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Time-space trends in cancer incidence in the Netherlands in 1989–2003

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Incidence of cancer may vary within a country and over time because of previous differences in exposure to risk factors or interventions for early detection (screening). This study describes time-space trends of incidence of common cancer sites across the Netherlands during the period 1989–2003 and speculates on the reasons for the observations. From the Netherlands Cancer Registry, World standardized incidence rates per municipality were smoothed calculating weighted averages for each 2 km by 2 km grid of the population mid-points of neighbouring municipalities and presented as map animations. Spatial relative changes in incidence were estimated by comparing the periods 1989–1994 and 1998–2003. Complete time-space trends can be found as map animations on http://maps.ikcnet.nl. The incidence of cervical and stomach cancer (for both sexes) decreased, being higher in the cities than in the rural areas during all periods and contrasting the trends in colorectal and breast cancer. The relative increase in incidence of lung cancer among females was highest in the rural north, but the incidence remained higher in the cities of the mid-west Netherlands. For males, there was a marked decrease in lung cancer incidence across the country since 1991. Incidence of melanoma increased, rates being twice as high in the coastal area than in the cities. Prostate cancer maps largely replicated the known history of PSA-testing in the Netherlands. Time-space cancer incidence patterns gave insight into effects of changes in exposure to risk determinants and early detection. The maps illustrate marked potential for cancer prevention at the national and regional level.

Key words: time-space trends; cancer incidence; risk determinants; early detection; map animations

The incidence of cancer is influenced by several factors and therefore changes continuously. The incidence of several cancer sites is known to be influenced by the intensity of exposure to risk factors and many of these cancers might therefore be avoidable.[1,2] Degree of urbanisation of the living environment, country of origin and socioeconomic status (SES) are indicators of exposure to these risk factors.

Furthermore, the introduction of new diagnostic methods or screening to recognise non-symptomatic cancers has led to an increase in incidence of some cancer sites.

Timing and extent of changes in the aforementioned factors vary over the country and thus can result in spatial differences in incidence. Speculations on the reasons of the observed changes will be clues into determinants (of the last 50 years), and avoidability of cancer, taking effects of early detection into account. We produced sets of maps and map animations (http://maps.ikcnet.nl) of changes in cancer incidence across the Netherlands during 1989–2003.

Our aim was to give an overview of the changes in incidence in the Netherlands since 1989, with some clues about the reasons for the observations taking the exposure to known risk factors or interventions for early detection (screening) into account. Since the data considering these factors is not available and directly linked to our data it was only possible to speculate about the reasons for the observed results.

Material and methods

The Netherlands Cancer Registry (NCR) is population-based and includes data on all newly diagnosed malignant cases since 1989. In 9 regions, all newly diagnosed malignancies are obtained from the automated pathology archive (PALGA). Other sources are the national patient hospital discharge registry, which accounts for up to 8% of the cases,[3] and radiotherapeutic and haematological departments. The regional cancer registries submit their data to the NCR, which is considered to be more than 95% complete, incompleteness being more likely due to elderly and outpatients with a clinical diagnosis only.[4] Specially trained registration clerks gather data concerning the patient (sex, date of birth), tumour characteristics (localisation, histological type, stage, size), and treatment characteristics. Narrow interpretation of the European privacy guideline of 1995 by Dutch privacy authorities and legislation does not allow for routine use of death certificates.

From the NCR, World standardized incidence rates (WSR) were calculated for the different cancer sites per municipality ($n = 458$). Cancer sites of interest were chosen based on known substantial trends in incidence, changes in exposure to risk factors and/or introduction, or alterations in screening interventions. Maps of cancer incidence were made based on these rates. For the cities with more than 100,000 inhabitants, the rates were presented as circles on the maps; the radius of the circle indicates the size of the population and the colour the WSR. Each step in colour scale corresponds to a 1.1-fold increase in the WSR. The rates for the remaining municipalities were smoothed to avoid chance variations.[4] For each 2 km by 2 km grid, a weighted average was calculated of the WSR of the population mid-points of neighbouring municipalities within 150 km to define the colour of that grid. The rates were inversely related to the distance (weight was 50% at 25 km) and directly weighted to the population size of the municipality.

The 15-year period was split into 4 overlapping periods of 6 years, *i.e.*, 1989–1994, 1992–1997, 1995–2000 and 1998–2003, making the map animations more continuous. The relative changes in WSR between the first and last period were also presented visually.

Results

In this article we present a selection of the cancer maps from a larger series of maps. Complete time-space trends can be found as map animations on http://maps.ikcnet.nl.

For the interpretation of these results, it is important to know that of the more than 16 million inhabitants of the Netherlands almost half of them are concentrated in the western, coastal region (mid-west) in the large cities such as Amsterdam, Rotterdam, The Hague and Utrecht (Fig. 1). The migrants (19% of the population of the Netherlands in 2003), residing mainly in the larger cities (Fig. 2), most often come from Morocco, Turkey, Surinam or the Netherlands Antilles.

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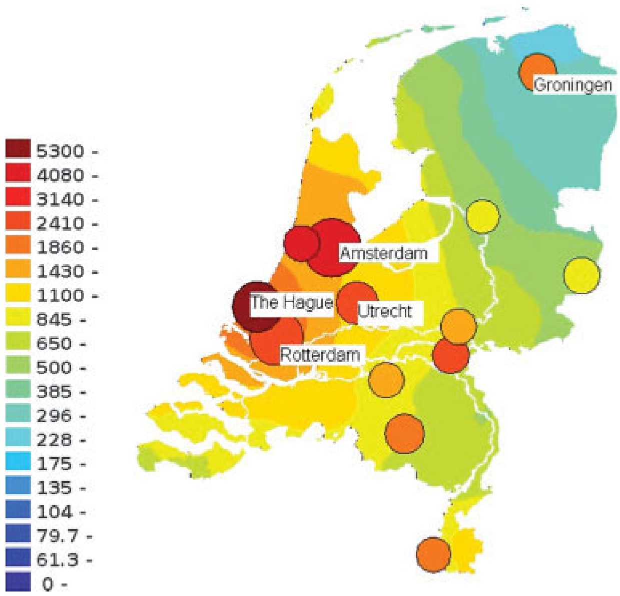

FIGURE 1 – The Netherlands: inhabitants per 100,000 persons in 2003. Source: Statistics Netherlands.

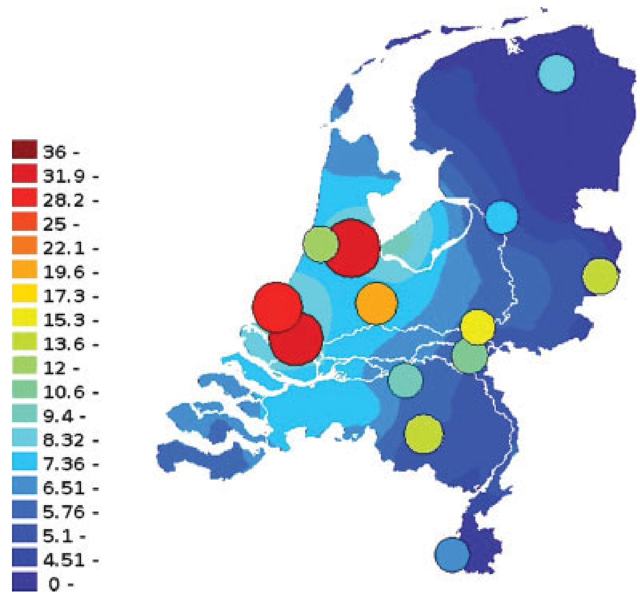

FIGURE 2 – The Netherlands: percentage immigrants in 2003. Source: Statistics Netherlands.

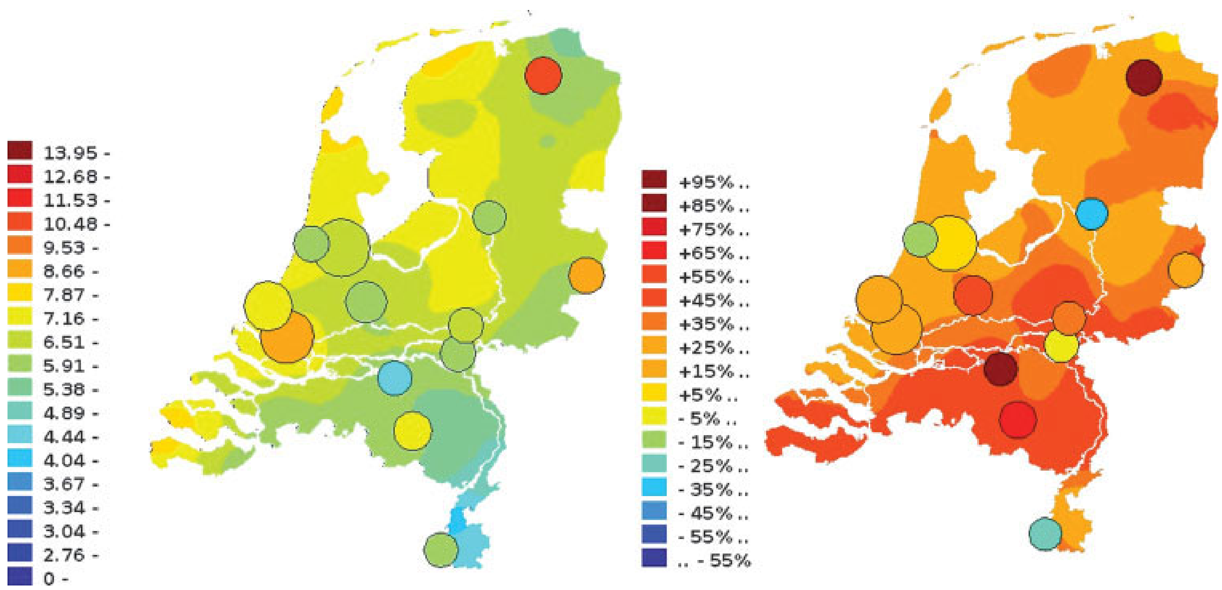

FIGURE 3 – Age-adjusted incidence of oesophageal cancer (World standard, per 100,000 person-years), 1998–2003 (left) and relative time-space trend in incidence from the period 1989–1994 to 1998–2003, males.

All cancers

Incidence among males remained almost stable at a rate of about 300 per 100,000 throughout the whole period. The incidence remained slightly higher in most cities although a decrease was seen in some large cities. Incidence among females increased from 226 per 100,000 in 1989 to 257 in 2003. A higher incidence was revealed in the larger cities and the mid-west compared to the rest of the country, which was more prominent for females than for males. There was a similar increase in incidence in females across the whole of the Netherlands.

Gastrointestinal tract

The incidence of oesophageal cancer increased on an average from 4.7 in 1989 to 8.0 per 100,000 males in 2003 and for females from 1.5 to 2.5. Incidence was lowest in the south of the country, both for males and females. There was a marked increase in incidence in the south-east and in the northern city of Groningen for males (Fig. 3).

Incidence of stomach cancer markedly decreased for males from 16 per 100,000 in 1989 to 10 in 2003 and for females from 6.3 per 100,000 in 1989 to 4.2 in 2003. Still a slight urban dominance in incidence remained. For males, the relative decrease in incidence in the mid-Netherlands tended to be smaller in the cities than in the rural areas. Still, the absolute decrease was larger in these cities: *e.g.* the absolute decrease in the city of Utrecht was 2.0 and in the surrounding areas of Utrecht 1.2 per 100,000, both yielding to a relative decrease of about 30%. For females, the urban dominance increased over time due to almost no decrease in many of the cities (Fig. 4).

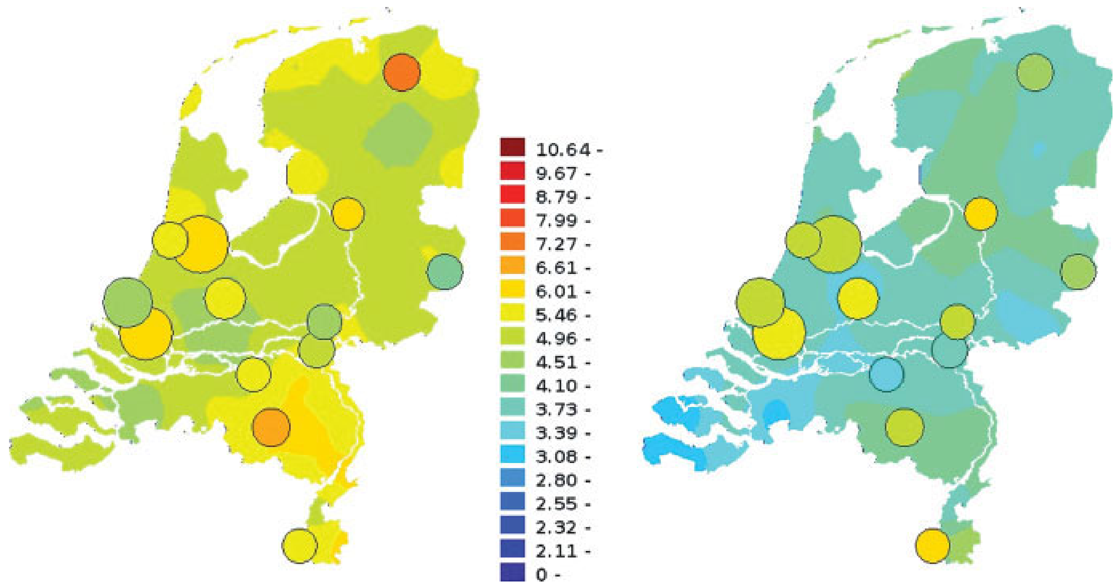

FIGURE 4 – Age-adjusted incidence of stomach cancer (World standard, per 100,000 person-years), 1989–1994 (left) and 1998–2003, females.

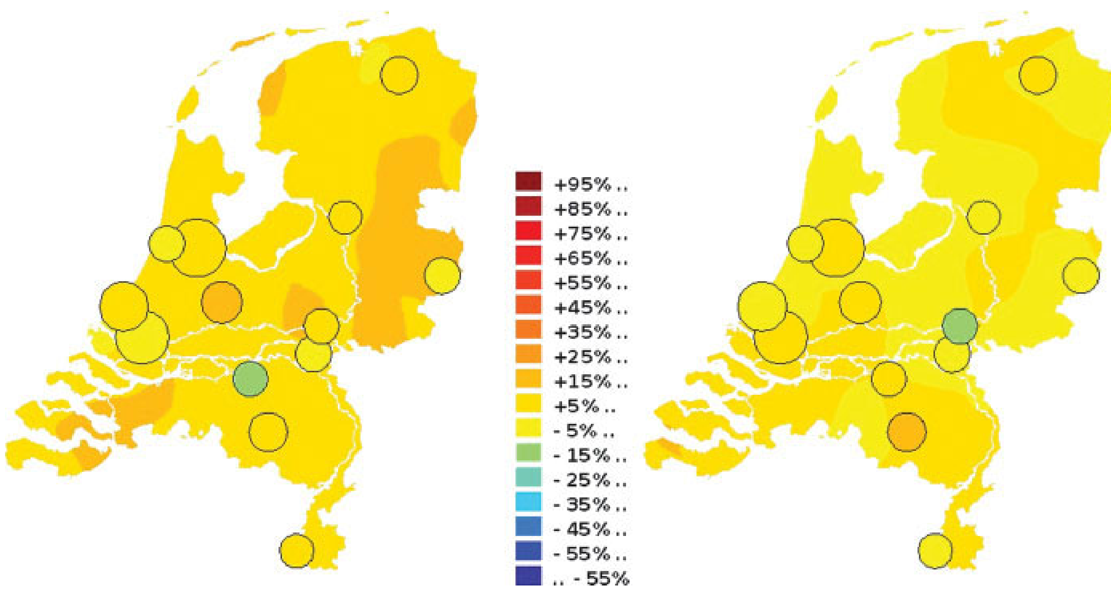

FIGURE 5 – Relative time-space trend in incidence of colorectal cancer from the period 1989–1994 to 1998–2003, males (left) and females.

From 1989 to 2003 a small increase in incidence of colorectal cancer was found from 35 to 40 among males and for females from 27 to 29 per 100,000. For both males and females, both the baseline incidence level and the relative increase in the rate tended to be slightly higher in the east, but the spatial variation was generally small (Fig. 5).

Lung cancer

A lower incidence of lung cancer among males was observed in 1989–1994 in the urban, western part of the Netherlands, followed by a decrease of 20–50% across the whole country, the difference between cities and rural areas becoming smaller (Fig. 6). For males, the overall incidence of lung cancer decreased from 74 per 100,000 in 1989 to 48 in 2003.

By contrast, the incidence of lung cancer among females increased from 12 per 100,000 in 1989 to 22 in 2003. The incidence was always highest in the largest cities, although its relative increase appeared to be slower than in many rural areas (Fig. 7).

Melanoma

The incidence of skin melanoma was highest along the western coast and lowest in several cities for both genders. It increased from 7.5 per 100,000 in 1989 to 10.4 in 2003 for males and from 10.7 to 14.7 among females. The relative difference in rates between west and east diminished as a result of a rapid increase in incidence rates, especially in the south-east of the country. Against the general strongly increasing trend, there was a decrease in some large cities (Fig. 8).

Female genital organs

Among Dutch females, the incidence of breast cancer increased from 73 per 100,000 in 1989 to 91 in 2003. The spatial differences

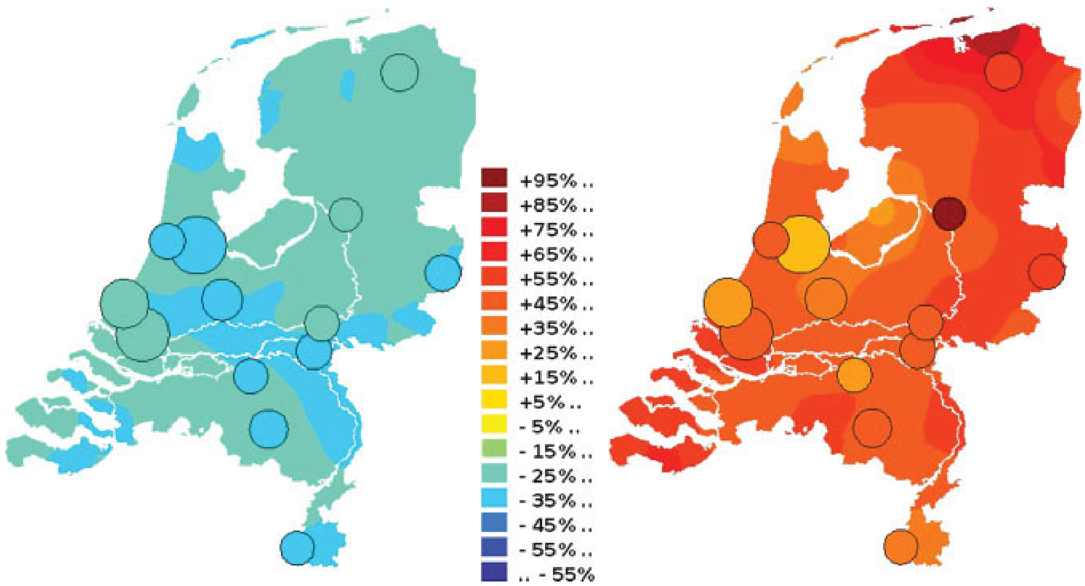

FIGURE 6 – Relative time-space trend in incidence of lung cancer from period 1989–1994 to 1998–2003, males (left) and females.

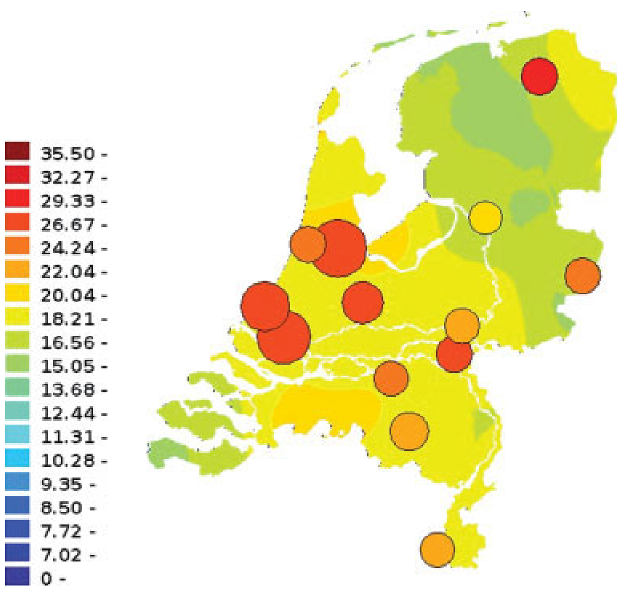

FIGURE 7 – Age-adjusted incidence of lung cancer (World standard, per 100,000 person-years), 1998–2003, females.

and relative changes were small. In the cities in the south-east, there was a tendency towards urban dominance over time.

Incidence of cervical cancer decreased from 7.2 per 100,000 in 1989 to 4.9 in 2003. Although the difference between urban and rural areas diminished during the whole period, the incidence in the cities generally remained higher than in rural surroundings (Fig. 9). Rates were lowest in the eastern regions.

Incidence of ovarian cancer decreased from 11 per 100,000 in 1989 to 8.3 in 2003. Although the decrease was manifest in the whole country, it was irregular, as was the urban–rural variation, exhibiting a lower incidence in some cities than in their suburban areas.

Male genital organs

The incidence of prostate cancer was generally lower in the cities than in the surrounding areas. The spatial change was similar, with a possibly higher increase around major urological centres like Nijmegen and Maastricht (Fig. 10). In the entire country, the incidence of prostate cancer increased from 39 per 100,000 in 1989 to 61 in 2003.

Incidence of testicular cancer increased from 3.9 per 100,000 in 1989 to 6.2 per 100,000 in 2003, remaining lowest in the cities of Rotterdam and The Hague in the west and especially increasing towards the north-east (Fig. 11).

Discussion

In this study we presented time-space variations in incidence of frequently occurring and rapidly changing cancer rates as maps, without administrative geographical boundaries. Spatial differences and time trends should generally be explained either by previous differences in exposure to risk factors and/or by early detection interventions. Logically, these trends do not necessarily follow administrative borders and may vary within a given region.

The overall cancer incidence rate was higher among urban populations as has been observed for many decades in numerous countries.[5,6] For males, the simultaneous decrease in the incidence of *e.g.* lung cancer in 1993–2003 and the increase in incidence of *e.g.* prostate cancer resulted in a relatively constant overall rate. The slight decrease in incidence in some large cities could be due to the well-documented increasing number of immigrants, with a lower incidence of certain sites of cancer (*e.g.* in the breast and colorectum) similar to the rates in their country of origin.[7,8]

Heavy drinking was fairly constant in the period 1989–2003, when it became higher among males (20%) than females (5%). There was also less drinking and smoking in the "Bible belt" going from the southwest to the middle of the Netherlands.[7]

Exposure to risk factors

Latency times of 20–50 years should be taken into account when considering exposure to relevant risk factors to explain time-space trends. For instance, the risk-increasing effect of smoking starts to show up more than 20 years after its start, while the first risk-decreasing effects of quitting (apparently on progression) can be seen quickly.[9] Males in the Netherlands, as in several other countries in Europe, started to stop smoking in the 1960s, which has resulted in a decrease in incidence of lung cancer among middle-aged males since the mid 1970s[9–11] and later at older age. The

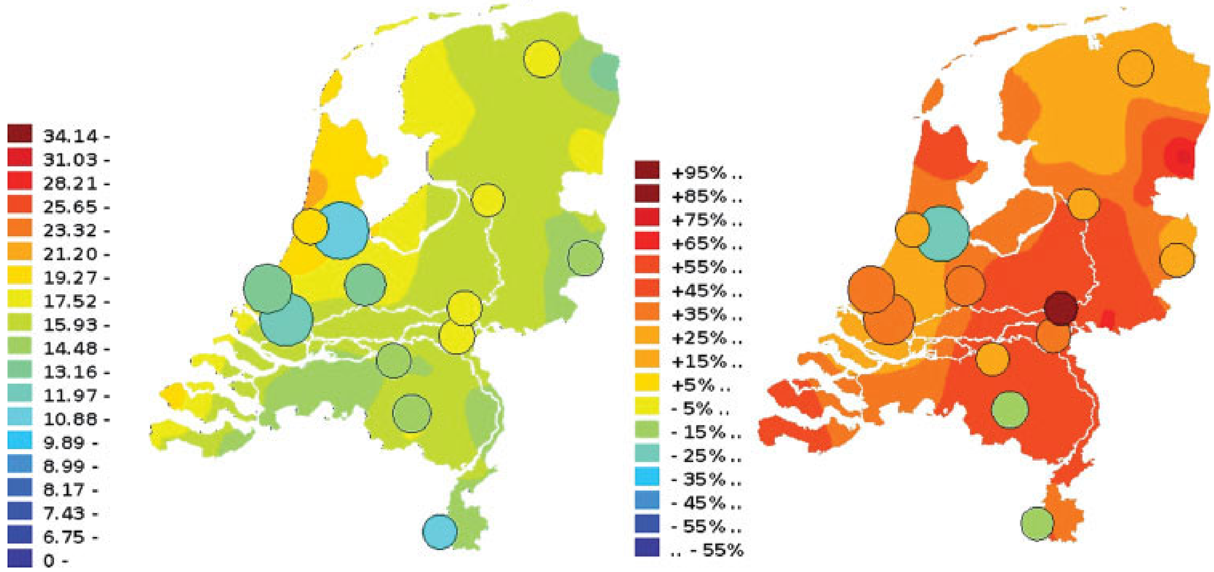

FIGURE 8 – Age-adjusted incidence of skin melanoma (World standard, per 100,000 person-years), 1998–2003 (left), and relative time-space trend in incidence from period 1989–1994 to 1998–2003, females.

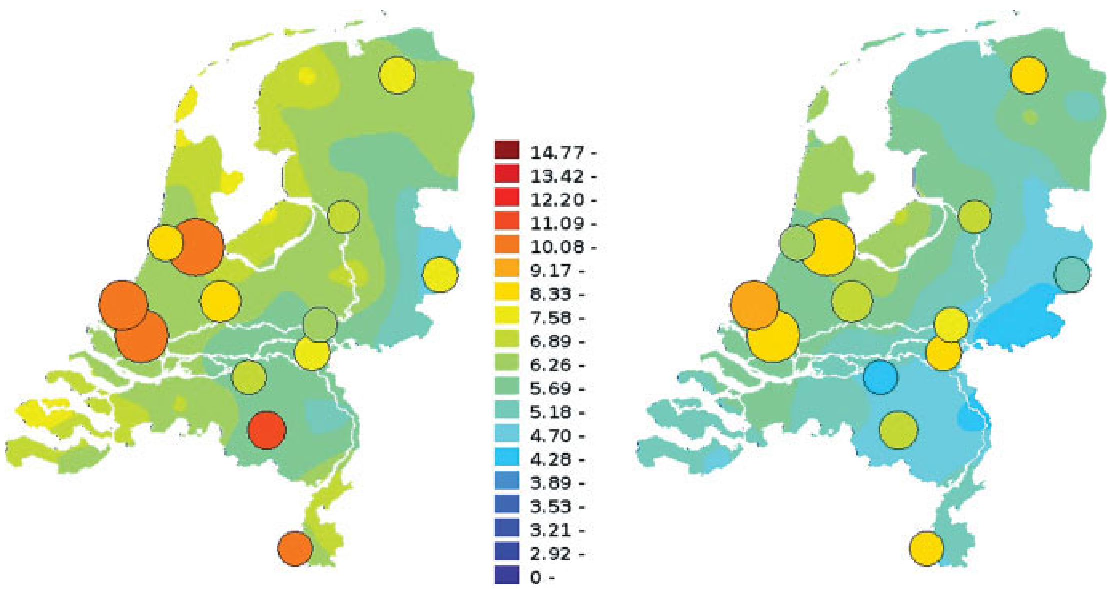

FIGURE 9 – Age-adjusted incidence of cervical cancer (World standard, per 100,000 person-years), 1989–1994 (left) and 1998–2003.

relative decrease in lung cancer incidence for males in the Netherlands from 90% in 1958 to 50% in 1980, decreasing further ever since, was about the same across the country, suggesting a homogeneous decline in smoking everywhere.[12] Following the increased smoking habits of Dutch women from 28% to 36% in 1980, rising more in groups of lower SES and education,[7,12] the increase in incidence of lung cancer among females was most marked in the urban, western part of the Netherlands and is clearly reflected in the cancer maps about 30 years later.

Although the relative increase in incidence was highest in the north-eastern rural part where female smoking increased in the late 1960s, the level remained less than half of that in the larger cities. Among males no such differences were found, implying that a strong effect of factors such as air pollution can be excluded.[13,14] Effects of current stop-smoking campaigns are likely to be seen at much shorter notice than of measures against starting to smoke.

Smoking is a risk factor not only for lung cancer but also for several other cancers, including oesophageal cancer. Given modest changes in alcohol use, the more intense smoking habits among women compared to men might partly explain the time-space trend in oesophageal cancer being so similar to lung cancer. The overall increase in the incidence of oesophageal cancer in the Netherlands resulted mainly from an increase in the incidence of adenocarcinoma from 1.3 per 100,000 in 1989 to 3.1 in 2003, representing 70% of all oesophageal cancers. Similar changes have been seen in other countries as well.[15,16] Other risk factors for oesophageal cancer are gastric reflux leading to Barrett's oesophagus,[18] obesity[19,20] and alcohol consumption (mainly associated with squamous cell carcinoma).[21] Of these factors, obesity is more common in the east-

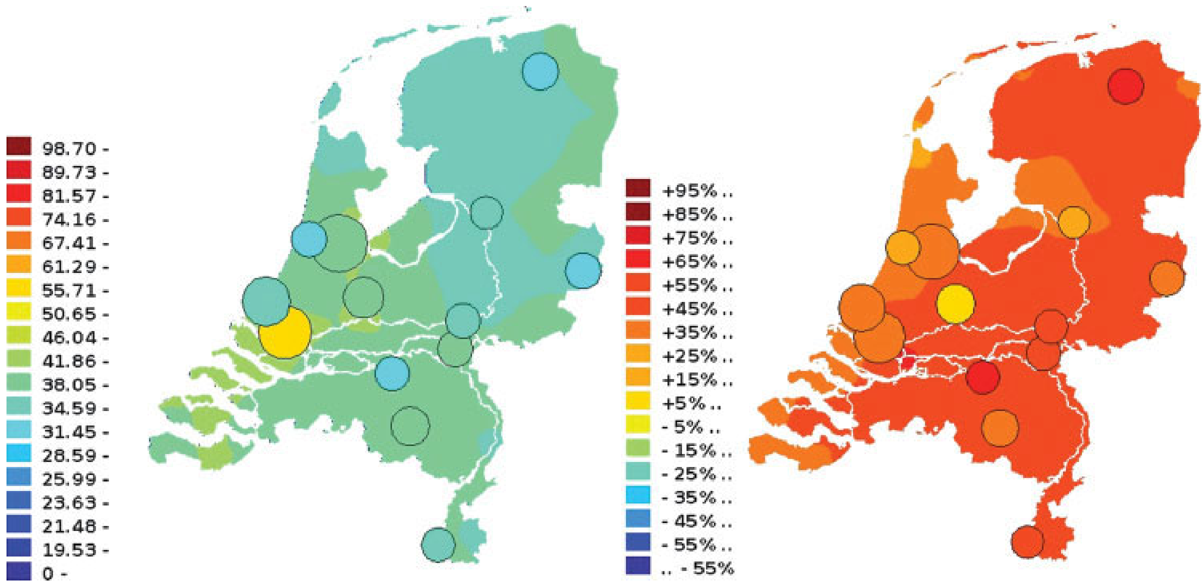

FIGURE 10 – Age-adjusted incidence of prostate cancer (World standard, per 100,000 person-years), 1992–1997 (left), and relative time-space trend in incidence from period 1989–1994 to 1998–2003.

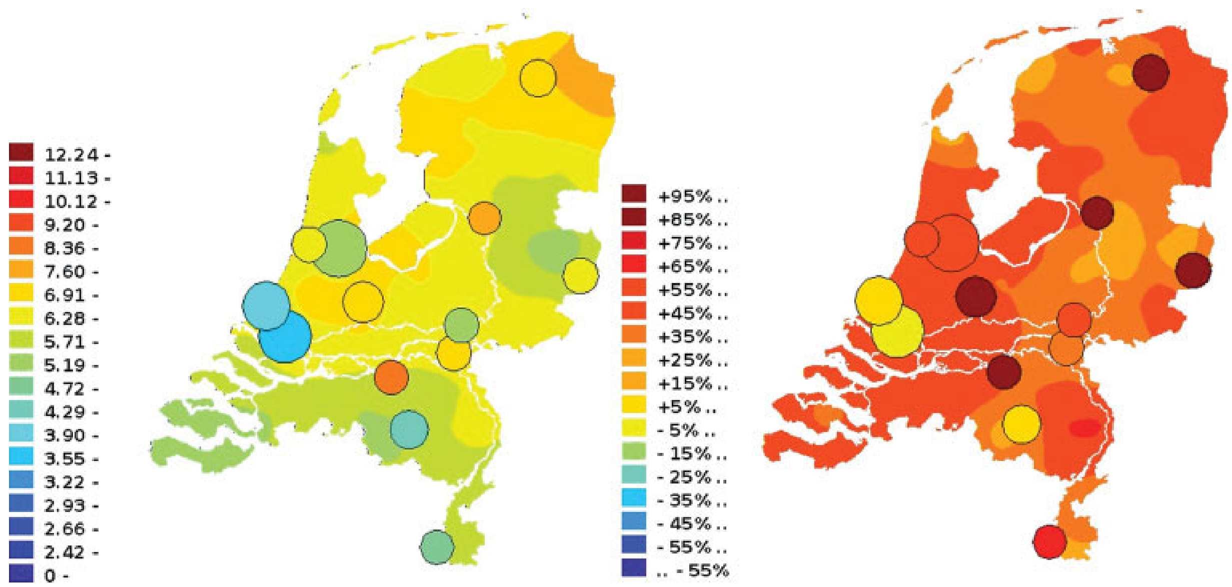

FIGURE 11 – Age-adjusted incidence of testicular cancer (World standard, per 100,000 person-years), 1998–2003 (left), and relative time-space trend in incidence from period 1989–1994 to 1998–2003.

ern parts of the Netherlands, where oesophageal cancer is yet rarest. Heavy drinking was fairly constant in the period 1989–2003, when it became higher among males (20%) than females (5%). There was also less drinking and smoking in the Bible belt going from the southwest to the middle of the Netherlands.[7]

The incidence of stomach cancer has decreased markedly during the last decades following changes in dietary patterns and the production, conservation and transportation of food, the large-scale use of refrigerators, the decreasing prevalence of *Helicobacter pylori*, the lower use of salt, and the increased consumption of fruit and vegetables. Although an inverse association between level of education and stomach cancer, partly related to lifestyle, has been found in the Netherlands and other countries,[22] geographical differences in the incidence of stomach cancer were modest, suggesting quite small variations in these lifestyle habits within the country.

For colorectal cancer, the most important risk factors include dietary habits (*e.g*. excess calory intake and consumption of red meat), lack of physical activity and a family history of colon cancer.[23–25] The higher incidence in the eastern part of the Netherlands could reflect the influence of such habits from Germany. Incidence of colorectal cancer in Germany appears to be 10–20% higher than in the Netherlands.[26] The higher (and markedly increased) percentage of obesity in the eastern part of the country may also play a role.[27] Trends in incidence of colorectal cancer also reflect the increasing proportion of migrants from low incidence countries: incidence rates in the early 2000s were less than 6 per 100,000 in Morocco, 9 in Turkey and 10 in Surinam.[26] The highest proportion of immigrants might also relate to the lower incidence in the largest cities. There has been a shift from high to low SES in overweight and unhealthy dietary habits resulting in an increase in incidence of colorectal cancer in the lower SES *e.g.* in Finland.[28] Screening activities with faecal occult blood testing have only been started in pilot studies recently and cannot affect the incidence rates shown in the present article.

Obesity may have a moderate association with ovarian cancer.[29] The relationship between fertility drugs and the cause of subfertility remains debatable.[30] The relation with oestrogen replacement therapy and an increased risk of ovarian cancer is more clear.[31] The use of oral contraceptives has a protective effect on the risk of ovarian cancer, which in the absence of other explanations can be seen as the main reason for the decline described in this article.[32] In the period 1995–1999, 40% of Dutch women used oral contraceptives, which varied from 46% in the southern part (Noord-Brabant) to 38% in the north (Groningen) and middle (Flevoland).[7] The increasing age at last birth in the Netherlands[27] could give some protection, but there are no data on spatial variations in this variable.[33] Other risk factors such as previous breast cancer[34] and a family history of breast cancer[35] will barely affect spatial trend.

The development of testicular cancer may be determined largely by influences in very early life. Prenatal factors such as low birth weight, older maternal age, low birth order as well as cryptorchidism generally convey an increased risk.[36,37] In the Netherlands, the mean age of the mother at delivery of the first child increased to 29 years in 2000.[7] Other possible risk factors are the carcinogenic effect of excess sex hormones and maternal lifestyle (*e.g.* smoking during pregnancy).[38] Would the increasing incidence of lung cancer in females some decades ago has mirrored the increase in incidence of testicular cancer now? Several studies have revealed that the geographical pattern of incidence is more closely associated with residence at birth than with residence at time of diagnosis, thus latency time and migration of young male patients should be taken into account when interpreting geographical trends.[39] Although in our study the most rapid increase was in some cities—incidence doubled in 10 years—generally the urban *versus* rural variations in incidence were irregular. As everywhere the risk of testicular cancer was higher in the most affluent areas compared to the most deprived areas, while there was little difference between urban and rural small areas; this argues against the influence of an environmental factor.[40]

The main risk factor for skin melanoma is intermittent exposure to UV radiation, especially at a young age.[41] For both males and females, incidence was lowest in the southeast of the Netherlands that hosts a lower proportion of people with fair skin.[42] The incidence was highest in the north-western coastal and lake areas where aquatic sports are practised and there are 10% more sun hours per year than in other parts of the country.[43] In 1989 a “Freckle bus” campaign along the midwestern seacoast of the Netherlands increased awareness of both the public as well as the general practitioners across the country, partly explaining the increase in incidence.[44] In the 1960s and 1970s, sunny (subtropical) holidays, mountaineering and skiing became more popular, primarily among higher SES classes who live outside the large cities like Amsterdam, Eindhoven and Maastricht in whom incidence of skin melanoma became higher. Increasing percentages of allochthonous people with skin type 3–4, a natural protection against UV radiation, might also be responsible for the lower incidence and the more rapid decrease in the larger cities. In the northern Netherlands (with more skin type 1–3) one tends to be more willing to get a quick tan than in the south.[45,46] The fact that incidence of skin melanoma was rather low in areas with the highest proportion of farmers is in line with the research finding that outdoor workers have a low risk of skin melanoma.[47]

Early detection interventions

Breast. An equivalent relative increase in incidence of breast cancer was found in all regions of the Netherlands. Diagnostic activity to reveal non-symptomatic breast cancer has been available to the same extent all over the country since 1990. Introduction of organised breast cancer screening started in 1974 in Utrecht in the centre and in Nijmegen in eastern Netherlands for women at age 50–64 and 40–74 years, respectively. This may explain the highest incidence rates found for this city. When the upper age limit shifted from 69 to 74 years in 1998, Nijmegen was the first to apply. The screening programme reached countrywide coverage gradually in the period 1990–1996. Lower attendance rates in the large cities in the west (about 15% lower than elsewhere), partly related to the presence of migrants affected the incidence of breast cancer negatively. Moreover, females from Turkey, Morocco and Surinam had an incidence rate of about 22–30 per 100,000 in 2002, being much lower than the 91 per 100,000 in the Netherlands.[26,48]

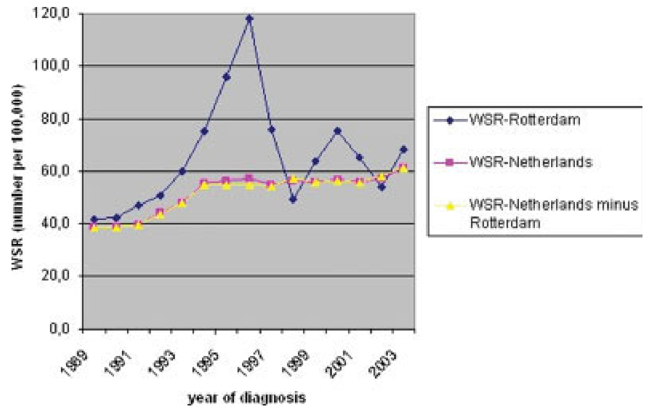

FIGURE 12 – Incidence of prostate cancer in Rotterdam and in the rest of the Netherlands (World standardized rates) from the period 1989–2003. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Breast cancer tends to be more common in high social economic classes, which can be linked to aspects of lifestyle.[28,49] The risk of breast cancer has increased with earlier menarche, older age at first birth and lower number of children, later age at menopause and postmenopausal hormonal therapy, which might be counteracted by more physical activity, less obesity and alcohol consumption,[49,53] all relevant exposures in the last 25 years.

Cervical cancer. The national PAP-smear screening program for cervical cancer, remodelled in 1996 (from a 3- to a 5-year interval), focuses on detection of pre-malignant lesions and is known to decrease the incidence.[51] Cervical cancer incidence was higher in areas with high population density, reflecting lifestyle changes such as a lower age at first intercourse and multiple sexual partners.[52] In the Netherlands, highest risks were found for cervical cancer among women born in Morocco and Surinam,[53] without being known whether the prevalence of high risk HPV infections among migrant women in the Netherlands is higher than among the native women, but an increase in the incidence of sexually transmitted diseases mainly among migrants was found in a study in Utrecht in the Mid-Netherlands.[54]

Prostate cancer. Although the average increase from the 1990s to the 2000s was similar all over the Netherlands, there were temporal peaks in the rates, the most striking being the one seen in the city of Rotterdam in southwest Netherlands in the period 1995–1998. This peak can be explained by the pilot study for PSA-screening which was started in 1994 in Rotterdam and surroundings (Fig. 12).[55,56] Partly simultaneously, partly later, the incidence (in fact the detection rate) of prostate cancer increased in the remaining parts of the country because of the increasing use of the PSA test as an opportunistic screening tool by urologists and general practitioners. Generally, the lower incidence among males in the cities reflects the difference in use of the PSA test, which is typical for the higher social economic class males.[57,58]

Conclusion

Evident spatial patterns in incidence and variation in the rate of change over time were revealed in the Netherlands for several cancer sites and they mostly complied with preceding changes in exposure to risk determinants (related to SES) and causal risk factors (smoking, UV light, dietary habits). Moreover, early detection/screening interventions have clearly affected the incidence for breast, cervical and prostate cancer as well as melanoma. All in all, our study also provides evidence for a large potential for prevention of cancer. Knowledge of regional variation in cancer incidence can support the planning of health care services on a regional basis.

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