gene occur in diverse human tumour types. *Nature* 1989, **342** 705–708.
43. Gaidano G, Ballerini P, Gong JZ, *et al.* p53 mutations in human lymphoid malignancies: association with Burkitts lymphoma and chronic lymphocytic leukemia. *Proc Natl Acad Sci USA* 1991, **88**, 5413–5417.
44. Stratton MR, Moss S, Warren W, *et al.* Mutation of the p53 gene is human soft tissue sarcomas: association with abnormalities of the RB1 gene. *Oncogene* 1990, **5**, 1297–1301.
45. Bartek J, Iggo R, Gannon J, Lane DP. Genetic and immunochemical analysis of mutant p53 in human breast cancer cell lines. *Oncogene* 1990, **5**, 893–899.
46. Romano JW, Ehrhart JC, Duthu A, Kim CM, Appella E, May P. Identification and characterization of a p53 gene mutation in a human osteosarcoma cell line. *Oncogene* 1989, **4**, 1483–1488.
47. Rodrigues NR, Rowan A, Smith MEF, *et al.* p53 mutations in colorectal cancer. *Proc Natl Acad Sci USA* 1990, **87**, 7555–7559.
48. Harlow E, Williamson NM, Ralston R, Helfman DM, Adams TE. Molecular cloning and *in vitro* expression of a cDNA clone for human cellular tumor antigen p53. *Mol Cell Biol* 1985, **5**, 1601–1610.

Acknowledgements—This research was supported by the Cancer Research Campaign. B.V. was supported by an EMBO long-term fellowship.

Eur J Cancer, Vol. 29A, No. 1, pp. 107–111, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00

Trends in Mortality from Malignant Cutaneous Melanoma in The Netherlands, 1950–1988

P.J. Nelemans, L.A.L.M. Kiemeney, F.H.J. Rampen, H. Straatman and A.L.M. Verbeek

This paper presents an analysis of trends in mortality from malignant melanoma of the skin in The Netherlands, 1950–1988. Statistical analyses show that time period effects are needed to describe the mortality trends in The Netherlands. Because this contrasts with reports from other countries, in which the trends were ascribed to a cohort effect only, log-linear models including the three factors age, time period and birth cohort, were fitted to the data. To be able to separate time period effects from birth cohort effects we assumed a mathematical function for the mortality rates in relation to age. The results obtained in this way indicate that time period effects increased up to 1970. An increase of birth cohort effects is seen for cohorts born between 1900 and 1955. For cohorts born after 1955 the mortality from melanoma seems to decrease. The most plausible explanation for the time period effect probably is improvement in death certification.
Eur J Cancer, Vol. 29A, No. 1, pp. 107–111, 1993.

INTRODUCTION

A RAPID RISE of incidence and of mortality from cutaneous malignant melanoma is reported from many countries in the world [1]. A doubling of incidence every 10–14 years is observed [2]. The increase in mortality is less than the rise in incidence. Mortality rates from the United States, England and Wales, and Canada studied by Lee, showed an annual increase of about 3% [3].

An international comparison of incidence rates (Fig. 1) shows that the Dutch population is at intermediate risk of getting a malignant melanoma of the skin [4]. Within the European Community The Netherlands belong to the countries in which the highest melanoma risk is seen [5]. Nationwide data about Dutch incidence of cancer over a longer period of time are not available. However, mortality data were published from 1950 onwards and can be studied for trends.

Time trends can be produced by two mechanisms, a time period effect and/or a birth cohort effect. In many countries a so-called age-cohort pattern was observed in both sexes. This means that starting with some specific birth cohort the mortality is increasing for successive birth cohorts (with a similar age profile) rather than for successive time periods. This observation of a birth cohort effect supports the idea that the rise of mortality and incidence of cutaneous malignant melanoma is real and not the result of better registration techniques.

This paper presents an analysis of the trends in melanoma mortality in The Netherlands, 1950–1988, using statistical methods described later.

Correspondence to P.J. Nelemans.
P.J. Nelemans, L.A.L.M. Kiemeney, H. Straatman and A.L.M. Verbeek are at the Department of Medical Informatics and Epidemiology, University of Nijmegen, Verlengde Groenestraat 75, 6525 EJ Nijmegen, The Netherlands; and F.H.J. Rampen is at the Department of Dermatology, Saint Anna Hospital, Oss, The Netherlands.
Revised 9 Mar. 1992; accepted 5 May 1992.

DATA AND METHODS

Mortality data

Numbers of persons with malignant melanoma of the skin as underlying cause of death from 1950 through 1988 were derived from annual publications of the Central Bureau of Statistics (CBS) [6]. Population information was also available from this

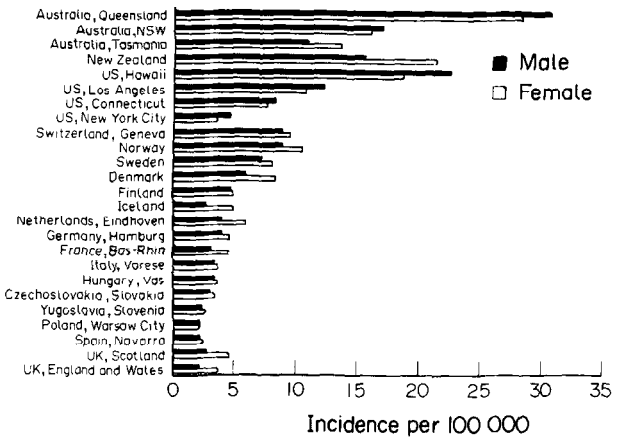

Fig. 1. Annual melanoma incidence rates for different countries, age-standardised to the world population [2].

source [7]. The numbers were organised by 5-year age groups and 5-year periods.

For statistical analysis the mortality rates were arranged in a two-way table by 5-year age groups and 5-year calendar periods [Table 1(a) and (b)]. Included in the analysis were eight time periods (from 1950–1954 to 1985–1988) and 14 age groups (from 15–19 years to 80–84 years). The last time period 1985–1988 was truncated to 4 years, because data on the year 1989 were not yet available at the time of analysis. The rates along the diagonals in these tables represent an approximation of the age-specific mortality rates of birth cohorts. In this way 21 birth cohorts can be defined: 1870–1874, 1875–1879, . . . until the cohort 1970–1974.

Statistical methods

To estimate the effects of age, time period and birth cohort on trend in mortality, a simultaneous analysis of these factors was performed by use of a statistical model. A rather simple model is the multiplicative one, where the mortality rate for a specific age–period–cohort combination is, apart from random fluctuation, described as a product of these three factors

$$Y_{apc} = \alpha_a \pi_p \tau_c, \text{ where}$$

Y_{apc} = mortality rate for age group a, born in period c, as experienced in period p,

α_a = parameters which describe the relationship between age group a (= 1, . . . , 14) and mortality,

π_p = parameters which describe the relationship between time period p (= 1, . . . , 8) and mortality,

τ_c = parameters which describe the relationship between birth cohort c (= 1, . . . , 21) and mortality.

Such a model is also called a log–linear model, because by taking the natural logarithm on both sides of the equality sign one obtains a linear model:

$$\log(Y_{apc}) = \log(\alpha_a) + \log(\pi_p) + \log(\tau_c).$$

Firstly, the age, period and cohort parameters are estimated, which give rise to expected mortality rates that are as close as possible to the observed rates in Table 1(a) and (b). Secondly, the discrepancies between observed and expected rates are examined to determine, whether the model describes the data adequately. The statistical procedure used for estimating the parameters is the maximum likelihood method. The software package GLIM was used for the computations [8]. The statistical analyses are based on the assumption that the age-specific number of deaths observed in specific time periods or in specific birth cohorts follow a Poisson distribution.

Goodness of fit of the various models was evaluated by examination of the deviances. When the model under consideration is true, the deviance is χ^2 distributed with the number of degrees of freedom equal to the number of cells minus the number of parameters used in the model. If a model gives an adequate description of the observed rates the deviance from the model is about equal to or less than the number of degrees of freedom. For a more detailed explanation of the log–linear models used we refer to papers of Clayton and Schifflers [9, 10].

A serious problem associated with age–period–cohort models is the basis lack of identifiability of these models [10]. It is not possible to obtain unique estimates of the parameters for period and cohort effects, because there are many sets of age, period and cohort parameters that describe the data well. The problem arises from the dependence between the age at diagnosis, year of birth, and year of diagnosis, the first being the difference between the third and second. The identifiability problem theoretically disappears by assuming a mathematical function

Table 1 (a). Male age-specific mortality rates per 100 000 in The Netherlands by registration period

	1950–54	1955–59	1960–64	1965–69	1970–74	1975–79	1980–84	1985–1988
15–19	0.00	0.09	0.15	0.14	0.21	0.07	0.19	0.08
20–24	0.05	0.15	0.38	0.23	0.34	0.31	0.22	0.42
25–29	0.10	0.57	0.51	0.51	0.90	0.63	0.97	0.88
30–34	0.51	0.80	0.47	0.90	1.14	1.27	1.48	1.52
35–39	0.36	0.69	1.34	1.19	1.29	1.28	2.45	2.39
40–44	0.37	0.85	1.33	1.18	2.03	2.61*	2.17	3.34
45–49	0.47	0.96	0.99	1.35	2.40	2.38	1.89	4.11
50–54	1.00	0.90	1.63	2.27	2.60	2.74	3.81	3.77
55–59	0.97	1.85	2.10	2.80	3.25	3.54	5.44	4.07
60–64	1.27	2.27	1.64	3.30	4.39	3.74	5.06	5.74
65–69	2.87*	1.54	2.76	3.74	3.51	3.84	5.42	6.65
70–74	1.74	2.34	3.67	4.80	4.15	4.47	4.22	6.76
75–79	1.09	3.07	3.15	6.14	5.05	6.80	8.54	7.87
80–84	2.87	3.20	6.61	4.81	10.1	6.25	5.83	11.1

*Cells omitted in the statistical analysis

Table 1 (b). Female age-specific mortality rates per 100 000 in The Netherlands by registration period

	1950–54	1955–59	1960–64	1965–69	1970–74	1975–79	1980–84	1985–1988
15–19	0.05	0.05	0.00	0.07	0.11	0.00	0.07	0.08
20–24	0.20	0.26	0.29	0.32	0.14	0.21	0.30	0.24
25–29	0.20	0.26	0.42	0.30	0.45	0.49	0.63	0.70
30–34	0.27	0.31	0.47	0.74	0.80	1.82*	1.22	1.23
35–39	0.46	0.73	0.62	0.68	1.69	1.38	1.37	1.39
40–44	0.48	0.53	1.35	1.77	1.21	1.00	1.92	2.25
45–49	0.51	1.45	1.54	2.04	1.63	1.80	1.85	3.07
50–54	0.81	0.91	1.60	1.98	1.89	2.18	3.15	2.88
55–59	0.66	1.26	1.67	2.26	2.58	3.33	3.25	3.48
60–64	1.30	1.13	1.70	2.50	2.74	2.92	3.63	3.56
65–69	1.83	2.17	2.05	2.41	3.26	5.12	4.75	4.13
70–74	2.26	2.55	3.34	3.18	4.02	4.11	4.48	6.10
75–79	1.49	2.54	4.90	4.35	5.12	3.96	6.43	6.80
80–84	1.48	2.79	5.59	7.09	6.65	8.17	6.74	7.02

for the age curve [10]. One mathematical function that can be chosen is, that mortality rates are proportional to a power of age so that the rates on the multiplicative scale are expressed as

$$Y_{apc} = a_m{}^k \pi_p \tau_c,$$

where a_m = the midpoint of the age group a and k is the power exponent. The logarithms of the rates can be expressed as

$$\log(Y_{apc}) = k \log(a_m) + \log(\pi_p) + \log(\tau_c).$$

Because of the assumption that the log mortality rate is linearly related to the logarithm of the midpoint of the age group, the models include only one parameter for age, i.e. k. In this paper we will refer to these models as the restricted models. In case of an adequate fit of these restricted models on the data, the mortality rates for birth cohorts relative to a reference cohort and the mortality rates for time periods relative to a reference period are identifiable.

RESULTS

In 1950 10 male and 10 female cases were registered with melanoma of the skin as underlying cause of death. In 1988 these numbers had increased up to 164 for men and 177 for women. Between 1950 and 1988 the annual age-standardised death rates have increased about 4-fold; from 0.41 to 1.89 per 100,000 for males and from 0.39 to 1.38 for females (Fig. 2).

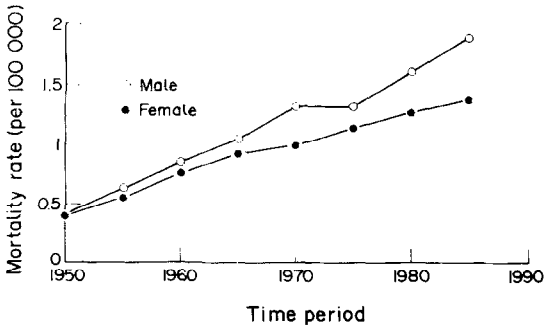

Fig. 2. Age-standardised (world population) mortality of cutaneous malignant melanoma per 100 000 population in The Netherlands, 1950–1988.

Table 2. Goodness of fit, as expressed by deviances in relation to the corresponding degrees of freedom, for log–linear models
$\log(Y_{apc}) = \log(\alpha_a) + \log(\pi_p) + \log(\tau_c)$

Factors included in the model	Men			Women		
	Deviance	D_f	P	Deviance	D_f	P
Age	604.3	96	0.00	401.9	97	0.00
Age + period	101.3	89	0.18	92.1	90	0.42
Age + cohort	102.2	76	0.02	89.9	77	0.15
Age+period+cohort	69.6	70	0.49	70.1	71	0.48

The mortality rates were age-standardised to the World Population by the direct method [4].

The statistical analyses comprised the ages 15–84 and the period 1950–1988. Because the total set of male mortality data was not fitted well by any of the models and even the deviance of the age–period–cohort model was fairly large, the cells with the largest standardised residuals in the age–period–cohort model were omitted. For men these cells represented age group 65–69 years in period 1950–1954 and age group 40–44 years in period 1975–1979 (Table 1a). For women, the cell representing age group 30–34 years in time period 1975–1979 was considered an outlier (Table 1b).

The results are summarised in Table 2, which presents the fit of various models to the data after omission of the cells which were considered as outliers. For both sexes the models with a time period effect gave a better fit than the models with a birth cohort effect. For men the best model is that with both a time period and a birth cohort effect. For women this full model was not really superior to the age–period model.

Table 3 presents the deviances and degrees of freedom for the restricted models, i.e. the models assuming a mathematical function for the age curve. It can be seen that the restricted age–period–cohort models still gave an adequate fit for both sexes. The best fitting slope k, i.e. power exponent, was 2.99 for men and 3.02 for women.

The now identifiable relative rates associated with successive time periods and birth cohorts, are presented in Figs 3 and 4, respectively. For calculation of relative rates for birth cohorts the estimate for the cohort born in the period 1920–1925 was

Table 3. Goodness of fit, as expressed by deviances in relation to the corresponding degrees of freedom, of log–linear models $\log(Y_{apc}) = k \log(a_m) + \log(\pi_p) + \log(\tau_c)$

Factors included in the model	Men			Women		
	Deviance	D_f	P	Deviance	D_f	P
Log (age)						
Log (age) + period	655.3	108	0.00	442.3	109	0.00
Log (age) + cohort	153.8	101	0.01	134.9	102	0.02
Log (age) +period+ cohort	130.0	88	0.00	121.9	89	0.01
	88.1	81	0.28	95.9	82	0.14

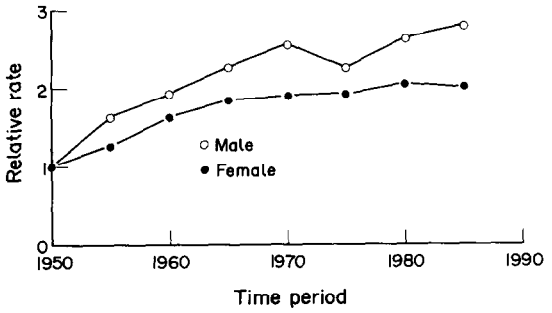

Fig. 3. Mortality rate for successive calendar periods for both sexes relative to time period 1950–1955. From models: $\log(Y_{apc}) = k\log(a_m) + \log(\pi_p) + \log(\tau_c)$.

used as reference, because this is one of the cohorts with the most complete data. A continuous increase of cohort effects is seen for cohorts born between 1900 and 1955. For cohorts born after 1955 the relative rates of dying from cutaneous melanoma decrease. The strongest increase of period effects is seen up to 1965 for women and up to 1970 for men. Thereafter it levels off.

DISCUSSION

A review of other trend studies on mortality from cutaneous malignant melanoma revealed that in many countries trends with time are best described by an age and birth cohort effect. In 1970 Lee *et al.* already noted from mortality data for the United States and for England and Wales that the increasing trends in deaths due to malignant cutaneous melanoma were compatible with a generation effect beginning with those born around the turn of the century [11]. The observation of a birth cohort effect led to the conclusion that it is unlikely that a systematic improvement in death certification is responsible for this rise [11]. This observation was confirmed by analyses of melanoma mortality rates in other countries [2, 12–14].

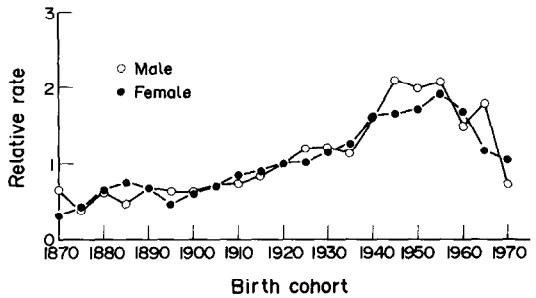

Fig. 4. Mortality rates for successive birth cohorts for both sexes relative to birth cohort 1920–1925. From models: $\log(Y_{apc}) = k\log(a_m) + \log(\pi_p) + \log(\tau_c)$.

By contrast, the results in the present study indicated, that models containing only age and cohort effects did not fit the Dutch mortality data. Period effects were needed to describe the trend in mortality rates in The Netherlands.

The age–period–cohort models for which we assumed a mathematical function for the age curve have the advantage that time period effects can be separated from birth cohort effects. Figure 3 shows that the effects of time period on mortality rates were largest up to 1970. Figure 4 suggests that the first birth cohorts which experienced increased exposure to the aetiological agent(s) were born at the beginning of this century. The continuous increase in cohort trend between 1900 and 1955 indicates that during this period the aetiological agent(s) became more widely distributed or that a change in life-style resulted in a greater probability to get exposed. The relative rates of dying from malignant melanoma seem to decrease for cohorts born after 1955. It must be noted that the estimates for the youngest cohorts are not as reliable as those for the more central cohorts. They are based on fewer cells and lower numbers of deaths and therefore are unstable. Definite conclusions cannot be based on these estimates. However, decreasing trend in melanoma mortality for younger birth cohorts was recently described for whites in the United States [15].

Period effects represent influences which affect the mortality rates in all age groups simultaneously. Period factors, which would increase reported mortality, are (a) changes in ICD-classifications, (b) improved death certification, e.g. transfer of deaths from non-melanoma skin cancers and/or organs to which the melanomas have metastasised, (c) changes in histopathological criteria and (d) increasing exposure of all age groups to an aetiological factor acting with a short latency period. Improvement in survival rates due to better therapy or detection of the disease in an earlier stage would lead to decreasing period effects.

Although four different *International Classifications of Diseases* were used during the period 1950–1988 (from ICD-6 to ICD-9), this cannot explain the increase in period trend, because there were no relevant changes in definition of melanoma of the skin. In The Netherlands there are no data available to verify to which extent improved death certification has contributed to the rise in recorded mortality due to melanoma. However, Roush *et al.* reported evidence that improvement in melanoma classification on death certificates occurred in the United States. In 1947, only 55% of the persons dying from skin cancer were correctly coded to the skin on the death certificate, whereas by 1970–1971, 88% of melanomas were correctly coded as cause of death [16]. Changes in histopathological criteria for the diagnosis of malignant melanoma, with a tendency to include borderline lesions previously diagnosed as benign, could cause an apparent rise in incidence rates, but cannot have a material impact on mortality rates because of the excellent prognosis of these lesions. Moreover, review of pigmented lesions in some studies revealed that only very few lesions classified as benign some decades ago are classified as malignant nowadays [16–19]. Because the cohort effect suggests an aetiological agent with a long latency period, the explanation that a causal factor with a short latency period increased mortality in all age groups simultaneously, seems a very unlikely explanation for the increasing period effects. So, the most plausible explanation for the increase in period trend

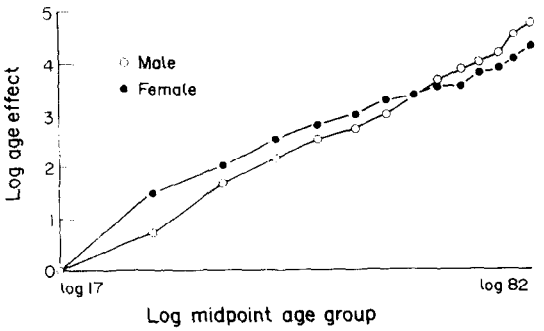

Fig. 5. Age-effects for men and women expressed as natural logarithms and plotted against the logarithms of the midpoints of age groups. The age effects were derived from age–period–cohort models: $\log(Y_{apc}) = \log(\alpha_a) + \log(\pi_p) + \log(\tau_c)$.

appears to be an improvement in certification of deaths due to melanoma. This would imply that part of the rise in recorded mortality is artefactual. For women the increase in period trend levels off after 1965 and for men, although less pronounced, after 1970. This might indicate that, like in the United States [16], the quality of death certification was rather good by that time and that further improvement affected recorded mortality rates to a lesser extent.

To cope with the identifiability problem an assumption was made about the form of the age curve. This assumption was based on a report of Doll, who observed that for several types of cancer incidence rates were proportional to the power of age [20]. Whether this assumption was acceptable with respect to the melanoma mortality rates observed in this study, was visually examined. In Fig. 5 the age effects, which were derived from the age–period–cohort models in Table 2, were plotted against the logarithms of the midpoints of age groups. As can be seen the curves are approximately straight lines indicating a linear trend. Furthermore, the assumption was confirmed by the age curves observed by Venzon *et al.* [12], who analysed melanoma mortality trends of five different populations. They found that two age curves, one for men and one for women, sufficed for all five populations studied. After plotting the age effects against age group midpoints, both on logarithmic scales, the curves were close to straight lines. The slopes for these age curves were 3.41 and 2.96 for men and women, respectively, and similar to those found for Dutch men (2.99) and women (3.02) in our study. Based on these observations it seems unlikely that the assumption about the age profile was arbitrary.

In conclusion, the observation that a time period effect was needed to describe the trend in melanoma mortality in The Netherlands suggests that part of the increase in recorded mortality from cutaneous melanoma is artefactual. An improvement in melanoma death certification may be the reason. Another part was explained by a birth cohort which indicates an increased exposure of more recent birth cohorts to an aetiological agent with a long latency period. Among birth cohorts born after 1955 mortality rates seem to decrease.

1. Lee JAH. Trend with time of the incidence of malignant melanoma of skin in white populations. In: Elwood JM, ed. *Melanoma and Naevi. Incidence, Interrelationships and Implications. Pigment Cell*, Vol. 9. Basel, Karger, 1988, 1–7.
2. Muir CS, Nectoux J. Time trends: malignant melanoma of skin. In: Magnus K, ed. *Trends in Cancer Incidence*. Causes and practical implications. Washington, Hemisphere Publishing, 1982, 365–385.
3. Lee JAH, Petersen GR, Stevens RG, Vesanen K. The influence of age, year of birth, and date on mortality from malignant melanoma in the populations of England and Wales, Canada and the white population of the United States. *Am J Epidemiol* 1988, **110**, 734–739.
4. Muir C, Waterhouse J, Mack T, Powell J, Whelan S, eds. Cancer incidence in five continents, Vol. 5. Lyon, IARC Scientific Publications No. 88, 1987.
5. Jensen OM, Estève J, Møller H, Renard H. Cancer in the European Community and its member states. *Eur J Cancer* 1990, **26**, 1167–1256.
6. Central Bureau of Statistics. Overledenen naar doodsoorzaak leeftijd en geslacht in het jaar 1950, 1951,. . .1988.
7. Central Bureau of Statistics. Bevolkingsaantallen naar leeftijd en geslacht in het jaar 1950, 1951,. . .1988.
8. Nelder JA, Wedderburn RWM. Generalised linear models, *JR Stat Soc* 1972, **135**, 370–384.
9. Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: Age–period and age–cohort models. *Stat Med* 1987, **6**, 449–467.
10. Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: The age–period–cohort model. *Stat Med* 1987, **6**, 469–481.
11. Lee JAH, Carter AP. Secular trends in mortality from malignant melanoma. *J Natl Cancer Inst* 1970, **45**, 91–97.
12. Venzon DJ, Moolgavkar SH. Cohort analysis of malignant melanoma in five countries. *Am J Epidemiol* 1984, **119**, 62–70.
13. Holman CDJ, James IR, Gatey PH, Armstrong BK. Analysis of trends in mortality from malignant melanoma of the skin in Australia. *Int J Cancer* 1980, **26**, 703–709.
14. Boyle P, Day NE, Magnus K. Mathematical modelling of malignant melanoma trends in Norway, 1953–1978. *Am J Epidemiology* 1983, **118**, 887–896.
15. Scotto J, Pitcher H, Lee JAH. Indications of future decreasing trends in skin-melanoma mortality among whites in the United States. *Int J Cancer* 1991, **49**, 490–497.
16. Roush GC, Schymura M, Holford TR. Patterns of invasive melanoma in the Connecticut Tumor Registry. Is the long-term increase real? *Cancer* 1988, **61**, 2586–2595.
17. Gordon LG, Lowry WS. Incidence and aetiology of melanoma. *Lancet* 1985, **I**, 583.
18. Philipp R, Hastings A,Briggs J, Sizer J. Are malignant melanoma time trends explained by changes in histopathological criteria for classifying pigmented skin lesions. *J Epidemiol Comm Health* 1987, **42**, 14–16.
19. van der Esch EP, Muir CS, Nectoux J, *et al.* Temporal change in diagnostic criteria as a cause of the increase of malignant melanoma over time is unlikely. *Int J Cancer* 1991, **47**, 483–490.
20. Doll R. The age distribution of cancer: implications for models of carcinogenesis. *JR Stat Soc* 1971, **134**, 133–166.

Acknowledgement—We thank Dr. J.P. Velema for his useful comments.