Birth Prevalence and Survival in Cystic Fibrosis*

A National Cohort Study in the Netherlands

Martijn G. Slieker, MD; Cuno S. P. M. Uiterwaal, MD, PhD; Maarten Sinaasappel, MD, PhD; Harry G. M. Heijerman, MD, PhD; Johan van der Laag, MD; and Cornelis K. van der Ent, MD, PhD

Background: Birth prevalence and survival in patients with cystic fibrosis (CF) in the Netherlands were last investigated > 30 years ago. However, since then the birth prevalence may have decreased because of genetic counseling and an increased number of newborns of non-European descent. Although survival of CF patients has increased worldwide, a significantly lower median age at death was recently reported in the Netherlands compared with data from the United States.

Objectives: To analyze birth prevalence and survival in CF patients in the Netherlands, and to compare this survival data with US CF data.

Design: Survey of all CF patients living in the Netherlands, and analysis of Dutch CF mortality statistics using data from the Dutch central statistics office, Statistics Netherlands (Voorburg, the Netherlands), and a comparison with Cystic Fibrosis Foundation (Bethesda, MD) patient registry data.

Setting: All CF centers in the Netherlands and the United States.


Measurements: Birth prevalence and birth cohort-specific survival.

Results: The overall birth prevalence of CF for 1974 to 1994 was 1 in 4,750 live births, which is a considerable decrease compared with 1961 to 1965 (1 in 3,600 live births). Estimated survival to 30 years increased from 6% in the 1950-to-1954 cohort, to 36% in the 1970-to-1973 cohort. Exact survival could be calculated from 1974 onwards. Survival to 15 years increased from 72% from the 1974-to-1979 cohort, to 91% in the 1985-to-1989 cohort. Survival in the United States in the 1980-to-1984 cohort was better compared to the Netherlands, but this difference has disappeared over subsequent cohorts.

Conclusions: The actual birth prevalence of CF in the Netherlands is clearly lower than it was 30 years ago. Survival in CF has dramatically improved. The difference in survival between the Netherlands and the United States, as observed in the cohorts born > 20 years ago, has disappeared. (CHEST 2005; 128:2309–2315)

Key words: birth prevalence; cystic fibrosis; survival

Abbreviations: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CI = confidence interval; UMCU = University Medical Center Utrecht

In the Netherlands, the birth prevalence of cystic fibrosis (CF) is estimated to be 1 in 3,600. This birth prevalence was estimated in a 1961-to-1965 birth cohort by means of an inquiry among medical specialists, and by analysis of hospital admission data, death certificates, and data of the national CF Foundation (Statistics Netherlands; Voorburg, the Netherlands). Because of improved methods of genetic counseling and an increased number of new-
borns of nonwestern (ie, Moroccan, Turkish, Indonesian, Surinamese, and Dutch Antillean) descent, the CF birth prevalence in the Netherlands may have decreased over the past decades. Survival in CF in the Netherlands was also determined >30 years ago, but survival has clearly improved since that time.

From 1974 onwards, reliable CF mortality data has been obtained from the Dutch national statistics office, Statistics Netherlands. Furthermore, nearly all CF patients are currently treated at one of the seven specialized CF centers in the Netherlands. Apart from improvement of care and life expectancy, centralized care has resulted in a better registration of patients with CF. The improved registration of both living CF patients and CF mortality enabled us to analyze CF birth prevalence and survival since 1965.

Fogarty et al\(^4\) compared median age at death from CF in 10 countries in North America, Europe, and Australasia. They described significant differences in survival between these countries, showing favorable results in the United States compared to Europe, including the Netherlands. However, a cross-sectional measure is unsuited for capturing subtle longitudinal survival trends.\(^5\)

In the last decade, national cohort survival data from US and UK CF centers, countries with relatively similar populations, have been published.\(^5\)–\(^8\) The question arises whether the Dutch cohort survival differs from survival from US and UK cohorts. This study estimates the birth prevalence of CF in the Netherlands and analyzes the survival in CF in birth cohorts from 1950 to 1989. Furthermore, the Dutch cohort survival data are compared with those from US and UK CF centers.

**Materials and Methods**

From 1995, nearly all Dutch CF patients are treated at one of seven CF centers in the Netherlands. Data on all CF patients living in the Netherlands on January 1, 2001, were obtained from these CF centers; duplicates were avoided by checking birth dates and postal codes. Patient numbers were similar to the patients in the Netherlands. Duplicates were avoided by checking birth dates and postal codes. Patient numbers were similar to the

From 1974 onwards, reliable CF mortality data has been obtained from the Dutch national statistics office, Statistics Netherlands. Furthermore, nearly all CF patients are currently treated at one of the seven specialized CF centers in the Netherlands. Apart from improvement of care and life expectancy, centralized care has resulted in a better registration of patients with CF. The improved registration of both living CF patients and CF mortality enabled us to analyze CF birth prevalence and survival since 1965.

Fogarty et al\(^4\) compared median age at death from CF in 10 countries in North America, Europe, and Australasia. They described significant differences in survival between these countries, showing favorable results in the United States compared to Europe, including the Netherlands. However, a cross-sectional measure is unsuited for capturing subtle longitudinal survival trends.\(^5\)

In the last decade, national cohort survival data from US and UK CF centers, countries with relatively similar populations, have been published.\(^5\)–\(^8\) The question arises whether the Dutch cohort survival differs from survival from US and UK cohorts. This study estimates the birth prevalence of CF in the Netherlands and analyzes the survival in CF in birth cohorts from 1950 to 1989. Furthermore, the Dutch cohort survival data are compared with those from US and UK CF centers.

**Materials and Methods**

From 1995, nearly all Dutch CF patients are treated at one of seven CF centers in the Netherlands. Data on all CF patients living in the Netherlands on January 1, 2001, were obtained from these CF centers; duplicates were avoided by checking birth dates and postal codes. Patient numbers were similar to the number of patients known to the Dutch CF Foundation, which is estimated to represent >98% of all Dutch CF patients. Since the 1990s, CF patients are treated according to consensus guidelines published by the Dutch CF Foundation, (Baarn, the Netherlands), which are similar to those propagated and suggested by the Cystic Fibrosis Foundation (Bethesda, MD).\(^5\) In all patients included in the present study, diagnosis was made by clinical evidence (pulmonary and/or GI manifestations typical for CF), confirmed by either an abnormal sweat chloride test result or CF genotype. In the Netherlands, there is neither mandatory prenatal screening nor newborn screening for CF.

Mortality data were obtained from the Department of Mortality Statistics of the Dutch central statistics office Statistics Netherlands. With the introduction of the International Classification of Diseases in 1974, CF was classified as a separate disease; therefore, mortality data on CF are available from 1974. There is no registration of elective terminations of pregnancies with the diagnosis of CF. In order to test the completeness of mortality statistics, data on 50 CF patients who died during the last 15 years (37 at the University Medical Center Utrecht [UMCU], 4 at home, and 9 at other hospitals) were retrieved from the hospital records of the UMCU. All 50 deaths could be found in the CF mortality statistics of Statistics Netherlands.

Using the survey data of living CF patients and the CF mortality statistics, the actual patient numbers could be calculated for each annual cohort after 1974. Annual survival data in these cohorts could be calculated from the mortality statistics. The survival of the pre-1974 cohorts can only be calculated for those who have survived after 1974. The size of the original cohorts was estimated by assuming a CF birth prevalence of 1 per 3,600 live births, as observed in the period from 1961 to 1965.\(^1\)

Five-year cohorts are used to give a reasonable sample size. Because for patients born after 1973 the exact survival could be calculated, the cohorts from 1970 to 1973 and from 1974 to 1979 were 4-year and 6-year cohorts, respectively. Because the numbers of patients are small, particularly in the early cohorts, survival rates were provided for both sexes together.

The life table was calculated using statistical software (SPSS version: 11.5; SPSS, Chicago, IL). Survival was analyzed using Cox proportional hazards model with age as the time scale.

**Results**

Table 1 gives total Dutch live births and estimated numbers of CF live births (based on a birth prevalence of 1 in 3,600)\(^1\) for different birth cohorts from 1950 to 1994. Actual numbers of CF live births for the birth cohorts from 1974 to 1994 are also shown. Figure 1 presents actual annual births of patients with CF between 1974 and 2000. The number of CF live births in the 1995-to-1999 cohort was 162; however, because of a diagnostic delay, this is probably an underestimation of the actual number of CF patients.\(^8\)

<table>
<thead>
<tr>
<th>Total Dutch Live Births, (\times 1,000)</th>
<th>Estimated CF Live Births, No.</th>
<th>Actual CF Live Births, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch Cohorts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1950–1954</td>
<td>1,146</td>
<td>318</td>
</tr>
<tr>
<td>1955–1959</td>
<td>1,174</td>
<td>326</td>
</tr>
<tr>
<td>1960–1964</td>
<td>1,233</td>
<td>343</td>
</tr>
<tr>
<td>1965–1969</td>
<td>1,208</td>
<td>336</td>
</tr>
<tr>
<td>1970–1973</td>
<td>875</td>
<td>243</td>
</tr>
<tr>
<td>1974–1979</td>
<td>1,065</td>
<td>296</td>
</tr>
<tr>
<td>1980–1984</td>
<td>877</td>
<td>244</td>
</tr>
<tr>
<td>1985–1989</td>
<td>925</td>
<td>257</td>
</tr>
<tr>
<td>1990–1994</td>
<td>985</td>
<td>274</td>
</tr>
</tbody>
</table>

The average overall birth prevalence of CF in 1974 to 1994 was 1 in 4,750 live births (95% confidence interval [CI], 1 in 5,100 to 1 in 4,440 births). Figure 2 presents the estimated (cohorts born before 1974) and actual (cohorts born after 1974) survival curves for the different cohorts. The estimated survival (SE) to 30 years increased from 6% (1%) in the 1950-to-1954 cohort, to 36% (3%) in the 1970-to-1973 cohort.

For the 1974-to-1979, 1980-to-1984, and 1985-to-1989 cohorts, the estimated survival (SE) to 15 years was 72% (3%), 77% (3%), and 91% (2%), respectively. The corresponding Cox proportional hazard ratios of the 1974-to-1979 and 1980-to-1984 cohorts, relative to the 1985-to-1989 cohort, were 3.5 (95% CI, 2.1 to 6.0) and 2.7 (95% CI, 1.5 to 4.7), respectively.

Figure 3 shows the improvement of survival rates...
from age 1 year in the subsequent birth cohorts, both in the Netherlands and in the United States (US data based on Cystic Fibrosis Foundation patient registry).\textsuperscript{7} In the 1980-to-1984 cohort, a clear difference in survival rate was observed in favor of the American patients; this difference, however, disappeared over the subsequent cohorts.

In the UK, for the 1980-to-1982 birth cohort, survival rates for boys and girls 10 years of age and 15 years of age were 88%/83% and 83%/77%, respectively.\textsuperscript{6} In the 1980-to-1982 Dutch cohort, survival to these ages was 82% and 76%, respectively (both sexes combined). In a 1983-to-1985 cohort, survival to age 10 years in UK boys/girls was 90%/90%, vs 89% for Dutch CF children.

**DISCUSSION**

We have presented data on birth prevalence and survival of CF patients from 1974 and gave estimates for the period from 1950 to 1973. In 1977, ten Kate\textsuperscript{1} published the birth prevalence of CF among live births in the Netherlands for the years 1961 to 1965. He identified CF patients by means of an inquiry among medical specialists and by analysis of hospital admission data, death certificates, and data of the national CF Foundation. This elaborate study yielded a birth prevalence of approximately 1 in 3,600 live births. The birth prevalence shown by ten Kate et al\textsuperscript{1} is significantly higher than the birth prevalence found in our study (average birth prevalence from 1974 to 1994, 1 in 4,750 live births). Several factors may explain this difference.

Firstly, the completeness of data collection may play a role. Our data depend on patient data collected by the seven Dutch CF centers and on CF mortality data collected by Statistics Netherlands. Since 1995, nearly all CF patients are treated at one of the seven specialized CF centers in the Netherlands; all of these centers transferred patient data to us. A comparison of our patient data with the number of patients known to the Dutch CF Foundation (estimated to represent > 98% of all Dutch CF patients) demonstrated that our data on living patients are at least complete for 98%.

A check on the completeness of the mortality statistics demonstrated that the mortality data of all 50 investigated CF patients could be found in the mortality statistics of Statistics Netherlands. Although the registration of mortality statistics seems to be complete, there might be underreporting due to prediagnosis mortality. However, in the study of ten Kate,\textsuperscript{1} there may be less reliable recordings of living subjects (he assumed patients with “probable” and “possible” CF to have CF) and dead subjects (no separate registration of CF by Statistics Netherlands because of lack of CF International Classification of Diseases coding).\textsuperscript{1}

Secondly, in the last decades, there has been an increasing immigration to (and to a lesser degree of emigration from) the Netherlands. Since most immigrants were from nonwestern countries with a lower CF fibrosis transmembrane conductance regulator (CFTR) mutation carrier frequency (e.g., Indonesia, Surinam, Dutch Antilles, Turkey and Morocco), this might have resulted in a lower CF birth prevalence over the last decades. In 1972 the number of inhabitants with a nonwestern background (first and second generation from Turkey or countries in Africa, South America and Asia, except Indonesia and Japan) in the Netherlands was 1%.\textsuperscript{10} In 2000, 16% of all newborns had at least one nonwestern parent (first generation).\textsuperscript{10} On the extreme assumption that from 1961 to 1965 0% of all newborns had a nonwestern parent and that the CFTR mutation carrier frequency in nonwestern parents is 0%, the
birth prevalence of 1 in 3,600 from 1961 to 1965 would decrease to 1 in 4,300 in the year 2000. This number is still different from a birth prevalence of 1 in 4,750 live births. Furthermore, the CFTR mutation carrier frequency in nonwestern parents is probably not completely zero. However, only data on first-generation nonwestern parents are available. Consequently, the actual number of children with nonwestern parents is substantially higher, therefore, the birth prevalence of CF may be < 1 in 4,300.

Thirdly, the increased and improved prenatal diagnosis and genetic counseling might have resulted in a lower CF birth prevalence. Scotet et al found a 22.6% global reduction of CF prevalence at birth after the introduction of prenatal diagnosis in couples related to a child with CF. Although prenatal diagnosis of CF has only been performed in the last 15 years, the general awareness that CF is an inheritable disease might have influenced family planning from an earlier date.

In a more recent study, de Vries et al found a CF carrier frequency of 1 in 32 in Dutch blood donors, corresponding to a birth prevalence of approximately 1 in 4,000. This is lower (although not statistically significant) than the birth prevalence of 1 in 3,600 this group had published earlier, but higher than the birth prevalence of 1 in 4,750 in our study. Farrell et al and Gregg et al observed a lower CF birth prevalence in a CF neonatal screening project than expected from carrier frequency. This may support the view that family planning influences the birth prevalence of CF. However, the birth rate of 1 in 4,690 live births for the pre-1990 cohorts together (from 1974 to 1989) was not significantly higher than the birth prevalence of 1 in 4,920 from 1990 to 1994. Furthermore, also in a recent study in Italy, no change was found in the birth prevalence of CF between 1988 and 2001.

In summary, it does not seem justified to assume that the actual CF birth prevalence in the Netherlands is still 1 in 3,600. Instead, a prevalence of 1 in 4,750 seems more realistic.

National cohort survival data of the United States and United Kingdom and data on median survival of western countries, including the Netherlands, have demonstrated a dramatic improvement in survival of CF patients during the past decades. Our study shows a similar dramatic improvement of survival for Dutch cohorts over the past decades. All successive cohorts demonstrate a higher survival rate than the previous one cohort, both for the estimated 1950-to-1973 cohorts and the 1974-to-1994 cohorts.

Because there is no single national registry of clinical or microbiological data of all Dutch patients, we were unable to directly analyze the cause of the observed improving survival of patients. Potential contributors to the better survival include improved nutritional management and dietary recommendations, new airway clearance techniques, new anti-pseudomonal antibiotics, and improved surgical techniques for meconium ileus. During the last decade, new pulmonary therapies were introduced, including more aggressive antibiotic treatments, dornase-alfa and tobramycin for inhalation. The establishment of specialized care centers may also have helped survival. However, other factors may also play a role. The representation of patients with mild disease is likely to increase over time due to an increase in the diagnosis of CF in patients with mild disease. However, because no Dutch CFTR mutation data have been published since 1994, a shift in severe/mild ratios of CFTR genotype could not be investigated.

Trends toward earlier diagnosis in CF might have led to more aggressive early care. Although the mean age of diagnosis in the Netherlands decreased from 27 months in the 1950s to 18 months in the 1960s, it appears to have stabilized between 14 and 18 months in later decades. Because, unlike in some other western countries, no national prenatal or newborn screening for CF in the Netherlands has been implemented, also in the last decade the age of diagnosis remained at approximately 14 months (unpublished data from the UMCU CF patient registry). Therefore, the improvement in survival in the Netherlands in the last decades is not due to earlier diagnosis.

Fogarty et al compared the median age at death from CF in 10 different countries and found substantial differences in survival. Median age at death was significantly higher in the United States compared with the Netherlands. However, median age at death is an indirect marker of current mortality experience. In a disease such as CF (for which life expectancy is consistently increasing), median age at death will invariably underestimate median survival.

The North American Cystic Fibrosis Foundation publishes yearly survival data of CF patients from the age of 1 year. Comparing the CF survival data between the United States and the Netherlands, a better survival could be demonstrated in the US patients compared to the Dutch patients in the 1980-to-1984 cohort (Fig 3); however, this difference has disappeared over the subsequent cohorts. Also, the difference in survival between the United Kingdom and the Netherlands found in the 1980-to-1982 cohort appeared to have disappeared for later cohorts. These findings stress the necessity of longitudinal survival studies in diseases for which life expectancy is consistently increasing, since cross-sectional studies fail to capture subtle changes in survival.
Apart from differences in the extent of underdiagnosis between nations, a number of other factors may explain the observed differences in survival in the older cohorts in the different countries. These factors include differences in socioeconomic status and variations in the distribution and virulence of pathogens. However, these factors are not significantly different between the Netherlands, the United States, and the United Kingdom.

Another explanation may be the difference in distribution of CF genotypes. In the Netherlands, the ΔF508 prevalence is 77% and the prevalence of severe mutations is 85% (percentage not determined, 12%). These percentages are higher than in the United States but similar to the United Kingdom.

Different studies reported that management of CF in specialized CF centers results in a better clinical outcome and survival. The introduction of specialized CF clinics differs internationally and might therefore partially explain the international difference in survival. Since approximately 1995, almost all Dutch CF patients are treated at one of the seven CF centers. The long-term effects of this centralized care will become apparent over the coming years.

In Denmark (with a population similar to the Netherlands), approximately 75% of all patients attend the Copenhagen CF center. Major differences in CF care between Denmark and the Netherlands include early institution of centralized care (since 1968), aggressive use of antibiotics in patients with chronic *Pseudomonas aeruginosa* infection and cohort isolation, separating patients with *P. aeruginosa* from patients without such colonization. In the Copenhagen CF center, a much better survival has been reported compared to our data and the US and UK data, with > 80% survival to 45 years from 1989 to 1993. Both the introduction of cohort isolation and the aggressive use of antibiotics have resulted in a lower incidence and prevalence of chronic *P. aeruginosa* infection in Denmark. However, although it is well accepted that chronic *P. aeruginosa* infection is a major risk factor for mortality in CF, the plausibility of the Danish survival data has been debated because of small patient numbers.

In conclusion, the actual birth prevalence of CF in the Netherlands is lower than the birth prevalence of CF estimated 30 years ago. Similar to other countries, the survival of patients with CF has dramatically increased over the past decades. The difference in survival between the Netherlands and the United States, as observed in the cohorts born > 20 years ago, has disappeared.

ACKNOWLEDGMENT: We thank all physicians of the Dutch CF centers for providing data on their CF patients and Mrs. I.M. Keij-Deerenberg (Department of Mortality Statistics of Statistics Netherlands) for providing CF mortality data.

REFERENCES

19. Dankert-Roelse JE, te Meeran GJ. Long term prognosis of patients with cystic fibrosis in relation to early detection by
20 Britton JR. Effects of social class, sex, and region of residence on age at death from cystic fibrosis. BMJ 1989; 298:483–487
26 Lewis PA. Inferences for health provision from survival data in cystic fibrosis. Arch Dis Child 1998; 79:297–299