Hypothesis/Commentary

Statins and Cancer Development

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Abstract

There is epidemiologic evidence that the hydrophilic 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitor pravastatin increases the incidence of some extrahepatic cancers, although this finding has been attributed to chance. We hypothesize that pravastatin is able to promote the development of cancer by causing an induction of HMG-CoA reductase and, hence, mevalonate synthesis in extrahepatic tissues. We have shown that mevalonate, the product of HMG-CoA reductase, promotes the growth of breast cancer cells. Because there is no uptake of pravastatin by most extrahepatic cells, this statin will be unable to mitigate the increase in mevalonate synthesis in extrahepatic tissues that accompanies the decrease in circulating cholesterol caused by its inhibition of hepatic HMG-CoA reductase. (Cancer Epidemiol Biomarkers Prev 2005;14(8):1897–8)

A disturbing increased incidence of cancers has been reported in two randomized controlled trials of the hydrophilic 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitor pravastatin—Prospective Study of Pravastatin in the Elderly at Risk (PROSPER; ref. 1) and Cholesterol and Recurrent Events (CARE; ref. 2). In the PROSPER trial, the reduction in deaths from vascular events was completely negated by the increase in deaths from cancer. In the CARE trial, breast cancer occurred in a significantly greater number of women treated with pravastatin. Randomized controlled trials of the lipophilic statins simvastatin (3) and lovastatin (4), however, have not shown an increased cancer incidence. The authors of both the PROSPER and CARE trials suggested that the increased incidence of cancer occurred by chance. Indeed, Shepherd et al. (5) suggest that the hydrophilic nature of pravastatin, which minimizes its uptake by extrahepatic tissues, should minimize its side effects. We hypothesize, however, that the absence of uptake of pravastatin by extrahepatic tissues indirectly mediates a cancer-promoting effect when coupled with the ability of this statin to lower serum cholesterol by inhibiting HMG-CoA reductase in the liver.

Both lipophilic and hydrophilic statins lower serum cholesterol concentrations by competitively inhibiting the activity of HMG-CoA reductase in the liver, resulting in reduced hepatic synthesis of mevalonate, a precursor of cholesterol. A decrease in serum cholesterol concentration causes a compensatory induction of HMG-CoA reductase and, hence, mevalonate synthesis in extrahepatic cells (6). We have recently shown that mevalonate promotes the growth in mice of tumors derived from human breast cancer cells, probably through enhanced proliferation (7). This result suggests that the induction of mevalonate synthesis in extrahepatic tissues that follows statin-mediated serum cholesterol reduction may promote the growth of occult neoplastic or preneoplastic cells (7). Indeed, in rodents, lowering of serum cholesterol by the unabsorbed bile acid–binding resin cholestyramine has been shown to promote mammary gland carcinogenesis (8, 9). There is evidence, however, that diffusion-mediated uptake of the lipophilic statins mitigates the increase in mevalonate synthesis in extrahepatic tissues that accompanies the decrease in serum cholesterol that they induce (10). Thus, lipophilic statins may be expected not to promote, and may even inhibit, cancer development. Indeed, no increased risk of cancer has thus far been reported in randomized controlled trials of the lipophilic statins (3, 4). In the follow-up to one trial, an indication of overall decreased risk of cancer death was seen in simvastatin users (11) and, in another, a significant reduction in incidence of melanomas was reported with lovastatin use (4). Several studies in rodents have also shown a protective effect of lipophilic statins on the growth of diverse tumor types (12-15) and on breast cancer cell growth in culture (16, 17).

Unlike the lipophilic statins, uptake of pravastatin by cells is mediated by a sodium-independent bile acid transporter (18). Because of the absence of this transporter on most extrahepatic cells (18), pravastatin has been shown to inhibit HMG-CoA reductase only in the liver and ileum, where the transporter is present (19), and does not inhibit the growth of breast cancer cells in culture (16, 17). Pravastatin, therefore, like cholestyramine, will be unable to mitigate the increase in mevalonate synthesis in extrahepatic tissues that accompanies the decrease in circulating cholesterol. Thus, increased mevalonate synthesis in extrahepatic tissues may explain the increased overall and site-specific risk of cancer that has been reported in some (1, 2), but not all (20-22), trials of pravastatin. This effect may be especially pronounced in the elderly that are expected to harbor a larger number of preneoplastic and occult neoplastic lesions that could be promoted by the increased mevalonate production and may help to explain the increased overall and site-specific risk of cancer in the PROSPER trial where the mean age of participants was 75 years.

A number of well-characterized rodent models are available for the experimental study of cancer. However, rats and mice that are commonly used in experimental cancer studies are generally unresponsive to the hypocholesterolemic effects of statins (23), precluding the use of these rodent models for direct investigation of our hypothesis. Studies of extrahepatic HMG-CoA reductase activity in pravastatin-treated humans would clearly be invasive, particularly because blood mononuclear

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leukocytes seem to transport pravastatin and, therefore, are not representative of most extrahepatic tissues in this regard (24). Evidence linking the putative induction of mevalonate synthesis in extrahepatic tissues by pravastatin to cancer risk will probably require the development of a new animal model.

We hypothesize that hydrophilic pravastatin promotes the development of cancer by causing an increase in mevalonate synthesis in extrahepatic tissues. It is important that differences in the pharmacologic properties of hydrophilic and lipophilic statins are recognized when considering extrahepatic effects of these compounds, including effects on extrahepatic cancers. Attempts to analyze the risk of cancer associated with statin use by performing meta-analyses in which trials of pravastatin and the lipophilic statins are pooled ignores the different effects of these two classes of statins on extrahepatic mevalonate synthesis and, therefore, on a biologically plausible mediator of cancer risk. Such oversight may temper findings of risk where one legitimately exists, or generalize and exaggerate risk without cause. There is clearly an urgent need for further controlled trials of the individual statins with inclusion of cancer mortality as a clinical end point.

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