

# Commentary

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## The statin-low cholesterol-cancer conundrum

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### Introduction

Hundreds of millions of people all over the globe are currently being administered statins because it is believed that their lipid lowering actions provide cardioprotective benefits. Adverse effects are considered uncommon and mild, and authors of numerous case-control studies of patients on statin treatment and matched, untreated individuals have even suggested a protective effect against numerous non-cardiovascular diseases, including cancer. In contrast, four controlled, randomized statin trials have resulted in a statistically significant increase of cancer in the treatment group; and several case-control and cohort studies have also shown a significant risk of cancer associated with statins. To add further confusion to this issue, meta-analyses of controlled, randomized statin trials have shown neither an increased nor a decreased risk of cancer.<sup>1</sup> Some of these discrepancies may result from the failure to recognize that the recordings of cancer in statin trials are biased for several reasons.

### The association between low cholesterol and cancer

Several cohort studies of healthy people have shown that low cholesterol is a risk marker for future cancer. The usual interpretation has been that the

association is secondary, because in most studies the association disappeared after having excluded early cancer cases. A common explanation has been that preclinical cancers might use cholesterol, which would lead to lower levels. However, when searching *Pubmed* with the words 'cancer AND cholesterol' we identified nine cohort studies including more than 140 000 individuals, where cancer was inversely associated with cholesterol measured 10–30 years earlier, and where the association persisted after exclusion of cancer cases appearing during the first 4 years (Table 1).<sup>2–10</sup> It seems unlikely that the liver would be unable to produce the extra cholesterol necessary for early tumor growth, considering that much larger amounts are steadily made for the constant renewal of our cells. Moreover, none of these cohort studies has been corrected for prior cholesterol-lowering treatment. Cancer was an adverse effect in WHO's clofibrate trial,<sup>11</sup> and clofibrate was one of the most popular cholesterol-lowering drugs before the advent of statins. Some high cholesterol participants in these cohort studies may well have had prior treatment with clofibrate and thus introduced a bias by diminishing the cancer differences between individuals with high and low cholesterol. This might even explain why many cohort studies have failed to show an association between low cholesterol and cancer and why a few have found a V- or

**Table 1** Nine cohort studies of healthy individuals, where low cholesterol, measured at least 10 years previously, was associated with cancer

	Number	Observation period; years (number of first years excluded)	Cancer types; listed in decreasing order	Incidence m/w	Mortality m/w	Adjusted for
Williams <i>et al.</i> <sup>2</sup>	5209	24 (6)	Colon; other types	*/ns		a,bw,ed,sm,sBT
Salmond <i>et al.</i> <sup>3</sup>	630	17 (5)	Not specified		*/*	
Schatzkin <i>et al.</i> <sup>4</sup>	12 548	10 (6)	Leukemia, lung, bladder, pancreas, cervix	**/ns	**/*	a,al,bw,d.
Törnberg <i>et al.</i> <sup>5</sup>	92 710	18–20 (11)	Not specified	ns/ns	**/ns	
Isles <i>et al.</i> <sup>6</sup>	15 262	12 (4)	Not specified	**/ns	**/ns	a,bw,d,sm,so
Kreger <i>et al.</i> <sup>7</sup>	5209	>30 (10)	Colon	**/none		al,BMI,g,sm
Schuit <i>et al.</i> <sup>8</sup>	3091	28 (5)	Mainly gastrointestinal		?/ns	
Chang <i>et al.</i> <sup>9</sup>	4338	18 (5)	Lung		ns/*	a,BMI,ed,sm
Steenland <i>et al.</i> <sup>10</sup>	14 407	17 (6)	Lung, breast, colorectal, prostate	*/none		a,al,BMI,sm,so

\* $P < 0.05$ ; \*\* $P < 0.01$ .

a, age; al, alcohol; bw, body weight; d, diet; dBT, diastolic blood pressure; ed, education; g, glucose intolerance, m/w, men/women; none, neither positive or inverse association; sBT, systolic blood pressure; sm, smoking; so, social group. The association between cancer and cholesterol was inverse in all studies, including those, where the association was non-significant.

a U-shaped association between cancer and cholesterol concentrations.

## Does statin treatment promote cancer?

In the first two simvastatin trials, 4S and HPS, cholesterol lowering increased non-melanoma skin cancer.<sup>12,13</sup> Since these associations were not significant, the increase was attributed to chance. However, if the figures from both trials are calculated together, the difference between the treatment and control groups does become statistically significant (256/12 454 vs. 208/12 459;  $P < 0.028$ ). In the CARE trial, 12 of 286 women in the pravastatin group but only one of 290 in the placebo group had breast cancer at follow-up ( $P = 0.002$ ).<sup>14</sup> Cancer was also reported more often in the PROSPER trial. The difference was obvious after 1 year, and it increased steadily during the trial period to become statistically significant after 4 years (245/2891 vs. 199/2913;  $P = 0.02$ ).<sup>15</sup> In the SEAS trial, 39/944 in the simvastatin/ezetimibe group but only 23/929 in the control group had cancer at follow-up ( $P = 0.05$ ).<sup>16</sup>

Cancer has been associated with statin treatment in several cohort and case-control studies as well. Matsuzaki *et al.*<sup>17</sup> followed 47 294 hypercholesterolemic Japanese patients on low dose (5–10 mg)

simvastatin per day for 6 years, and found that the number of cancer deaths was more than three times higher in patients whose total cholesterol was  $< 160$  mg/dl at follow-up compared with those whose cholesterol was normal or high ( $P < 0.001$ ). In a case-control study by Iwata *et al.*<sup>18</sup> 13.3% of patients with lymphoid malignancies had been treated with statins compared with 7.3% of control individuals with non-malignant diseases matched for age and sex ( $P < 0.001$ ). In a retrospective study of 388 men with prostate cancer and 1552 matched controls Chang *et al.*<sup>19</sup> found an increasing cancer risk with increasing cumulative statin dose ( $\chi^2$  for linear trend 7.23;  $P = 0.007$ ). In a case-control study by Agalliou *et al.*,<sup>20</sup> obese men taking statins had an increased risk of prostate cancer compared with obese non-users (OR = 1.5, 95% CI 1.0–2.2), with a stronger association for long-term use (OR = 1.8, 95% CI 1.1–3.0). In accordance, a retrospective analysis by Ritch *et al.*<sup>21</sup> found that among 1261 patients who had undergone radical prostatectomy, those on statins were more likely to have an elevation of biochemical tests that suggested recurrent cancer ( $P < 0.05$ ), and also a more aggressive cancer type reflected as a higher Gleason sum ( $P < 0.05$ ) than non-users. Finally, Hoffman *et al.*<sup>22</sup> found that of 83 patients with bladder cancer, the tumor became more aggressive in 53% of those who took statins, in contrast to only 18% for non-users ( $P = 0.004$ ).

## Interpretation bias

The discrepancy between these findings and the lack of an association between cancer and statin treatment seen in the meta-analyses can be explained in several ways.

In a review of experimental carcinogenicity in rodents, Newman and Hulley<sup>23</sup> found that both fibrates and statins produced cancer after a short time at serum levels close to those achieved in clinical trials. In humans, the lag time between initial exposure to carcinogens and clinical diagnosis is much longer than for rodents. For example, bronchial cancer rarely surfaces after only 10 years of heavy smoking. As almost all statin trials have lasted only 5 years or less, not enough time may have elapsed to demonstrate their carcinogenicity. Consistent with this, most cancers that have occurred with statistical significance have been those most likely to be detected early (skin, lymphoid, breast, prostate and bladder cancer), or because they have appeared in individuals who were already at a higher risk.

Furthermore, the meta-analyses noted above have a bias, since non-melanoma skin cancers, the easiest malignancies to detect early, were not included. The reason for this is that following the publication of HPS, authors of statin trials have not reported the number of this cancer category.

In the CARE trial,<sup>16</sup> where breast cancer was seen significantly more often in the treatment group, some of these were recurrences. The risk of cancer is much higher in patients who previously had this cancer, but it has not been possible to analyze the number of recurrences in the meta-analyses,<sup>22</sup> because after the publication of CARE, patients with a history of malignancy have been excluded.

Cancer is also more prevalent in the elderly. The increased incidence in the PROSPER trial is therefore alarming because that trial included only people above the age of 71 years. Subgroup analyses of individuals at greater risk than normal, such as smokers and those over 70 years of age would seem to be appropriate, but has never been reported in any trial or meta-analysis to the best of our knowledge.

The reasons for excluding cancer patients in the trials are not obvious, because statins have been claimed to protect against cancer together with a variety of other non-cardiovascular diseases. This notion is based on case-control studies in which the incidence of cancer in people with low cholesterol was compared with the incidence in patients receiving statins. As low cholesterol may predispose to cancer and as those on statins have lived most of their lives with high cholesterol, it is impossible to

draw any valid conclusions from such studies. Furthermore, adherence to statins is low, in particular when prescribed for primary prevention. For example, in a Canadian study that included 85 020 patients without heart disease, 75% were no longer taking statins on 2-year follow-ups.<sup>24</sup> Thus, failure to correct for adherence would also contribute to a falsely low number of adverse effects.

A more accurate appraisal would be to relate the number of cancer cases to the achieved blood cholesterol concentration, as was done by Matsuzaki *et al.*<sup>17</sup> They found that cancer deaths had tripled in those whose cholesterol was the lowest at follow-up compared with the others. In a meta-analysis of 15 randomized controlled statin trials Alsheikh-Ali *et al.*<sup>25</sup> noted the same phenomenon. There was no significant increase of cancer, but non-melanoma skin cancer was not included, and the mean trial length was only 4.4 years. However, there was a statistically significant and inverse association between on-treatment low-density-lipoprotein cholesterol (LDL-C) and cancer incidence, both in the statin and in the control arms. Compared with control patients, statin-treated patients achieved lower levels of LDL-C while maintaining a similar risk for cancer, suggesting that the cholesterol-lowering effect of statins was not associated with an increased risk of cancer or might even be protective.

## Possible mechanisms of action and the role of lipoproteins

There are several possible mechanisms behind the inverse association between cholesterol and cancer. Either the statins are carcinogenic by themselves, or low cholesterol resulting from statin therapy may weaken the body's defenses against cancer, or unknown factors may be carcinogenic and at the same time lower cholesterol.

The first possibility is utterly complicated, because unlike the vast majority of known carcinogens, the statins are neither mutagenic nor genotoxic.<sup>23</sup> If they are carcinogenic, the reason may be their disruption of immune system function, for instance by increasing the number of regulatory T cells.<sup>26</sup> Another possibility is that the statins may enhance the genotoxicity of other substances.<sup>27</sup> However, arguments have also been presented in favor of a cancer-protective effect.<sup>28</sup> This is obviously a difficult problem to study because of the many biochemical pathways that are blocked by the statins. We have abstained from analyzing this issue because of its complexity and because

these ideas are speculative and are based solely on laboratory experiments.

The arguments in favor of the second possibility, that low cholesterol may increase risk, are more compelling, and are also supported by human studies. The strongest argument is the collection of cohort studies listed in Table 1, all of which were started before cholesterol-lowering treatment became popular. Also other studies indicate that low cholesterol, or rather a low concentration of the lipoproteins, may be crucial.

More than 50 years ago several research groups found that carcinogenic hydrocarbons are rapidly bound by lipoproteins<sup>29</sup> suggesting that cells of people with high blood cholesterol may have less exposure to carcinogens and thus be protected against cancer. But the lipoproteins may protect in another way.

One hundred years ago Ellermann and Bang succeeded in transferring leukemia from one chicken to another by cell-free tissue filtrates, and shortly thereafter Peyton Rous isolated the sarcoma virus of hens. More recently, compelling links have been found between human papilloma virus and cervical cancer, between Epstein–Barr virus and Burkitt’s lymphoma, between T-cell leukemia virus and lymphoma and between hepatitis B-virus and liver cancer.<sup>30</sup> It has been estimated that 15–20% of human cancers may have a viral etiology, and there is increasing evidence that certain bacteria may play a similar role.<sup>31</sup> These findings are crucial because the lipoproteins partake in the immune defense system by binding and inactivating microorganisms and their toxic products.<sup>32,33</sup>

In 1939, Todd *et al.* discovered that a serum factor named antistreptolysin-S was not an antibody, as previously thought, because its titer fell in patients with rheumatic fever at the peak of clinical symptoms. Humphrey localized it to the lipid fraction of the blood, and since then more than a dozen research groups have documented that antistreptolysin-S is identical with the lipoproteins and constitutes a non-specific host defense system able to bind and neutralize not only streptolysin-S, but also other endotoxins and a large number of bacteria and virus species.<sup>32</sup> For instance, test tube studies have shown that human low density lipoprotein (LDL) inactivates up to 90% of *Staphylococcus aureus* alpha-toxin, and an even larger fraction of bacterial lipopolysaccharide (LPS).<sup>32</sup> In accordance, hypocholesterolemic rats injected with LPS had a markedly increased mortality compared with normal rats, which could be ameliorated by injecting purified human LDL; and hypercholesterolemic mice challenged with LPS or live bacteria had an 8-fold increase of LD<sub>50</sub> compared with normal mice.<sup>32</sup>

Superti *et al.* confirmed that all human subclasses of lipoproteins were able to inhibit the infectivity and hemagglutination by SA-11 rotavirus, and complex formation was visualized by electron microscopy.<sup>32</sup>

It has been shown that apolipoprotein B, the primary lipoprotein of LDL and very-low-density-lipoprotein (VLDL) performs an innate defense effector against *Staphylococcus aureus* infections in mice,<sup>34</sup> but there may be other mechanisms as well, because several studies have shown that also HDL partake in the immune defense system.<sup>32</sup>

There are many clinical observations relating lipoproteins to infectious diseases. Low cholesterol is associated with respiratory and gastrointestinal disease, most of which have an infectious origin, and low cholesterol is also a risk factor for HIV, AIDS, mortality due to postoperative abdominal infections, and sepsis.<sup>35</sup> These associations have also been explained with the argument that low cholesterol is secondary to the infection. However, when Iribarren *et al.*<sup>36</sup> followed more than 100 000 healthy individuals for 15 years, they found that those who had low cholesterol at the start had significantly more hospital admissions due to an infectious disease.<sup>36</sup> Obviously, the low cholesterol, which was recorded at a time when these people were healthy, could not have been caused by a disease that they had not yet encountered.

The role played by the lipoproteins in innate immunity is in accordance with the findings of Sijbrands *et al.*<sup>37</sup> They tracked the ancestors of Dutch people with familial hypercholesterolemia and identified a large number of individuals with a 50% chance of having this genetic abnormality. They searched official records of deaths and found that before the year 1900 the presumed heterozygotes for hypercholesterolemia lived longer than the average Dutchman. At that time, the most common cause of death was infectious disease. The authors therefore suggested that high cholesterol protected against infections. As some cancers are caused by microorganisms, high cholesterol may protect people with familial hypercholesterolemia against cancer as well. Support for this idea comes from a cohort study by Neil *et al.*<sup>38</sup> of 2871 patients with familial hypercholesterolemia recruited between 1980 and 1998. Their standardized mortality ratio for cancer, calculated from the ratio of the number of deaths observed to the number expected in the general population of England and Wales, was significantly lower (0.6, 95% CI 0.4–0.8).<sup>38</sup> The authors suggested that the cause was cholesterol-lowering treatment together with a more healthy lifestyle. Considering that no controlled, randomized cholesterol-lowering trial has succeeded in lowering

cancer morbidity or mortality, neither by diet nor drugs, it seems more likely that the lower cancer mortality rates in these individuals resulted from the protection afforded by their high cholesterol.

All lipoproteins are able to neutralize the effects of micro-organisms<sup>31,32</sup> and may therefore be carcinoprotective. For instance, several cohort and case-control studies have found that low high-density-lipoprotein cholesterol (HDL-C) is associated with future cancer, especially liver, lung and breast cancer. A meta-analysis of 24 statin trials, in which baseline HDL-cholesterol had been recorded, also showed a strong and significant inverse relationship between baseline HDL-C and the rate of incident cancer.<sup>39</sup>

Benn *et al.*<sup>40</sup> recently reported that people with genetically low LDL-cholesterol do not have an increased risk of cancer, and they therefore assumed that the association between cancer and cholesterol was secondary. However, information was neither provided about the number of people whose low LDL-cholesterol was inherited nor concerning the particle size of LDL-cholesterol. LDL-particles vary in size; a high number of the small particles, but not of the large ones, is a risk marker for cardiovascular disease, suggesting that small and large particles may have different functions. There is also good reason to suspect that the large particles are more effective both as transporters of toxic compounds and as participants in immune system activities.

## Conclusion

The interrelationships between cholesterol, the lipoproteins and cancer are complicated and demand more research. Long-term follow-up of patients taking statins and subjects with similar cholesterol levels not receiving such therapy may be useful. Subgroup analyses of people who are at greater risk such as smokers and the elderly would also be desirable. To avoid adherence bias, the number of cancer cases in statin-treated people should be related to the LDL cholesterol level achieved. Statin studies in experimental animals have been limited to rodents and expanding these to species more closely related to humans might provide better information. Analyses of national cancer registers can be misleading, because cancer mortality may reflect the combined result of the increasing use of statin drugs and decreasing smoking and other harmful lifestyle habits. Despite the latter, the incidence of non-melanoma skin cancer in the USA has on average increased by 4.2% per year between 1992 and 2006.<sup>41</sup> This particular issue should be given high priority considering that millions of healthy people,

including both children and adults, are presently taking statin drugs, and concerted efforts are being made to increase their use for primary prevention.

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