 years after quitting.[5,6] Among lung cancers diagnosed in Sweden in 2021, only 13% were diagnosed in never smokers (https://cancercentrum.se/samverkan/cancerdiagnoser/lunga-och-lungsack/kvalitetsregister).

Smoking histories in the Nordic populations are country-specific, as has been reviewed.[7] Like in other populations, men adopted the habit of smoking first, and many Finnish (FI) and Danish (DK) men were smokers after World War II. Swedish (SE) men started at a moderate level and were able to reduce their smoking frequency to 15% by the early 2000s; later their smoking frequency was lower than that of SE women.[8,9] Smoking levels in DK and Norwegian (NO) men and women have remained highest in the Nordic countries (www.pnlee.co.uk/ISS.htm). Smoking is not only a risk

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factor of lung cancer but it also worsens survival by interfering with radiation therapy, particularly if continued after lung cancer diagnosis.[10–12] Other risk factors for lung cancer include occupational exposures, air pollution, radon, and family history and possibly also type 2 diabetes.[13–19]

We assessed relative survival in lung cancer in the Nordic countries over a 50-year period from 1971 to 2020 with a focus on changes in survival times. The study describes "real world" state of cancer control in these countries which guarantee health care to the residents with minimal out-of-pocket costs. In addition to the standard 1- and 5-year survival, we showed data for conditional 5/1-year survival and annual changes in survival.

Methods

The data were obtained from NORDCAN database 2.0.[20,21] The database was accessed at the International Agency for Cancer (IARC) website (https://nordcan.iarc.fr/en),[22] and the available tools were used to extract data on incidence, mortality and 1- and 5-year survival. NORDCAN uses International Classification of Diseases (ICD) version 10 codes for cancer.

Using the NORDCAN, we extracted data on 1- and 5-year relative survival, and the follow-up was extended until death, emigration or loss of follow-up, or to the end of 2020. Survival data for relative survival were available from 1971 onwards and the NORDCAN analysis was based on the cohort survival method for the first nine 5-year periods, and a hybrid analysis combining period and cohort survival in the last period 2016–2020; in the hybrid analysis in the last 5-year period, data are used from the penultimate 5-year period to make up 5-years of survival, as detailed.[20] Age-standardized relative survival was estimated using the Pohar Perme estimator.[23] Age-standardization was performed by weighting individual observations using external weights as defined on the IARC website. Age groups 0 to 89 were considered. The national life tables were used to calculate the expected survival. Statistical modeling and data visualizations were performed using R statistical software (https://www.r-project.org) in the R studio environment (https://posit.co/) (code available at https://github.com/filip-tichanek/nord_lung). The detailed methods have been published.[24]

For comparisons with other up-to-date lung cancer survival data we used the US Surveillance, Epidemiology and End Results (SEER) data for years 2012–18 on Non-Hispanic whites through (https://seer.cancer.gov/statistics-network/explorer/application.html?site=1anddata_type=1andgraph_type=2andcompareBy=sexandchk_sex_3=3andchk_sex_2=2andrate_type=2andrace=1andage_range=1andhdn_stage=101andadvopt_precision=1andadvopt_show_ci=onandhdn_view=0andadvopt_display=2#graphArea).

Results

Incidence and Mortality in the Nordic Countries

Age-standardized (world) incidence and mortality trends for lung cancer for the period 2011 to 2020 are reported in Table 1. Male incidence rates were highest for DK at 38.5/100,000 and lowest for SE at 17.8/100,000. The female rate for

Table 1 Age-Standardized Incidence (A) and Mortality (B) in Lung Cancer per 100,000 from 2011 to 2020, Separately for Males (Left Part) and Females (Right Part)

Males	ASR (World)	Cum. risk % [0–74]	Females	ASR (World)	Cum. Risk % [0–74]
A) Case numbers					
Denmark, 23,843	38.5	4.7	Denmark, 23,889	36.5	4.6
Finland, 17,493	28.2	3.5	Finland, 10,133	14.0	1.8
Norway, 16,561	32.1	3.9	Norway, 14,924	27.5	3.6
Sweden, 20,026	17.8	2.2	Sweden, 21,817	19.0	2.5
B) Death numbersity					
Denmark, 18,727	28.9	3.3	Denmark, 17,755	24.7	3.0
Finland, 14,604	22.8	2.8	Finland, 7771	10.0	1.3
Norway, 11,896	22.3	2.6	Norway, 9878	16.9	2.1
Sweden, 18,125	15.0	1.7	Sweden, 18,205	14.1	1.8

DK was only slightly lower than the male rate but the lowest female rate was for FI at 14.0/100,000. Mortality rates were lower than the incidence rates but correlated with each other.

Relative Survival in the Nordic Countries and USA

Figure 1 shows relative 1-, 5/1- and 5-year lung cancer survival in DK men (a) and women (e), in FI men (b) and women (f), in NO men (c) and women (g) and in SE men (d) and women (h). Even though the female plots had the same shape as the male ones, the female rates were higher. Initially, the DK rates were below the other countries but a strong increase in survival started after the year 2000. Finland was the only country for which 5/1-year conditional survival was much lower than the 1-year survival, and overall Finland lagged behind the other countries in survival improvements after the year 2000.

Table 2 lists survival rates in 1- and 5-year periods, and the country-specific rates can be compared. In the latest period (2016–20) 1-year lung cancer survival had reached over 50% for men (FI only 43%) and about 60% for women (FI 52.4%). Contemporary 5-year survival was best for NO men (26.6%, significantly better than that in the other

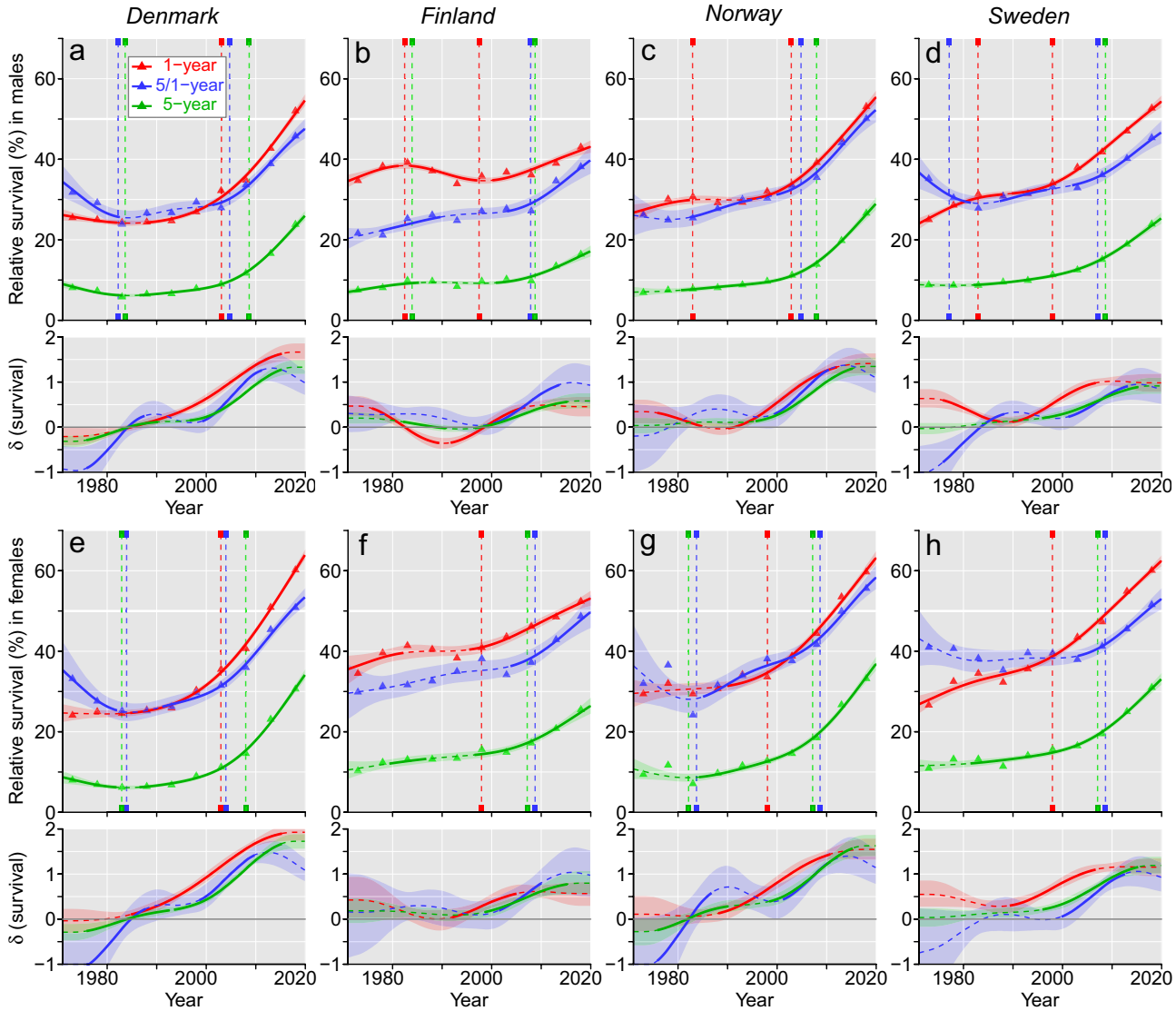

Figure 1 Relative 1-, 5/1- and 5-year survival rates of lung cancer in Denmark (**a** and **e**), Finland (**b** and **f**), Norway (**c** and **g**) and Sweden (**d** and **h**), separately for males (**a**–**d**) and females (**e**–**h**). The vertical lines mark a detectable change in the survival trends ("breaking points") and the bottom curves show estimated annual changes in survival. The curves are solid if there is >95% plausibility that the curve grows or declines. Shadow areas indicate 95% credible interval derived from GAM. All curves are color coded (see the insert).

Table 2 1-Year (a) and 5-Year (b) Relative Survival % [95% Confidence Interval] in Lung Cancer from 1971 to 2020, Separately for Males (Left) and Females (Right)

	Male Cancers				Female Cancers			
	Denmark	Finland	Norway	Sweden	Denmark	Finland	Norway	Sweden
(a) 1-year								
1971–1975	25.5 [24.3–26.7]	34.7 [33.4–36.0]*	26.4 [24.6–28.3]*	25.0 [23.9–26.1]*	24.1 [22.1–26.3]	34.5 [31.3–37.9]	29.4 [26.2–33.1]	26.6 [24.7–28.7]*
1976–1980	25.0 [24.0–26.0]	38.3 [37.2–39.5]	30.1 [28.5–31.7]	28.6 [27.5–29.8]*	25.0 [23.4–26.8]	39.6 [36.9–42.6]	32.0 [29.1–35.2]	32.5 [30.5–34.7]
1981–1985	24.3 [23.3–25.2]	39.2 [38.1–40.4]	30.7 [29.3–32.2]	31.3 [30.1–32.4]	24.6 [23.3–26.1]	41.4 [38.9–44.2]	29.4 [27.1–32.0]	34.5 [32.7–36.4]
1986–1990	24.4 [23.4–25.3]	37.1 [35.9–38.3]	29.2 [27.9–30.5]	30.8 [29.6–31.9]	25.4 [24.2–26.7]	40.5 [38.1–43.0]	30.7 [28.6–32.8]	32.3 [30.7–34.0]*
1991–1995	24.7 [23.8–25.7]*	33.9 [32.8–35.1]	29.3 [28.1–30.7]*	31.4 [30.3–32.6]*	25.9 [24.8–27.1]*	38.3 [36.2–40.6]	34.2 [32.3–36.1]	35.6 [34.1–37.1]*
1996–2000	26.9 [26.0–27.9]*	35.8 [34.6–37.1]	32.0 [30.8–33.3]	34.1 [33.0–35.4]*	30.3 [29.2–31.4]*	40.9 [38.9–43.0]	33.6 [32.0–35.3]*	39.4 [38.0–40.9]*
2001–2005	32.2 [31.2–33.2]*	36.8 [35.6–38.1]	33.6 [32.3–34.9]*	38.0 [36.8–39.2]*	35.5 [34.4–36.6]*	43.6 [41.7–45.6]	38.8 [37.3–40.4]*	43.5 [42.2–44.7]*
2006–2010	34.8 [33.8–35.9]*	36.1 [34.8–37.4]*	39.2 [37.9–40.5]*	41.8 [40.6–43.0]*	40.6 [39.5–41.6]*	46.2 [44.4–48.0]	44.4 [43.0–45.8]*	47.3 [46.1–48.5]*
2011–2015	42.7 [41.6–43.8]*	39.0 [37.7–40.3]*	44.9 [43.6–46.2]*	47.0 [45.8–48.2]*	50.9 [49.9–52.0]*	48.5 [46.9–50.2]*	53.5 [52.2–54.9]*	54.9 [53.8–56.1]*
2016–2020	52.0 [50.8–53.1]	43.0 [41.7–44.3]	53.1 [51.8–54.5]	52.7 [51.5–54.0]	60.2 [59.2–61.3]	52.4 [50.8–54.1]	59.7 [58.4–61.1]	60.1 [59.0–61.2]
(b) 5-years								
1971–1975	8.1 [7.3–9.0]	7.5 [6.8–8.3]	6.9 [5.8–8.2]	8.8 [8.1–9.6]	8.0 [6.6–9.7]	10.3 [8.2–12.9]	9.4 [7.1–12.5]	10.9 [9.5–12.5]
1976–1980	7.3 [6.7–8.0]	8.1 [7.5–8.8]*	7.5 [6.5–8.5]	8.7 [7.9–9.5]	6.9 [5.9–8.1]	12.4 [10.6–14.5]	11.7 [9.7–14.1]	13.2 [11.7–15.0]
1981–1985	5.8 [5.2–6.4]	9.9 [9.1–10.7]	7.8 [6.9–8.8]	8.7 [8.0–9.5]	6.2 [5.5–7.1]	13.1 [11.3–15.1]	7.1 [5.8–8.7]	13.2 [11.9–14.6]
1986–1990	6.5 [6.0–7.1]	9.7 [9.0–10.6]	8.1 [7.3–9.1]	9.5 [8.8–10.3]	6.4 [5.7–7.2]	13.2 [11.5–15.1]	9.7 [8.4–11.3]	11.4 [10.3–12.6]*
1991–1995	6.6 [6.0–7.2]*	8.4 [7.7–9.2]	8.8 [8.0–9.7]	9.9 [9.2–10.7]	6.8 [6.1–7.6]*	13.4 [11.9–15.2]	11.6 [10.3–13.1]	14.1 [13.0–15.2]
1996–2000	7.9 [7.3–8.6]	9.7 [9.0–10.6]	9.7 [8.8–10.6]	11.3 [10.5–12.2]	9.0 [8.2–9.7]*	15.6 [14.1–17.3]	12.8 [11.6–14.1]	15.6 [14.6–16.7]
2001–2005	9.0 [8.3–9.7]*	10.2 [9.4–11.1]	11.2 [10.3–12.1]*	12.5 [11.7–13.4]*	11.2 [10.5–12.0]*	14.9 [13.5–16.4]	14.6 [13.5–15.9]*	16.5 [15.6–17.5]*
2006–2010	11.7 [11.0–12.5]*	9.8 [9.0–10.7]*	13.9 [13.0–15.0]*	15.1 [14.1–16.1]*	14.6 [13.9–15.5]*	17.2 [15.8–18.7]*	18.5 [17.3–19.7]*	19.5 [18.6–20.5]*
2011–2015	16.6 [15.8–17.5]*	13.5 [12.5–14.5]*	19.8 [18.7–21.0]*	18.9 [17.9–19.9]*	23.1 [22.2–24.0]*	20.8 [19.4–22.3]*	26.7 [25.5–28.0]*	25.0 [24.0–26.1]*
2016–2020	23.8 [22.8–25.0]	16.4 [15.2–17.6]	26.6 [25.3–28.0]	23.9 [22.7–25.1]	30.6 [29.5–31.8]	25.5 [23.8–27.2]	33.2 [31.8–34.6]	31.0 [29.8–32.2]

Note: *Significant (non-overlapping 95% CLs) increase between the marked and the next period.

countries) and worst in Finland (16.4%); for women, the order was the same, NO on top (33.2%) and FI in the bottom (25.5%). Female 1- and 5-year survival was significantly better than male survival in all countries; the mean differences were 7.9 % units for 1-year and 7.3 % units for 5-year survival (means for the four countries). For 5-year survival the 50-year improvement was best for NO men (19.7 % units) and women (23.8 % units) and worst for FI men and women (9.1 and 15.2 % units). For Norway, 5-year survival improved more than 3.5-fold over the 50-year period, while improvement in Finland was only 2.2–2.5 fold; 50-year improvement in 1-year survival in Finland lagged even more behind as improvement was only 1.2–1.5 fold compared to more than 2-fold improvements in the other countries.

Data from Table 3 enabled estimation of the magnitude of survival improvements after year 1 to year 5 over the 50-year period. Improvement in 5/1-year survival has been somewhat less than that for 1-year survival (Table 2), and in 2016–20 somewhat less patients died in the first year compared to the subsequent 4 years.

According to the US SEER database for Non-Hispanic whites, 5-year survival in 2012–18 was 19.2% for men and 27.0% for women.

Discussion

We documented an improvement in lung cancer survival. One-year survival doubled and 5-year survival tripled in the 50-year study period in DK, NO and SE patients. The improvement in survival was slow until about the year 2000, at which point all survival metrics improved and continued to improve over the remainder of the study period. Importantly, the improvement in 5/1-year survival was only slightly slower than that for 1-year survival. All Nordic datasets showed a consistently better survival for women compared to men. Survival in women in the last period was longer by more than 7 % units (mean of all countries) for both 1- and 5-year survival. We reported earlier that lung cancer is one of the few solid cancers with a sex difference in survival.[25] Sex difference in lung cancer survival has been the subject of many studies and the female advantage after treatment has been confirmed, with sex being the only factor associated with the improved survival.[26]

Table 3 5/1-Year (4-Year Conditional) Survival % in Lung Cancer from 1971 to 2020, Separately for Males (Left) and Females (Right)

	Male Cancers				Female Cancers			
	Denmark	Finland	Norway	Sweden	Denmark	Finland	Norway	Sweden
1971–1975	31.8	21.6	26.1	35.2	33.2	29.9	32.0	41.0
1976–1980	29.2	21.1	24.9	30.4	27.6	31.3	36.6	40.6
1981–1985	23.9	25.3	25.4	27.8	25.2	31.6	24.1	38.3
1986–1990	26.6	26.1	27.7	30.8	25.2	32.6	31.6	35.3
1991–1995	26.7	24.8	30.0	31.5	26.3	35.0	33.9	39.6
1996–2000	29.4	27.1	30.3	33.1	29.7	38.1	38.1	39.6
2001–2005	28.0	27.7	33.3	32.9	31.5	34.2	37.6	37.9
2006–2010	33.6	27.1	35.5	36.1	36.0	37.2	41.7	41.2
2011–2015	38.9	34.6	44.1	40.2	45.4	42.9	49.9	45.5
2016–2020	45.8	38.1	50.1	45.4	50.8	48.7	55.6	51.6

In order to understand the reasons behind the increased survival, we searched clinical reports on lung cancer diagnostics and treatment from the Nordic countries. In Sweden, the proportion of adenocarcinoma has continuously increased and by 2021 it made up some 55% of all lung cancers, followed by squamous cell carcinoma (<20%) and small cell carcinoma (>10%). The trend in histological distribution of lung cancer has been similar in the other countries.[27–29] According to a national lung cancer report for Sweden in 2021, over 50% of patients were diagnosed with metastasis but the majority of patients with good performance status (WHO grades up to 2) were offered some form of treatment; half of all diagnoses were in the age group 70 to 79 years (https://cancercentrum.se/samverkan/cancerdiagnoser/lunga-och-lungsack/kvalitetsregister). In Norway in the period 1997–2011 about half of lung cancers were diagnosed with metastases and there was a time-dependent increase in resection rates from 16.3% in 1997–99 to 23.8% in 2009–11.[27] According to a later NO study, curative treatment increased from 22.9% of the patients in 2001 to 37.9% in 2016, including 20.6% operations, 8.5% conventional radiotherapy, and 8.8% stereotactic radiotherapy.[30] Computed tomography (CT) has been the major imaging tool for lung cancer and it has contributed to incidental findings of early stage lung cancers.[31] Positron emission tomography (PET) was introduced in Sweden in 1990 and together with thorax-CT it has become a diagnostic tool for most lung cancer patients.[27–29] A further improvement in the diagnostic armamentarium was endobronchial ultrasound bronchoscopy (EBUS) which Sweden started using after the year 2000.[28]

Surgery, often minimally invasive surgery, is the main therapeutic modality for early-stage lung cancer, supported by radio- or chemotherapy and more recently by targeted therapy or immunotherapy.[29,32,33] Non-small cell lung cancer develops resistance toward chemotherapy and targeting radiation needs to be adjusted to movements because of breathing. Surgery, chemotherapy with platinum and other compounds, targeted therapy (eg, epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangement) and immunotherapy are currently the treatments of choice; immunotherapy is widely used as single agent, if the tumor is PDL1+ or tumor mutation burden is high.[28,32,33] A common way to use immunotherapy nowadays is to combine it first line with chemotherapy.[28,32] Small cell carcinoma may initially respond well to chemotherapy and radiation, but has usually metastasized before diagnosis, making surgery ineffective.[32]

In the Nordic countries, national treatment guidelines have been issued for lung cancer and major organizational changes have been instituted in cancer care. Treatment has been centralized, care pathways for patients have been facilitated and increasing numbers of patients are seen by multidisciplinary teams.[28,34]

Differences in survival between the countries were not large (excluding the poor performer, Finland) but they were systematic in that 5-year survival was best in NO men and women, and the improvement over 50 years was also largest in Norway. More patients have been diagnosed in the early stages. Lung cancer is not the only cancer for which survival in Finland is lagging behind the other Nordic countries.[23,25] Although there are likely many reasons for this, the deep economic crisis in Finland in the 1990s has probably cast a long shadow on health care, and relative health care funding

(Finland 7.0%, Sweden 9.3%, Denmark 8.4%, Norway 9.0%, www.oecd-ilibrary.org 2019) and the absolute national resources are lagging behind the other Nordic countries.[35] Finland is yet to set up a national cancer plan which Denmark already enacted in 2001 and Norway and Sweden later.[23] According to data.oecd.org, Finland clearly had the least computed tomography (CT) scanners per 100,000 inhabitants in 2021 (Finland 17, Sweden 28, Norway 30, Denmark 44). This might serve as a surrogate for early lung cancer detection. Smoking histories appear not to explain sex or country differences in survival. While male smoking frequencies were historically higher than female ones, the differences equalized toward the end of the 1980s and smoking levels have remained relatively high in Denmark and NO men and women and Swedish men have been non-smoking champions[36] (www.pnlee.co.uk/ISS.htm).

In a large international study on cancer survival for the years 2010–2014, Japan reported the best 5-year survival in lung cancer at 33% (both sexes).[37] Some countries, including Sweden, reached survival in the range of 20–30% but the largest group, also including also Denmark, Finland and Norway, reached survival in the range of 10–19%. However, since that study, the development has been fast in Denmark, Norway and Sweden, and 5-year survival in these countries was higher than that reported in the US SEER database for Non-Hispanic whites in 2012–18 which was 19.2% for men and 27.0% for women. One reason for the positive development in the Nordic countries, as well as in most developed countries, has been the gradual increase in adenocarcinoma, a common histology in nonsmokers, which is characterized by higher survival than that for lung cancer overall (adenocarcinoma in SEER 24.5% for men and 34.6% for women).

The limitation of the present study is the lack of pathological information about lung cancer at diagnosis and any treatment information. However, the advantages of the NORDCAN data are its uniquely long follow-up time from high-level cancer registries. It is not feasible to assume that comparable pathological data were available over 50 years, and even the closely collaborating Nordic cancer registries have difficulties in comparing data on tumor characteristics (stage).[38] Lacking stage data do not allow assessment of the contribution of early detection to increasing survival. However, comparison of 1- and 5/1-year survival allows assessment of the death rates between periods 0–1 and 1–5 years of diagnosis.

The previous studies on lung cancer survival ascribe the progress to multifactorial causes including earlier and more precise diagnostics, improved and more active treatment, and better organization of patient care.[23,27–29] Also, the gradual shift in lung cancer histology from squamous cell carcinoma to a more tractable adenocarcinoma should contribute to a survival benefit.[28,33] The title of one of these studies "Lung cancer survival in Norway, 1997–2011: from nihilism to optimism" epitomized the combined contribution of many positive factors.[27] It is curious that these studies did not observe the major trend change that took place after the year 2000 toward a sustained improvement in survival. The probable reason is that these studies covered shorter periods instead of the 50-year time span of the present study supplemented with a detailed analysis of annual changes.

In conclusion, we could document a very positive development in lung cancer survival after the year 2000. Since then, all survival metrics showed almost linear increases and, importantly, there was no indication of slowing down of the improvement. Because half of lung cancer is diagnosed at a metastatic stage, the improvement in 5- and 5/1-year survival appears to be reassuring that some metastatic lung cancers are also successfully treated. The possible contribution of immunotherapy to survival may be too early to evaluate since the data of the last 5-year period (2016–20) are not independent but a hybrid estimate with the penultimate period.

Data Sharing Statement

Aggregated data from a publically accessible database were used. Full statistical R code is available at https://github.com/filip-tichanek/lungs.

Ethics

Anonymous data from a publically available database were used posing no ethical issues. The IARC website on NORDCAN describes under "About the project" that "Data in NORDCAN is freely available"; IARC is an intuition of the World Health Organization. The Finnish regional ethical committee instructions state that "[…] ethical approval is normally not required, as stipulated by the legislation, for example in simple interview research or research based on patient records and/or registers-based research, as long as the patients' identity is not violated." (translated from Finnish).

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Disclosure

AH is a shareholder in Targovax ASA. AH is an employee and shareholder in TILT Biotherapeutics Ltd. The other authors declared no conflict of interest.

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