Statin Use and Risk of Lymphoid Neoplasms: Results from the European Case-Control Study EPILYMPH

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Abstract

Background: **Statins, drugs used to treat dyslipidemia, may have anticancer properties. We have evaluated lymphoma risk associated with regular statin use in an international case-control study.**

Methods: **This case-control study included 2,362 cases of incident B- and T-cell lymphoma from Czech Republic, France, Germany, Ireland, Italy, and Spain and 2,206 hospital or population controls. Information on drug use, diagnosis at admission (for hospital controls), and putative risk factors for lymphoma was collected with personal interviews. Hospital controls admitted for diseases possibly entailing use of statins were excluded from the analysis.**

Results: **The odds ratio for regular statin use was 0.61 (95% confidence interval, 0.45-0.84); all major lymphoma subtypes showed similarly decreased risks. Decreased risks were observed in all centers. Duration of statin use was not associated with a greater reduction in the risk of lymphoma. Use of other lipid lowering drugs, such as fibrates, did not significantly modify the risk of lymphoma (odds ratio, 0.75; 95% confidence interval, 0.44-1.27).**

Conclusion: **Statin use was associated with an important reduction in lymphoma risk, adding to the growing evidence of anticancer properties of this group of drugs. These results are reassuring for the increasing number of patients taking statins on a regular basis.** (Cancer Epidemiol Biomarkers Prev 2006;15(5):921–5)

Introduction

Statin-class drugs (i.e., lovastatin, simvastatin, atorvastatin, fluvastatin, pravastatin, cerivastatin, and rosuvastatin) were first marketed in 1987 and are now widely used for the treatment of hypercholesterolemia and for prevention of ischemic heart disease in high-risk patients. Statins reduce cholesterol synthesis in the liver through the inhibition of 3-hydroxy-3-methylglutaryl CoA reductase and the blockade of the mevalonate pathway. The use of statins has experienced an average 36% annual increase in Europe during the period of 1997 to 2002, and they are now among the best-selling drugs in Western countries (1). Statins are generally well tolerated but may cause potentially serious side effects, such as liver dysfunction and rhabdomyolysis (2).

During preclinical and clinical development of statin-class drugs, animal studies showed an increased risk of cancer in rodents exposed to statins at doses similar to those used in humans (3). This raised an initial concern on the human carcinogenicity of statins. Interestingly, the commonly used statin pravastatin caused malignant lymphomas in mice at doses that ranged from 0.5- to 5-fold the maximum recommended dose for humans (3). In addition, subjects expressing the glucose-6-phosphate dehydrogenase-deficient phenotype, a genetic condition leading to reduced availability of NADPH required for 3-hydroxy-3-methylglutaryl CoA reductase activity and therefore to decreased cholesterol synthesis, were found to have an increase in deaths from malignant lymphoma (4).

Two randomized clinical trials in humans have subsequently found a suggestion of an increased incidence of cancer among subjects treated with statins. In the Cholesterol and Recurrent Events Trial, breast cancer was more common among users of pravastatin (1 case among placebo receivers and 12 cases among pravastatin receivers; $P = 0.002$), but there were no significant differences among lymphoma and leukemia incidence (10 cases in the placebo group and 8 in pravastatin group (5). In the Prospective Study of Pravastatin in the Elderly at Risk study, a significant 25% increase in the incidence of any cancer was observed (6).

However, most studies in humans have not found an increased risk of cancer in statin users, and some even suggest a decreased risk. Three reviews of the major published statin clinical trials (7-9) showed no modification of the risk of cancer, although the follow-up was short (3-5 years). The 10-year follow-up of the Scandinavian Simvastatin Survival Study showed a nonsignificant 20% decreased risk of cancer among those originally enrolled in the simvastatin arm of the randomized trial (10). A recent case-control study conducted in Israel found a significantly reduced risk of colorectal cancer among subjects that had used statins during at least 5 years

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J. Fortuny and S. de Sanjosé had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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(11). Some studies have assessed the relation of statins with lymphoma risk. A population-based cohort study showed a significant 14% reduction in the incidence of any cancer among users of statins and a nonsignificant 12% reduction in the risk of lymphatic and hematopoietic cancers (12). A population-based case-control study found a suggestion of a decreased risk for several subtypes of lymphoma among users of any cholesterol-lowering drug (13). Finally, one population-based case-control study found an overall 50% decreased risk of non-Hodgkin's lymphoma among users of statins, although the association did not exist for long-term users of statins (14).

In western countries, lymphomas are, as a whole, the third most common malignancy in women and the fifth in men (15). Alterations in immune competence and some viral infections are strongly related with an increased risk of lymphoma, but information on other risk factors is scarce, and most cases have no known cause.

To study the possible relation of chronic statin use with the risk of lymphoma, we have used the data of an international case-control study designed to assess the effect of several putative risk factors for lymphomas.

Materials and Methods

The EPILYMPH multicenter case-control study was carried out in 6 countries and 22 centers (6 centers in Germany, 2 in Italy, 4 in Spain, 6 in Ireland, 3 in France, and 1 in Czech Republic) from 1998 to 2004. A common core protocol and interview were used in all countries. The study includes 2,362 incident lymphoma cases and 2,465 controls.

Cases were defined as all consecutive patients having a first diagnosis of lymphoid malignancy during the study period in the participating hospitals. The diagnosis of lymphoma was verified by histology, and 99% of them were supplemented by immunohistochemistry tests and flow cytometry. Cases were categorized according to the WHO Classification for Neoplastic Diseases of the Lymphoid Tissues and included all B-cell, T-cell, and natural killer cell neoplasms as well as Hodgkin's lymphoma (16). Subjects with a diagnosis of uncertain malignant potential, such as post-transplant lymphoproliferative disorder or monoclonal gammapathies of undetermined significance, were excluded. The distribution of the 2,362 cases by major histology entities was 1,858 B-cell lymphomas (including 281 multiple myelomas, 410 chronic lymphocytic leukemias, 493 diffuse large B-cell lymphomas, 251 follicular lymphomas, and 423 other and unspecified hystologies), 136 T-cell lymphomas, 289 Hodgkin's lymphomas, and 79 other and unspecified lymphomas.

Controls were identified at the time of diagnosis of the cases and were sampled from the general population based on census lists in Italy and Germany. In the other countries, controls were recruited from the same hospital as the cases. In all instances, controls were frequency matched to the cases by age (±5 years), gender, and study center. In hospital-based studies, controls were excluded if the main reason for the hospitalization at the time of recruitment was cancer, organ transplant, and/or systemic infection.

Informed consent was obtained from all subjects before enrollment, and the Institutional Review Boards of participating centers approved the study. Overall participation rate was 87% for cases and 68% for controls. Refusal to participate ranged from 7% to 18% among cases, 34% to 56% among population controls, and 4% to 40% among hospital controls.

Standardized interviews were conducted by trained personnel to collect data on sociodemographic characteristics, lifetime medical history of common diseases, family history of cancer and genetic diseases, smoking, alcohol, lifetime X-ray exposure, regular use of medication, UV light exposure, and lifetime occupational history.

A wide range of admission diagnoses for hospital controls were included in the study, and some of them may lead to higher use of statins than what would be expected in the general population. To deal with this potential limitation, two groups of hospital controls were a priori defined based on their probability of being statin users. A ''high-probability'' group (group 1) consisted of control subjects whose admission diagnoses were either directly related to the use of lipid-lowering drugs (i.e., hyperlipidemia and coronary heart disease), were a risk factor for coronary heart disease (i.e., metabolic syndrome: obesity, diabetes mellitus, and hypertension), or were related to gall bladder stones. A ''similar-to-general-population'' group (group 2) included controls whose admission diagnoses were deemed unrelated to the use of statins and other hypolipemiants. Control group 1 was excluded from analysis unless otherwise specified (n = 259). Thus, of the 2,455 initial controls, 1,046 were population based, and 1,419 were hospital based. Of the later, 1,160 had admission diagnoses unrelated to statin use. Questionnaire information on lifetime drug consumption was available for cases and controls. Chronic use was defined as usage once per week for a year or more. Participants in the study reported a total of 9,809 separate instances of medication use. These were manually recoded into active principles of interest by a clinical pharmacologist who was unaware of the case/control status of the subjects. Among all drugs reported in the questionnaire, 269 were lipid-lowering drugs, and these were divided into statins and other lipid-lowering drugs. Statins were further coded as pravastatin and other statins. Statin use is likely to be associated to nonsteroidal anti-inflammatory drug use (i.e., aspirin) because both are commonly prescribed to patients with cardiovascular disease. It is well known that aspirin use is protective for several cancers. To adjust for potential confounding, a variable indicating whether the subject had ever been a regular user of any nonsteroidal anti-inflammatory drug, including aspirin, was created.

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) as the measure of association between specific variables and the occurrence of lymphoma. All models were adjusted for age (in quintiles), gender, and center. Duration of statin use was categorized based on the tertiles of years of statin use among the controls. $P_{\text{linear trend}}$ for statin exposure was computed excluding the nonuser category to assess the trend only among exposed subjects. Subjects who had smoked al least one cigarette a day for at least 6 months were considered regular smokers. To adjust for potential socioeconomic confounding, an education variable with three levels (i.e., low, medium, and high) was used.

The data were analyzed using Stata 8.2 Special Edition.

Results

Table 1 summarizes the sociodemographic characteristics of our study population. No statistically significant differences were seen among cases and controls for these variables. Statin drugs had been regularly used by 3.1% of the cases and 5.4% of controls (11.6% of group 1 controls, 4.3% of group 2 controls, and 5.2% of population controls). Although the abovementioned hospital control group 1 had a higher prevalence of statin use than population-based control group ($P < 0.0001$), prevalence of statin use was similar among hospital control group 2 and population-based controls ($P = 0.84$).

Table 2 summarizes the risk of lymphoma among lipid lowering drug users. The OR for regular statin use was 0.61 (95% CI, 0.45-0.84). We did not observe an inverse trend in lymphoma risk by duration of statin use. We found no evidence of a significant association between other lipid-lowering drug use with the risk of lymphoma (OR, 0.75; 95%

Table 1. Distribution of age, gender, country, and education among cases and controls

	Cases *n* (%), *N* = 2,362	Controls *n* (%), *N* = 2,465
Gender		
Female	1,038 (44)	1,143 (46)
Male	1,324 (56)	1,322 (54)
Age (quintiles), y		
<41	487 (21)	510 (21)
41-54	452 (19)	495 (20)
55-63	474 (20)	488 (20)
64-71	527 (22)	529 (21)
>71	420 (18)	443 (18)
Missing	2 (0.1)	0 (0.0)
Country		
Germany	710 (30)	710 (29)
Italy	262 (11)	336 (14)
Spain	591 (25)	631 (26)
France	298 (13)	276 (11)
Ireland	208 (9)	208 (8)
Czech Republic	293 (12)	304 (12)
Highest school level		
Secondary school	1,084 (46)	1,122 (46)
High school	926 (39)	991 (40)
University	331 (14)	338 (14)
Missing	21 (1)	14 (1)

CI, 0.44-1.27). Risk estimates for pravastatin use (7 cases and 16 controls) showed no significant difference from the risk estimates for all statins (OR, 0.35; 95% CI, 0.14-0.86). When educational level (as a marker of socioeconomic status) was added to the model, the risk estimates for statin use remained unchanged (OR, 0.62; 95% CI, 0.46-0.85). Neither adjustment for smoking status (OR, 0.60; 95% CI, 0.44-0.82) nor adjustment for nonsteroidal anti-inflammatory drug use (OR, 0.65; 95% CI, 0.48-0.89) changed the risk estimates for statin use.

When control group 1 was included in the analysis, statin use was also associated with a decreased risk of lymphoma (OR, 0.55; 95% CI, 0.41-0.73).

Figure 1 shows the risk of lymphoma among users of statins by type of study and country, using population-based and non–statin-related controls (group 2) only. Statin use was inversely associated with risk of lymphoma both among population and hospital-based studies (OR, 0.53; 95% CI, 0.33-0.85 and OR, 0.72; 95% CI, 0.48-1.09, respectively). There was heterogeneity among countries for the effect of statins on lymphoma risk ($P_{\text{heterogeneity}} = 0.03$). The heterogeneity was not due to a different pattern between centers but rather to a different magnitude of the inverse association. A sensitivity analysis, excluding countries one by one, provided consistent evidence of a decreased risk of lymphoma in statin users (OR, 0.55-0.68, $P < 0.05$ for all).

Table 3 shows the risk of lymphoma subtypes in relation to statin use. Similar risk estimates were seen for all main histologic groups. The risk estimate for B-cell lymphomas was 0.61 (95% CI, 0.44-0.84). Similarly, T-cell lymphoma (OR, 0.74; 95% CI, 0.29-1.86) and Hodgkin's lymphoma (OR, 0.74; 95% CI, 0.26-2.07) were less frequent among regular statin users.

Discussion

In our study, statin use was associated with a reduced risk of lymphoma, with a similar reduction for all major histologic subtypes. Pravastatin, which was related to an increased risk of lymphoma in mice when given at low doses, was also associated with a reduced risk of lymphoma in this study. Adjustment for smoking and nonsteroidal anti-inflammatory drug use did not alter these risk estimates. Use of other lipid-lowering drugs (such as fibrates) was not associated with a significantly decreased risk of lymphoma. There were no significant differences in risk estimates between studies using hospital controls and population-based controls.

An association of statin drugs with cancer has been identified in several previous studies in *in vivo* models. Newman et al. reported several malignant neoplasias associated with the use of statins in animal studies before 1994 (3). Hepatocellular carcinomas, lymphomas, and thyroid carcinomas seemed more frequently among statin-treated animals. Additionally, a variety of benign proliferative lesions were also seen in rodents: pulmonary adenomas, stomach papillomas, hepatocellular adenomas, Harderian gland adenomas, and thyroid adenomas. The authors concluded that these drugs should be used with caution and that only patients at high short-term risk of coronary heart disease should have statins prescribed, as no evidence was available on the long-term risk-benefit balance for patients at low risk of coronary heart disease. However, 17 years after the first statins were marketed, neither a strong evidence of an increased risk of cancer among statin users nor a plausible biological explanation for their putative carcinogenicity have been proposed.

There was particular interest in the assessment of breast cancer risk among users of statins, as some studies had found a moderate increase in the incidence of this cancer (17, 18). Subsequent studies have not confirmed this increased risk (12), and some have even suggested a decreased risk of breast cancer among exposed women (19). On the other hand, there is growing experimental evidence of a number of pleiotropic effects of statins that have raised interest in using them as chemopreventive drugs in cancer intervention trials. Different

Table 2. Risk of lymphoma and use of statins or other hypolipemiants

	Basic model,* group 1† controls excluded		
	No. cases (%)	No. controls (%)	OR (95%CI)
Statin use			
Never	2,288 (97)	2,103 (95)	1.00 (reference)
Ever	74 (3)	103 (5)	0.61 (0.45-0.84)
Duration of statin use, y			
≤2	27 (1)	35 (2)	0.66 (0.40-1.10)
2-6.25	24 (1)	35 (2)	0.59 (0.35-1.00)
>6.25	17 (1)	24 (1)	0.61 (0.33-1.15)
$P_{\text{linear trend}} = 0.58$			
Missing	6	9	0.51 (0.18-1.46)
Other hypolipemiants use			
Never	2,333 (99)	2,177 (99)	1.00 (reference)
Ever	29 (1)	29 (1)	0.75 (0.44-1.27)

*Basic model includes matching variables age (quintiles), gender, and country.
†Group 1 includes hospital controls whose admission diagnoses were directly related to the use of statins (hypercholesterolemia, dyslipidemia, and coronary heart disease), risk factors for coronary heart disease (i.e., metabolic syndrome obesity, diabetes mellitus, and hypertension), and gallstones.

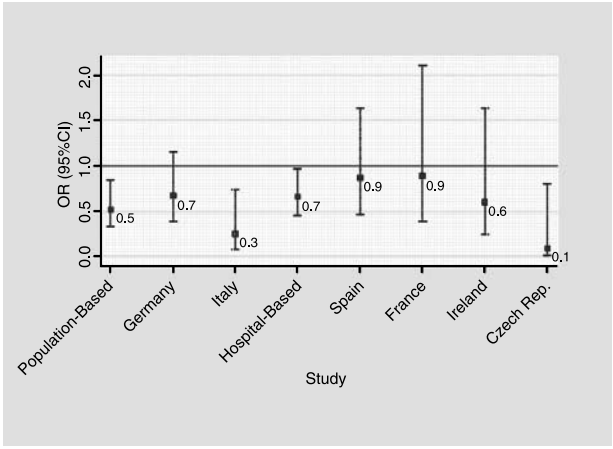

Figure 1. Risk of lymphoma and statin use by country and type of study. Model adjusted for age and gender. Group 1 controls excluded.

pathways by which statins could reduce cancer risk have been suggested and seem to involve blockade of the mevalonate pathway and the subsequent lack of posttranscriptional modification of apoptosis-inducing proteins, such as Bcl-2, Mcl-1, and nuclear factor-κB among others (20). This process ultimately favors apoptosis of cancer cells (21). These mechanisms have been specifically linked to apoptosis in multiple myeloma and other B-cell lymphomas (22-24). For other neoplasms, alternative mechanisms of statin anticancer activity have been suggested, involving inflammation or immunomodulation.

The EPILYMPH Study has several strengths: transnational setting, very large sample size, high-quality exposure and pathology assessment, and expert drug use evaluation. Nevertheless, our analysis has also several potential shortcomings. Hospital-based studies evaluating the effect of drugs on the risk of a given disease might be especially susceptible to selection bias. Controls drawn from a hospital may be on the average less healthy individuals than population controls and thus more prone to be regular drug users. Therefore, risk estimates from such studies may overestimate the protective effect of drugs and underestimate any increased risks associated to drug use. Our study included controls enrolled from hospitals (in Spain, France, Ireland, and Czech Republic) and from the general population (in Germany and Italy). We used population-based controls as the reference group in the estimation of the actual prevalence of lipid-lowering drug use in our population study base. The 5.1% prevalence of statin use among population controls was similar to that reported by other comparable studies (12, 17, 19). Our primary analysis only included controls with admission diagnoses unrelated to statin use and from population-based studies because prevalence of statin use was higher in the a priori defined hospital control group 1. There were relatively few controls included in group 1 (n = 259) compared with group 2 (n = 1,143) or the population-based controls (n = 1,046), and their exclusion did not affect either the precision of the risk estimates nor their value.

Lymphoma risk reductions associated with statin use showed significant heterogeneity across countries. However, a formal sensitivity analysis, excluding countries one by one, showed consistently statistically significant decreased risks for lymphoma in statin users (OR, 0.55-0.68). The Italian and Czech substudies were different from the rest of studies (i.e., the inverse association was stronger in these two countries). The overall risk of lymphoma for statin users was 0.76 (95% CI, 0.54-1.07) if both countries were excluded from the analysis. No differences in gender or age distribution existed between these two countries and the other four countries, and they did not use the same source of controls (Italians used population-based controls and Czechs hospital based). Despite heterogeneity, a protective effect of statin use was detected in all countries. The explanation for the observed heterogeneity, thus, remains unclear but could be related to different patterns in statin prescription among countries, genetic background of the population, and random variation because of small numbers in individual studies.

Recall bias is another potential threat to the validity of case-control study results. In our study, however, we do not expect it to differentially affect cases and controls, as patients are unlikely to relate lipid-lowering therapy to lymphoma risk. Moreover, the use of hospital controls greatly reduces the differences in recall, as both cases and controls are interviewed in similar conditions (i.e., when admitted to a hospital (25). In addition, statins are used on a chronic basis and most patients are not likely to suspend them once they have started the therapy, as cholesterol levels would rapidly increase to pretreatment levels. This is shown by the fact that only nine subjects were past users of statins. Recall bias is probably lower for drugs used on a daily basis than for drugs sporadically used or drugs suspended long time ago. However, a residual degree of misclassification cannot be completely ruled out, although it would probably tend to underestimate the observed protective effect of statin use, as cases are generally more prone to have a better recall, especially in population-based studies (25).

Bias due to an increased probability of hypercholesterolemia diagnosis, and statin treatment, because of medical consultation due to undiagnosed lymphoma (for cases) or to the condition that will ultimately lead to hospital admission (for controls) is possible in this kind of studies. To account for this bias, we did an alternative analysis, excluding drug use that took place during the year before the enrollment in the study and lymphoma risk estimates for statin users that were similar (OR, 0.64; 95% CI, 0.46-0.90).

Table 3. Risk of selected lymphoma subtypes and statin use

	Total no.	Ever users of statins	OR* (95% CI)
Controls	2,206	103	1.00 (reference)
Cases			
B-cell lymphomas	1,858	65	0.61 (0.44-0.84)
Myeloma	281	8	0.47 (0.22-0.99)
CLL and SLL	410	22	0.83 (0.51-1.34)
Diffuse large cell lymphoma	493	17	0.69 (0.40-1.17)
Follicular lymphoma	251	10	0.80 (0.40-1.56)
Marginal and MALT lymphoma	126	5	0.79 (0.31-2.00)
T-cell lymphoma	136	5	0.74 (0.29-1.86)
Hodgkin's lymphoma	289	4	0.74 (0.26-2.07)

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small cell lymphocytic leukemia.
*Model adjusted by age, gender, and country (group 1 controls excluded).

If hypercholesterolemia was independently protective for lymphoma, confounding by indication could explain our findings. We have not been able to assess the risk of lymphoma in relation to cholesterol levels in our study, but no published evidence exists supporting this hypothesis. It could also be speculated that statin use could be a marker of an underlying genetic trait that would reduce the risk of lymphoma and increase the probability of being treated with statins. Although this scenario is theoretically possible, it is an unlikely explanation because of the convincing biological evidence linking statins to a reduced lymphoma risk by promotion of antiapoptotic activities or other anti-inflammatory-related mechanisms (20-24).

In conclusion, statin use was associated with an important reduction in lymphoma risk, adding to the growing evidence of anticancer properties of statin drugs. These results are reassuring for the increasing number of patients taking statins on a regular basis, but replication is needed before clinical implications can be drawn.

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References

1. Walley T, Folino-Gallo P, Schwabe U, Van Ganse E. Variations and increase in use of statins across Europe: data from administrative databases. Br Med J 2004;328:385–6.
2. Goodman and Gilman's. The pharmacological basis of therapeutics. 10th edition. New York: McGraw Hill; 2001.
3. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. JAMA 1996;275:55–60.
4. Cocco P, Todde PF, Fornera S, Manca P, Sias AR. Mortality in a cohort expressing the glucose-6-phosphate dehydrogenase deficiency. Blood 1998; 91:706–9.
5. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.
6. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–30.
7. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. JAMA 1997;278:313–21.
8. Bjerre LM, LeLorier J. Do statins cause cancer? A meta-analysis of large randomized clinical trials. Am J Med 2001;110:716–23.
9. Pfeffer MA, Keech A, Sacks FM, et al. Safety and tolerability of pravastatin in long-term clinical trials: prospective pravastatin pooling (PPP) project. Circulation 2002;105:2341–6.
10. Strandberg TE, Pyorala K, Cook TJ, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet 2004;364:771–7.
11. Poynter JN, Gruber SB, Higgins PDR, et al. Statins and the risk of colorectal cancer. N Engl J Med 2005;352:2184–92.
12. Friis S, Poulsen AH, Johnsen SP, et al. Cancer risk among statin users: a population-based cohort study. Int J Cancer 2005;114:643–7.
13. Beiderbeck AB, Holly EA, Sturkenboom MC, Coebergh JW, Stricker BH, Leufkens HG. Prescription medications associated with a decreased risk of non-Hodgkin's lymphoma. Am J Epidemiol 2003;157:510–6.
14. Zhang Y, Holford TR, Leaderer B, et al. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control 2004;15:419–28.
15. Ferlay, Bray F, Pisani P, Parkin D. GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide. 5th ed. Lyon: IARC Press; 2001.
16. Jaffé HS, Harris NL, Stein H, Vardiman JW. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2001.
17. Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Shapiro S. Statin use and the risk of breast and prostate cancer. Epidemiology 2002;13:262–7.
18. Beck P, Wysowski DK, Downey W, Butler-Jones D. Statin use and the risk of breast cancer. J Clin Epidemiol 2003;56:280–5.
19. Boudreau DM, Gardner JS, Malone KE, Heckbert SR, Blough DK, Daling JR. The association between 3-hydroxy-3-methylglutaryl conenzyme A inhibitor use and breast carcinoma risk among postmenopausal women: a case-control study. Cancer 2004;100:2308–16.
20. Schonbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? Circulation 2004;109:18–26.
21. Graaf MR, Richel DJ, van Noorden CJF, Guchelaar HJ. Effects of statins and farnesyltransferase inhibitors on the development and progression of cancer. Cancer Treat Rev 2004;30:609–41.
22. van de Donk NWCJ, Schotte D, Kamphuis MMJ, et al. Protein geranylgeranylation is critical for the regulation of survival and proliferation of lymphoma tumor cells. Clin Cancer Res 2003;9:5735–48.
23. van de Donk NWCJ, Kamphuis MMJ, van Kessel B, Lokhorst HM, Bloem AC. Inhibition of protein geranylgeranylation induces apoptosis in myeloma plasma cells by reducing Mcl-1 protein levels. Blood 2003;102:3354–62.
24. Gronich N, Drucker L, Shapiro H, Radnay J, Yarkoni S, Lishner M. Simvastatin induces death of multiple myeloma cell lines. J Investig Med 2004;52:335–44.
25. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies. II. Types of controls. Am J Epidemiol 1992;135: 1029–41.