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Increased risk of fatal prostate cancer may explain the rise in mortality in the Netherlands

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Background	Several lines of evidence suggest that, as a result of improved diagnostic techniques, the increase in incidence of prostate cancer is due largely to increased detection of subclinical cases. Between 1971 and 1989, a considerable increase in incidence was found in Southeastern Netherlands among men aged under 60 years without an improvement in prognosis. We hypothesized that in addition to the increase due to increased detection, a genuine increase in incidence has occurred in the last two decades and that this should be reflected in national mortality rates.
Methods	Age-specific and age-adjusted mortality rates were calculated to determine whether mortality due to prostate cancer continued to increase after 1990. Using log-linear Poisson modelling according to Clayton and Schifflers, we estimated the contribution of period and cohort effects to prostate cancer mortality between 1955 and 1994.
Results	The age-adjusted mortality increased from 22 in 1955–1959 to 33 per 10^5 in 1990–1994 (European standardized rate). For men under 65, the rates stabilized after 1989. The age-cohort model fitted the data better than the age-period model. Therefore, the increase in mortality can be explained largely by the increasing risk for successive birth cohorts for men born until 1930. However, more frequent reporting of prostate cancer as the underlying cause of death (partly attributable to a decline in competing causes of death) may have occurred as well.
Conclusions	Our findings suggest an increased risk of fatal prostate cancer in The Netherlands between 1955 and 1994.

Keywords	Prostate cancer, mortality, statistical modelling, birth cohorts, trends
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The incidence of prostate cancer has increased considerably over the past decades in most industrialized countries,[1] including The Netherlands.[2,3] Mortality rates for prostate cancer have increased to a lesser extent.[1,2] More than 6300 cases of prostate cancer are now detected annually in The Netherlands, whereas the number of deaths due to prostate cancer amounted to 2374 in 1994.[3] An increase in mortality due to prostate cancer was found in consecutive birth cohorts, on the basis of mortality data up to 1989.[4] The prognosis for prostate cancer patients has improved in several countries, e.g. the US[5] and Sweden,[6] presumably due to earlier diagnosis and increased detection of preclinical cases.[6] In Southeastern Netherlands, the overall 5-year relative survival improved slightly, but it declined for patients aged 40–59 from 65% (95% CI : 47–83%) in 1975–1979 to 48% (95% CI : 34–62%) in 1985–1989.[7] A decline in survival of prostate cancer patients below 60 years was also observed in other countries in this period, e.g. in Sweden.[6] We hypothesized that a real increase in risk may have occurred in the 1980s in the most recent birth cohorts, i.e. men born between 1920 and 1935. We chose to analyse mortality data, because trends in mortality due to prostate cancer are less likely to be influenced by changes in diagnostic procedures than trends in the incidence. In addition to calculation of age-specific and age-adjusted mortality trends, we performed an age-period-cohort analysis using national data up to 1994 to determine whether mortality due to prostate cancer continued to increase after 1989 in The Netherlands and if this can be explained by either period or birth cohort effects.

Methods

The underlying cause of every death has been reported to Statistics Netherlands since 1900. The number of men recorded as having died of prostate cancer and the age-specific number of

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Table 1 Relationship between age, period and cohort. (For illustration, birth cohort 1900–1909 is shown in *Italic*)

	Period							
Age	1955–1959 (1)	1960–1964 (2)	1965–1969 (3)	1970–1974 (4)	1975–1979 (5)	1980–1984 (6)	1985–1989 (7)	1990–1994 (8)
55–59 (1)	1895–1904 (6)	*1900–1909 (7)*	1905–1914 (8)	1910–1919 (9)	1915–1924 (10)	1920–1929 (11)	1925–1934 (12)	1930–1939 (13)
60–64 (2)	1890–1899 (5)	1895–1904 (6)	*1900–1909 (7)*	1905–1914 (8)	1910–1919 (9)	1915–1924 (10)	1920–1929 (11)	1925–1934 (12)
65–69 (3)	1885–1894 (4)	1890–1899 (5)	1895–1904 (6)	*1900–1909 (7)*	1905–1914 (8)	1910–1919 (9)	1915–1924 (10)	1920–1929 (11)
70–74 (4)	1880–1898 (3)	1885–1894 (4)	1890–1899 (5)	1895–1904 (6)	*1900–1909 (7)*	1905–1914 (8)	1910–1919 (9)	1915–1924 (10)
75–79 (5)	1875–1884 (2)	1880–1889 (3)	1885–1894 (4)	1890–1899 (5)	1895–1904 (6)	*1900–1909 (7)*	1905–1914 (8)	1910–1919 (9)
80–84 (6)	1870–1879 (1)	1875–1884 (2)	1880–1889 (3)	1885–1894 (4)	1890–1899 (5)	1895–1904 (6)	*1900–1909 (7)*	1905–1914 (8)

Table 2 List of models fitted consecutively using methods described by Clayton and Schifflers[10,11]

Models considered	Equations of the model	Values of indices
Age (A)	$E[\ln Y_a] = a_a$	a = 1,2,...,5,6
Age + Drift (AD)	$E[\ln Y_{ap}] = a_a + \delta p$ or $E[\ln Y_{ac}] = a_a + \delta c$	p = 1,2,...,7,8 c = A − a + p, c = 1,...,13
Age + Period (AP)	$E[\ln Y_{ap}] = a_a + \pi_p$	as before
Age + Cohort (AC)	$E[\ln Y_{ac}] = a_a + \tau_c$	as before
Age + Period + Cohort (APC)	$E[\ln Y_{apc}] = a_a + \pi_p + \tau_c$	as before

The mortality rate Y_{ap} is fully specified as being the rate for age group a and cohort c, since c = A − a + p, where A is the number of age groups. The left-hand side of the equation is the expected value of the natural log of the mortality rate. The right-hand side of the equation is a linear combination of the effects of some or all of the factors: age, period and cohort.

males in the Dutch population were abstracted from the annual publications of Statistics Netherlands for the years 1955–1994.[8,9] Four revisions of the International Classifications of Disease (ICD) were used in this period. In the Sixth and Seventh Revisions, ICD code 177 was used as the definition for prostate cancer, in the Eighth and Ninth Revisions ICD code 185. The definitions for the two codes were essentially the same.

For statistical analysis, the number of deaths and the number of males in The Netherlands were compiled into 5-year age groups and 5-year calendar periods of death. Mortality rates were calculated for these groups per 100 000 person-years. We adjusted the rates for age according to the European Standard Population. Ages below 55 were ignored in the analysis, because less than one per cent of prostate cancer deaths occur in this group.[3] The relation between the indexed age groups (a = 1–6), periods (p = 1–8) and cohorts (c = 1–13) is shown in Table 1. To estimate the separate effects of age (A), calendar period (P) and birth cohort (C) on the trend in mortality, a series of models containing the terms listed in Table 2 was fitted sequentially, using the methods described by Clayton and Schifflers.[10,11] The GENMOD procedure of the statistical package SAS was used. To test the goodness-of-fit of the models with the observed mortality rates and to test the models against one another, deviances and differences of deviances with appropriate degrees of freedom were used.[10,11] We allowed for extra Poisson variation in the final AC model.[12]

Results

The number of cases and person-years of all observations used in the analyses are displayed in Table 3. The age-adjusted mortality due to prostate cancer increased gradually from 22 in 1955–1959 to 26 in 1965–1969, stabilized in the early 1970s and then further increased to 33 in 1990–1994 (Figure 1) The increase occurred initially in all age groups, but after 1989 only in the oldest age groups (Figure 2). The age-specific mortality rate declined slightly in 1990–1994 for men under 65. The results of statistical modelling of the observed rates are summarized in Tables 4 and 5. If a model is valid, the deviance is χ^2 distributed with DF degrees of freedom. Large values of the deviance compared with DF indicate a lack of fit. The AP-model gave a poor fit, resulting in a *P*-value for the goodness-of-fit of 0.014. The AC-model fitted somewhat better ($P = 0.038$) than the AP-model ($P = 0.014$). The fully parameterized age-period-cohort model did not fit the data better than the AC-model: the difference in deviances was not significant ($P = 0.088$) (Table 5). The age-period-cohort model fitted the data better than the AP-model ($P = 0.026$), but not better than the AC-model, also when allowing for extra-Poisson variation (F-test: $P = 0.30$) (Table 6). We, therefore, conclude that the AC-model with extra-Poisson variation provided a good description of the data (Figure 3). The plot of the standardized deviance residuals of the AC-model with extra-Poisson variation and the AC-model without extra-Poisson variation showed only small differences in the two types of residuals and no (extreme) outliers (Figure 4).

Discussion

Two main findings can be derived from our analyses. Firstly, mortality due to prostate cancer in The Netherlands continued to increase up to the period 1990–1994 and this increase can be described largely by an increased risk for consecutive birth cohorts since 1875. Secondly, prostate cancer mortality ceased to increase for men under 65 after 1989.

The poor fit of the Age-Drift model indicated non-regular period and cohort effects. Although the fully parameterized age-period-cohort model gave the best description of the data, this model is difficult to interpret. Because there are too many parameters in this model, age, period and cohort effects cannot be distinguished.[11] Since the AC-model was not significantly worse, an AC-model with extra Poisson variation describes the data reasonably well, suggesting birth cohort effects.

Mortality due to prostate cancer increased between 1975 and 1988 in most European countries (by 5–10% per 5-year period),

Table 3 Number of deaths due to prostate cancer and person-years of observation in The Netherlands, 1955–1994

	55–59	60–64	65–69	70–74	75–79	80–84
a) No. of deaths						
1955–1959	95	229	514	837	1036	867
1960–1964	116	245	591	898	1299	1133
1965–1969	132	325	654	1078	1512	1425
1970–1974	138	314	689	1089	1553	1514
1975–1979	140	339	799	1338	1693	1674
1980–1984	163	410	879	1433	1889	1832
1985–1989	210	529	919	1581	2116	2112
1990–1994	195	519	1062	1766	2319	2496
	55–59	**60–64**	**65–69**	**70–74**	**75–79**	**80–84**
b) Person-years of observation						
1955–1959	1 244 347	1 055 747	845 088	640 646	423 388	218 827
1960–1964	1 382 245	1 156 572	940 699	707 939	475 594	257 087
1965–1969	1 462 469	1 274 451	1 015 380	771 006	521 280	290 946
1970–1974	1 506 338	1 343 825	1 110 544	819 823	554 929	316 949
1975–1979	1 580 498	1 388 582	1 171 273	895 203	588 620	336 228
1980–1984	1 710 417	1 462 326	1 218 130	948 617	644 259	360 135
1985–1989	1 757 563	1 588 469	1 284 758	997 095	688 909	386 452
1990–1994	1 821 150	1 369 635	1 417 716	1 073 638	736 525	424 506

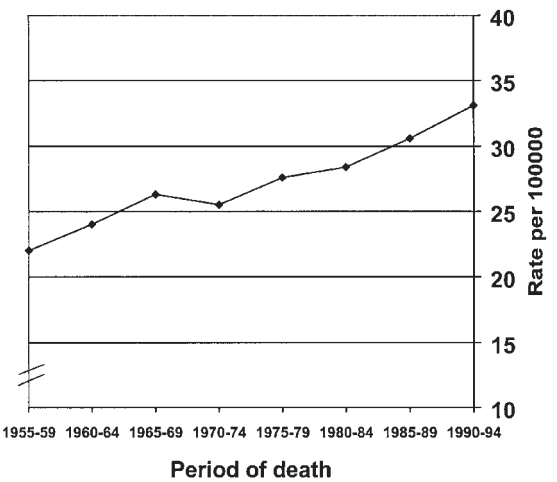

Figure 1 Age-adjusted mortality due to prostate cancer in The Netherlands, 1955–1994. (European Standardized Rate)

Figure 2 Age-specific mortality rates for prostate cancer in The Netherlands, 1955–1994

Table 4 Goodness-of-fit tests of the models

Model	Deviance	Degrees of freedom	*P*-value
Age	418.5	42	<0.001
Age + Drift	75.2	41	<0.001
Age + Period	55.9	35	0.014
Age + Cohort	45.1	30	0.038
Age + Period + Cohort	34.1	24	0.083

Table 5 Successive testing of models[a]

Testing models	Difference in deviance	Degrees of freedom	*P*-value
Age + Drift versus Age	343.3	1	<0.001
Age + Period versus Age + Drift	19.3	6	0.004
Age + Cohort versus Age + Drift	30.1	11	0.002
Age + Period + Cohort versus Age + Period	21.8	11	0.026
Age + Period + Cohort versus Age + Cohort	11.0	6	0.088

[a] The F-value for a test of the APC-model versus the AC-model in the presence of extra Poisson variation[12] was [(45.1 – 34.1)/6]/[34.1/24] = 1.29 with 6 degrees of freedom for the numerator and 24 degrees of freedom for the denominator (*P*-value is 0.30).

The F-value for a test of the APC-model versus the AP-model in the presence of extra Poisson variation[12] was [(55.9 – 34.1)/11]/[34.1/24] = 1.39 with 11 degrees of freedom for the numerator and 24 degrees of freedom for the denominator (*P*-value is 0.24).

except for Portugal, Spain and Yugoslavia.[1] This increase did not occur in a specific age group. Furthermore, an increasing cumulative mortality risk (30–74 years) was found for consecutive birth cohorts after 1910 (up to the 1940 birth cohort) in Denmark and Norway and to a lesser extent in Germany, Belgium, UK and The Netherlands.[1] In Norway, mortality due to prostate

Table 6 Parameters of the Age-Cohort model on the log scale (Table 2) with and without extra Poisson variation

Age	Parameters	SE[a]	SE (extra Poisson variation)	Cohort	Parameters	SE	SE (extra Poisson variation)
55–59	–9.14	0.072	0.088	1875	–0.56	0.087	0.106
60–64	–8.08	0.081	0.099	1880	–0.45	0.082	0.101
65–69	–7.09	0.080	0.098	1885	–0.35	0.081	0.099
70–74	–6.28	0.080	0.098	1890	–0.34	0.081	0.099
75–79	–5.56	0.080	0.098	1895	–0.31	0.080	0.098
80–84	–4.97	0.080	0.098	1900	–0.31	0.080	0.098
				1905	–0.25	0.080	0.098
				1910	–0.20	0.080	0.098
				1915	–0.18	0.080	0.098
				1920	–0.13	0.080	0.099
				1925	–0.06	0.081	0.099
				1930	0.04	0.085	0.104
				1935	0.0	–	–

[a] Standard error.

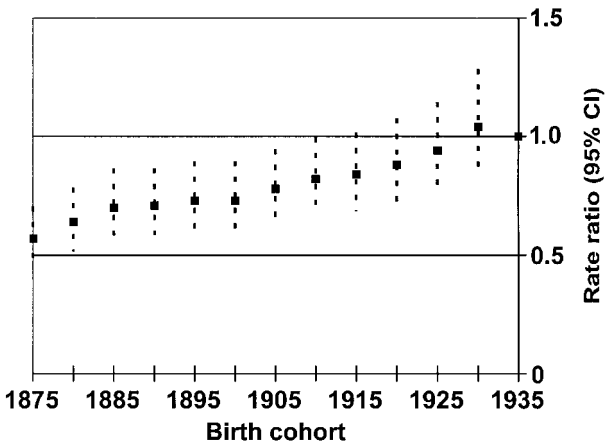

Figure 3 Relative risk of mortality due to prostate cancer per birth cohort in The Netherlands and 95% confidence intervals, based on the Age-Cohort model (birth cohort 1935 is reference cohort)

cancer increased to a similar extent as the incidence between 1957 and 1991, which was more pronounced in men under 60 years, but without a birth cohort effect.[13] On the other hand, no notable increases in mortality were reported for Northern Sweden between 1974 and 1989[14] or Isère (France) between 1979 and 1990.[15]

Analyses with mortality data available up to 1983 in Spain showed an increase in the risk for men born before 1891–1896, followed by a stabilization.[16] On the basis of mortality data up to 1991 from the database of the World Health Organization, a pattern of an increasing risk was shown for men born around 1910 and earlier, followed by a slow increase (France, Canada, Australia) or stabilization (US, UK).[17] In a recent report concerning mortality in Europe, a cohort effect was found in most countries, which was most pronounced in Poland, Hungary, Greece and Spain. In some countries (e.g. Belgium, Denmark) there was a hint of reversal of trends in the cohorts of men born around 1940. Calendar period effects were negligible in most countries.[18]

Our results suggest that the risk of clinical prostate cancer has increased in The Netherlands. There could, however, be other reasons for our findings. Because the unequivocal determination of the cause of death is particularly difficult for the oldest subjects, changes in coding practices may have influenced the frequency of reporting prostate cancer as the underlying cause of death, against the background of the rising incidence of prostate cancer and the decline in mortality due to cardiovascular disease,[19] male lung cancer[20] and benign prostatic hyperplasia.[21] This would, however, have resulted in stronger period than cohort effects. Nevertheless, the finding of an AC-model that fits might be explained in a different manner. If increased detection and consequently increased reporting of prostate cancer as the cause of death affect successive birth cohorts to different extents, changes in diagnostic procedures could mimic a cohort effect under some circumstances. For prostate cancer, incidence rates would have been more prone to spurious cohort effects, because increasing detection of subclinical prostate cancer is more likely to affect the incidence of prostate cancer than mortality. Since the prevalence of 'latent' prostate cancer at autopsy increases rapidly with age,[22] a higher detection rate is, indeed, likely to be more pronounced for older than younger ages. A spurious cohort effect on mortality rates could only be found if the vast majority of 'latent' cases of prostate cancer resulted in the reporting of prostate cancer as the underlying cause of death, but this does not seem to be a plausible assumption.

Delayed diagnosis resulting in a worse prognosis is not a likely explanation for increased mortality, because, in fact, an increasing proportion of cases was detected at an organ-confined stage.[2] Furthermore, curative radiotherapy was applied increasingly.

If the mortality rate for prostate cancer has increased over the past decades, it seems that the contribution of increased detection to the increase in incidence is generally overestimated. However, the incidence of prostate cancer has been higher than the mortality attributable to this disease since the 1970s and the trend has been a steady increase.[2] As a consequence, the mortality/incidence ratio in The Netherlands was 0.52 in 1990 and 0.38 in 1994.[3] Therefore, it seems likely that an increase in

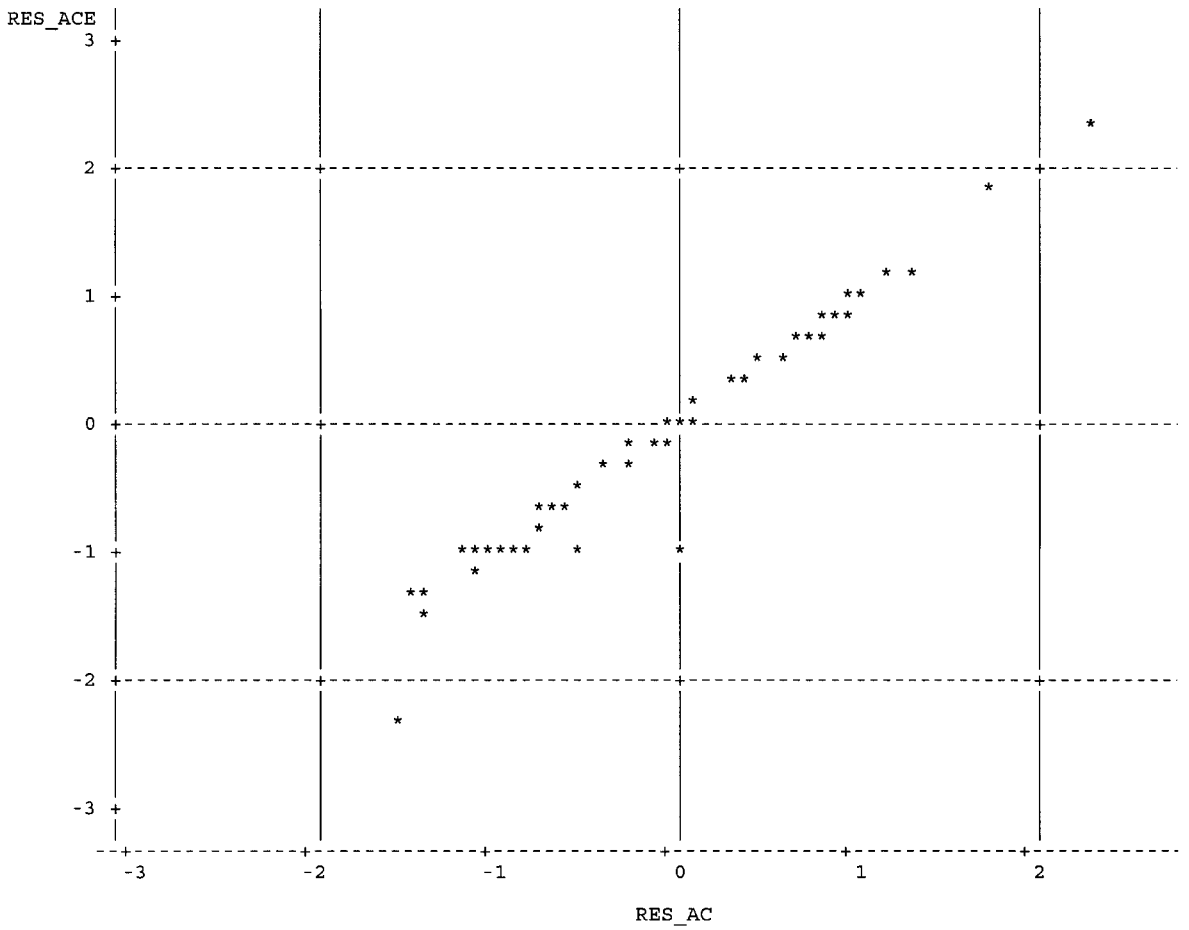

Figure 4 Plot of standardized deviance residuals of the Age-Cohort-model without extra Poisson variation (Res-ac) (x-axis) and the Age-Cohort-model with extra Poisson variation (Res-ace) (y-axis)

the risk of clinical prostate cancer has occurred in addition to a considerable artificial increase in the incidence.

However, a cause for this increased risk has not been established yet. Major genetic factors are responsible for approximately 9% of cases.[23] High dietary fat intake is one of the few rather consistently reported risk factors, but the evidence on alcohol intake, physical activity, vitamin D and risk factors *in utero* is still inconclusive.[24,25]

In conclusion, mortality due to prostate cancer has continued to increase, which can be explained to a large extent by an increasing risk for successive birth cohorts up to those born around 1930. Analyses of mortality in other European countries point into the same direction.

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