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Review

Statins and cancer: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 6 April 2008
Received in revised form
29 May 2008
Accepted 20 June 2008
Available online 15 August 2008

Keywords:
Statins
Neoplasms
Cancer
Systematic review
Meta-analysis

ABSTRACT

Background: Systematic reviews on the association between statin therapy and cancer have focused on randomised trials without assessing the quality of evidence. We aimed to review the overall evidence taking study quality into consideration.

Methods: Publications of original studies on the effect of statin treatment on cancer in adult patients were searched on MEDLINE, EMBASE and CENTRAL databases upto October 2007. Our search yielded 37 eligible original studies out of 3607 references. Five studies were additionally found through manual search. Thus, 42 studies were included in the analyses: 17 randomised controlled trials, 10 cohort studies, and 15 case-control studies.

Findings: Statins had no effect on the overall incidence of cancer (median risk ratio (RR) 0.96, range 0.72 to 1.2), or on the incidence of lung (median RR 0.92, range 0.83 to 3.0), breast (median RR 1.04, range 0.74 to 19) or prostate cancer (median RR 0.96, range 0.33 to 1.7). They seemed to protect from stomach (median RR 0.59, range 0.40 to 0.88) and liver cancer (median RR 0.62, range 0.33 to 1.2), and from lymphoma (median RR 0.74, range 0.28 to 2.2). They increased the incidence of both melanoma (median RR 1.5, range 1.3 to 1.7) and non-melanoma skin cancer (median RR 1.6, range 1.2 to 2.2). The effect varied, yet inconsistently, by statin type. The median follow-up time was 4 years. The strength of evidence was mostly weak.

Interpretation: The evidence suggests that statins do not have short-term effects on cancer risk. The evidence on potentially protective or harmful effects is inconclusive. High quality cohort studies with long follow-up are needed to resolve the issue.

1. Introduction

Statins (HMG-CoA-reductase inhibitors) have become the most popular drugs used for high cholesterol because of their efficacy and few side-effects. Randomised controlled trials (RCT's) have shown that statins improve the blood lipid profile and decrease a number of cardiovascular diseases and mortality from coronary heart disease.[1] There has been a growing interest in statins because of their possible anticancer effects.[2] Statins have antiproliferative, proapoptotic, anti-invasive and radiosensitising effects.[3] They inhibit the mevalonate pathway that leads the critical changes in cell function. Anticancer effect is also associated with mutations of activated RAS-proteins in colorectal and pancreatic cancers as well as in lung cancers and leukaemia. Statins may have a cytostatic effect on cancer cells and prolong the survival of

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.06.025

cancer patients.[4] They also act as antioxidative, anti-inflammatory and angiogenic drugs[5] and could therefore both prevent and promote cancer cell growth.

The authors of recent meta-analyses have mainly concluded that statins do not affect the overall risk of cancer[1,5–8] or the risk of major cancer subtypes either.[1,5–7,9–11] Two meta-analyses included observational studies,[6,12] all other meta-analyses focused on RCT's. In only one meta-analysis had the authors assessed the quality of included studies.[9] Instead, many authors carried out various kinds of sensitivity analyses.

RCTs are considered to provide the best evidence on the effects of any intervention, yet it does not mean that we are allowed to neglect the evidence provided by other study designs. One of the shortcomings of RTCs is that they do not reflect the real-life mixed use of drugs. There is much concern about the validity of meta-analyses in general and how strong conclusions can be based on them, mainly due to the fact that meta-analyses themselves are observational in nature. Even though the methodology on how to carry out systematic reviews and meta-analyses is still in progress, it can be argued that the assessment of study quality is vital for rigorous meta-analyses.

The aim of this study was to systematically review and evaluate the evidence on the association between statin therapy and cancer. The information will be utilised later as a basis of hypothesis formulation for a nationwide study on cancer risk among statin users in Finland with exact information of types and amounts of statins used by them. Therefore, the target population in this meta-analysis was defined as middle-aged Northern European.

2. Materials and methods

2.1. Search

We attempted to find all publications of original studies on the effect of statin treatment on cancer in adult patients. Potentially eligible studies, upto October 2007, were searched in the electronic databases MEDLINE, EMBASE and Cochrane CENTRAL. The following medical subject headings and free text keywords were used: 'hydroxymethylglutaryl-CoA reductase inhibitors', 'statin', 'atorvastatin', 'fluvastatin', 'lovastatin', 'pravastatin', 'simvastatin', 'rosuvastatin', 'cancer', 'malignant neoplastic disease', 'human', 'trial', 'cohort study'. Additional studies were sought by manual search through reference lists of relevant reviews and other publications, and the authors' personal libraries.

2.2. Study selection and data extraction

One reviewer (JK) determined the eligibility of retrieved studies according to predetermined criteria, consulting the other authors when necessary. No language restrictions were imposed. Inclusion criteria were: an original study comparing statin treatment with an inactive control (placebo or no statins), adult study participants (18 years or older), cancer incidence reported, and follow-up over 1 year. Studies on cerivastatin and those describing statin treatment in cancer or transplant patients were excluded. One reviewer extracted the data on a predetermined form. In case a trial had multiple treatment arms with different doses of a statin, the numbers of cancer cases in those arms were combined. We did not approach the authors on studies that did not report cancer outcomes.

2.3. Assessment of strength of evidence

One reviewer (JK) assessed the strength of evidence according to predetermined criteria and cut-off points which were set in consensus by all authors. First, the quality of each study, and the quality and applicability of the results were evaluated. Study quality was determined based on the definition of the base population of eligible participants (e.g. all consecutive patients with myocardial infarction, or volunteers recruited by an announcement), and the definition and measurement of the predictor (e.g. statin type, dosage, placebo) and outcome (e.g. cancer type, diagnostic criteria, information self-reported or register-based).

The quality of the results was determined based on sample size, randomisation, allocation of treatment, blinding, compliance, drop-outs, losses to follow-up, missing data, follow-up time, effect measure, and potential confounders. The applicability of the results was determined based on country, setting, age, sex, race and coverage (i.e. the number of study participants divided by the number of the eligible ones in the base population). Applicability assessment needs the target population to be defined; in this meta-analysis, it was deemed middle-aged Northern European.

Secondly, the overall strength of evidence was assessed on each separate outcome. The strength was based on study design, study quality, the quality and applicability of the results, and the homogeneity in between the studies (Table 1). The homogeneity was evaluated based on the similarity of study populations, predictors, outcomes, follow-up times, risks among the controls, effect measures, effect sizes (benefit, no effect, harm), and continuity of effect sizes (whether the results of different studies could be thought of as arising from the same source population in a statistical sense).

2.4. Statistical analyses

The effect measures of interest were the risk ratio (RR) and the rate difference (RD) per 100,000 person-years between the statin treated patients and the control ones. Odds ratios were assumed to be approximate risk ratios. Median RRs with ranges are reported. In addition, mean RRs and their 95% confidence intervals were calculated using the inverse variance method. Assessment was hierarchical, so that summary effect measure was determined based on those studies that provided the highest level of evidence. Studies providing weaker strength were excluded from calculations.

3. Results

3.1. Description of studies

Our search yielded 69 potentially relevant publications out of 3607 references (Fig. 1). These publications described 57 original studies: 33 RCTs, 10 cohort studies, 13 case-control

Table 1 – Criteria for strength of evidence on intervention

Strength of evidence	Study design	Minimum study quality	Minimum results quality	Minimum results applicability	Number of studies	Homogeneity Index[a]
Good	RCT, RCCT	Good	Good	Moderate	3	6/8 (2/3)
Moderate	RCT, RCCT	Moderate	Moderate	Moderate	2	5/8 (2/3)
	CT, CO, NCC	Good	Good			
Weak	RCT, RCCT	Weak	Weak	Weak	1	4/8 (1/2)
	CT, CO, NCC	Moderate	Moderate			
	CC	Good	Good			
Very weak	CS	Weak	Weak	Weak	1	3/8 (1/2)

RCT = Randomised controlled trial; RCCT = Randomised controlled crossover trial; CT = Clinical trial; CO = Cohort study; NCC = Nested case-control study; CC = Case-control study; CS = Cross-sectional study.

a First fraction expresses the number of factors (e.g. population, outcome, follow-up time) that need to be homogenous in between the studies. The latter fraction expresses the number of studies that need to be similar, in order for the factor in question to be considered homogenous.

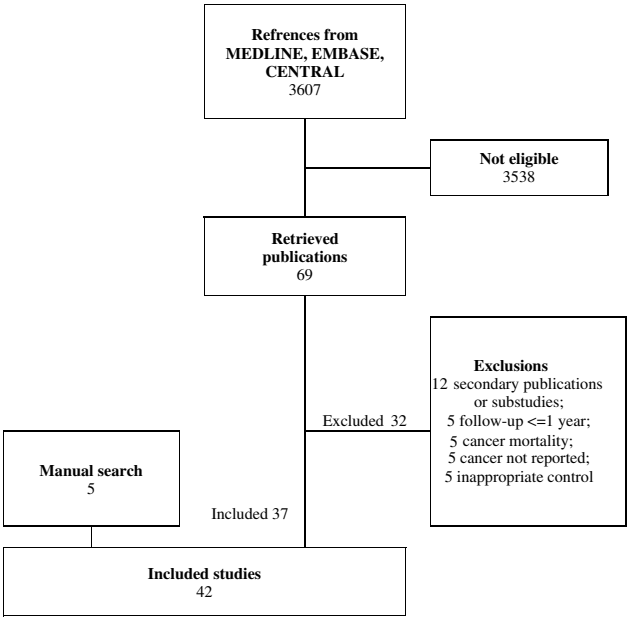

Fig. 1 – Literature search flow.

studies, and one cross-sectional study. Publications were considered to describe one study if they used the same study population. Three randomised controlled trials, one cohort study, and the cross-sectional study were excluded due to short or non-existent follow-up time. Four trials and one cohort study reported other clinical outcomes but not cancer. Five trials reported only fatal cancer cases and were therefore excluded. Five trials had inappropriate control groups. Five eligible trials were found by manual search. Altogether, 42 studies were included in this meta-analysis.[13–54] Especially for large trials, necessary information on study design and baseline characteristics was acquired from separate publications.[55–71]

The characteristics of the studies included are shown in Tables 2 and 3. The studies had been published between 1993 and 2007. The population size in the studies varied from 250 to 483,733, and the number of cases from 2 to 22,512. In the RCTs, the study populations were predominantly male; in the observational studies, the gender distribution was more even. Overall, the age ranged from 18 to at least 100 years, yet the participants were mostly middle-aged. Most of the studies evaluated the effects of atorvastatin, lovastatin, pravastatin and simvastatin. No study reported findings on rosuvastatin. The follow-up time ranged from 2 to 12 years (median 4 years).

In the RCTs, cancer was always listed among the adverse events, and the rigour in the endpoint assessment of cancer varied. Eight trials had a central endpoint committee, yet it was usually unclear if cancer diagnoses were adjudicated centrally. Two trials used registers and the rest did not provide information on the outcome assessment concerning cancer. Out of the 25 observational studies included in this review, information on cancer was based on register data in 19 studies and on self-reporting and clinical records in the others.

3.1.1. *Quality and applicability of studies*

Study quality was moderate to good in all studies, being mainly moderate in trials and mainly good in observational studies. Result quality was good in one trial and in nine observational studies and moderate in 13 trials and 14 observational studies. The applicability of studies was moderate to good in all studies. Overall, only one study[25] could have provided strong evidence on cancer. Respectively, 17 studies[13–20,22,26–29,33,38,40,41] could have provided moderate evidence, 15 studies[21,23,24,30–32,34–37,39,42,43,45,46] weak evidence and nine studies[44,47–54] only very weak evidence.

3.2. *Effects of statins on cancer*

3.2.1. *Any statin*

The number of studies available for analysis varied from 1 to 17 (Table 4). The median risk ratio between statin treatment and the control treatment on different cancer outcomes varied from 0.39 to 1.6, and the median rate difference per 100,000 person-years from –50 to 69.

The effect estimates did not seem to depend on publication year but more on study design (Fig. 2). The effect estimates were close to null effect in RCTs, cohort studies and nested case-control studies. Case-control studies focusing on one cancer site at a time have a tendency to show RRs below unity for statin use with the exception of one study on lymphoid malignancies[49] that shows significant excess for statin use.

Table 2 – Study characteristics: trials and cohort studies

Study	Year of publication	Statin	Cancer outcome	Start of recruitment	Follow up (years)	Treated n/N	Controls n/N	Crude RD per 100,000 person-years	Crude RR
Randomised controlled trials									
MARS[13]	1993	L	Any	1985	2.2	6/123	5/124	384	1.2
SSSS[14]	1994	S	Any	1988	5.4	103/2223	102/2221	8	1.0
KAPS[15]	1995	P	Any	1990	3	1/224	1/223	–1	1.0
REGRESS[16]	1995	P	Any	1989	2	3/450	3/434	–12	0.96
WOSCOPS[17]	1995	P	Any not nmsc	1989	4.9	116/3302	106/3293	60	1.1
CAIUS[18]	1996	P	Any	1991	3	3/151	4/154	–204	0.76
CARE[19]	1996	P	Any	1989	5	172/2081	161/2078	103	1.1
LCAS[20]	1997	L	Any	1993	2.5	12/214	16/215	–734	0.75
AFCAPS /TexCAPS[21]	1998	L	Any not nmsc	1990	5.2	252/3304	259/3301	-42	0.97
LIPID[22]	1998	P	Any	1990	6.1	379/4512	399/4502	–76	0.95
GISSI[23]	2000	P	Any not nmsc	1993	2.0	16/2138	24/2133	–186	0.67
LIPS[24]	2002	P	Any	1996	3.9	46/822	49/818	–101	0.93
MRC_BHF HPS[25]	2002	S	Any not nmsc	1994	5	814/10269	803/10267	21	1.0
PROSPER[26]	2002	P	Any not nmsc	1997	3.2	245/2891	199/2913	513	1.2
Beishuizen[27]	2004	CS	Any	1999	2	4/125	4/125	0	1.0
PHYLLIS[28]	2004	P	Any	1990s	2.6	1/254	1/254	0	1.0
GDDS[29]	2005	A	Any	1998	4	39/619	44/636	–154	0.91
Cohort studies									
Beck[30]	2003	FLPS	Breast	1989	4.2	188/13592	691/53880	332[a]	1.1[a]
Cauley[31]	2003	FLPS	Breast	1992	6.8	6/284	234/6952	–190	0.31[a]
Friis[32]	2005	ACFLPS	Any not nmsc	1989	3.3	398/12251	22114/322503	–1093	0.86[a]
NHS[33]	2005	ns	Breast	1994	6	152/15370	1472/59534	–247	0.96[a]
Wei[34]	2005	ns	Colorectal	1984	~3[b]	18/213	188/2425	233	1.1[a]
Cauley[35]	2006	AFLPS[c]	Breast	1993	6.7	297/11710	4086/144641	–43	0.91[a]
CPS-II[36]	2006	FLPS	Colorectal	1997	4	183/23360	601/103426	51	1.0[a]
HPFS[37]	2006	ns	Prostate	1990	12	322/2847	2257/27796	266	0.96[a]
Boudreau[38]	2007	ACFLPRS	Breast	1990	6.4	401/6836	2306/85952	497	1.1[a]
Setoguchi[39]	2007	ACFLPS	Colorectal	1994	2.9	190/24439	59/7284	–11	0.96[a]

Note: Each study might have reported several cancer outcomes. The outcome with most cases has been included in this table.

n/N = No. of cases in the group; RD = Rate difference; RR = Risk ratio; A = Atorvastatin; C = Cerivastatin; F = Fluvastatin; L = Lovastatin; P = Pravastatin; R = Rosuvastatin; S = Simvastatin; nmsc = Non-melanoma skin cancer; ns = Not specified.

a Adjusted values reported by authors.

b Approximately, follow-up time not reported clearly by authors.

c Authors mentioned 'other' statins but did not specify further.

Table 3 – Study characteristics: case-control studies

Study	Year of publication	Statin	Cancer outcome	Start of data collection	Intervention (years)	Cases *n/N*	Controls *n/N*	Crude OR	Adjusted OR
Nested case-control studies									
Blais[40]	2000	LPS	Any	1989	nr	nr/542	nr/5420	. . .	0.72
Graaf[41]	2004	ACFPS	Any	1991	nr	144/3080	986/16711	0.79	0.80
Kaye[42]	2004	ns	Any	1987	2.4	256/3244	1066/14844	1.1	1.0
Vinogradova[43]	2007	ACFPS	Colorectal	1995	∼2	538/5686	2424/24982	0.98	0·93
Case-control studies									
Boudreau[44]	2004	ns	Breast	1997	3.7	112/961	119/983	0.96	0.90
Zhang[45]	2004	ns	Lymphoma	1996	nr	37/601	71/717	0.62	0.50
Poynter[46]	2005	ns	Colorectal	1998	nr	120/1953	234/2015	0.53	0.57
Shannon[47]	2005	AFLS	Prostate	2001	∼2	30/90	93/176	0.63	0.35
EPILYMPH[48]	2006	ns	Lymphoma	1998	∼4	74/177	2288/4391	0.80	0.61
Iwata[49]	2006	FPS	Lymphoma	1995	4	29/218	31/437	1.9	2.5
Landgren[50]	2006	ns	Myeloma	1996	nr	7/179	59/691	0.46	0.40
Coogan[51]	2007	ns	Colorectal	1991	nr	35/726	190/3842	0.97	0.80
Coogan[52]	2007	ACFLPRS	Colorectal	2001	∼3	457/1759	523/1752	0.87	0.92
Robertson[53]	2007	ns	Colorectal	1989	nr	125/5582	1509/55834	0.83	nr
Khurana[54]	2007	ACFLPRS	Lung	1998	∼3	1994/7280	161668/476453	0.81	0.55

Note: Each study might have reported several cancer outcomes. The outcome with most cases has been included in this table. n/N = No. of exposed in the group; OR = Odds ratio; A = Atorvastatin; C = Cerivastatin; F = Fluvastatin; L = Lovastatin; P = Pravastatin; R = Rosuvastatin; S = Simvastatin; ns = Not specified; nr = Not reported.∼ = Approximately, intervention time not reported clearly by authors.

Table 4 – Effects of statins on cancer

Cancer[a]	Strength of evidence	RR					RD per 100,000 years
		k/K	N_k	Median [range]	Mean (95% CI)	k	Median [range]
All cancers							
Any[13–16,18–20,22,24,27–29,40–42]	Weak[b]	15/15	67432	0.96 [0.72 to 1.2]	0.93 (0.77–1.1)	12	–6 [–734 to 384]
Any excl. nmsc[14,17,25,26,21,23,32]	Moderate	4/7	37379	1.1 [0.94 to 1.3]	1.1 (0.82–1.4)	4	41 [–51 to 534]
Respiratory							
Lung[15,21,23,32,39–42,56,51,54]	Weak[b]	9/11	391216	0.92 [0.83 to 3.0]	1.0 (0.73–1.4)	6	0 [–25 to 148]
Respiratory ns[17,25,26]	Moderate	3/3	32935	1.1 [0.96 to 1.1]	1.1 (0.70–1.6)	3	23 [–7 to 54]
Breast[19,22,26,33,38,70[A]]	Moderate	6/17	177866	1.0 [0.74 to 19]	1.3 (0.92–1.7)	6	15 [–103 to 628]
Genitourinary							
Gynecological							
Ovarian[42]	Weak	1/1	501	1.0	1.00 (0.25–3.93)	.	.
Uterus[40,42,51]	Weak	2/3	715	0.39 [0.30 to 0.50]	0.37 (0.13–1.09)	.	.
Gynaecological ns[32,42,70]	Weak	3/3	172633	0.93 [0.91 to 1.1]	0.97 (0.55–1.71)	2	–8 [–23 to 8]
Prostate[15,21,32,37,40–42,56,70,47,51]	Weak[b]	9/11	231893	0.96 [0.33 to 1.7]	0.99 (0.77–1.27)	6	–14 [–149 to 43]
Urinary tract							
Kidney[41,42,70,51]	Weak	3/4	21369	1.0 [0.27 to 1.0]	0.79 (0.39–1.6)	1	2
Bladder[21,41,42,70,51]	Weak	4/5	29903	1.1 [0.82 to 1.2]	0.99 (0.63–1.6)	2	–13 [–31 to 6]
Urinary tract ns[40,42,56]	Weak	3/3	8413	0.93 [0.43 to 1.1]	0.86 (0.46–1.6)	1	-6
Genitourinary ns[17,25,26]	Moderate	3/3	32935	1.0 [0.95 to 1.2]	1.0 (0.70–1.5)	3	0 [–25 to 37]
Gastrointestinal							
Upper GI							
Oesophageal[42]	Weak	1/1	530	0.80	0.80 (0.16–3.9)	.	.
Stomach[41,42]	Weak	2/2	1296	0.59 [0.40 to 0.88]	0.64 (0.23–1.8)	.	.
Upper GI ns[56,70]	Weak[b]	2/2	27113	1.4 [1.2 to 1.7]	1.3 (0.77–2.3)	2	33 [23 to 43]
Colorectal							
Colon[21,40–42,46,51,52]	Weak	4/7	10815	0.93 [0.83 to 1.2]	1.0 (0.61–1.7)	1	29
Rectum[41,42,46,51,52]	Weak	2/5	1026	0.88 [0.48 to 1.6]	1.1 (0.45–2.5)	.	.
Colorectal ns[19,56,70[B]]	Moderate	3/13	31272	0.60 [0.57 to 0.87]	0.74 (0.47–1.2)	3	–50 [–87 to –33]
Gastrointestinal ns[14,17,19,25,26[C]]	Moderate	5/7	41538	1.0 [0.92 to 1.5]	1.1 (0.75–1.5)	5	6 [–10 to 222]
Liver[19,32]	Weak	2/2	338913	0.62 [0.33 to 1.2]	0.85 (0.27–2.7)	2	–4 [–10 to 2]
Pancreas[41,42,51,57]	Weak	2/4	1175	0.84 [0.80 to 0.89]	0.83 (0.32–2.1)	.	.
Haematological							
Myeloma[50]	Very weak	1/1	870	0.40	0.40 (0.12–1.3)	.	.
Lymphoma[21,40,41,45,48,49,51]	Weak	4/7	8745	0.74 [0.28 to 2.2]	0.68 (0.38–1.2)	1	6
Leukaemia[51]	Very weak	1/1	4095	1.1	1.1 (0.37–3.3)	.	.
Lymphoma or leukaemia[19,70]	Weak[b]	2/2	24695	1.0 [0.80 to 1.3]	1.1 (0.59–2.1)	2	0 [–19 to 19]
Haematological ns[25,32]	Weak	2/2	355290	1.0 [0.88 to 1.2]	1.1 (0.63–1.9)	2	3 [–18 to 23]
Central nervous system[25]	Weak	1/1	20536	1.7	1.7 (0.60–4.9)	1	10
Skin							
Melanoma[19,70,21,42]	Moderate	2/4	24695	1.5 [1.3 to 1.7]	1.6 (0.71–3.5)	2	12 [10 to 14]
Non-melanoma[14,25,21,23]	Moderate	2/4	24980	1.6 [1.2 to 2.2]	1.3 (0.86–2.1)	2	69 [58 to 80]
Skin ns[40,41]	Weak	2/2	1789	0.71 [0.63 to 0.81]	0.74 (0.32–1.7)	.	.

RR = Risk ratio; RD = Rate difference; nmsc = Non-melanoma skin cancer; ns = Not specified; GI = Gastrointestinal; k/K = No. studies providing best evidence out of all eligible studies; RDs are generally based on less evidence, because it cannot be calculated for case-control data; Nk = Total no. of participants in the studies providing best evidence.

a References for studies given in superscript; studies with lower quality given in brackets; A:[21,30–32,35,39–42,44,51,70]; B:[32,34,36,39,42,43,46,51–53]; C:[23,32]

b Strength of evidence decreased due to the heterogeneity of studies.

The strength of evidence was at most moderate but mostly weak. Moderate evidence could be found on respiratory, breast, colorectal, genitourinary, gastrointestinal, melanoma and non-melanoma skin cancer, and any cancer excluding non-melanoma skin cancer. The strength of evidence was reduced to weak due to heterogeneity on prostate, upper gastrointestinal cancer and lymphoma or leukaemia as well as any cancer. Strength was borrowed from lower-quality studies in leukaemia.

3.2.2. *Different statins*

Only those cancer outcomes for which there was evidence on at least three different statins are reported here. The number of eligible studies varied from 1 to 6 (Table 5). The median risk ratio between statin treatment and the control treatment on different cancer outcomes varied from 0.34 to 0.91 for atorvastatin, from 0.34 to 1.2 for fluvastatin, from 0.52 to 1.7 for lovastatin, from 0.58 to 1.7 for pravastatin, and from 0.67 to 1.6 for simvastatin. Respectively, the median rate difference per

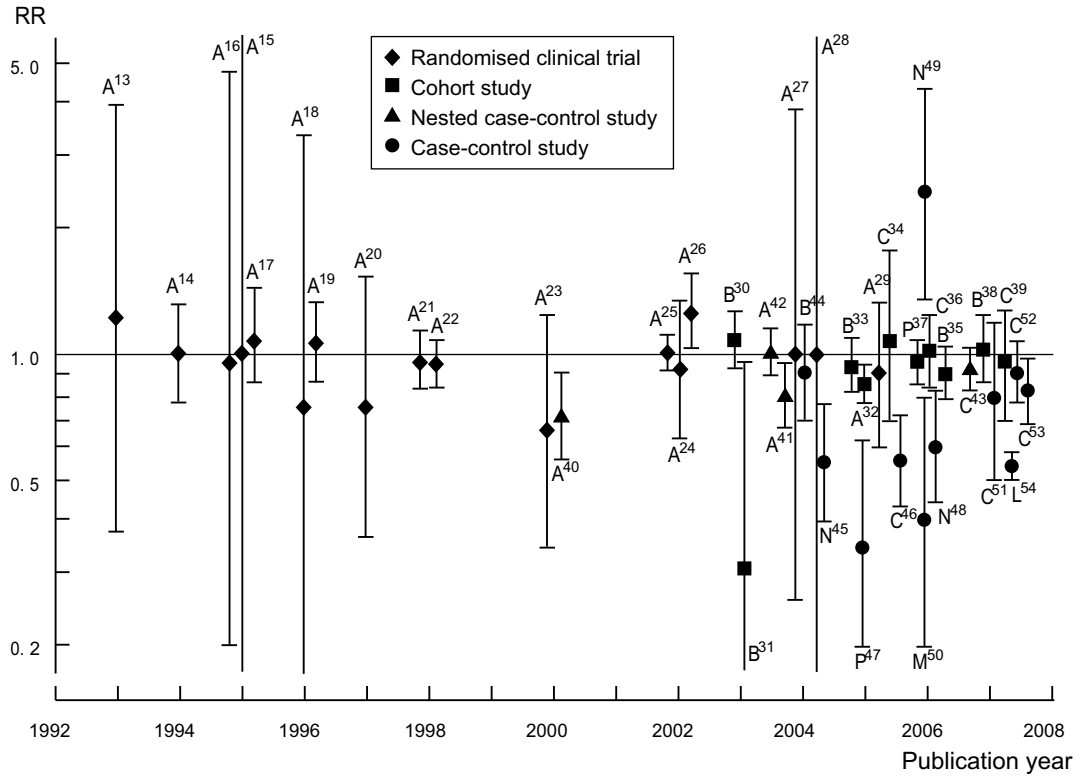

Fig. 2 – Relative risk estimates, with 95% confidence interval bars, for statin users in comparison with reference population, by publication year and study type. Case-control studies emerged in the 2000s and show greater effects than the other study types which may partly be due to both publication bias and methodological issues inherent to study design. *Note*: The risk estimates are only superficially comparable between studies because both the intervention and outcome vary, especially in observational studies. See Table 2 for relative risks (i.e. risk ratios and odd ratios). References for studies are given in superscript. Cancer types: A=Any (studies 17, 21, 23, 25, 26 and 32 excluded non-melanoma skin cancer); B = Breast; C = Colorectal; L = Lung; M = Melanoma; N = Lymphoma; P = Prostate.

100,000 person-years varied from –76 to 384 for lovastatin, from –68 to 148 for pravastatin, and from –103 to 69 for simvastatin. The strength of evidence was moderate for pravastatin on breast and colorectal cancer, and for simvastatin on non-melanoma skin cancer. Otherwise, the level of evidence was mostly weak.

4. Discussion

We analysed the data from 17 randomised controlled clinical trials and 25 observational studies in order to evaluate the effect of statins on cancer in adult patients. Our findings resemble those of others who have stated that there is no evidence that statins would have a clinically significant effect on overall cancer incidence, or on respiratory, breast, colorectal, gastrointestinal, genitourinary, or prostate cancer.[1,5,7–10] On the other hand, in a review on 20 case-control studies, statins were associated with a decreased risk of any, lung and prostate cancer.[12] Any indication on potential harm or benefit in our review is based on weak evidence except for skin cancer.

We found moderate evidence that statins are associated with an increased risk of melanoma and non-melanoma skin cancer, whereas other authors have generally concluded that there is no apparent association between statins and the risk of melanoma,[1,5–7,11] or that a preventive effect of statins is not excluded.[9,12] All reviews have used the same trials as the basis of evidence, the weighted summary estimate of relative risk varying from 0.84 to 1.0. Baigent and colleagues[1] had information on 14 RCTs, the others[5–7,11] from four to six trials. Baigent and colleagues did not report trial-specific risk estimates for melanoma, even though they had access to the unpublished results of all included trials. Two other reviews[9,10] also had some unpublished data at hand. The trial-specific relative risks reported in the reviews ranged from 0.33 to 2.3. The reason for the contradiction between our conclusion and those of the other reviewers lies evidently in the number and quality of studies included and in the methodology applied in the meta-analysis.

When using hierarchical quality-based methods in evaluation (as in the present review), it is reasonable to believe that the review suffers less from potential publication bias because high quality studies tend to become published more often than low quality ones[72] and thus the best evidence is more readily and more completely obtainable for the reviewers. The quality of studies and results varied, and only one study[25] was of high enough quality and applicability to be able to contribute strong evidence on cancer. (Note that strong evidence requires at least three such studies.) The trials included in our meta-analysis were designed to study the efficacy of statins on cardiovascular endpoints; cancer was

Table 5 – Effects of statins on cancer by statin type

Cancer[a]	Strength of evidence	RR				RD per 100,000 years	
		k/K	N_k	Median [range]	Mean (95% CI)	k	Median (range)
Any cancer							
Atorvastatin[29]	Weak	1/1	1255	0.91	0.91 (0.42–2.0)	1	–154
Fluvastatin[20,24]	Weak	2/2	1640	0.84 [0.75 to 0.93]	0.87 (0.47–1.6)	2	–417 [–734 to –101]
Lovastatin[13]	Weak	1/1	247	1.2	1.2 (0.35–4.2)	1	384
Pravastatin[15,16,18,19,22,28]	Moderate	6/6	15317	0.98 [0.76 to 1.2]	0.98 (0.72–1.3)	6	–6 [–204 to 103]
Simvastatin[14]	Weak	1/1	4444	1.0	1.0 (0.55–1.9)	1	8
Any cancer excl. nmsc							
Lovastatin[21]	Weak	1/1	6605	0.97	0.97 (0.60–1.6)	1	–42
Pravastatin[17,23,26]	Moderate[b]	3/3	16670	1.1 [0.67 to 1.3]	1.1 (0.72–1.6)	3	60 [–186 to 534]
Simvastatin[14,25]	Moderate	2/2	24980	0.97 [0.94 to 1.0]	0.99 (0.73–1.4)	2	–15 [–51 to 21]
Breast							
Atorvastatin[44]	Very weak	1/1	1776	0.80	0.80 (0.29–2.2)	.	.
Fluvastatin[44]	Very weak	1/1	1752	1.1	1.1 (0.36–3.3)	.	.
Lovastatin[21,44,51]	Weak	1/3	997	1.4	1.4 (0.52–4.0)	1	153
Pravastatin[19,22,26,44,51]	Moderate	3/5	5092	1.7 [1.0 to 19]	3.3 (1.7–6.3)	3	148 [1 to 628]
Simvastatin[70,44,51]	Weak	1/3	5082	0.74	0.74 (0.34–1.6)	1	–103
Prostate							
Atorvastatin[47]	Very weak	1/1	302	0.34	0.34 (0.04–2.6)	.	.
Fluvastatin[47]	Very weak	1/1	302	0.34	0.34 (0.04–2.6)	.	.
Lovastatin[21,47,51]	Weak	1/3	5608	1.0	1.0 (0.55–1.8)	1	6
Pravastatin[15,56,51]	Weak	2/3	7024	0.75 [0.33 to 1.7]	1.3 (0.55–3.3)	2	–53 [–149 to 43]
Simvastatin[70,47,51]	Weak	1/3	15454	1.0	1.0 (0.57–1.8)	1	0
Colorectal							
Atorvastatin[43,52]	Weak	1/2	30468	1.1	1.1 (0.64–1.9)	.	.
Fluvastatin[43]	Weak	1/1	30468	1.2	1.2 (0.52–2.8)	.	.
Lovastatin[52]	Very weak	1/1	2641	1.7	1.7 (0.63–4.7)	.	.
Pravastatin[19,56,43,52]	Moderate	2/4	10736	0.58 [0.57 to 0.60]	0.58 (0.28–1.2)	2	–68 [–87 to –50]
Simvastatin[43,70,52]	Weak	2/3	51004	0.85 [0.83 to 0.87]	0.85 (0.57–1.3)	1	-33
Lymphoma							
Fluvastatin[49]	Very weak	1/1	596	0.72	0.72 (0.06–8.8)	.	.
Lovastatin[21]	Weak	1/1	6605	1.1	1.1 (0.38–3.1)	1	6
Pravastatin[48,49]	Very weak	2/2	5051	1.0 [0.35 to 2.9]	1.2 (0.51–2.9)	.	.
Simvastatin[49]	Very weak	1/1	612	0.67	0.67 (0.15–3.0)	.	.
Melanoma							
Lovastatin[21]	Weak	1/1	6605	0.52	0.52 (0.19–1.4)	1	–76
Pravastatin[19]	Weak	1/1	4159	1.3	1.3 (0.33–5.3)	1	10
Simvastatin[70]	Weak	1/1	20536	1.7	1.7 (0.65–4.5)	1	14
Non-melanoma skin cancer							
Lovastatin[21]	Weak	1/1	6605	1.0	1.0 (0.63–1.7)	1	39
Pravastatin[23]	Weak	1/1	4271	1.0	1.0 (0.14–7.1)	1	0
Simvastatin[14,25]	Moderate	2/2	24980	1.6 [1.2 to 2.2]	1.3 (0.86–2.1)	2	69 [58 to 80]

Findings shown only on outcomes where there is evidence on at least three different statins. RR = Risk ratio; RD = Rate difference; nmsc = Non-melanoma skin cancer; k/K = No. studies providing best evidence out of all eligible studies; N_k = Total no. of participants in the studies providing best evidence.

a References for studies given in superscript; studies with lower quality given in brackets.

b Strength borrowed from lower-quality studies.

considered an adverse event and was reported, and probably also measured, with varying rigor. The observational studies, instead, had been specially designed to study statins' association with cancer. The evaluation of strength of evidence also relies on how well the studies report details relevant to the topic. In many cases, the evidence might actually be stronger than it appears, as more precise and important information may be left out from the publication. Authors, reviewers and editors often consider that the discussion with expert opinions on the quality and importance of the findings is the most important section of an article. For a critical reader or author of a review, however, the information on those characteristics that affect study quality, results quality and applicability is most crucial.

We did not approach the authors of potentially eligible studies to acquire more information on study details and can-

cer outcomes for practical reasons. This has decreased the number of studies included in our meta-analysis, but their inclusion would probably not have changed our conclusions. Bonovas and colleagues[5] had included seven such studies. The total number of participants of those studies is 3699 and the total number of cases 117. Freeman and colleagues[10] had approached the authors of original studies and had been provided with missing information from 20 out of 36 studies.

The definition of outcome varied from study to study. Combining studies would have increased the total number of studies for a respective cancer type, but the heterogeneity would also have increased. In the evaluation method we used, cumulating heterogeneous sets of low quality studies does not increase the strength of evidence.

We do not believe that we have missed any important published literature. Ideally, all included studies are selected via systematic searches from electronic databases. Because the indexing of publications will probably never be thoroughly complete, especially on the secondary or adverse outcomes, a manual search and the existence of 'gray' literature must be accepted to some extent. Five out of 42 studies included in our review represented this 'gray' literature, which can be considered acceptable.

The evidence so far is rather reassuring that statins do not increase the risk of cancer in the short-term. Cancer is an endpoint that needs to be followed-up for at least 10 years; over half of the studies included in this study had an intervention time less than 5 years and only one reached 10 or more years. The effect of potential lead time bias is bigger the shorter the follow-up time is. The evidence at this point in time is far from convincing, especially that statins are usually intended to be used for the rest of one's life. For similar reasons, it is also too early to say whether some statins might have a protective effect for some cancer types.

There has been a change from RCTs to observational studies (Fig. 2). In the future, new long-term RCTs are not likely to be started, which emphasises the role of good quality population-based cohort studies as a source of most reliable evidence on the effects of statins. The use of statins is ever-spreading and we do need to continue the follow-up and assessment of their long-term effects. Other authors have raised two topics that we did not try to explore but definitely require more investigation; namely, it is possible that statins are associated with increased risk of cancer in the elderly,[73] and in patients in whom the achieved LDL cholesterol level is low.[74] Just by rigorously re-analysing the RCTs with follow-up for at least 3 years, we would be wiser on these topics. More evidence must also be gathered and evaluated for each statin type separately.

In summary, the evidence suggests that statins do not have any short-term effects on cancer but the strength of evidence is mostly weak. Evidence on long-term effects is lacking. We need more high quality cohort studies with longer follow-up. Weak evidence should not be accepted as a basis for definite conclusions that determine clinical practice.

Conflict of interest statement

None declared.

Acknowledgement

This work is financially supported by the Finnish Cancer Society.

REFERENCES

1. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**(9493):1267–78.
2. Chan KK, Oza AM, Siu LL. The statins as anticancer agents. *Clin Cancer Res* 2003;**9**(1):10–9.
3. Thibault A, Samid D, Tompkins AC, et al. Phase I study of lovastatin, an inhibitor of the mevalonate pathway, in patients with cancer. *Clin Cancer Res* 1996;**2**(3):483–91.
4. Simons M. Molecular multitasking: Statins lead to more arteries, less plaque. *Nat Med* 2000;**6**(9):965–6.
5. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Statins and cancer risk: A literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. *J Clin Oncol* 2006;**24**(30):4808–17.
6. Browning DR, Martin RM. Statins and risk of cancer: A systematic review and metaanalysis. *Int J Cancer* 2007;**120**(4):833–43.
7. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: A meta-analysis. *JAMA* 2006;**295**(1):74–80.
8. Roberts CG, Guallar E, Rodriguez A. Efficacy and safety of statin monotherapy in older adults: A meta-analysis. *J Gerontol A Biol Sci Med Sci* 2007;**62**(8):879–87.
9. Dellavalle RP, Drake A, Graber M, et al. Statins and fibrates for preventing melanoma. *Cochrane Database Syst Rev* 2005:CD003697.
10. Freeman SR, Drake AL, Heilig LF, et al. Statins, fibrates, and melanoma risk: A systematic review and meta-analysis. *J Natl Cancer Inst* 2006;**98**(21):1538–46.
11. Stein EA, Corsini A, Gimpelewicz CR, Bortolini M, Gil M. Fluvastatin treatment is not associated with an increased incidence of cancer. *Int J Clin Pract* 2006;**60**(9):1028–34.
12. Taylor ML, Wells BJ, Smolak MJ. Statins and cancer: A meta-analysis of case-control studies. *Eur J Cancer Prev* 2008;**17**(3):259–68.
13. Blankenhorn DH, Azen SP, Kramsch DM, et al. for the MARS Research Group. Coronary angiographic changes with lovastatin therapy: The Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med* 1993;**119**(10):969–76.
14. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
15. Salonen R, Nyyssonen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS): A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation* 1995;**92**(7):1758–64.
16. Jukema JW, Bruschke AVG, Van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995;**91**(10):2528–40.
17. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New Engl J Med* 1995;**333**:1301–7.

18. Mercuri M, Bond MG, Sirtori CR, et al. Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic Mediterranean population: The Carotid Atherosclerosis Italian Ultrasound Study. *Am J Med* 1996;**101**:627–34.
19. Sacks FM, Pfefeer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *New Engl J Med* 1996;**335**(14):1001–9.
20. Herd JA, Ballantyne CM, Farmer JA, et al. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *Am J Cardiol* 1997;**80**(3):278–86.
21. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;**279**:1615–22.
22. The Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *New Engl J Med* 1998;**339**:1349–57.
23. Marchioli R. Results of the low-dose (20 Mg) pravastatin GISSI Prevenzione Trial in 4271 patients with recent myocardial infarction: Do stopped trials contribute to overall knowledge? *Ital Heart J* 2000;**1**:810–20.
24. Serruys PW, de FP, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: A randomized controlled trial. *JAMA* 2002;**287**:3215–22.
25. Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002;**360**(9326):7–22.
26. Shepherd J, Blauw GJ, Murphy MB, et al. PROSPER-study-group. Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER): A randomised controlled trial. *Lancet* 2002;**360**:1623–30.
27. Beishuizen ED, Van De Ree MA, Jukema JW, et al. Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. *Diabetes Care* 2004;**27**(12):2887–92.
28. Zanchetti A, Crepaldi G, Bond MG, et al. Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis: Principal results of PHYLLIS - A randomized double-blind trial. *Stroke* 2004;**35**(12):2807–12.
29. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**(3):238–48.
30. Beck P, Wysowski DK, Downey W, Butler-Jones D. Statin use and the risk of breast cancer. *J Clin Epidemiol* 2003;**56**(3):280–5.
31. Cauley JA, Zmuda JM, Lui LY, et al. Lipid-lowering drug use and breast cancer in older women: A prospective study. *J Women's Health* 2003;**12**(8):749–56.
32. Friis S, Poulsen AH, Johnsen SP, et al. Cancer risk among statin users: A population-based cohort study. *Int J Cancer* 2005;**114**(4):643–7.
33. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Serum lipids, lipid-lowering drugs, and the risk of breast cancer. *Arch Intern Med* 2005;**165**:2264–71.
34. Wei JT, Mott LA, Baron JA, Sandler RS. Reported use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors was not associated with reduced recurrence of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 2005;**14**(4):1026–7.
35. Cauley JA, McTiernan A, Rodabough RJ, et al. Statin use and breast cancer: Prospective results from the Women's Health Initiative. *J Natl Cancer Inst* 2006;**98**(10):700–7.
36. Jacobs EJ, Rodriguez C, Brady KA, Connell CJ, Thun MJ, Calle EE. Cholesterol-lowering drugs and colorectal cancer incidence in a large United States cohort. *J Natl Cancer Inst* 2006;**98**(1):69–72.
37. Platz EA, Leitzmann MF, Visvanathan K, et al. Statin drugs and risk of advanced prostate cancer. *J Natl Cancer Inst* 2006;**98**(24):1819–25.
38. Boudreau DM, Yu O, Miglioretti DL, Buist DS, Heckbert SR, Daling JR. Statin use and breast cancer risk in a large population-based setting. *Cancer Epidemiol Biomarkers Prev* 2007;**16**(3):416–21.
39. Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation* 2007;**115**(1):27–33.
40. Blais L, Desgagne A, LeLorier J. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: A nested case-control study. *Arch Intern Med* 2000;**160**(15):2363–8.
41. Graaf MR, Beiderbeck AB, Egberts AC, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. *J Clin Oncol* 2004;**22**(12):2388–94.
42. Kaye JA, Jick H. Statin use and cancer risk in the General Practice Research Database. *Br J Cancer* 2004;**90**(3):635–7.
43. Vinogradova Y, Hippisley-Cox J, Coupland C, Logan RF. Risk of colorectal cancer in patients prescribed statins, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors: Nested case-control study. *Gastroenterology* 2007;**133**(2):393–402.
44. Boudreau DM, Gardner JS, Malone KE, Heckbert SR, Blough JR, 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**(11):2308–16.
45. 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.
46. Poynter JN, Gruber SB, Higgins PD, et al. Statins and the risk of colorectal cancer. *N Engl J Med* 2005;**352**(21):2184–92.
47. Shannon J, Tewoderos S, Garzotto M, et al. Statins and prostate cancer risk: A case-control study. *Am J Epidemiol* 2005;**162**(4):318–25.
48. Fortuny J, de SS, Becker N, et al. Statin use and risk of lymphoid neoplasms: Results from the European case-control study EPILYMPH. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(5):921–5.
49. Iwata H, Matsuo K, Hara S, et al. Use of hydroxy-methyl-glutaryl coenzyme A reductase inhibitors is associated with risk of lymphoid malignancies. *Cancer Sci* 2006;**97**(2):133–8.
50. Landgren O, Zhang Y, Hoar Zahm S, Inskip P, Zheng T, Baris D. Risk of multiple myeloma following medication use and medical conditions: A case-control study in Connecticut women. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(12):2342–7.
51. Coogan PF, Rosenberg L, Strom BL. Statin use and the risk of 10 cancers. *Epidemiology* 2007;**18**(2):213–9.
52. Coogan PF, Smith J, Rosenberg L. Statin use and risk of colorectal cancer. *J Natl Cancer Inst* 2007;**99**(1):32–40.
53. Robertson DJ, Larsson H, Friis S, Pedersen L, Baron JA, Sorensen HT. Proton pump inhibitor use and risk of colorectal cancer: A population-based, case-control study. *Gastroenterology* 2007;**133**(3):755–60.
54. Khurana V, Bejjanki HR, Caldito G, Owens MW. Statins reduce the risk of lung cancer in humans: A large case-control study of US veterans. *Chest* 2007;**131**(5):1282–8.

55. Downs JR, Clearfield M, Tyroler HA, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): Additional perspectives on tolerability of long-term treatment with lovastatin. *Am J Cardiol* 2001;**87**(9):1074–9.
56. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med* 2007;**357**(15):1477–86.
57. Khurana V, Sheth A, Caldito G, Barkin JS. Statins Reduce the risk of pancreatic cancer in humans: A case-control study of half a million veterans. *Pancreas* 2007;**34**(2):260–5.
58. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: Early safety and efficacy experience. *Eur Heart J* 1999;**20**:725–41.
59. Strandberg TE, Pyörälä K, Cook TJ, et al. 4S-Group. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). *Lancet* 2004;**364**:771–7.
60. The LIPID Study Group. Design features and baseline characteristics of the LIPID (Long-Term Intervention With Pravastatin in Ischaemic Disease) Study: A randomized trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. *Am J Cardiol* 1995;**76**:474–9.
61. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: The LIPID Trial follow-up. Lancet 2002; 359(9315): 1379-87.
62. West of Scotland Coronary Prevention Study Group. A coronary primary prevention study of Scottish men age 45-64 years: Trial design. *J Clin Epidemiol* 1992;**45**:849–60.
63. The West of Scotland Coronary Prevention Study Group. Computerised record linkage: Compared with traditional patient follow-up methods in clinical trials and illustrated in a prospective epidemiological study. *J Clin Epidemiol* 1995;**48**(12):1441–52.
64. The Scandinavian Simvastatin Survival Study Group. Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction. *Am J Cardiol* 1993;**71**:393–400.
65. Downs JR, Beere PA, Whitney E, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): Design and rationale. *Am J Cardiol* 1997;**80**(287):293.
66. Shepherd J, Blauw GJ, Murphy MB, et al. on behalf of the PROSPER Study Group. The design of a Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *Am J Cardiol* 1999;**84**:1192–7.
67. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003;**348**:891–9.
68. Baron JA, Beach M, Mandel JS, et al. for the Calcium Polyp Prevention Study Group. Calcium supplements for the prevention of colorectal adenoma. *N Engl J Med* 1999;**340**:101–7.
69. Greenberg ER, Baron JA, Tosteson TD, et al. for the Polyp Prevention Study Group. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med* 1994;**331**:141–7.
70. HPS Collaborative Group. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: A randomised placebo-controlled trial [ISRCTN48489393]. *BMC Medicine* 2005;**3**(6):1–21.
71. Calle EE, Rodriguez C, Jacobs EJ, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: Rational, study design and baseline characteristics. *Cancer* 2002;**94**:2490–501.
72. Scherer RW, Langenberg P, von EE. Full publication of results initially presented in abstracts. *Cochrane Database Syst Rev* 2007:MR000005.
73. Bonovas S, Sitaras NM. Does pravastatin promote cancer in elderly patients? *A meta-analysis. CMAJ* 2007;**176**(5):649–54.
74. Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: Insights from large randomized statin trials. *J Am Coll Cardiol* 2007;**50**(5):409–18.