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Incidence trends in lung and bladder cancers in the Nordic Countries before and after the smoking epidemic

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ABSTRACT

Cigarette smoking epidemic which started before the World War II completely changed the cancer landscape, and hugely increased the incidence in cancers which were responsive to tobacco smoke carcinogens, such as lung and urinary bladder cancers. Reliable incidence data spanning the stepwise spreading epidemic are rare, but the Nordic cancer registries are unique sources in being able to catch the pre-epidemic situation especially in the female population where smoking became more prevalent after the War. We used data from the NORDCAN database which were provided by the cancer registries of Denmark, Finland, Norway and Sweden for the analysis of incidence changes in lung and bladder cancers from year 1943 (Denmark), from 1953 (Finland and Norway) and from 1960 (Sweden) until year 2016. The results were compared to the global cancer data available from the International Agency for Research on Cancer (IARC). The analyses revealed three novel observations relevant to the smoking epidemic. I) Bladder cancer incidence for Finnish women diagnosed in the 1950s, when the smoking prevalence was very low, was 1.2/100,000 (world standard rate) which is below the present lowest continental rate of 2.0/100,000 for Latin American women. II) Among Norwegian women diagnosed in the 1950s the lung-to-bladder incidence ratio was 0.64, probably benchmarking the incidence rates prior to the smoking epidemic. III) Our analysis among Swedish men, who have had the lowest smoking prevalence in Europe, showed an epochal crossing of lung and bladder cancer incidence rates before year 2015. Thus, the data suggest that the approaching of the incidence rates for lung and bladder cancer can be expected in the course of the abating smoking epidemic.

INTRODUCTION

The epidemic of smoking cigarettes started in industrialized countries before World War II and the cigarette consumption expansion was followed by a parallel increase in lung cancer mortality a few decades later (1, 2). The habit of smoking penetrated various populations at different rates and males adopted smoking generally earlier than women (www.pnlee.co.uk/ISS.htm). We know well how smoking has modelled the cancer panorama, but what it was before the epidemic or what it might be after the epidemic is uncertain because reliable sources of data are limited (3, 4). Cancer registries of the Nordic Countries Denmark, Finland, Norway and Sweden were started in the 1950s (Denmark in 1943) to cover the whole population in countries with universal health care systems (5). Data from these sources are collected into the NORDCAN database which we use here as a window to look into the past to estimate pre-smoking incidence of lung and bladder cancers and into the future of an abating smoking epidemic.

Relative risks for tobacco-related lung cancer are of the order of 10 to 20 in active cigarette smokers compared to non-smokers, and they remain at levels of 3 to 5 after 20 years of quitting smoking (6, 7). Active smokers have a relative risk for bladder cancer of about 4 to 5 compared to non-smokers (6, 8, 9). In former smokers the risk is typically 2 to 3, depending on the time since quitting, and it may take at least 30 years to reach the incidence level of non-smokers (6, 8, 9). The risks for both cancers are typically in the higher risk range for men and in the lower range for women (10). The changing composition of cigarettes and tobacco have apparently lowered the risk of lung cancer by about 20% but increased the risk of bladder cancer by 30% (11, 12). Population attributable fractions of smoking in UK for year 2015 were estimated at 74.1% for male and 70.2% for female lung cancer, and at 46.0% for male and 41.5% for female bladder cancer (13). The other considered risk factors for lung cancer were occupation (20.5% for men and 4.3% for women), radiation (4.7 and 5.0%) and air pollution (7.8% for men and women); the combined estimates were 81.9 and 75.0%, respectively (of note, they were not additive). For bladder cancer occupation (7.1 and 1.9%) and radiation (2.1 and 1.8%) constituted the additional risk factors for a total of 50.8 and 43.6% (13). Other risk factors such as type 2 diabetes and family history were not considered (14, 15).

To put the incidence data on lung and bladder cancers in a perspective, we collected smoking prevalence rates for the four Nordic Countries, which have quite different past patterns of smoking (www.pnlee.co.uk/ISS.htm) (16, 17). At around 1960, about half of Swedish men smoked, compared to about 60% for Norwegian and 70% for Danish men (18); the proportion was 55% for Finnish men which had decreased since the World War II (19). In Swedish men smoking prevalence dropped to 15% by the early 2000s (17, 20). The drop of smoking prevalence was initially fast in Finnish men but it remained at 30% into the early 2000s. In Norwegian and Danish men, the decrease was slow but by early 2000s the prevalence reached 35% (www.pnlee.co.uk/ISS.htm) (18). The smoking prevalence in Swedish women was around 30% in 1960 and it slowly decreased towards 20% in the early 2000s when it exceeded the male

prevalence (20). For Norwegian and Danish women the history resembled the Swedish one, with the exception that the Danish prevalence was initially over 40% and the prevalence in both countries remained at 30-35% into the early 2000s (www.pnlee.co.uk/ISS.htm) (18, 21). Among Finnish women the trend was opposite, starting at <5% in 1960 and ending up at the Swedish level of 20% in the early 2000s (www.pnlee.co.uk/ISS.htm)(20). Not only histories of smoking prevalence differ but also the types of consumed products, including adoption of the ‘low tar’ filter cigarettes. Products other than manufactured cigarettes (hand rolled cigarettes, pipe and cigars) have been common in Norway and earlier in Denmark but rare in Sweden and Finland (22)(www.pnlee.co.uk/ISS.htm). Thus the Nordic population offers a variety of smoking patterns, including the lowest smoking prevalence in Europe for Swedish men and among the highest for Danish women (17, 23).

Incidence trends for lung and bladder cancers were analyzed using the NORDCAN database from the earliest available years (1940s and 1950s) through 2016.

MATERIALS AND METHODS

We used the NORDCAN database which is a compilation of data from the high-level Nordic cancer registries as described (5, 24) (<https://NORDCAN.iarc.fr/en/database#bloc2>). Data were available from Denmark since 1943, Finland and Norway since 1953 and Sweden since 1960. Mortality data were collected from the same source but the starting year was 1951 for Denmark and 1952 for Sweden. In the database, lung cancer codes are C33-C34; bladder cancer is part of urothelial cancers covered by the codes C65-68 (cancers of the pelvis, ureter, bladder), D09.0-1, D30.1-9, D41.1-9 (in situ and tumors of undefined behavior at these sites). Coding practices for bladder cancer have been internationally variable as far as consideration of benign lesions. In NORDCAN the coding should be unified except that Denmark included tumors of unknown grade and ‘papilloma’ in bladder coding already in the 1950s (5).

The vast majority of urothelial cancers are located in the bladder (90-95% of all) with the upper urinary tract (renal pelvis and ureter) accounting for the rest (25). For simplicity and the dominance of a single entity, we call these cancers as ‘bladder cancer’. Urothelial cancers share risk factors, including smoking (6, 25, 26).

For incidence analysis and in any incidence comparisons, the world standard population was used in age adjustment. In some graphs 3-year smoothing was used because of small case numbers.

In some analyses we used databases at the International Agency for Research on Cancer (IARC), including ‘Cancer Today’ [Cancer Today \(iarc.fr\)](http://CancerToday.iarc.fr) and the Cancer Incidence in Five Continents (CI5) XI with incidence data from years 2008 to 2012.

RESULTS

Lung and bladder cancer incidence rates for males in the Nordic countries are shown in **Fig. 1**. The incidence rates of the two cancers are presented in the same panel to facilitate rate comparisons. In **Fig. 1A** the rates for Denmark and Finland show very large but narrowing lung-to-bladder ratios in the two countries. While in Finland the lung-to-bladder ratio was 8-fold at its peak, around 1970, it gradually decreased to less than 2-fold in 2016. For Denmark, the ratio was constantly 2-fold between 1943 and 1980, but then decreases to 1.5 in 2016. The Danish incidence peaks for lung and bladder cancers were separated by less than a decennium while the time interval was more than doubled for Finland. In **Fig. 1B** the same male data are shown for Norway and Sweden (note different scales for the Y-axes). Similar to Denmark, the Norwegian lung cancer rate was initially twice the bladder cancer rate, but the difference narrowed with time. While the graph for lung cancers reached a broad maximum at around 2000, bladder cancer rate kept on increasing. For Sweden, the rate difference was initially also 2-fold but it started declining after 1980 due to declining lung cancer rates, and the graphs cross before year 2015 (arrow).

Female incidence data for lung and bladder cancers in the Nordic Countries are shown in **Fig. 2**. It is a noteworthy, in difference to the male rates, that the female rates for both cancers started with an initial plateau phase. The Danish rates of lung and bladder cancers started close to each other but ended up in 2016 with a lung cancer rate 4.5-fold higher than the bladder cancer rate (**Fig. 2A**). For Finland, the starting level for bladder cancer in the 1950s was around 1/100,000, lowest for all recorded rates. The difference between rates for lung and bladder were initially about 2-fold but widened to about 4-fold. The Norwegian and Swedish lung and bladder cancer rates started at similar levels but lung cancer rates shot up in 1975, particularly in Norway and ended up at 3.5-fold over the rate for bladder cancer (**Fig. 2B**). In Sweden, the difference in 2016 was close to 3-fold.

Because of unique possibility to query incidence data far back in pre-smoking (or minimal smoking) time, were analyzed female lung and bladder cancer rates from the 5 earliest years available (Table 1). The incidence for lung cancer was lowest, 1.8/100,000, in Norway, and doubled in the other countries. For bladder cancer, the Finnish rate of 1.2/100,000 was the lowest and the Swedish rate the highest, 3.2/100,000. The rates for lung cancer exceeded those for bladder cancer (lung-to-bladder ratios Denmark 1.3, Finland 3.1, Sweden 1.2), with the exception of Norway, where the lung-to-bladder ratio was 0.64. Mortality rates from the earliest available year are also shown; the years overlap with the years for the incidence data for Finland and Norway, but for Denmark are later and Sweden earlier than the incidence data. The Swedish bladder cancer mortality was 1.1/100,000, which suggested a minimal influence by smoking in the early 1950s. The death rate for bladder cancer in the other Nordic Countries was also below 2.0/100,000.

DISCUSSION

The novel observations include gauging of the likely pre-smoking incidence rates for lung cancer in Norwegian women (1.8/100,000) and for bladder cancer in Finnish women (1.2/100,000). We observed probably the epochal landmark for a developed country, the crossing of rates for bladder and lung cancers in Swedish men. Other findings were declining male lung cancer rates which were not followed by declining bladder cancer rates in Norway and Sweden, and time-dependent widening of incidence rates for female lung and bladder cancers following the onset of the smoking epidemic. The major limitation of the study is the ecological extrapolation for smoking prevalence.

The unique aspect of cancer registration in the Nordic Countries was that it started nation-wide earlier than in other countries (not considering some early regional registers) in the world. However there is always concern about the accuracy and coverage of the historical data; low rates may indicate poor coverage of cases. In the Nordic Countries cancer registration and death registration are independent recording systems, although the cancer registries may search causes of death records (5). Thus the consistency of incidence and mortality data in Table 1, considering the small shifts in timing, provides evidence on the reliability of the data.

Another question about the tenet of the study is whether we indeed were able to gauge cancer rates before the influence of smoking. The incidence trends of lung and bladder cancers for Finnish and Norwegian women were flat from 1953 to about 1965, and started to rise thereafter, indicating an influence of a new risk factor (smoking). For Norwegian women exact smoking histories are available by birth cohorts (27). These can be used to estimate the smoking prevalence in birth cohorts/age groups that could have contributed to lung cancer in the 1950s; the estimate is below 10%. Accordingly, the incidence of lung cancer in Norwegian women at 1.8/100,000 (**Table 1**), is at the level of lowest global female rates ranging from 1.0 to 1.9/100,000 in individual cancer registries in South Africa, India and Algeria (in years 2008-20212, IARC CI5). Smoking rates among Finnish women were very low until the 1960s and the low bladder cancer rates in the 1950s should reflect the negligible smoking prevalence in the early parts of the century. Why were then lung cancer rates for Finnish women 3 times higher than those for bladder cancer in the 1950s? We do not know, but the overwhelming use of wood for heating and cooking, and the Finnish habit of at least weekly bathing in a wood-heated sauna might have been associated with lung cancer risk in a study on Finnish men (28). The Finnish bladder cancer rate of 1.2/100,000 (**Table 1**) is at the level of the lowest current global rates in developed countries (Californian American Indians and Korean immigrants, IARC CI5); yet some lower rates are reported from some cancer registries in developing countries but with questions about diagnostic comparability and coverage (29).

Surpassing of lung cancer incidence by bladder cancer incidence, which took place among Swedish men before 2015, is probably unique for the global cancer experience in the aftermath of the smoking epidemics. A related sentinel finding among Norwegian women showed that in the 1950s the lung-to-bladder cancer incidence ratio was 0.64. This may indicate that before the

smoking epidemic, the incidence of bladder cancer may have exceeded that of lung cancer. The Swedish male data are now showing the similar situation in the terminal phase of the smoking epidemic. The global lung-to-bladder cancer incidence ratio is estimated at 2.2 for men and 4.0 for women (IARC [Cancer Today](#)). The ratios are highest in Asia, 5.5 (men) and 10.0 (women), intermediate in Europe (2.2 and 3.9) and North America (2.0 and 6.4) and lowest in Africa (1.4 for men and women).

Even though the rates for lung cancer in Swedish men peaked in the early 1980s and in Norwegian men at around 2000, the rates for bladder cancer kept on increasing (**Fig. 1**). The changing composition of manufactured cigarettes and tobacco has most likely changed the relative incidence of smoking-related lung and bladder cancers, because smoking of ‘low tar’ cigarettes are thought to reduce the risk of lung cancer (20%) but increase the risk of bladder cancer (30%) (11, 12). Hand-rolled cigarettes were popular in Norway and their tar (and nicotine) content was high, 34 mg/cig compared to manufactured cigarettes, 14 mg/cig (22). Another difference between the Nordic countries is the common use of smokeless tobacco “snus” by Swedish, and also Norwegian men, while the habit is rare in Finland and Denmark (20, 30-32). However, the female trends in lung and bladder cancer appear quite different from the male trends. This is reflected in the female lung-to-bladder cancer incidence ratios, which increased systematically in the four Nordic Countries, starting from about equal rates and increasing to 3-4.5, in spite of some 8-fold incidence difference between the highest (Denmark) and the lowest (Finland) rates (**Fig. 2**). While lung cancer increased throughout the follow-up period, the increase in bladder cancer incidence peaked in Denmark and Finland in the early 1990s.

The very high Finnish lung cancer rate, peaking in 1970, was most likely due to the wartime and post-war heavy smoking. In contrast to other Nordic Countries, the war involved a large proportion of Finnish men, and 5 cigarettes belonged to the daily ration of every soldier. Heavy smokers supplemented their tobacco stores with locally grown *Nicotiana Rustica* (high in nicotine and tar), which originated from Russia with name ‘makhorka’. It has been speculated that the Finnish habit of regular sauna bathing, in a part of the population in ‘smoke sauna’ without direct exhaust, and dusty stoves with wood as the predominant fuel contributed to lung cancer risk, probably preferentially more than to risk of bladder cancer (28). This would explain the very high incidence ratios of Finnish male lung and bladder cancer (8-fold, **Fig. 1**). It would also explain the 3-fold higher lung-to-bladder cancer incidence ratios for Finnish women in the 1950s, as discussed above. The lung-to-bladder cancer incidence ratio for Danish men was about 2-fold.

In conclusion, comparisons of lung and bladder cancer rates over a long time span revealed that in the early 1950s, i.e., before adoption of smoking among Finnish women, the incidence of bladder cancer was 1.2/100,000, at the level of the lowest known global rates. In the same period, the incidence in lung cancer among Norwegian women was the lowest currently known, and it was even lower than that for bladder cancer (lung-to-bladder ratio 0.64). The other epochal finding was documented for Swedish men, whose bladder cancer incidence overtook lung cancer

incidence before 2015, probably as a first population achieving this during the declining the smoking epidemic. Among men, decreasing lung cancer rates did not translate into decreasing bladder cancer rates among Swedes and Norwegians whereby other risk factors, such as snus, may operate. The results suggest some benchmark incidence targets for lung and bladder cancers, which may be achieved when the smoking epidemic can be overcome in the current populations.

AUTHOR CONTRIBUTIONS

Design: KH, OH.

Acquisition of data: KH, EL

Statistical analysis and interpretation: KH, EL, AH, AF, BL, OH.

Manuscript writing: KH and OH.

Approval of the final text: All authors

ETHICAL ISSUES

Aggregated data from a publically accessible database were used posing no ethical issues.

CONFLICT OF INTEREST

A.H. is shareholder in Targovax ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

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DATA ACCESS AND SHARING

Publically available NORDCAN data can be accessed at (<https://NORDCAN.iarc.fr/en/database#bloc2>).

FIGURE LEGENDS

Fig. 1. Age-adjusted incidence rates for lung and bladder cancer in Danish and Finnish men (A) and in Norwegian and Swedish men (B) from the earliest available year to 2016. The arrow in B

shows the epochal crossing of lung and bladder cancer incidence rates in Sweden. Note the different scales for the Y-axes.

Fig. 2. Age-adjusted incidence rates for lung and bladder cancer in Danish and Finnish women (A) and in Norwegian and Swedish women (B).

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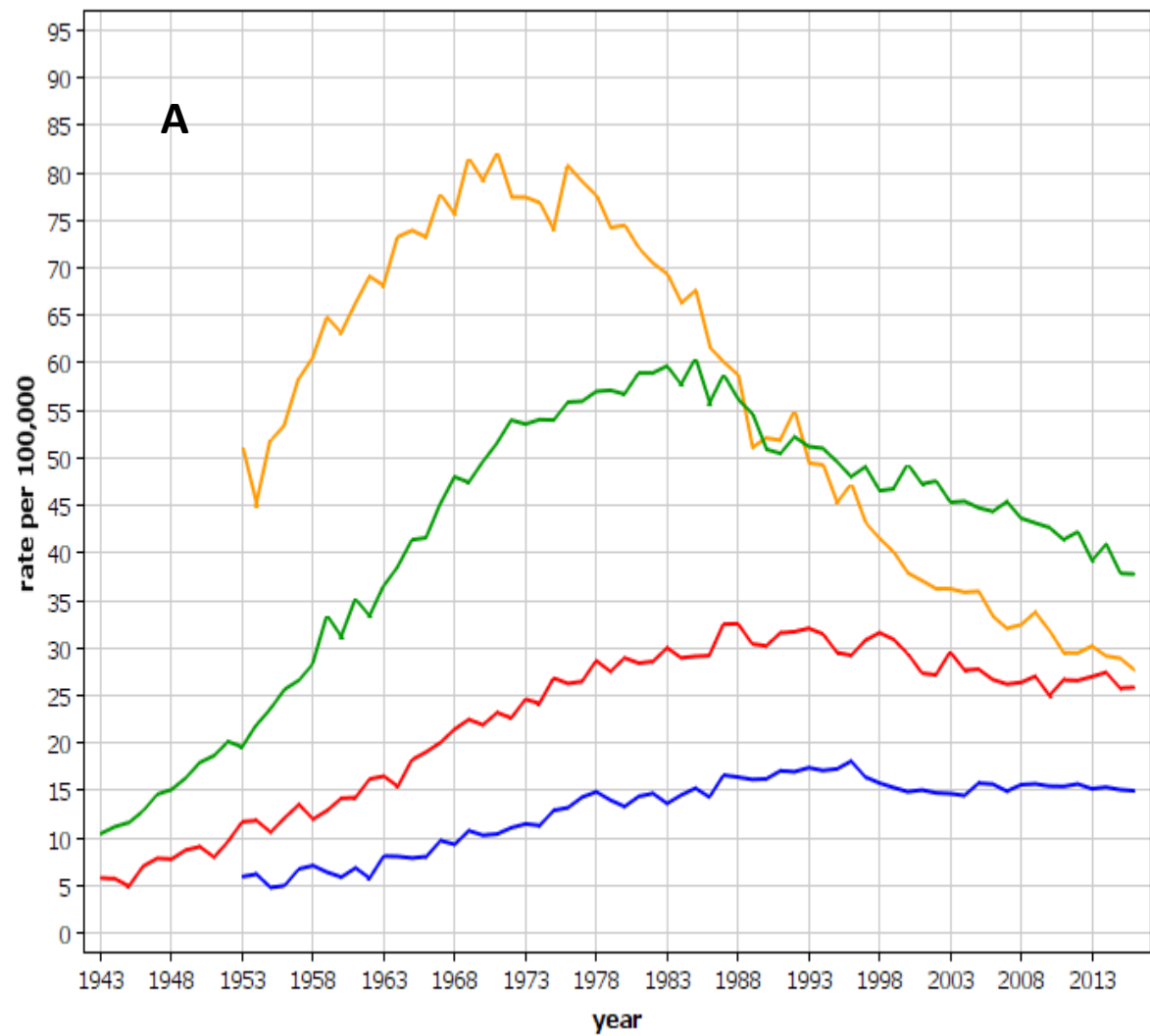
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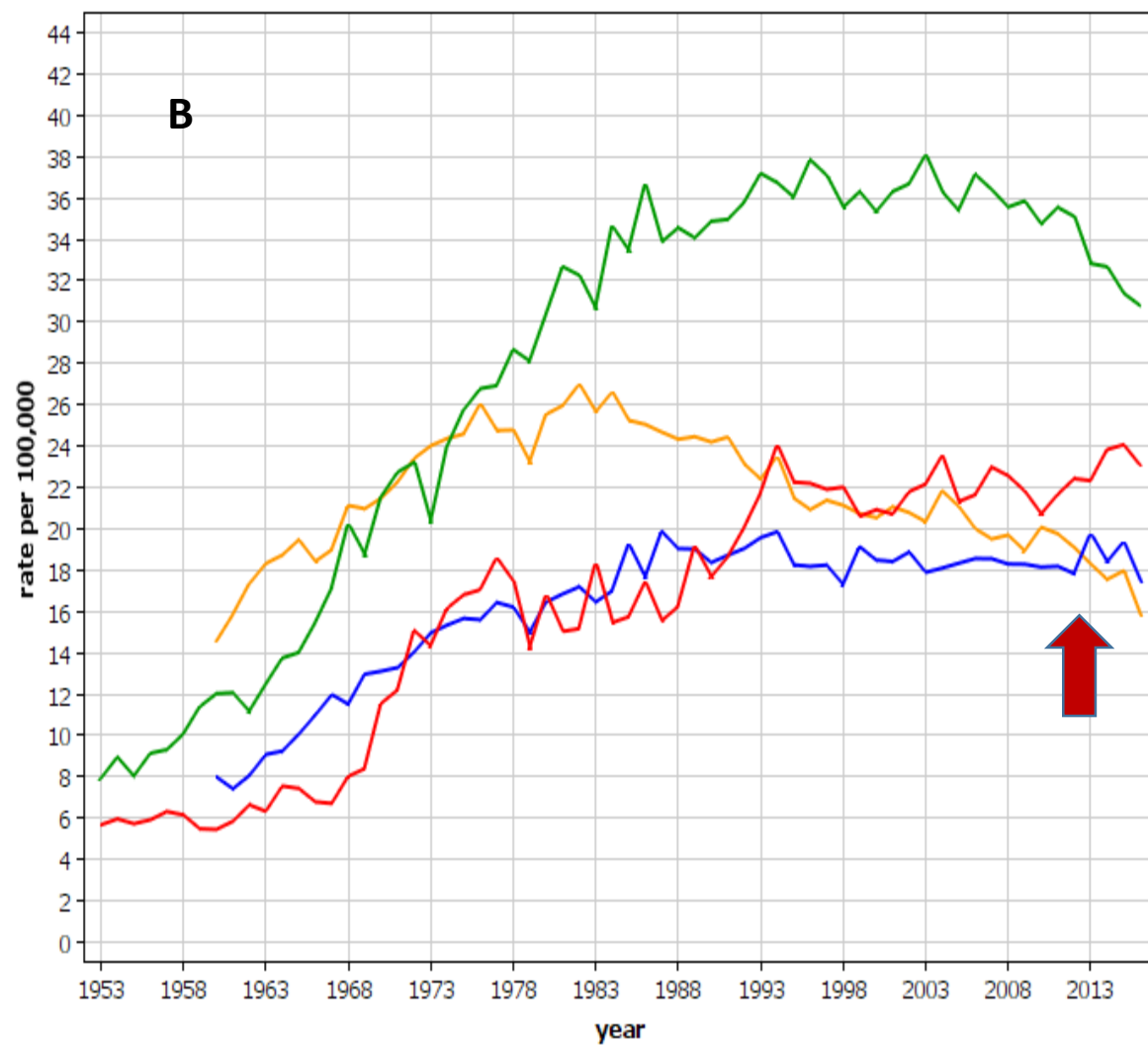
Table 1. Annual incidence and mortality rates for female lung and bladder cancers in the Nordic Countries based on the earliest available data from the NORDCAN database. SD, standard deviation.

Country (years)	Lung cancer		Bladder cancer	
	cases	per 100,000 [SD]	cases	per 100,000 [SD]
Incidence				
Denmark (1943-7)	405	3.3 (0.17)	308	2.5 (0.15)
Finland (1953-7)	482	3.7 (0.17)	152	1.2 (0.10)
Norway (1953-7)	216	1.8 (0.12)	379	2.8 (0.15)
Sweden (1960-4)	1180	3.8 (0.11)	1018	3.2 (0.10)
Mortality				
Denmark (1951-5)	593	4.1 (0.17)	274	1.8 (0.11)
Finland (1953-7)	441	3.4 (0.16)	114	1.3 (0.13)
Norway (1953-7)	301	2.4 (0.14)	227	1.7 (0.11)
Sweden (1952-6)	974	3.7 (0.12)	310	1.1 (0.06)

Fig. 1

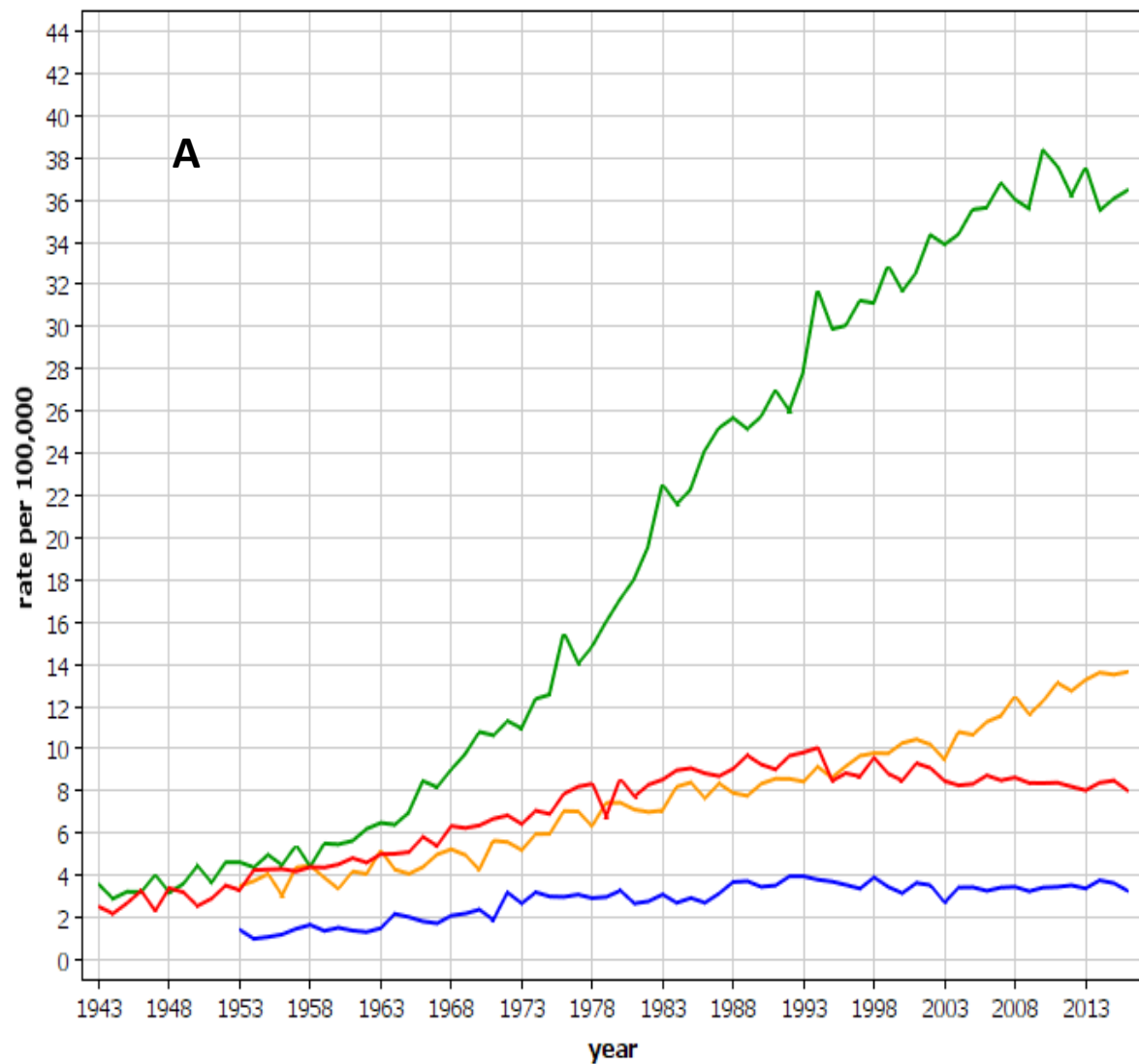


■ Denmark , Bladder etc. ■ Denmark , Lung ■ Finland , Bladder etc. ■ Finland , Lung

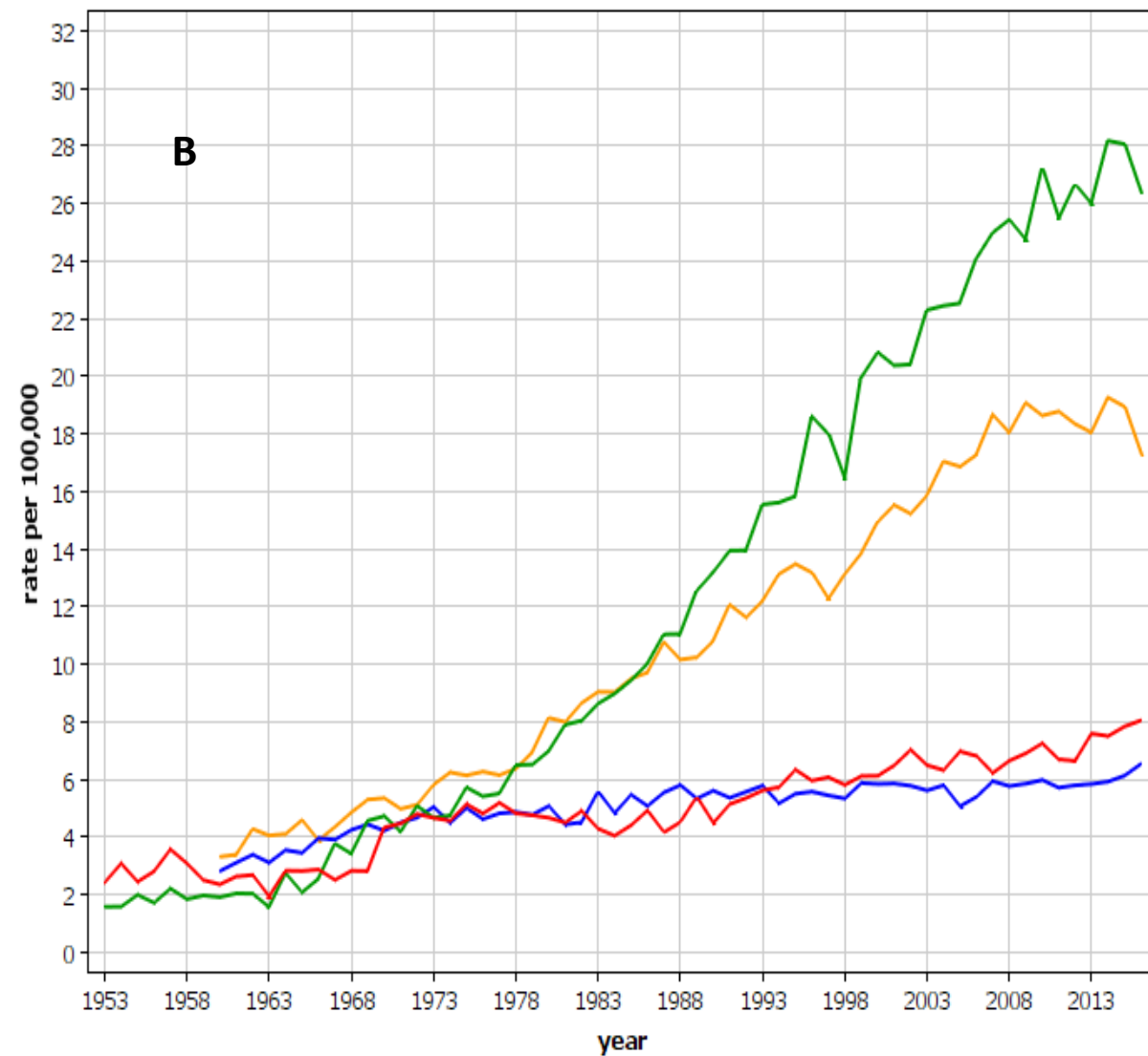


■ Norway , Bladder etc. ■ Norway , Lung ■ Sweden , Bladder etc. ■ Sweden , Lung

Fig. 2



■ Denmark , Bladder etc. ■ Denmark , Lung ■ Finland , Bladder etc. ■ Finland , Lung



■ Norway , Bladder etc. ■ Norway , Lung ■ Sweden , Bladder etc. ■ Sweden , Lung