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Recent trends and future projections of lymphoid neoplasms – a Bayesian age–period–cohort analysis

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Abstract

Objectives: A steady increase in incidence of lymphoid neoplasms has been reported, especially for non-Hodgkin's lymphoma (NHL). Using high-quality incidence data from 1973–1992 in nine population-based cancer registries (Alberta, Bombay, Denmark, Israel, New Zealand, Osaka, Oxford, Slovenia, Utah), we have examined past increases in specific lymphoid neoplasms. Further, by using a Bayesian age–period–cohort approach, we have calculated 5-, 10- and 15-year projections for each group of lymphoid neoplasms.
Results: NHL incidence increased in all centers by an average of 77% in men and 66% in women between 1973 and 1992. Fifteen-year projections of these rates to 2003–2007 indicate that they will increase by an average of 55% among men and 79% among women. High projected incidence rates above 15/100,000 in men and 10/100,000 in women are expected in Alberta, Denmark, Israel, New Zealand, Oxford, and Utah by 2003–2007. The one notable exception was among men from Osaka, where no increase was projected. Modest increases in leukemia and multiple myeloma rates were observed in most of the nine registries with further projected increases by 2007. Projected incidence rates of Hodgkin's disease indicated little change.
Conclusion: Increases in NHL rates are occurring worldwide and provide no evidence of peaking. A key assumption in the projected rates is that the effect of environmental agents determining the trends during 1973–1992 will remain stable during the subsequent projection period.

Introduction

The incidence of lymphoid neoplasms is increasing in most parts of the world. A comparison of cancer registry information between 1982 and 1992 [1, 2] indicates that non-Hodgkin's lymphoma (NHL) is increasing at an average annual rate of 4–5% each year, implying a doubling of NHL incidence every 20 years. This upward trend is observed in all geographic regions covered by cancer registration, and is not restricted to any particular age group or sex, or to predominantly rural or urban areas. The reason for the increase has attracted much speculation but there is no clear explanation for it. Less dramatic increases have been observed for both multiple myeloma and leukemia [3] while rates for Hodgkin's disease appear to be stable or perhaps declining.

The classification of lymphoid neoplasms and the diagnostic procedures used have changed over the past three decades. Greater awareness of the disease and sensitivity of diagnostic methods may have resulted in more cases being detected. While this may account for part of the increase in lymphoid neoplasms in the 1960s and 1970s, especially NHL, it cannot explain more recent increases that have occurred [4]. The recent AIDS epidemic is another possible explanation, with an increasing number of AIDS-related lymphomas. However, these represent only a very small proportion of all lymphomas in most regions. For example, a specialist lymphoma registry in Cote-d'Or, France, detected a 10% annual increase in NHL from 1980 to 1989 that was completely independent of the HIV virus [5].

The analysis of trends in incidence between distinct geographic regions is likely to further our understanding of the etiology of lymphomas and may provide clues for the reasons behind the increasing incidence. We have therefore examined trends in Hodgkin's disease, NHL,

myeloma, and leukemia using recent data from nine high-quality cancer registries from around the world. Furthermore, we have adopted a Bayesian non-parametric age–period–cohort approach to make projections of future rates of lymphoid neoplasms up to 2007. Based on the assumption that past trends will continue into the future, these estimates give an indication of how the increase in the incidence of lymphoid neoplasms is likely to develop.

Methods

Incidence data for Hodgkin's disease (ICD-9 201), NHL (ICD-9 200 and 202), multiple myeloma (ICD-9 203), and leukemia (ICD-9 204-208) were obtained from the publications *Cancer Incidence in Five Continents*, volumes II–VII [1, 2, 6–9] for approximate 5-year periods of 1963–67, 1968–72, 1973–77, 1978–82, 1983–87, and 1988–1992. All registries with incidence data for lymphoid neoplasms over at least a 20-year period were identified and the quality and completeness of registration was assessed based on measures of the high proportion of cases which were reported to be histologically verified and the low proportion identified from death certificates only. These two measures provide indications of a high quality of diagnosis and completeness of ascertainment. A final selection of nine cancer registries was made to ensure geographic coverage of central, northern, and western Europe; the United States and Canada; the Middle East; Oceania; and eastern and southern Asia. The exact time periods for which data are available varied slightly between registries (Table 1). These data are stratified by sex and 5-year age groups (0–4, 5–9,...,70–74). Ages of 75 years and above were excluded due to the unreliability of death certification in these age groups. Cancer registries which satisfied the selection criteria were not available from several regions, including Africa, Mediterranean Europe, or South America.

Age–period–cohort models

For a given age group in a given period we can calculate the approximate year of birth, known as the cohort. Age–period–cohort models describe incidence rates in terms of age, period effects (which apply to all people at a certain point in time), and cohort effects (factors affecting a group of people born around the same time). The form of the model, given in the Appendix, belongs to the family of generalized linear models. Projections based on extrapolating classical estimates of age, period, and cohort effects require the analyst to make parametric assumptions [10] and are sensitive to variation in the most recent cohort effects, which can be unstable due to small numbers. The approach presented here uses non-parametric smoothing to reduce variation, hence improving the precision of the projections.

Bayesian methods combine prior knowledge with observed data to derive a posterior distribution, from which we can draw inferences about model parameters and functions of these parameters (*i.e.* rates). The use of Bayesian methods has been limited in the past because the posterior distribution is usually difficult or impossible to evaluate. Recent advances in computer-intensive techniques have overcome this problem and it is now possible to draw large samples from the posterior distribution and estimate quantities of interest by taking averages of these samples. The Bayesian approach used here allows us to incorporate *a-priori* belief about the smoothness of the age, period, and cohort effects [11]. This is achieved by specifying an autoregressive prior

Table 1. Incidence data analysed by registry and volume

Registry	Volume					
	II[a]	III[b]	IV	V	VI	VII
Alberta, Canada	1963–66	1969–72	1973–77	1978–82	1983–87	1988–92
Bombay, India	1964–66	1968–72	1973–75	1978–82	1983–87	1988–92
Denmark	1963–67	1968–72	1973–76	1978–82	1983–87	1988–92
Israel, all Jews	–	1967–71	1972–76	1977–81	1982–86	1988–92
New Zealand, non-Maori	1962–66	1968–71	1972–76	1978–82	1983–87	1988–92
Osaka, Japan	–	–	1973–77	1979–82	1983–87	1988–92
Oxford, UK	1963–66	1968–72	1974–77	1979–82	1983–87	1988–92
Slovenia	–	1968–72	1973–76	1978–81	1982–87	1988–92
Utah, USA	–	–	1973–77	1978–82	1983–87	1988–92

[a] Note that, due to changes in coding practises, data from volume II were excluded from analyses of NHL and leukemia.
[b] In the case of Denmark, data from volume III were also excluded from analyses of NHL and leukemia due to changes in coding practises.

Table 2. Smoothed and projected age-standardized rates with 90% credible intervals for NHL

	Alberta	Bombay	Denmark	Israel	New Zealand	Osaka	Oxford	Slovenia	Utah
Males									
1968–72	5.08	2.05	–	7.67	5.16	–	3.87	2.38	–
1973–77	6.29	2.42	4.54	8.05	5.80	3.64	4.68	3.00	6.78
1978–82	7.69	2.78	5.72	8.53	6.49	4.46	5.62	3.76	8.19
1983–87	9.00	3.19	7.05	8.81	7.35	5.18	6.85	4.60	9.78
1988–92	10.34	3.61	8.79	10.77	8.47	5.26	8.73	5.61	11.51
1993–97	**11.85**	**4.01**	**11.00**	**12.81**	**9.74**	**5.31**	**11.08**	**6.81**	**13.41**
	(10.09–13.65)	**(3.46–4.61)**	**(9.75–12.46)**	**(10.44–17.20)**	**(8.59–11.19)**	**(4.14–6.42)**	**(9.61–13.40)**	**(5.65–8.10)**	**(11.42–15.63)**
1998–2002	**13.47**	**4.41**	**13.89**	**15.10**	**11.18**	**5.27**	**14.01**	**8.26**	**15.54**
	(9.73–18.09)	**(3.27–5.80)**	**(10.77–18.01)**	**(9.54–28.06)**	**(8.70–14.80)**	**(3.11–8.06)**	**(10.46–20.70)**	**(5.72–11.49)**	**(11.35–21.00)**
2003–07	**15.31**	**4.82**	**17.71**	**17.54**	**12.79**	**5.19**	**17.64**	**9.98**	**17.82**
	(7.91–27.77)	**(2.62–8.45)**	**(10.55–30.07)**	**(6.45–60.12)**	**(7.67–22.34)**	**(1.80–13.09)**	**(9.61–37.49)**	**(4.86–19.23)**	**(9.51–32.68)**
Females									
1968–72	3.87	1.21	–	6.27	4.03	–	2.62	1.34	–
1973–77	4.63	1.44	2.80	5.93	4.22	1.83	3.20	1.73	6.00
1978–82	5.95	1.71	3.72	6.17	4.52	2.27	3.92	2.23	6.36
1983–87	6.41	2.07	4.79	6.79	5.16	2.78	4.74	2.87	6.99
1988–92	7.30	2.49	5.89	8.85	6.13	3.24	5.77	3.70	8.08
1993–97	**8.37**	**2.99**	**7.28**	**11.36**	**7.29**	**3.78**	**7.03**	**4.77**	**9.09**
	(6.02–11.86)	**(2.55–3.52)**	**(6.07–8.38)**	**(8.95–15.28)**	**(6.23–8.89)**	**(3.17–4.35)**	**(6.06–8.19)**	**(3.96–5.73)**	**(7.43–12.43)**
1998–2002	**9.54**	**3.58**	**9.01**	**14.57**	**8.74**	**4.42**	**8.56**	**6.15**	**10.11**
	(4.62–20.68)	**(2.66–4.95)**	**(6.21–12.19)**	**(8.54–27.27)**	**(6.33–13.15)**	**(3.08–5.91)**	**(6.38–11.49)**	**(4.40–8.71)**	**(6.75–18.98)**
2003–07	**10.89**	**4.31**	**11.09**	**18.70**	**10.71**	**5.22**	**10.30**	**7.98**	**11.13**
	(2.35–54.22)	**(2.36–8.17)**	**(5.37–20.68)**	**(5.76–65.79)**	**(5.41–23.70)**	**(2.59–9.66)**	**(5.73–18.54)**	**(4.09–15.76)**	**(4.65–37.61)**

model which smooths effects on each time scale, preventing parameter estimates from differing too much from those in adjacent time bands. The expected value for each effect is based on an extrapolation from its two immediate predecessors. The autoregressive model extrapolates period and cohort effects forward to make projections for rates in future periods. (Age effects are not extrapolated since the age groups of interest in future periods do not change.) Problems in identifying and interpreting individual parameters, caused by the linear relationship between age, period, and cohort effects in these models, do not affect projected rates.

For fitted and projected age-standardized rates samples of 8000 were drawn from the posterior distribution. These samples are summarized by their median, and 90% credible intervals are calculated from the 5th and 95th percentiles, after excluding the initial 500 iterations as "burn-in" [12]. Further details regarding the implementation of the Bayesian model are contained in the Appendix. This method has been compared with three alternative models for both incidence and mortality data, and a variety of different cancer sites by comparing the performance of empirical projections [13]. Overall, the Bayesian projections outperformed all other methods considered. This method is also robust – it was found to work well in situations where other approaches failed, such as when the numbers of observed cases are very small.

Results

For each of the four neoplastic groups age-standardized rates were calculated from the fitted age-specific rates using the world population [2] for ages 0–74. Tables 2–5 present standardized rates for periods in which data were observed (normal font) and projected rates for the next three periods (bold). Ninety percent credible intervals for the projections are given in parentheses. As the length of projection increases so does the associated uncertainty, and this is reflected by the width of the credible intervals.

NHL incidence shows increasing trends in all registries, and these trends are projected to continue into the future (with the exception of Osaka for males) (Table 2). Particularly high rates are predicted by 2003–07 in Utah for males (17.82/100,000) and females (11.13/100,000), Denmark for males (17.71/100,000) and Israel for females (18.70/100,000), reflecting percentage increases from 1988–92 of up to 111%. Comparatively low observed rates for females in Slovenia are expected to increase by 116% in the same time period. When Hodgkin's disease and NHL were combined and

Table 3. Smoothed and projected age-standardized rates with 90% credible intervals for Hodgkin's disease

	Alberta	Bombay	Denmark	Israel	New Zealand	Osaka	Oxford	Slovenia	Utah
Males									
1963–67	3.27	0.80	3.11	–	3.13	–	3.15	–	–
1968–72	3.12	1.00	2.93	2.45	2.92	–	3.05	2.41	–
1973–77	2.98	1.28	2.73	2.42	2.73	0.56	2.91	2.21	1.93
1978–82	2.82	1.19	2.61	2.51	2.44	0.51	2.73	2.12	1.99
1983–87	2.70	1.18	2.60	2.69	2.14	0.47	2.57	2.11	2.04
1988–92	2.63	1.22	2.69	2.93	1.87	0.45	2.45	2.16	2.08
1993–97	**2.59**	**1.27**	**2.79**	**3.21**	**1.67**	**0.45**	**2.33**	**2.24**	**2.13**
	(2.12–3.15)	**(0.84–1.99)**	**(2.40–3.40)**	**(2.72–3.78)**	**(1.29–2.07)**	**(0.35–0.58)**	**(1.92–2.82)**	**(1.77–2.88)**	**(1.62–2.77)**
1998–2002	**2.55**	**1.33**	**2.92**	**3.52**	**1.49**	**0.46**	**2.23**	**2.37**	**2.17**
	(1.79–3.68)	**(0.53–3.71)**	**(2.15–4.32)**	**(2.58–4.79)**	**(0.90–2.24)**	**(0.30–0.72)**	**(1.55–3.18)**	**(1.55–3.77)**	**(1.36–3.43)**
2003–07	**2.53**	**1.43**	**3.05**	**3.84**	**1.35**	**0.50**	**2.12**	**2.56**	**2.21**
	(1.27–5.07)	**(0.20–11.89)**	**(1.65–6.54)**	**(2.09–7.02)**	**(0.51–3.08)**	**(0.22–1.16)**	**(1.04–4.32)**	**(1.15–6.10)**	**(0.96–5.11)**
Females									
1963–67	1.75	0.44	2.00	–	1.55	–	1.38	–	–
1968–72	1.96	0.48	1.90	2.36	1.62	–	1.50	1.50	–
1973–77	1.94	0.51	1.76	2.16	1.80	0.31	1.63	1.39	3.50
1978–82	1.76	0.53	1.65	2.12	1.81	0.25	1.78	1.33	2.96
1983–87	1.66	0.55	1.59	2.29	1.67	0.23	1.97	1.31	2.53
1988–92	1.75	0.58	1.57	2.66	1.42	0.23	2.22	1.33	2.15
1993–97	**1.81**	**0.61**	**1.55**	**3.05**	**1.26**	**0.24**	**2.50**	**1.36**	**1.83**
	(1.25–3.01)	**(0.48–0.78)**	**(1.29–1.92)**	**(2.49–4.03)**	**(0.78–1.83)**	**(0.16–0.35)**	**(2.04–3.11)**	**(1.03–1.82)**	**(1.39–2.37)**
1998–2002	**1.88**	**0.64**	**1.53**	**3.41**	**1.15**	**0.27**	**2.81**	**1.41**	**1.58**
	(0.89–5.49)	**(0.42–0.99)**	**(1.09–2.32)**	**(2.28–6.05)**	**(0.44–2.41)**	**(0.14–0.53)**	**(1.96–4.22)**	**(0.89–2.38)**	**(0.98–2.45)**
2003–07	**1.95**	**0.66**	**1.52**	**3.74**	**1.06**	**0.33**	**3.17**	**1.47**	**1.36**
	(0.38–16.63)	**(0.30–1.51)**	**(0.75–3.40)**	**(1.64–11.20)**	**(0.15–4.91)**	**(0.11–1.22)**	**(1.58–6.83)**	**(0.63–3.79)**	**(0.56–3.10)**

reanalysed, similar increasing trends were still observed and projected, confirming that increases in reported cases of NHL are not simply due to misclassification with Hodgkin's disease.

Hodgkin's disease incidence appears to be stable or decreasing in most of the registries considered (Table 3). Exceptions are Israel (males and females) and Oxford (females), where the high incidence rates observed for the period 1988–92 are expected to increase by up to 43% by the period 2003–07. The very low rates observed in Osaka are expected to increase at a similar rate among females. Decreasing trends observed in certain countries such as New Zealand (males and females) and Utah (females) are likely to continue.

Generally increasing trends are also observed in incidence rates of multiple myeloma and, on the whole, these trends are expected to continue up to 2003–07 (Table 4). Exceptions are Osaka (males) and Oxford (females), for which rates are expected to peak in 1993–97 and 1998–2002 respectively, then decline. By 2003–07 the highest rates are expected to be in Utah and Oxford for males, and in New Zealand and Alberta for females. The most striking relative increases in projected rates are expected in females. In Alberta, Denmark, and New Zealand percentage increases in incidence rates of about 40% are expected between 1988–92 and 2003–07. Decreasing trends are observed and expected to continue in Israel (males and females) and Utah (females).

For most of the registries considered, leukemia incidence rates appear to be relatively stable and even decreasing in some cases (Table 5). Exceptions are Oxford and, to a lesser extent, New Zealand, where observed and projected rates show a strong upward trend. Projected rates for Oxford reach 13.13/100,000 for males by 2003–07, and 11.63/100,000 for females, reflecting increases from 1988–92 of 79% and 119%, respectively. Smoothed observed rates in New Zealand of 8.23/100,000 and 5.67/100,000 for males and females in 1988–92 are projected to increase by 22% and 29%, respectively, by 2003–07.

Discussion

The striking observation from this analysis concerns the consistency of the increase in NHL between 1968 and 1992, which was reported in all nine cancer registries for both men and women, and in the increase in projected rates up to 2007. The other notable result includes the modest increase which was observed in most regions for multiple myeloma.

Table 4. Smoothed and projected age-standardized rates with 90% credible intervals for multiple myeloma

	Alberta	Bombay	Denmark	Israel	New Zealand	Osaka	Oxford	Slovenia	Utah
Males									
1963–67	1.40	0.44	2.24	–	2.16	–	1.67	–	–
1968–72	1.73	0.55	2.23	1.76	2.31	–	1.92	0.98	–
1973–77	2.07	0.70	2.20	1.99	2.45	0.83	2.20	1.25	1.97
1978–82	2.40	0.81	2.24	2.14	2.59	0.97	2.46	1.55	2.35
1983–87	2.76	0.87	2.32	2.11	2.79	1.09	2.73	1.82	2.76
1988–92	3.02	0.96	2.46	1.98	2.93	1.14	3.00	2.06	3.16
1993–97	**3.28**	**1.05**	**2.62**	**1.85**	**3.09**	**1.16**	**3.27**	**2.25**	**3.53**
	(2.52–4.03)	**(0.79–1.48)**	**(2.27–3.11)**	**(1.34–2.32)**	**(2.58–3.67)**	**(0.92–1.40)**	**(2.73–3.95)**	**(1.74–2.89)**	**(2.69–4.63)**
1998–2002	**3.53**	**1.13**	**2.81**	**1.73**	**3.26**	**1.10**	**3.57**	**2.36**	**3.87**
	(2.07–5.18)	**(0.65–2.29)**	**(2.10–3.93)**	**(0.92–2.73)**	**(2.30–4.53)**	**(0.71–1.60)**	**(2.55–5.08)**	**(1.48–3.70)**	**(2.39–6.27)**
2003–07	**3.75**	**1.21**	**3.01**	**1.62**	**3.45**	**1.01**	**3.86**	**2.37**	**4.17**
	(1.37–8.10)	**(0.38–5.01)**	**(1.67–5.87)**	**(0.45–4.25)**	**(1.75–6.54)**	**(0.43–2.12)**	**(2.02–7.58)**	**(1.02–5.55)**	**(1.74–10.00)**
Females									
1963–67	1.36	0.47	1.48	–	1.46	–	0.99	–	–
1968–72	1.51	0.55	1.46	1.66	1.58	–	1.18	1.00	–
1973–77	1.64	0.65	1.47	1.63	1.69	0.58	1.37	1.05	2.04
1978–82	1.76	0.75	1.54	1.62	1.80	0.68	1.57	1.13	1.95
1983–87	1.89	0.82	1.71	1.59	1.96	0.73	1.82	1.24	1.86
1988–92	2.04	0.88	1.88	1.54	2.13	0.78	2.14	1.37	1.71
1993–97	**2.22**	**0.92**	**2.05**	**1.52**	**2.32**	**0.84**	**2.43**	**1.48**	**1.52**
	(1.76–2.77)	**(0.69–1.19)**	**(1.73–2.49)**	**(1.20–1.89)**	**(1.95–2.80)**	**(0.61–1.10)**	**(1.99–3.03)**	**(1.15–1.98)**	**(1.10–2.04)**
1998–2002	**2.42**	**0.97**	**2.22**	**1.51**	**2.54**	**0.90**	**2.56**	**1.56**	**1.29**
	(1.58–3.61)	**(0.56–1.50)**	**(1.56–3.29)**	**(0.97–2.31)**	**(1.84–3.59)**	**(0.46–1.56)**	**(1.77–3.91)**	**(1.01–2.67)**	**(0.75–2.12)**
2003–07	**2.62**	**1.00**	**2.40**	**1.50**	**2.77**	**0.94**	**2.46**	**1.62**	**1.03**
	(1.16–5.62)	**(0.35–2.35)**	**(1.16–5.17)**	**(0.65–3.45)**	**(1.50–5.46)**	**(0.26–3.12)**	**(1.22–5.48)**	**(0.71–4.46)**	**(0.39–2.61)**

Table 5. Smoothed and projected age-standardized rates with 90% credible intervals for leukemia

	Alberta	Bombay	Denmark	Israel	New Zealand	Osaka	Oxford	Slovenia	Utah
Males									
1968–72	7.06	2.81	–	6.52	6.89	–	4.94	5.28	–
1973–77	7.23	3.04	6.95	6.52	7.03	4.34	5.03	5.54	7.80
1978–82	7.47	3.30	7.48	6.38	7.13	4.83	5.34	5.77	7.77
1983–87	7.60	3.56	8.11	6.17	7.64	5.18	6.00	6.04	7.66
1988–92	7.39	3.79	8.20	6.05	8.23	5.37	7.35	6.34	7.40
1993–97	**7.27**	**4.00**	**8.33**	**5.96**	**8.78**	**5.53**	**8.88**	**6.66**	**7.13**
	(5.89–8.40)	**(3.53–4.54)**	**(6.81–9.58)**	**(5.19–6.89)**	**(7.54–10.56)**	**(4.79–6.27)**	**(7.31–11.77)**	**(5.65–7.79)**	**(5.93–8.44)**
1998–2002	**7.14**	**4.20**	**8.45**	**5.88**	**9.35**	**5.65**	**10.77**	**6.99**	**6.85**
	(4.69–9.56)	**(3.27–5.40)**	**(5.52–11.36)**	**(4.46–7.91)**	**(6.81–13.69)**	**(4.21–7.37)**	**(7.21–18.96)**	**(5.11–9.47)**	**(4.80–9.42)**
2003–07	**7.03**	**4.43**	**8.59**	**5.81**	**10.08**	**5.79**	**13.13**	**7.34**	**6.57**
	(3.14–13.22)	**(2.65–7.47)**	**(3.69–16.43)**	**(3.37–10.52)**	**(5.19–21.37)**	**(3.20–10.08)**	**(5.57–39.75)**	**(4.00–13.50)**	**(3.24–12.50)**
Females									
1968–72	4.64	2.40	–	5.22	4.53	–	4.02	4.72	–
1973–77	4.97	2.50	4.95	4.98	4.75	3.28	3.77	4.61	5.09
1978–82	5.27	2.57	5.15	4.76		3.45	3.74	4.32	5.18
1983–87	5.51	2.68	5.38	4.45	5.21	3.53	4.03	3.99	5.27
1988–92	5.48	2.77	5.31	4.09	5.67	3.58	5.30	3.81	5.35
1993–97	**5.50**	**2.86**	**5.27**	**3.78**	**6.15**	**3.65**	**6.87**	**3.58**	**5.49**
	(4.33–6.48)	**(2.45–3.29)**	**(4.33–6.10)**	**(3.20–4.36)**	**(5.32–7.36)**	**(3.13–4.21)**	**(5.08–10.35)**	**(2.94–4.73)**	**(4.43–6.67)**
1998–2002	**5.50**	**2.96**	**5.25**	**3.49**	**6.67**	**3.74**	**8.93**	**3.35**	**5.70**
	(3.41–7.60)	**(2.19–3.90)**	**(3.48–7.11)**	**(2.52–4.62)**	**(5.00–9.57)**	**(2.73–4.98)**	**(4.71–21.06)**	**(2.29–5.76)**	**(3.85–8.29)**
2003–07	**5.53**	**3.08**	**5.26**	**3.25**	**7.29**	**3.85**	**11.63**	**3.13**	**6.11**
	(2.24–10.66)	**(1.67–5.43)**	**(2.38–9.96)**	**(1.71–5.74)**	**(3.98–14.60)**	**(2.02–7.03)**	**(3.00–62.76)**	**(1.43–9.11)**	**(2.89–12.96)**

Table 6. Percentage increases in fitted incidence rates for NHL, stratified by age group and overall (ages 0–74), for periods observed (smoothed) and periods projected

	Alberta	Bombay	Denmark	Israel	New Zealand	Osaka	Oxford	Slovenia	Utah	Weighted average
Males										
Observed	1969–72 to 1988–92	1968–72 to 1988–92	1973–76 to 1988–92	1967–71 to 1988–92	1968–71 to 1988–92	1973–77 to 1988–92	1968–72 to 1988–92	1968–72 to 1988–92	1973–77 to 1988–92	–
Age group										
0–19	73.08	−13.83	95	−10.39	48.35	35.82	87.94	102.38	26.73	–
20–49	85.42	64.699	117.09	26.04	63.01	24.75	127.69	130.25	56.22	–
50–74	119.83	121.59	84.08	59.46	66.44	56.09	128.63	148.69	83.10	–
Overall	**103.54**	**76.10**	**93.61**	**40.42**	**64.15**	**44.51**	**125.58**	**135.71**	**69.76**	–
Projected	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07
Age group										
0–19	43.40	−28.37	68.33	21.98	42.02	−5.66	80.24	59.12	18.21	23.91
20–49	36.84	21.004	103.72	37.99	43.08	−0.68	79.69	68.70	35.50	48.28
50–74	53.47	49.092	97.82	80.66	54.61	−0.18	112.47	84.45	66.21	61.61
Overall	**48.07**	**33.52**	**101.48**	**62.86**	**51.00**	**−1.33**	**102.06**	**77.90**	**54.82**	**55.40**
Females										
Observed	1969–72 to 1988–92	1968–72 to 1988–92	1973–76 to 1988–92	1967–71 to 1988–92	1968–71 to 1988–92	1973–77 to 1988–92	1968–72 to 1988–92	1968–72 to 1988–92	1973–77 to 1988–92	–
Age group										
0–19	73.74	106.12	87.60	15.95	119.19	98.26	81.38	188.37	21.49	–
20–49	89.70	98.26	115.38	38.20	60.83	59.89	112.40	181.06	15.93	–
50–74	86.88	110.66	110.04	44.95	42.86	84.08	126.83	173.24	48.38	–
Overall	**88.63**	**105.79**	**110.36**	**41.15**	**52.11**	**77.05**	**120.23**	**176.12**	**34.67**	–
Projected	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07	1988–92 to 2003–07
Age group										
0–19	38.41	72.28	61.67	90.89	136.34	87.94	72.24	125.00	28.94	82.51
20–49	37.49	74.40	76.03	90.01	83.62	67.54	52.84	117.13	36.85	72.48
50–74	53.17	71.45	93.64	122.64	60.30	48.39	89.46	111.61	40.94	79.40
Overall	**49.18**	**73.09**	**88.29**	**111.30**	**74.71**	**61.11**	**78.51**	**115.68**	**37.75**	**78.78**

The percentage increases in both observed and projected NHL rates were further explored by calculating them within three age bands (0–19, 20–49, and 50–74 years) (Table 6). For males we see that percentage increases, in both observed and projected incidence rates, are generally higher in older age groups. This is reflected by the average percentage increases for projections, which are three times higher in the 50–74 age group compared to the 0–19 age group (62% *vs* 24%). The pattern is not so clear for females, with percentage increases in both observed and projected rates often decreasing with increasing age group. However, for the three registries with the highest projected rates for females by 2003–07 (Israel, Utah, and Denmark), the greatest observed and projected percentage increases do tend to occur in the age band 50–74. We also note that the overall average projected increase is higher for females (79%) than males (55%).

For other lymphoid neoplasms, past rates for Hodgkin's disease and leukemia have been relatively stable and may be expected to remain so, whereas some relatively moderate increases in multiple myeloma appear to be occurring. The most notable exception to these trends is for leukemias in Oxford, where large increases are projected between 1992 and 2007 of 78% in men (from 7.35 to 13.13) and 119% among women (from 5.30 to 11.63). Inspection of age-specific rates for Oxford suggests that increases across all age groups in the last two periods of observed data (1983–87 and 1988–92) may explain the increasing trends in projected rates. Smoothed age-standardized male leukemia rates increase by 12% between 1978–82 and 1983–87, and by a further 23% by 1988–92. These figures compare with increases of 2% and 6% between the first three periods of observed data. The corresponding female leukemia rates increase by 8% between 1978–82 and 1983–87, and

by 32% between 1983–87 and 1988–92, while rates actually decrease between the first three periods of observed data. The elevated rate of increase observed for both sexes in the periods 1983–87 and 1988–92 is carried forward by the autoregressive model, and the relative increases between the last period of observed data and the three periods of projected data remains steady at 21% for males and 30% for females. While the observed increases in registered incidence may reflect real changes in disease incidence, the possibility of improved diagnosis or reporting should not be excluded, and the projections should be treated with due caution.

Consistency of the increasing NHL rates in all nine populations adds further weight to this, reflecting a real increase in disease incidence and not an artefact of diagnostic trends or ascertainment. On further examination both age–period and age–cohort models gave reasonable fits to the data in most cancer registries, indicating that the increasing incidence is due to a mixture of period and cohort effects (data not shown). The underlying increase in the incidence is likely to be due to one or more exposures with a wide and increasing distribution, although more prevalent in western as opposed to Asian populations. Candidates for such an agent include increasing exposure to ultraviolet light as well as increasing exposure to other possible immunostimulatory agents including solvents and pesticides. Regarding future projections to 2007, the underlying assumption is that the trends in exposure agents responsible for this increase in NHL incidence will remain stable. While cohort effects are often behavioral and tend to be relatively stable, period effects are liable to change and the validity of these assumptions is therefore unknown. However they do indicate that, if true, the incidence of NHL is likely to continue increasing rapidly, especially in those countries which already have a high incidence.

Appendix

For each age group a ($a = 1,\ldots,A$) and period p ($p = 1,\ldots,P$) we have the observed number of cases d_{ap} and the number of person-years n_{ap}. We assume that d_{ap} has a Poisson distribution and that its mean μ_{ap} can be modeled as follows:

$$\log(\mu_{ap}) = \log(n_{ap}) + \alpha_a + \beta_p + \gamma_c.$$

The cohort c ($c = 1,\ldots,C$) indicates the approximate year of birth and is fixed by a and p ($c = A + p - a$). In our analyses A is always 9 but P and C depend on the number of years for which data are available. We define prior distributions for age, period, and cohort effects which smooth each point on its two preceding points. Note that the first two effects on each scale are given non-informative priors.

$$\alpha_1 \sim \text{Normal}(0, 1000000 \cdot \sigma_\alpha^2)$$
$$\alpha_2 \sim \text{Normal}(0, 1000000 \cdot \sigma_\alpha^2)$$
$$\alpha_a|\alpha_{1,\ldots,a-1} \sim \text{Normal}(2\alpha_{a-1} - \alpha_{a-2}, \sigma_\alpha^2) \quad a > 2$$

$$\beta_1 \sim \text{Normal}(0, 1000000 \cdot \sigma_\beta^2)$$
$$\beta_2 \sim \text{Normal}(0, 1000000 \cdot \sigma_\beta^2)$$
$$\beta_p|\beta_{1,\ldots,p-1} \sim \text{Normal}(2\beta_{p-1} - \beta_{p-2}, \sigma_\beta^2) \quad p > 2$$

$$\gamma_1 \sim \text{Normal}(0, 1000000 \cdot \sigma_\gamma^2)$$
$$\gamma_2 \sim \text{Normal}(0, 1000000 \cdot \sigma_\gamma^2)$$
$$\gamma_e|\gamma_{1,\ldots,c-1} \sim \text{Normal}(2\gamma_{c-1} - \gamma_{c-2}, \sigma_\gamma^2) \quad c > 2$$

This model is not based on parametric assumptions, and the hyperparameters σ_α^2, σ_β^2, and σ_γ^2, which control the degree of smoothing, are given non-informative priors so that results reflect purely evidence from the data. The model was implemented using the BUGS software [12] to draw Markov chain Monte Carlo samples of age-specific and age-standardized rates for each period. The median and percentiles (5th, 95th) of the age-standardized rates (excluding the initial 500 iterations) are tabulated in the results section.

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