

Statins and fibrates for preventing melanoma (Review)

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[Intervention Review]

Statins and fibrates for preventing melanoma

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ABSTRACT

Background

Effective treatment for advanced melanoma is lacking. While no drug therapy currently exists for prevention of melanoma, in vitro, case-control, and animal model evidence suggest that lipid-lowering medications, commonly taken for high cholesterol, might prevent melanoma.

Objectives

To assess the effects of statin or fibrate lipid-lowering medications on melanoma outcomes.

Search strategy

We searched the Cochrane Skin Group Specialised Register (February 2003), CENTRAL (*The Cochrane Library* Issue 1, 2005), MEDLINE (to March 2003), EMBASE (to September 2003), CANCERLIT (to October 2002), Web of Science (to May 2003), and reference lists of articles. We approached study investigators and pharmaceutical companies for additional information (published or unpublished studies).

Selection criteria

Trials involving random allocation of study participants, where experimental groups used statins or fibrates and participants were enrolled for at least four years of therapy.

Data collection and analysis

Three authors screened 109 abstracts of articles with titles of possible relevance. We then thoroughly examined the full text of 72 potentially relevant articles. We requested unpublished melanoma outcomes data from the corresponding author of each qualifying trial.

Main results

Statins and fibrates for preventing melanoma (Review)

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We identified 16 qualifying randomised controlled trials (RCTs) (7 statin, 9 fibrate). Thirteen of these trials (involving 62,197 participants) provided data on incident melanomas (6 statin, 7 fibrate). A total of 66 melanomas were reported in groups receiving the experimental drug and 86 in groups receiving placebo or other control therapies. For statin trials this translated to an odds ratio of 0.90 (95% confidence interval 0.56 to 1.44) and for fibrate trials an odds ratio of 0.58 (95% confidence interval 0.19 to 1.82).

Subgroup analyses failed to show statistically significant differences in melanoma outcomes by gender, melanoma occurrence after two years of participation in trial, stage or histology, or trial funding. Subgroup analysis by type of fibrate or statin also failed to show statistically significant differences, except for the statin subgroup analysis which showed reduced melanoma incidence for lovastatin, based on one trial only (odds ratio 0.52, 95% confidence interval 0.27 to 0.99).

Authors' conclusions

The melanoma outcomes data collected in this review of RCTs of statins and fibrates does not exclude the possibility that these drugs prevent melanoma. There was a 10% and 42% reduction for participants on statins and fibrates, respectively, however these results were not statistically significant. Until further evidence is established, limiting exposure to ultraviolet radiation remains the most effective way to reduce the risk of melanoma.

PLAIN LANGUAGE SUMMARY

Currently there is no clear evidence that cholesterol drugs reduce melanoma risk.

Some studies have suggested that medicines (such as statins and fibrates) taken to lower blood cholesterol may reduce the risk of melanoma skin cancer. Our review of 16 studies did not find any clear evidence to support such a suggestion, but we cannot exclude a useful effect of such drugs until more studies become available.

BACKGROUND

Several lines of evidence suggest that the lipid-lowering medications commonly taken for high cholesterol may prevent melanoma. This review examined whether melanoma occurred less frequently in people who had taken the type of lipid-lowering medications known as statins and fibrates, compared with those who had not.

Definitions: Melanoma and non-melanoma skin cancer

Skin cancer is commonly divided into two forms: melanoma and non-melanoma skin cancer. Melanoma is a disease that primarily occurs in people of lighter skin colour and occurs when pigment cells known as melanocytes grow in an uncontrolled fashion (Armstrong 1996). Normally, melanocytes endow the skin with its natural colour and account for the formation of naevi (moles). Non-melanoma skin cancer also favours people of lighter skin colour, but involves the squamous and basal cells of the skin rather than melanocytes. While melanoma accounts for only 4% of skin cancer cases, it accounts for roughly 79% of skin cancer deaths in the US (<http://www.cancer.org>), largely owing to its tendency to metastasise to other parts of the body, including the liver, lungs, and brain. The limited success of available treatments and high

cost of therapies used to treat advanced melanoma leave many, especially those at high risk of developing melanoma, eagerly awaiting the discovery of a means of prevention (Walsh 2000).

Melanomas are often recognized by using the 'ABCDE' (asymmetry, borders, colour, diameter, evolving) memory guide: one looks for skin growths that are Asymmetrical (one half does not look like the other half), that have ragged, irregular Borders, that contain unusual Colours (red, white or blue) or irregular coloration, that have a large Diameter (are larger than a pencil eraser, or approximately 6 mm) and that are changing or Evolving (Thomas 1998). For people with numerous moles, the 'ugly duckling' rule may also be a useful way to help distinguish a potentially dangerous melanoma from a benign lesion. That is, a malignant melanoma may raise suspicion simply because it looks different from surrounding moles (Grob 1998). Because of the importance of early diagnosis of melanoma in determining prognosis, all changing, itching, and bleeding growths deserve timely evaluation by a health care professional.

Epidemiology and impact

The incidence of malignant melanoma continues to rise in the US, and constitutes a substantial public health problem (Rigel 2000;

Weinstock 2000). The American Cancer Society estimates that in 2004 there will be 55,100 new cases of malignant melanoma, and 7910 deaths due to the disease in the US (ACS 2004). Because of its high rate of occurrence in young adults, melanoma ranks second only to adult leukaemia in years of potential life lost from adult-onset cancer (Albert 1990). The annual direct costs of treating newly diagnosed melanoma in the US were estimated to be US\$ 563 million more than 5 years ago and are likely to have increased with the rising incidence (Tsao 1998).

Causes

Several population studies have suggested that melanoma is most clearly associated with ultraviolet (UV) light exposure, and that sunburn is the sun exposure variable most consistently associated with melanoma (Armstrong 1996; Lim 1999). Other melanoma risk factors identified include age (increasing risk with increasing age), race (white non-Hispanic > white Hispanic > Black or Asian), family history, number of moles (increasing risk with increasing number of moles), and gender (male > female) (Armstrong 1996; Berwick 1998). Additional factors have also been associated with melanoma: red or blond hair, pre-skin cancer lesions (actinic keratoses), marked freckling of the upper back, 3 or more blistering sunburns prior to age 20, 3 or more years with outdoor summer jobs during teen years, and use of artificial tanning devices (Rigel 1995; Swerdlow 1988). Many of these factors may simply be substitute markers for total/intermittent ultraviolet radiation dose. Some argue that many melanoma risk factors are yet to be discovered (Begg 2001).

Prognosis

The two most important factors in determining whether a melanoma is likely to spread to other parts of the body are whether ulceration (bleeding) is present and the depth of the tumour in the skin. Ten-year survival for patients with non-ulcerated localized melanomas, less than one millimetre (mm) in depth, is 88% (Balch 2001). If ulceration is present, the 10-year survival drops to 83%. Ten-year survival for melanoma 1 to 2 mm deep drops to 79% without ulceration and 64% with ulceration. In the most advanced category of localized melanoma, deeper than 4 mm with ulceration, 10-year survival drops to 32%. Patients with melanoma that has spread to multiple locations in the skin have a 10-year survival of 16% while those with metastases to the lungs have a 10-year survival of 3% (Balch 2001).

Why it is important to do this review

Chemoprevention is the use of medications to prevent a disease. For example, tamoxifen is considered a chemopreventive agent for

breast cancer in women at high risk of developing the disease. No medication is currently recognized as preventing melanoma.

The cells of many cancers, including melanoma, use cholesterol in a different way to non-cancerous cells (Fumagalli 1964; Littman 1966; Versluis 1996). Therefore, medications that alter cholesterol levels may slow or stop tumour growth, enhance the anti-cancer effects of chemotherapy, or possibly even prevent cancer (Buchwald 1992; Lenz 1997). In support of this theory, lovastatin, a medication commonly prescribed to people with high cholesterol levels, has displayed antitumour activity in experimental models of numerous cancers, including melanoma (Jani 1995; Prassanna 1996).

Case-control results suggest a role for statins in cancer prevention (Graaf 2004; Sleijfer 2005). In addition, results from two large, double-blind, placebo-controlled, multi-year clinical trials of lipid-lowering agents for heart disease, have reported significantly fewer melanomas occurring in people taking lipid-lowering medications (AFCAPS 1998; VA-HIT 1999). The numbers of all other cancers, including prostate, colon, lung, lymphoma, bladder, and breast cancer, were not significantly different between groups of participants. The two studies used two different types of lipid-lowering medications: lovastatin, a member of the statin (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor) drug class, and gemfibrozil, a member of the fibrate (fibric acid derivative) drug class. Statins and fibrates are thought to lower cholesterol in different ways (inhibition of cholesterol synthesis versus interaction with the peroxisome-proliferator-activated receptor alpha, PPAR-alpha). Lovastatin and gemfibrozil have no known shared molecular mechanisms of action. However both lovastatin and gemfibrozil are associated with liver cancer in rodents (Newman 1996). Because of concern about the possibility of a similar association with cancer in humans and because meta-analysis of randomised clinical trials has suggested that lipid-lowering medications might increase rates of death not due to heart disease (Criqui 1991; Muldoon 1990), cancer incidence and death rates have been monitored in many clinical trials using these medications.

At the cellular level, lovastatin has been shown to slow the growth and proliferation of melanoma cells grown in the laboratory as well as to induce melanoma cell death (Feleszko 1998; Feleszko 2002; Nordenberg 1996; Shellman 2005). Lovastatin also dramatically decreased the number of melanoma lung metastases in mice injected with melanoma cells (Jani 1995). Recently, the fibrate drug fenofibrate was shown to significantly decrease melanoma metastases in hamsters (Grabacka 2004).

Unfortunately, evidence of effectiveness in vitro and in animal models does not necessarily translate to a similar effect in humans. Moreover, a drug's ability to slow the growth or spread of tumour cells may not correlate with a role in prevention. However, such evidence, together with lower observed melanoma rates in clinical trials, substantiates the appropriateness of further evaluation. The need for investigation of possible chemopreventive agents is

heightened too by the inadequacy of currently available treatment for advanced melanoma. A systematic review of all available randomised, controlled, clinical trial evidence is thus called for to formally evaluate whether drugs such as lovastatin and gemfibrozil reduce melanoma risk in humans.

While lipid-lowering medications may hold promise for preventing melanoma, as well as other more common diseases, the use of these medications is not without risk; therefore randomised, controlled clinical trials need to be performed before preventive or therapeutic use in melanoma can be recommended (Dellavalle 2003).

OBJECTIVES

To assess the relationship between use of statins or fibrates (lipid-lowering medications) and melanoma incidence.

METHODS

Criteria for considering studies for this review

Types of studies

- a) Trials involving random allocation of study participants to the experimental and placebo or non-placebo control group(s).
- b) Experimental groups using statins or fibrates in isolation; we excluded studies with other medication differences between the experimental and control groups.
- c) Trials must have enrolled participants for at least four years of therapy, given that benefits of the intervention may require long-term exposure (Petitti 2000).

Types of participants

Participants of any qualifying trial were included in the review. The majority of participants had coronary artery disease and were enrolled in included trials for purposes of evaluating cardiovascular endpoints.

Types of interventions

Eligible interventions included statin or fibrate medications taken by mouth. We included trials with both placebo and non-placebo control arms for comparison.

Types of outcome measures

Primary outcomes

Melanoma incidence occurring during trial participation (number of people per year diagnosed with a new melanoma).

Secondary outcomes

1. Incidence of melanomas with poor prognosis (> 3 mm thick and ulcerated).
2. Incidence of dysplastic naevi (a mole with atypical architecture or cellular features), confirmed by histological report.
3. Overall cancer incidence (tumours of any organ).
4. Mortality due to melanoma.

We added mortality due to melanoma as an outcome after publication of the protocol. It merits investigation because it is the outcome a person diagnosed with melanoma seeks to avoid.

Search methods for identification of studies

We searched for studies and did not impose any language restrictions.

Electronic searches

We searched the following databases (1975 to 2003).

- a) The Cochrane Skin Group Specialised Register, which contains citations from an ongoing comprehensive programme of handsearching of dermatology journals and conference proceedings, was searched in February 2003 using the following terms: melanoma and (fibrate* or (HMG-CoA and reductase* and inhibitor*) or statin* or (lipid and lower*)).
- b) Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2005) see Appendix 1 for the search strategy.
- c) MEDLINE (from 1966 to March 2003) see Appendix 2 for the search strategy.
- d) EMBASE (from 1980 to September 2003) see Appendix 3 for the search strategy.
- e) CANCELIT (from 1975 to October 2002) see Appendix 4 for the search strategy.
- f) Web of Science-Science Citation Index (from 1970 to May 2003) see Appendix 5 for the search strategy.

Searching other resources

References from published studies

We examined references from published studies for additional relevant trials.

Unpublished literature

We requested unpublished, ongoing trials, and conference abstract information via correspondence with trial authors and pharmaceutical companies.

Data collection and analysis

Selection of studies

One author (AD) checked all database results and selected articles with titles of possible relevance. Three authors (AD, RD, LS) screened abstracts from the selected articles, allowing articles with appropriate abstract contents to proceed to full article review. We then thoroughly reviewed the full text of articles potentially meeting inclusion criteria and assessed and recorded their methodological quality. We resolved any disagreement by discussion between the authors.

Data extraction and management

At least two of the six independent authors (AD, LH, EH, KJ, RD, LS) extracted the data and discrepancies were resolved by consensus.

Assessment of risk of bias in included studies

Assessment of methodological quality

Six independent authors (AD, LH, EH, KJ, RD, LS) assessed methodological quality. At least two authors reviewed each article. We extracted information about the methods, interventions, outcomes, and results of each trial using a data extraction form. We obtained missing data from the trial authors whenever possible.

Table 1. Numbers of participants and incidence calculations

Trial	Group	No. Participants (T)	No. Participants (C)	Trial length (years)	Prtpcnts x Yrs (T/C)	Melanoma/pers/ (T)	Melanoma/pers/Yr (C)
4S 1994	Statin	2221	2223	5.4	11993 / 12004	7 / 11993 = .00058	3 / 12004 = .00025
ALLHAT 2002	Statin	5170	5185	4.8	24816 / 24888	-	-
AFCAPS 1998	Statin	3304	3301	5.2	17181 / 17165	14 / 17181 = .00081	27 / 17165 = .00157

We judged articles as A-adequate, B-unclear, or C-inadequate in each of the following categories.

Randomisation procedure:

A-based on a clear description of how the random numbers were generated; B-unclear; C-not based on validly generated random numbers.

Allocation concealment:

A-third party or opaque sealed envelopes; B-unclear; C-open list, day of week or quasi-randomised.

Intention-to-treat:

A-intention to treat analysis with minimal missing data; B-unclear; C-intention to treat analysis not performed or performed with substantial missing data.

Blinding of participants:

A-patient is blinded; B-unclear; C-patient is aware of allocation.

Blinding of outcomes assessors:

A-assessor is blinded or independent; B-unclear; C-assessor is aware of allocation.

Dealing with missing data

We requested missing data from trial authors, including:

a) Summary of melanoma outcomes

- Number of participants and duration of trial (Table 1).

Table 1. Numbers of participants and incidence calculations (Continued)

MAAS 1993	Statin	193	188	4.0	772 / 752	0 / 772 = 0	0 / 752 = 0
LIPID 1998	Statin	4512	4502	6.1	27523 / 27462	30 / 27523 = .00109	28 / 27462 = .00102
CARE 1996	Statin	2081	2078	5.0	10405 / 10390	4 / 10405 = .00038	3 / 10390 = .00029
WOSCOP 1995	Statin	3302	3293	4.9	16180 / 16136	4 / 16180 = .00025	6 / 16136 = .00037
BIP 2000	Fibrate	1548	1542	6.2	9598 / 9560	2 / 9598 = .00021	6 / 9560 = .00063
CDP 1986	Fibrate	1103	2789 (lactose)	6.2	6839 / 17292	2 / 6839 = .00029	3 / 17292 = .00017
ROP 1992	Fibrate	361	359	4.0	1444 / 1436	-	-
HHS 1987	Fibrate	2051	2030	5.0	10255 / 10150	1 / 10255 = .00010	0 / 10150 = 0
DIS 1991	Fibrate	379	760	5.0	1895 / 3800	-	-
WHO 1973	Fibrate	5331	10414	5.3	28254 / 55194	0 / 28254 = 0	0 / 53794 = 0
LEADER 2002	Fibrate	783	785	4.6	3602 / 3611	1 / 3602 = .00028	1 / 3611 = .00028
VA-HIT 1999	Fibrate	1264	1267	5.1	6446 / 6462	1 / 6446 = .00016	9 / 6462 = .00139
BECAIT 1998	Fibrate	47	45	5.0	235 / 225	0 / 235 = 0	0 / 225 = 0

- Participant drop-outs (Table 2) i.e. people who stop taking their study medication before a study endpoint. This may be due to side effects, personal decisions, moving away from the study centre, etc. These people can still be contacted by the study investigators.

Table 2. Additional study characteristics

Trial acronym	Full trial name	Country	Study drug	Control	Treatment (M/F)	Control/other (M/F)	Dropout total (T/C)	Follow-up loss (T/C)
4S 1994	Scandinavian Simvastatin Survival Study (4S)	Norway, Denmark, Finland, Iceland, Sweden	Simvastatin	Placebo	1814 / 407	1803 / 420	10.4% / 13.0%	0.0% / 0.0%
ALLHAT 2002	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	US, Puerto Rico, Virgin Islands, Canada	Pravastatin	Usual care	2659 / 2511	2645 / 2540	22.6% / 32.0%	2.2% / 2.7%
AFCAPS 1998	Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS)	US	Lovastatin	Placebo	2805 / 499	2803 / 498	29.3% / 37.0%	
MAAS 1993	Multi-centre Anti-Atheroma Study (MAAS)	Netherlands, Sweden, UK, Germany, Belgium, France	Simvastatin	Placebo	171 / 22	165 / 23	25.4% / 28.7%	
LIPID 1998	Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Australia, New Zealand	Pravastatin	Placebo	3756 / 756	3742 / 760	19% / 24%	

Table 2. Additional study characteristics (Continued)

CARE 1996	Cholesterol and Recurrent Events Trial (CARE)	Canada, US	Pravastatin	Placebo	1790 / 291	1787 / 291	2% / 8%	
WOSCOF 1995	West of Scotland Coronary Protection Study (WOSCOF)	UK	Pravastatin	Placebo	3302 / 0	3293 / 0	29.6% / 30.8%	
BIP 2000	Bezafibrate Infarction Prevention Study (BIP)	Israel	Bezafibrate	Placebo	1412 / 136	1413 / 129	23% / 26%	
CDP 1986	Coronary Drug Project (CDP)	US, Puerto Rico	Clofibrate	Placebo (lactose). There were other arms i.e. estrogen, dextrothyroxine and niacin, but no data was provided.	1103 / 0	2789 / 0 2220/0 1110/0 1119/0	5.6% / 6.1%	
ROP 1992	Rate of Progression (ROP)	Italy	Bezafibrate	Unclear if placebo or usual care	199 / 162	194 / 165	0.8% / 3.1%	
HHS 1987	Helsinki Heart Study (HHS)	Finland	Gemfibrozil	Placebo	2051 / 0	2030 / 0	31.3% / 28.5%	0.0% / 0.0%
DIS 1991	Diabetes Intervention Study (DIS)	Germany	Clofibrate	Placebo and intensified health education	379 (M + F)	760 (M + F)	11.9% / 11.3%	

Table 2. Additional study characteristics (Continued)

WHO 1973	World Health Organization Study (WHO)	UK, Czechoslovakia, Hungary	Clofibrate	Placebo	5331 / 0	10414 / 0	34.4% / 32.8%	/	
LEADER 2002	Lower Extremity Arterial Event Reduction Trial (LEADER)	UK	Bezafibrate	Placebo	783 / 0	785 / 0	48.7% / 52.5%	/	1.5% / 1.1%
VA-HIT 1999	Veterans Affairs Cooperative Studies Program High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)	US	Gemfibrozil	Placebo	1264 / 0	1267 / 0	29% / 29%		
BECAIT 1998	Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)	Sweden	Bezafibrate	Placebo	47 / 0	45 / 0	10.6% / 13.3%	/	

- Participants lost to follow up (Table 2).
- Melanoma incidence (Table 3).

Table 3. Melanoma incidence and source of information

Trial	Published (T/C)	Unpublished (T/C)	Reason Undisclosed	Melanoma/pers/yr (T)	Melanoma/pers/yr (C)
4S 1994	-	7 / 3	-	0.00058	.00025

Table 3. Melanoma incidence and source of information (Continued)

ALLHAT 2002	-	-	Declined pending publication of research	-	-
AFCAPS 1998	14 / 27	-	-	0.00081	0.00157
MAAS 1993	-	0 / 0	-	0.0	0.0
LIPID 1998	-	30 / 28	-	0.00109	0.00102
CARE 1996	4 / 3	-	-	0.00038	0.00029
WOSCOP 1995	-	4 / 6	-	0.00025	0.00037
BIP 2000	-	2 / 6	-	0.00021	0.00063
CDP 1986	-	2 / 3	-	0.00029	0.00017
ROP 1992	-	-	None provided	-	-
HHS 1987	1 / 0	-	-	0.00010	0.0
DIS 1991	-	-	None provided	-	-
WHO 1973	-	0 / 0	-	0.0	0.0
LEADER 2002	-	1 / 1	-	0.00028	0.00028
VA-HIT 1999	1 / 9	-	-	0.00016	0.00139
BECAIT 1998	-	0 / 0	-	0.0	0.0

b) Data source

- Published versus unpublished obtained via correspondence with trial authors (Table 3).

c) All information available on the histology of incident melanoma and ensuing work-up including:

- Breslow depth (Table 4).

Table 4. Additional melanoma diagnosis data provided by trial authors

Trial	Treatment group	Clark Level	Breslow depth	Stage	Histological subtype	Trial yr diagnosis	Gender	Ulc/Sent Lymph Node
LIPID 1998	Control (Placebo)	-	-	-	-	5	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	3	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	6	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	3	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	6	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	4	Male	-
LIPID 1998	Control (Placebo)	IV	-	-	-	7	Male	-
LIPID 1998	Control (Placebo)	I	-	-	-	5	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	3	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	5	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	2	Male	-

Table 4. Additional melanoma diagnosis data provided by trial authors (Continued)

LIPID 1998	Treatment (Pravastatin)	II	-	-	-	3	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	6	Male	-
LIPID 1998	Treatment (Pravastatin)	IV	-	-	-	4	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	1	Male	-
LIPID 1998	Control (Placebo)	IV	-	-	-	2	Male	-
LIPID 1998	Control (Placebo)	-	-	-	Superficial spreading	4	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	4	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	7	Female	-
LIPID 1998	Control (Placebo)	-	-	-	Nodular	3	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	5	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	6	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	4	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Male	-

Table 4. Additional melanoma diagnosis data provided by trial authors (Continued)

LIPID 1998	Treatment (Pravastatin)	-	-	-	-	2	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	5	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	4	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Male	-
LIPID 1998	Control (Placebo)	V	-	-	-	3	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	6	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	7	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	3	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	6	Male	-
LIPID 1998	Control (Placebo)	III	-	-	-	7	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Male	-

Table 4. Additional melanoma diagnosis data provided by trial authors (Continued)

LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	2	Female	-
LIPID 1998	Control (Placebo)	-	-	-	-	7	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	7	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Female	-
LIPID 1998	Treatment (Pravastatin)	II	-	-	-	3	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	7	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	3	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	3	Male	-
LIPID 1998	Control (Placebo)	III	-	-	Superficial spreading	3	Male	-
LIPID 1998	Treatment (Pravastatin)	III	-	-	-	1	Female	-

Table 4. Additional melanoma diagnosis data provided by trial authors (Continued)

LIPID 1998	Control (Placebo)	-	-	-	-	5	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	3	Male	Cervical lymph nodes
LIPID 1998	Control (Placebo)	-	-	-	Superficial spreading	5	Male	-
LIPID 1998	Treatment (Pravastatin)	II	-	-	-	1	Male	-
LIPID 1998	Control (Placebo)	-	-	-	Superficial spreading	5	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	4	Male	-
LIPID 1998	Control (Placebo)	-	-	-	-	3	Male	-
LIPID 1998	Treatment (Pravastatin)	-	-	-	-	5	Female	-
VA-HIT 1999	Control (Placebo)	-	-	-	-	5	Male	-
VA-HIT 1999	Control (Placebo)	-	-	-	-	2	Male	-
VA-HIT 1999	Control (Placebo)	-	-	-	-	5	Male	-
VA-HIT 1999	Control (Placebo)	-	-	-	-	2	Male	-
VA-HIT 1999	Control (Placebo)	-	-	-	-	2	Male	-
VA-HIT 1999	Control (Placebo)	-	-	-	-	2	Male	-

Table 4. Additional melanoma diagnosis data provided by trial authors (Continued)

VA-HIT 1999	Control (Placebo)	-	-	-	-	2	Male	-
VA-HIT 1999	Control (Placebo)	-	-	-	-	5	Male	-
VA-HIT 1999	Control (Placebo)	-	-	-	-	1	Male	-
VA-HIT 1999	Treatment (Gemfibrozil)	-	-	-	-	6	Male	-
CARE 1996	Control (Placebo)	-	-	-	-	5	Male	-
CARE 1996	Control (Placebo)	-	-	-	-	2	Male	-
CARE 1996	Control (Placebo)	-	-	-	-	4	Male	-
CARE 1996	Treatment (Pravastatin)	-	-	-	-	5	Male	-
CARE 1996	Treatment (Pravastatin)	-	-	-	-	2	Male	-
CARE 1996	Treatment (Pravastatin)	-	-	-	-	3	Male	-
CARE 1996	Treatment (Pravastatin)	-	-	-	-	3	Male	-
WOSCOP 1995	Control (Placebo)	-	-	Metastatic	-	-	Male	Axillary
WOSCOP 1995	Control (Placebo)	-	-	-	Choroidal	-	Male	-

Table 4. Additional melanoma diagnosis data provided by trial authors (Continued)

WOSCOP 1995	Control (Placebo)	-	-	-	Lentigo maligna melanoma	-	Male	-
WOSCOP 1995	Control (Placebo)	-	0.75 mm	-	Superficial spreading	-	Male	-
WOSCOP 1995	Control (Placebo)	-	0.8 mm	-	Superficial spreading	-	Male	-
WOSCOP 1995	Control (Placebo)	-	-	-	Superficial spreading	-	Male	-
WOSCOP 1995	Treatment (Pravastatin)	-	-	-	Choroidal	-	Male	-
WOSCOP 1995	Treatment (Pravastatin)	-	4.0 mm	-	Nodular	-	Male	-
WOSCOP 1995	Treatment (Pravastatin)	-	0.0 mm	Stage 0	-	-	Male	-
WOSCOP 1995	Treatment (Pravastatin)	-	0.92 mm	Stage I	-	-	Male	-
BIP 2000	Control (Placebo)	I	0.0 mm	Stage 0 (In-situ)	-	6	Male	-
BIP 2000	Control (Placebo)	-	-	Stage III	Nodular melanoma	1	Male	-
BIP 2000	Control (Placebo)	-	-	Stage IV	-	4	Male	-
BIP 2000	Control (Placebo)	-	-	Metastatic	-	1	Male	-
BIP 2000	Treatment (Bezafibrate)	-	-	Stage III	Superficial spreading	2	Male	-

Table 4. Additional melanoma diagnosis data provided by trial authors (Continued)

BIP 2000	Treatment (Bezafibrate)	-	-	-	-	6	Male	-
CDP 1986	Control (Lactose placebo)	-	-	-	-	6	Male	-
CDP 1986	Control (Lactose placebo)	-	-	-	-	6	Male	-
CDP 1986	Treatment (Clofibrate)	-	-	-	-	6	Male	-
CDP 1986	Treatment (Clofibrate)	-	-	-	-	4	Male	-
LEADER 2002	Control (Placebo)	-	0.0 mm	Stage 0 (In-situ)	Lentigo maligna melanoma	5	Male	-
LEADER 2002	Treatment (Bezafibrate)	-	0.0 mm	Stage 0 (In-situ)	Lentigo maligna melanoma	2	Male	-

- Clark level (Table 4).
- Histological type of melanoma (lentigo maligna, acral lentiginous, superficial spreading, and nodular) (Table 4).
- Presence or absence of ulceration (Table 4).
- Sentinel lymph node status (Table 4).
- Stage (Table 4).
- Site of diagnosis (not available to protect patient confidentiality).
- Additional melanoma diagnosis data (provided by trial author) (Table 4).
- Mortality due to melanoma, collected from published and unpublished data from correspondence with study authors (Table 5).

Table 5. Mortality due to melanoma

Trial	Deaths (T)	Deaths (C)	Death rate (T/C)	Death post trial (T)	Death post trial (C)	Source
LIPID 1998	2	4	0.00007 / 0.00015	0	0	Unpublished
WOSCOP 1995	1	0	0.00006 / 0.0	0	0	Unpublished
BIP 2000	0	0	0.0 / 0.0	0	0	Unpublished
CDP 1986	0	0	0.0 / 0.0	1 (1 died 6 years post trial)	6 (2 died < 1 year post trial, 3 died 6 years post trial, 1 died 7 years post trial)	Unpublished

d) Exposure to statins and fibrates prior to initiation of trial participation for participants with melanoma

e) Information other than histological reports used to identify melanoma outcomes in the trials

We offered a monetary incentive (US\$ 50 for each unpublished melanoma) to offset costs associated with providing data. Published funding source (Table 6) and overall cancer incidence and mortality data from qualifying trials is presented (Table 7).

Table 6. Funding

Trial	Funding Type	Funding Source
4S 1994	Pharmaceutical	Merck Research Laboratories
ALLHAT 2002	Both	National Heart, Lung and Blood Institute, Pfizer, AstraZeneca and Bristol-Myers Squibb
AFCAPS 1998	Pharmaceutical	Merck & Co Inc. and SPECTRUM Pharmaceutical Research Corporation
MAAS 1993	Pharmaceutical	Merck Sharp & Dohme Research Laboratories
LIPID 1998	Both	Bristol-Myers Squibb Pharmaceutical Research Institute and the National Heart Foundation of Australia
CARE 1996	Pharmaceutical	Bristol-Myers Squibb Pharmaceutical Research Institute

Table 6. Funding (Continued)

WOSCOP 1995	Pharmaceutical	Bristol-Myers Squibb Pharmaceutical Research Institute
BIP 2000	Pharmaceutical	Boehringer Mannheim GmbH
CDP 1986	Non-Pharmaceutical	National Heart, Lung and Blood Institute
ROP 1992	Unknown	Unknown
HHS 1987	Pharmaceutical	Warner-Lambert Company
DIS 1991	Non-Pharmaceutical	National Diabetes Care Service of the former GDR
WHO 1973	Non-Pharmaceutical	British Heart Foundation, the Albert D. Lasker Foundation of New York City and Ministries of Health in Hungary and Czechoslovakia
LEADER 2002	Non-Pharmaceutical	Medical Research Council and British Heart Foundation
VA-HIT 1999	Pharmaceutical	Parke-Davis (division of Warner-Lambert Co.)
BECAIT 1998	Both	Boehringer Mannheim GmbH, Swedish Heart-Lung Foundation and Karolinska Institute

Table 7. Overall cancer incidence and mortality

Trial	Incidence (T)	Incidence (C)	Incidence rate (T/C)	Deaths (T)	Deaths (C)	Death rate (T/C)
4S 1994	-	-	-	33	35	0.015 / 0.016
ALLHAT 2002	369 (pravastatin)	378 (usual care)	0.071 / 0.073	163	148	0.032 / 0.029
AFCAPS 1998	252 (lovastatin)	259 (placebo)	0.076 / 0.078	-	-	-
MAAS 1993	-	-	-	-	-	-
LIPID 1998	403 (pravastatin)	417 (placebo)	0.089 / 0.093	128	141	0.028 / 0.031
CARE 1996	172 (pravastatin)	161 (placebo)	0.083 / 0.077	-	-	-
WOSCOP 1995	116 (pravastatin)	106 (placebo)	0.035 / 0.032	44	49	0.013 / 0.015
BIP 2000	85 (bezafibrate)	91 (placebo)	0.055 / 0.059	-	-	-
CDP 1986	-	-	-	11	27	0.010 / 0.010
ROP 1992	-	-	-	-	-	-
HHS 1987	31 (gemfibrozil)	26 (placebo)	0.015 / 0.013	31	26	0.015 / 0.013
DIS 1991	-	-	-	2	5	0.005 / 0.007

Table 7. Overall cancer incidence and mortality (Continued)

WHO 1973	-	-	-	58	83	0.011 / 0.008
LEADER 2002	-	-	-	47	47	0.060 / 0.060
VA-HIT 1999	125 (gemfibrozil)	138 (placebo)	0.099 / 0.109	45	51	0.036 / 0.040
BECAIT 1998	-	-	-	-	-	-

Data synthesis

Analysis

We analysed the effects of statins and fibrates separately. A detailed description of individual studies and their potential inadequacies is presented in the 'Characteristics of included studies' table and in the 'Assessment of risk of bias in included studies' section. We used a random effects model and odds ratios (OR with 95% confidence intervals (CI)) to estimate pooled treatment effects. We have expressed the results in terms of presence or absence of a melanoma diagnosis.

Due to lack of participant-specific data, we were not able to adjust for differences in the length of follow-up in the different study arms and we did not adjust melanoma incidence for study drop-outs. We calculated melanoma incidence using the following formula: (number of incident melanomas in study arm)/(number of persons in study arm)(duration of trial in years).

Subgroup analysis and investigation of heterogeneity

If moderate statistical heterogeneity was observed ($I^2 > 50\%$), we used sensitivity analyses to examine the effects of excluding the following study subgroups: studies with less than 500 participants, studies with pharmaceutical industry funding, and studies with lower reported methodological quality.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Results of the search

Automated searches produced 4405 unique published paper titles indicating trials that may have involved the use of statins or fibrates in RCTs. From the initial results, 109 trials qualified for abstract assessment based on title relevance. Of these, we excluded 37 trials

after abstract review and examined 72 trials by reviewing the full paper. Sixteen trials met all qualifications (see 'Characteristics of included studies') and we included them. The key publications for each trial appear in the tables giving the characteristics of included and excluded studies.

Included studies

Of the 16 qualifying trials, 7 were statin trials and 9 were fibrate trials. None of the qualifying trials collected cancer incidence as a primary outcome. Seven of the 16 trials enrolled only men. Two trials excluded participants with cancer (BECAIT 1998; DIS 1991). Trials were conducted in nearly 20 different countries (Table 2).

Three different statins were employed in the qualifying trials (lovastatin, pravastatin, and simvastatin), with treatment doses ranging from 20 to 40 mg per day. The fibrate trials used 3 types of fibrates (bezafibrate, clofibrate, and gemfibrozil) and daily dosages ranged from 400 to 1800 mg.

We sent the corresponding author of each qualifying trial a packet of forms asking for additional data on any participant who developed melanoma. Nine of the qualifying trials provided unpublished melanoma incidence data and seven provided participant-specific data (Table 4). Methods of validation of melanoma diagnosis were frequently unreported. The only trial which used other (non statin or fibrate) treatment arms provided melanoma incidence data on the fibrate treatment and placebo arms only, thus we could only use these two arms for our analysis (CDP 1986).

Excluded studies

We excluded 56 trials (see 'Characteristics of excluded studies') based on failure to meet inclusion criteria (was not randomised, used drugs in addition to statins or fibrates, had a mean participant treatment duration of less than four years).

Risk of bias in included studies

We evaluated each study for quality according to the following assessment criteria: descriptions of randomisation, concealment, intention-to-treat, blinding of participants, and blinding of assessors (Table 8).

Table 8. Methodological quality

Trial	Randomisation	Concealment	Intention to Treat	Blinding of Particip	Blinding Assessors
4S 1994	A-Based on clear description of how random numbers were generated	A-Third party or opaque sealed envelopes	A-Intention to treat analysis with minimal missing data	A-Patient is blinded	A-Assessor is blinded or independent
ALLHAT 2002	A-Based on clear description of how random numbers were generated	A-Third party or opaque sealed envelopes	A-Intention to treat analysis with minimal missing data	C-Patient is aware of allocation	C-Assessor is aware of allocation
AFCAPS 1998	B-Unclear	B-Unclear	A-Intention to treat analysis with minimal missing data	A-Patient is blinded	A-Assessor is blinded or independent
MAAS 1993	B-Unclear	B-Unclear	A-Intention to treat analysis with minimal missing data	A-Patient is blinded	A-Assessor is blinded or independent
LIPID 1998	A-Based on clear description of how random numbers were generated	B-Unclear	A-Intention to treat analysis with minimal missing data	A-Patient is blinded	A-Assessor is blinded or independent
CARE 1996	A-Based on clear description of how random numbers were generated	A-Third party or opaque sealed envelopes	A-Intention to treat analysis with minimal missing data	A-Patient is blinded	A-Assessor is blinded or independent
WOSCOP 1995	A-Based on clear description of how random numbers were generated	B-Unclear	A-Intention to treat analysis with minimal missing data	A-Patient is blinded	A-Assessor is blinded or independent
BIP 2000	B-Unclear	B-Unclear	A-Intention to treat analysis with minimal missing data	A-Patient is blinded	A-Assessor is blinded or independent
CDP 1986	A-Based on clear description of how random numbers were generated	A-Third party or opaque sealed envelopes	B-Unclear	A-Patient is blinded	A-Assessor is blinded or independent

Table 8. Methodological quality (Continued)

ROP 1992	B-Unclear	B-Unclear	B-Unclear	B-Unclear	B-Unclear
HHS 1987	A-Based on clear description of how random numbers were generated	A-Third party or opaque sealed envelopes	A-Intention to treat analysis with minimal missing data	A-Patient is blinded	A-Assessor is blinded or independent
DIS 1991	B-Unclear	B-Unclear	B-Unclear	A-Patient is blinded	A-Assessor is blinded or independent
WHO 1991	B-Unclear	B-Unclear	A-Intention to Treat Analysis with Minimal Missing Data	A-Patient is blinded	A-Assessor is blinded or independent
LEADER 2002	B-Unclear	B-Unclear	A-Intention to Treat Analysis with Minimal Missing Data	A-Patient is blinded	A-Assessor is blinded or independent
VA-HIT 1999	A-Based on clear description of how random numbers were generated	B-Unclear	A-Intention to Treat Analysis with Minimal Missing Data	A-Patient is blinded	A-Assessor is blinded or independent
BECAIT 1998	A-Based on clear description of how random numbers were generated	B-Unclear	B-Unclear	A-Patient is blinded	A-Assessor is blinded or independent

Allocation

phone call centre. The 11 other studies did not fully describe allocation concealment.

Randomisation

Nine of the 16 studies gave clear descriptions of how random numbers were generated: 7 trials utilized a block randomisation design (4S 1994; BECAIT 1998; CDP 1986; HHS 1987; LIPID 1998; VA-HIT 1999; WOSCOP 1995), 1 trial randomised by telephone through a call centre (CARE 1996), and 1 trial used both a block design and call centre (ALLHAT 2002). The remaining seven studies did not fully specify how random numbers were generated for randomisation.

Allocation concealment

Five studies clearly described the method of allocation concealment: 4S 1994 used sequential assignment of pre-packaged test medications; the drug supplier for the HHS 1987 trial dispensed packages in numerical order; CDP 1986 used a 3 party and opaque sealed envelopes; ALLHAT 2002 and CARE 1996 used a tele-

Blinding

All but two of the studies blinded both participants and assessors to the assigned treatment groups. ALLHAT 2002 did not conceal allocation from the participant or assessor and ROP 1992 did not clearly state if there was blinding.

Since melanoma incidence was not a primary outcome of any of the qualifying studies the effect of randomisation and selection bias, blinding of outcome assessment and detection bias, handling of losses and attrition bias, and non-blinding of the ALLHAT 2002 trial are difficult to predict or assess. Two trials excluded participants with a history of cancer (BECAIT 1998; DIS 1991), which may have led to lower melanoma incidence in these trials. Rates for dropout (i.e. people who stop taking their study medication before a study endpoint but who can still be contacted by the study investigators) ranged from 2% to 30.8% in statin trials and 0.8% to 52.5% in fibrate trials (Table 2). The CDP trial dropout rates were provided by author correspondence. Four of the

16 trials included rates for loss to follow up (i.e. participants with whom the study loses contact) which ranged from 0% to 2.7% (Table 2). Twelve of the 16 trials had separate pre-trial publications dedicated specifically to describing trial design.

Selective reporting

Intention to treat analysis

Twelve of the studies performed intention-to-treat (ITT) analysis. Four studies did not clearly state if ITT analysis was used (BECAIT 1998; CDP 1986; DIS 1991; ROP 1992).

Effects of interventions

Primary Outcome

Melanoma incidence (number of people per year diagnosed with a new melanoma)

We identified sixteen qualifying RCTs (7 statin, 9 fibrate) of which 13 provided data on incident melanomas (6 statin, 7 fibrate) (Table 9). Fifty-nine incident melanomas were collectively reported in published trial papers (20 statins and fibrates, 39 placebo or other control therapies) and an additional 93 were identified in unpublished data via correspondence with trial authors (46 statins and fibrates, 47 placebo or other control therapies) (Table 3). Rates of melanoma incidence varied from 0.0 to 0.0016 melanomas per person per year (Table 3).

Table 9. Trials and melanoma incidence by medication

Lovastatin (T/C)	Pravastatin (T/C)	Simvastatin (T/C)	Bezafibrate (T/C)	Clofibrate (T/C)	Gemfibrozil (T/C)
AFCAPS 1998 (14 / 27); Post Trial 2 Years (12 / 22)	CARE 1996 (4 / 3); Male (4 / 3), Female (0 / 0); Post Trial 2 Years (2 / 2)	4S 1994 (7 / 3)	BECAIT 1998 (0 / 0); Male (0 / 0), Female (0 / 0)	CDP 1986 (2 / 3); Male (2 / 3); Post Trial 2 Years (2 / 2)	HHS 1987 (1 / 0); Male (1 / 0)
	LIPID 1998 (30 / 28); Male (26 / 27), Female (4 / 1); Post Trial 2 Years (20 / 18)	MAAS 1993 (0 / 0); Male (0 / 0), Female (0 / 0)	BIP 2000 (2 / 6); Male (2 / 6), Female (0 / 0); Post Trial 2 Years (1 / 2)	WHO 1973 (0 / 0); Male (0 / 0)	VA-HIT 1999 (1 / 9); Male (1 / 9); Post Trial 2 Years (1 / 3)
	WOSCOP 1995 (4 / 6); Male (4 / 6)		LEADER 2002 (1 / 1); Male (1 / 1)		

Two trials had previously reported statistically significantly fewer incident melanomas in treated participants (AFCAPS 1998; VA-HIT 1999). However none of the nine studies providing unpub-

lished melanoma incidence data had significantly fewer incident melanomas in treated people. Three trials have not provided data on melanoma incidence: ALLHAT 2002, DIS 1991, and ROP

1992. The investigators from the [ALLHAT 2002](#) study have stated they will not release this data until publication of a manuscript reporting cancer incidence in their study. The investigators from the [DIS 1991](#) study have stated that this Cochrane review does not possess high enough Institutional Review Board clearance to allow access to their data. The investigators from the [ROP 1992](#) study corresponded but did not provide the requested melanoma outcomes data.

1. Statins or fibrates versus control

Based on all acquired data, we found no significant association between lower melanoma incidence and the use of statins (odds ratio 0.90, 95% confidence interval 0.56 to 1.44; Analysis 1.1) or fibrates (odds ratio 0.58, 95% confidence interval 0.19 to 1.82; Analysis 2.1)

We performed limited stratified data analysis by:

- (a) type of statin (six studies; Analysis 1.1)
- (b) type of fibrate (seven studies; Analysis 2.1)
- (c) gender of the participant (ten studies; Analysis 3.1)
- (d) melanoma incidence after two years of participation (six studies; Analysis 4.1)

(e) trial funding (13 studies; Analysis 5.1).

This analysis also failed to show statistically significant differences in all cases, except for the statin subgroup analysis which showed reduced melanoma incidence for lovastatin. However, we only included one trial in the analysis (odds ratio 0.52, 95% confidence interval 0.27 to 0.99; Analysis 1.1) ([AFCAPS 1998](#)). From the lovastatin results, 244 people need to be treated (NNT) for 5 years to prevent 1 melanoma.

Secondary Outcomes

We could not analyse the secondary outcomes due to low event rates or lack of information.

1. Incidence of melanomas with poor prognosis (> 3 mm thick and ulcerated)

Of the 152 reported melanomas, Breslow depth was only provided for 8, Clark level for 12 and melanoma stage for 10 ([Table 4](#)).

2. Incidence of dysplastic naevi (a mole with atypical architecture or cellular features), confirmed by histological report

There was no information reported for dysplastic naevi ([Table 10](#)).

Table 10. Dysplastic naevus incidence

Trial	Dysplastic Naevi
4S 1994	None
ALLHAT 2002	None
AFCAPS 1998	None
MAAS 1993	None
LIPID 1998	None
CARE 1996	None
WOSCOP 1995	None
BIP 2000	None
CDP 1986	None
ROP 1992	None
HHS 1987	None

Table 10. Dysplastic naevus incidence (Continued)

DIS 1991	None
WHO 1973	None
LEADER 2002	None
VA-HIT 1999	None
BECAIT 1998	None

3. Overall cancer incidence (tumours of any organ)

Overall cancer incidence rates ranged from 0.015 to 0.099 and 0.013 to 0.109 in the treatment and control groups respectively, and cancer death rates ranged from 0.005 to 0.060 and 0.007 to 0.060 in the treatment and control groups respectively (Table 7).

4. Mortality due to melanoma

Melanoma death rates ranged from 0.0 to 0.00011 in both the treatment and control groups (Table 5).

DISCUSSION

Summary of main results

This review examined the association of therapy (statins or fibrates) with an unanticipated secondary outcome (melanoma prevention). Two trials had previously reported statistically significantly fewer incident melanomas in treated participants (AFCAPS 1998; VA-HIT 1999). However, we found that additional unpublished data (melanoma incidence from trials that had not published this data) did not yield statistically significant evidence to support or exclude this association. More studies are needed to obtain sufficient power to exclude a potentially clinically useful effect.

Potential biases in the review process

The dangers of publication bias were highlighted in this review. Both studies finding a significant decrease in melanoma incidence associated with drug therapy (AFCAPS 1998; VA-HIT 1999) published these results while only 2 of 11 studies showing no significant association published their results (Table 3). This underscores the danger of drawing conclusions using only published data. Systematic reviews are often hindered by lack of access to unpublished data of qualifying trials. To minimize this barrier, our study contacted investigators possessing potentially relevant

unpublished data and offered a monetary incentive for the provision of melanoma data (US\$ 50 for each unpublished melanoma). Two studies requested payment of the monetary incentive offered (CDP 1986; WOSCOP 1995), and one study deemed the money essential for the retrieval of the melanoma outcomes data requested (CDP 1986). Additionally, we have no information on melanoma development in participants lost to follow up. Because event rates are so small, the potential impact of missing data could be substantial.

Given the lack of evidence to exclude the hypothesis that statins and fibrates prevent melanoma, further work to continue this investigation is needed. Corroborating evidence for fibrate use for melanoma prevention or treatment is minimal, however evidence for statin use for melanoma prevention or treatment continues to build: cohort studies support reduced risk of melanoma in people taking statins (Dellavalle 2003) and in vitro, statins induce melanoma apoptosis (cell death) and increase the cell killing effects of drugs used for melanoma chemotherapy (Feleszko 1998; Feleszko 2002; Nordenberg 1996). Animal model data and in vitro work also suggest that statins might reduce melanoma migration potential and metastasis (Collisson 2003; Jani 1995). Thus this meta-analysis supports further research into the potential use of statins for melanoma prevention and the utility of testing statins as therapy, especially if combined with chemotherapy to produce synergistic effects (Sleijfer 2005). Given the paucity of effective therapies for advanced melanoma, Phase I and II clinical trials combining statins with chemotherapy might still appear reasonable to test whether this drug combination is tolerable and if so, more effective than current chemotherapy alone.

The systematic review had several limitations. The data came from 13 trials with mostly male participants using 6 different drugs. Cancer was not a primary endpoint of most of the included trials. Not all primary participant data regarding melanoma diagnosis was available. At least 1 item of histological data (such as Breslow depth, Clark level, histological subtype) was reported for only 32 out of 152 melanomas preventing exploration of the potential impact of use of statins or fibrates on variables at diagnosis. No data on dysplastic naevi, a marker of melanoma risk, was reported and studies may not have randomised the participants equally by

the various risk factors for melanoma (e.g. dysplastic naevi).

AUTHORS' CONCLUSIONS

Implications for practice

The melanoma outcomes data collected by this study from randomised, controlled trials of statins or fibrates does not exclude the hypothesis that these drugs prevent melanoma. There was a 10% reduction in melanoma incidence for people on statins and a 42% reduction for those on fibrates, however these results were not statistically significant. Until further evidence is established, limiting exposure to ultraviolet radiation remains the most effective way to reduce the risk of melanoma.

Implications for research

While this meta-analysis does not exclude the potential use of statins or fibrates in isolation for melanoma prevention, it does call for further exploration of the use of these drugs in melanoma therapy. Whether these drugs can inhibit metastasis or augment the effect of chemotherapeutic agents in advanced melanoma still merits further investigation (Collisson 2003; Grabacka 2004; Sleijfer 2005). This lack of evidence warrants further work assessing the role of statins and fibrates in melanoma.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

4S 1994

Methods	AC: sequential assignment of pre-packaged test medications RS: block randomisation B: double-blind ITT	
Participants	4444 randomised (2221 treatment, 2223 control), male and female, 35 to 70 yrs of age	
Interventions	Simvastatin (10 to 40 mg qd) vs placebo	
Outcomes	Melanoma incidence provided by author correspondence [1°- Death, major coronary events]	
Notes	5.4 yrs mean f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

AFCAPS 1998

Methods	AC: unclear RS: unclear B: double-blind ITT	
Participants	6605 randomised (3304 treatment, 3301 control), male and female, 45 to 73 yrs of age	
Interventions	Lovastatin (20 to 40 mg qd) vs placebo	
Outcomes	Melanoma incidence published [1°- First acute major coronary event]	
Notes	5.2 yrs mean f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

ALLHAT 2002

Methods	AC: telephone call centre RS: block randomisation and call centre B: none ITT	
Participants	10355 randomised (5170 treatment, 5185 control), male and female, 66 yrs mean age	
Interventions	Pravastatin (40 mg qd) vs usual care	
Outcomes	Melanoma incidence not provided [1°- All causes mortality, CHD events]	
Notes	4.8 yrs mean f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

BECAIT 1998

Methods	AC: unclear RS: block randomisation B: double-blind	
Participants	92 randomised (47 treatment, 45 control), male only, 45 yrs of age or younger	
Interventions	Bezafibrate (200 mg TID) vs placebo	
Outcomes	Melanoma incidence provided by author correspondence [1°- Change in lumen diameter]	
Notes	5 yrs f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

BIP 2000

Methods	AC: unclear RS: unclear B: double-blind ITT	
Participants	3090 randomised (1548 treatment, 1542 control), male and female, 45 to 74 yrs of age	
Interventions	Bezafibrate (400 mg qd) vs placebo	
Outcomes	Melanoma incidence provided by author correspondence [1°- Fatal MI, non-fatal MI or sudden death]	
Notes	6.2 yrs mean f/u; 32 pts were excluded after randomisation	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

CARE 1996

Methods	AC: telephone call center RS: telephone call centre B: double-blind ITT	
Participants	4159 randomised (2081 treatment, 2078 control), male and female, 21 to 75 yrs of age	
Interventions	Pravastatin (40 mg qd) vs placebo	
Outcomes	Melanoma incidence published [1°- Death from coronary heart disease or MI]	
Notes	5 yrs median f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

CDP 1986

Methods	AC: third party and opaque sealed envelopes RS: block randomisation B: double-blind
Participants	8341 randomised (2220 estrogen, 1110 dextrothyroxine, 1103 clofibrate, 1119 niacin, 2789 lactose), male only, 30 to 64 yrs of age
Interventions	Estrogen (2.5 mg qd) vs estrogen (5.0 mg qd) vs dextrothyroxine (6 mg qd) vs clofibrate (1.8 g qd) vs niacin (3.0 mg qd) vs placebo (lactose qd)
Outcomes	Melanoma incidence provided by author correspondence [1°- Mortality (all causes), CAD, CUD, CNS dz, Infxn]
Notes	6.2 yrs median f/u (5.4 yrs mean f/u for clofibrate; 5.3 yrs mean f/u for lactose)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

DIS 1991

Methods	AC: unclear RS: unclear B: double-blind
Participants	1139 randomised (379 treatment, 760 control), male and female, 30 to 55 yrs of age
Interventions	Clofibrate (1.6 g qd) vs placebo vs placebo and intensified health education
Outcomes	Melanoma incidence not provided [1°- IHD, MI, or cardiac death]
Notes	5 yrs f/u

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

HHS 1987

Methods	AC: drug supplier dispensed packages in numerical order RS: block randomisation B: double-blind ITT	
Participants	4081 randomised (2051 treatment, 2030 control), male only, 40 to 55 yrs of age	
Interventions	Gemfibrozil (600 mg BID) vs placebo	
Outcomes	Melanoma incidence published [1°- MI (fatal and non-fatal)]	
Notes	5 yrs mean f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

LEADER 2002

Methods	AC: unclear RS: unclear B: double-blind ITT	
Participants	1568 randomised (783 treatment, 785 control), male only, 68 yrs mean age	
Interventions	Bezafibrate (400 mg qd or qod if creatine 135 to 149 mmol/l) vs placebo	
Outcomes	Melanoma incidence provided by author correspondence [1°- CHD (fatal or nonfatal)]	
Notes	4.6 yrs median f/u; one clinic was excluded because of poor "quality data"	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

LIPID 1998

Methods	AC: unclear RS: block randomisation B: double-blind ITT	
Participants	9014 randomised (4512 treatment, 4502 control), male and female, 62 yrs median age	
Interventions	Pravastatin (40 mg qd) vs placebo	
Outcomes	Melanoma incidence provided by author correspondence [1°- Mortality from CHD]	
Notes	6.1 yrs mean f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

MAAS 1993

Methods	AC: unclear RS: unclear B: double-blind ITT	
Participants	381 randomised (193 treatment, 188 control), male and female, 55 yrs mean age	
Interventions	Simvastatin (20 mg qd) vs placebo	
Outcomes	Melanoma incidence provided by author correspondence [1°- Change in width of segments measured by coronary angiography]	
Notes	4 yrs f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

ROP 1992

Methods	AC: unclear RS: unclear B: unclear	
Participants	720 randomised (361 treatment, 359 control), male and female, 55 to 60 yrs of age	
Interventions	Bezafibrate (400 mg qd) vs control (unclear if placebo or usual care)	
Outcomes	Melanoma incidence not provided [1°- rate of progression from one class of stenosis to the next]	
Notes	4 yrs f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

VA-HIT 1999

Methods	AC: unclear RS: block randomisation B: double-blind ITT	
Participants	2531 randomised (1264 treatment, 1267 control), male only, 64 yrs mean age	
Interventions	Gemfibrozil (1200 mg qd) vs placebo	
Outcomes	Melanoma incidence published [1°- Nonfatal MI or CAD death]	
Notes	5.1 yrs of f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

WHO 1973

Methods	AC: unclear RS: unclear B: double-blind ITT	
Participants	15745 randomised (5331 treatment, 10414 control), male only, 30 to 59 yrs of age	
Interventions	Clofibrate (1.6 g qd) vs placebo (olive oil capsules)	
Outcomes	Melanoma incidence provided by author correspondence [1°- Ischaemic Heart disease (fatal and non-fatal) and death from all causes]	
Notes	5.3 yrs f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

WOSCOP 1995

Methods	AC: unclear RS: block randomisation B: double-blind ITT	
Participants	6595 randomised (3302 treatment, 3293 control), male only, 45 to 64 yrs of age	
Interventions	Pravastatin (40 mg qd) vs placebo	
Outcomes	Melanoma incidence provided by author correspondence [1°- Nonfatal MI, death from CHD]	
Notes	4.9 yrs mean f/u	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Methods

AC: method of allocation concealment

RS: method of generating randomisation sequence

B: blinding (participant, clinician, outcome assessment)

ITT= Intention-to-treat analysis

Participants:

exp=experimental
 Outcomes:
 1°= Primary outcome
 Notes:
 f/u = Follow-up years
 vs = versus
 pts = patients
 qd = every day

Characteristics of excluded studies *[ordered by study ID]*

Albert 2001	Mean Patient Treatment Period < 4 Years
Arad 2001	Lipid-Lowering Agent Not Used in Isolation
Arntz 2000	Mean Patient Treatment Period < 4 Years
Athyros 2002	Mean Patient Treatment Period < 4 Years
Avellone 1993	Mean Patient Treatment Period < 4 Years
Ballantyne 2001	Mean Patient Treatment Period < 4 Years
Bays 2003	Mean Patient Treatment Period < 4 Years
Campeau 1997	Lipid-Lowering Agent Not Used in Isolation
Carmena 1996	Mean Patient Treatment Period < 4 Years
Chung 2001	Mean Patient Treatment Period < 4 Years; No Randomisation
Colhoun 2004	Mean Patient Treatment Period < 4 Years
Corominas 1993	Mean Patient Treatment Period <4Years
DAIS Invest 2001	Mean Patient Treatment Period <4Years
Davidson 2000	Mean Patient Treatment Period < 4 Years
Diercks 2000	Lipid-Lowering Agent Not Used in Isolation
Elkeles 1998	Mean Patient Treatment Period <4Years
ENCORE 2003	Mean Patient Treatment Period < 4 Years

(Continued)

Garcia-Otin 2002	Mean Patient Treatment Period < 4 Years
Gentile 2000	Mean Patient Treatment Period < 4 Years
GISSI 2000	Mean Patient Treatment Period < 4 Years
Hagenaars 2001	Mean Patient Treatment Period < 4 Years
Hanefeld 1999	Mean Patient Treatment Period < 4 Years
Holdaas 2003	Lipid-Lowering Agent Not Used in Isolation
HPSCG 2002	Lipid-Lowering Agent Not Used in Isolation
Humphries 1998	Mean Patient Treatment Period < 4 Years
Hunninghake 2001	Mean Patient Treatment Period < 4 Years
Illingworth 2001	Mean Patient Treatment Period < 4 Years
Ito 2001	Mean Patient Treatment Period < 4 Years
J-CLAS 1997	Mean Patient Treatment Period < 4 Years
Jones 1998	Mean Patient Treatment Period < 4 Years
Kawaguchi 2002	Mean Patient Treatment Period < 4 Years
Kim 2001	Mean Patient Treatment Period < 4 Years
MacMahon 2000	Mean Patient Treatment Period < 4 Years
Markwood 2001	Mean Patient Treatment Period < 4 Years
McKenney 1998	Mean Patient Treatment Period < 4 Years
McPherson 2001	Mean Patient Treatment Period < 4 Years
Michels 2002	Mean Patient Treatment Period < 4 Years; No Randomisation
MIRACL 2001	Mean Patient Treatment Period < 4 Years
Muls 2001	Mean Patient Treatment Period < 4 Years
Newcastle 1971	Mean Patient Treatment Period < 4 Years

(Continued)

Ose 1999	Mean Patient Treatment Period < 4 Years
Pauciullo 2000	Mean Patient Treatment Period < 4 Years
PCABGTI 2003	Lipid-Lowering Agent Not Used in Isolation
Santos 2001	Mean Patient Treatment Period < 4 Years
Sawayama 2002	Mean Patient Treatment Period < 4 Years
Schwartz 2001	Mean Patient Treatment Period < 4 Years
Shepherd 2002	Mean Patient Treatment Period < 4 Years
Sirtori 1996	Mean Patient Treatment Period < 4 Years
SSP 1971	Mean Patient Treatment Period < 4 Years
Stelmach 1993	Mean Patient Treatment Period < 4 Years; No Randomisation
Syvanne 1997	Mean Patient Treatment Period < 4 Years
Teo 2000	Lipid-Lowering Agent Not Used in Isolation
VA Coop 1973	Mean Patient Treatment Period < 4 Years
Vichayanrat 2002	Mean Patient Treatment Period < 4 Years; No Randomisation
Wenke 1997	Lipid-Lowering Agent Not Used in Isolation
West 1996	Mean Patient Treatment Period < 4 Years

Characteristics of ongoing studies *[ordered by study ID]*

ASCOT 2001

Trial name or title	ASCOT Study
Methods	
Participants	40 to 79 yrs of age with hypertension

ASCOT 2001 (Continued)

Interventions	Atorvastatin (10 mg qd) vs placebo
Outcomes	1° - Non-fatal MI and fatal CHD
Starting date	2001
Contact information	Alison Adderkin a.adderkin@imperial.ac.uk +44 (0)20 7594 3447
Notes	

LDS 2004

Trial name or title	LDS 2004
Methods	
Participants	40 to 75 yrs of age with T2 DM, LDL 1.5<4.1 mmol/L, triglyceride <4.5 mmol/L, no CV disease
Interventions	Cerivastatin (0.4 mg qd) with micronised fenofibrate (200 mg qd) vs placebo
Outcomes	(unclear) Cardiovascular events
Starting date	unclear
Contact information	lds@dtu.ox.ac.uk +44 (0)1865 857257
Notes	

RESPECT 2003

Trial name or title	RESPECT
Methods	
Participants	65 to 80 yrs of age without documented CHD or stroke
Interventions	Cerivastatin (0.4 or 0.8 mg qd) vs placebo
Outcomes	1° - Time until first stroke and/or first primary cardiac event
Starting date	2003

RESPECT 2003 (Continued)

Contact information	Respect@medizin.uni-koeln.de +49 221 46867 0
Notes	

TNT 2005

Trial name or title	TNT Study
Methods	
Participants	35 to 75 yrs of age with CHD, LDL < 3.4 mmol/L
Interventions	Atorvastatin (10 mg qd) vs atorvastatin (80 mg qd)
Outcomes	1° - Major cardiovascular event; 2° - Major coronary event (death from CHD)
Starting date	1998
Contact information	jclarosa@downstate.edu
Notes	

DATA AND ANALYSES

Comparison 1. Statins versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Melanoma incidence	6	31198	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.56, 1.44]
1.1 Lovastatin	1	6605	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.27, 0.99]
1.2 Pravastatin	3	19768	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.65, 1.62]
1.3 Simvastatin	2	4825	Odds Ratio (M-H, Random, 95% CI)	2.34 [0.60, 9.06]

Comparison 2. Fibrates versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Melanoma incidence	7	30999	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.19, 1.82]
1.1 Bezafibrate	3	4750	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.11, 1.75]
1.2 Gemfibrozil	2	6612	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.02, 11.11]
1.3 Clofibrate	2	19637	Odds Ratio (M-H, Random, 95% CI)	1.69 [0.28, 10.11]

Comparison 3. Statins and fibrates versus control: subgroup analysis by gender

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Melanoma incidence	10	50767	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.54, 1.44]
1.1 Male (statins)	3	17670	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.59, 1.51]
1.2 Female (statins)	2	2098	Odds Ratio (M-H, Random, 95% CI)	4.04 [0.45, 36.20]
1.3 Male (fibrates)	7	30734	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.19, 1.82]
1.4 Female (fibrates)	1	265	Odds Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 4. Statins and fibrates versus control: subgroup analysis after two years of participation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Melanoma incidence	6	29291	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.53, 1.26]
1.1 Melanoma incidence after 2 years (statins)	3	19778	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.49, 1.33]
1.2 Melanoma incidence after 2 years (fibrates)	3	9513	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.24, 3.08]

Comparison 5. Statins and fibrates versus control: subgroup analysis by funding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Melanoma incidence	13	62197	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.52, 1.29]
1.1 Nonpharmaceutical	3	21205	Odds Ratio (M-H, Random, 95% CI)	1.45 [0.32, 6.52]
1.2 Pharmaceutical	8	31886	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.32]
1.3 Both	2	9106	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.64, 1.79]

WHAT'S NEW

Last assessed as up-to-date: 14 August 2005.

4 October 2008	Amended	Converted to new review format.
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HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 4, 2005

15 August 2005	New citation required and conclusions have changed	Substantive amendment.
26 July 2005	Amended	Minor update.

CONTRIBUTIONS OF AUTHORS

Link with editorial base-RD

Review correspondence-all

Draft protocol-RD,KN, LS

Search for trials-MG, AD, KN

Obtain copies of trials-AD

Select trials to include-RD, AD, EH, LS

Extract data from trials-AD, DK, LH

Enter data into RevMan-AD, LH

Carry out analysis-all

Interpret analysis-all

Draft final review-RD, AD, EH, LH, LS

Update review-RD, LS

DECLARATIONS OF INTEREST

Robert Dellavalle has received the independent, peer reviewed Atorvastatin Research Award (www.arawards.com, US\$ 50,000 US/year, 7/1/03-6/30/05, funded by Pfizer Pharmaceuticals), to support research exploring gene expression in tumors from persons exposed and unexposed to statins. He also purchased 50 shares of Merck common stock in 1991 and, despite the recommendations of many financial advisors, has not sold them yet. Both Merck and Pfizer manufacture statins.

SOURCES OF SUPPORT

Internal sources

- University of Colorado Department of Medicine small grant to Lisa Schilling, USA.
- University of Colorado Cancer Center start up funds to Robert Dellavalle, USA.
- University of Colorado Health Sciences Center and Denver Veterans Affairs Medical Center for access to the Internet and other resources, USA.

External sources

- Health Services Research Award in Faculty Development in Primary Care (grant 5D14HP00153) to Lisa Schilling, USA.
- National Institutes of Health grants T32 AR07411 to Kathryn Johnson and Eric Hester, USA.
- National Institutes of Health K-07 grant CA92550 to Robert Dellavalle, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticholesteremic Agents [*therapeutic use]; Clofibrilic Acid [*therapeutic use]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [*therapeutic use]; Melanoma [*prevention & control]; Randomized Controlled Trials as Topic; Skin Neoplasms [*prevention & control]

MeSH check words

Humans