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Lipid-Lowering Medication and Risk of Cancer

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ABSTRACT. Low or declining levels of serum cholesterol have been associated with increased mortality from cancer. We conducted a population-based cohort study of 1882 patients from one Danish county who received lipid-lowering drugs between January 1, 1991 and December 31, 1994. During the follow-up period of up to 4 years, 41 cancers were observed among users of lipid-lowering drugs, with 42.9 expected, to yield an age- and sex-standardized incidence ratio of 1.0 (95% confidence interval, 0.7–1.3). Although limited by small numbers and short follow-up period, examination by site of cancer and type of drug provided no evidence of an association. Further research is needed, however, with longer follow-up to assess more fully any potential cancer risk with these medications. *J CLIN EPIDEMIOL* 52;2:167–169, 1999. © 1999 Elsevier Science Inc.

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INTRODUCTION

There is good evidence that intentional lowering of serum cholesterol in patients with high levels significantly reduces the incidence of myocardial infarction and mortality from cardiovascular disease [1–3]. There remains, however, uncertainty about the possible harmful effects of reduced levels of blood cholesterol [4]. Thus, low or declining levels of serum cholesterol have been associated in some studies with increased mortality from cancer [5–7], and other studies have suggested an excess risk of cancer associated with certain cholesterol-lowering drugs [8–10]. Here we examine the incidence of cancer in a population-based cohort of users of lipid-lowering drugs as compared with the rate of cancer in the general population.

PATIENTS AND METHODS

We used the population-based pharmacoepidemiological prescription database of the County of North Jutland, Denmark, which was started on January 1, 1991, to link 25,257 prescriptions for lipid-lowering drugs with 1882 individuals up to December 31, 1994. During this period, the population of the county was around 487,000 inhabitants, representing approximately 9% of the total Danish population.

The tax-supported insurance program of the National Health Service of Denmark refunds 50% of the cost of lipid-lowering drugs prescribed by doctors and based on a medical indication. From the computerized accounting system maintained by Danish pharmacies, data on prescriptions are transferred to the central health insurance administration, and the pharmacies are reimbursed. In the County of North Jutland, prescription data are also transferred to the pharmacoepidemiological prescription database, which includes the customers' personal identification number (which incorporates data of birth), the type of drug prescribed according to the anatomical therapeutic chemical (ATC) classification system [11], and the date of prescription [12,13]. Use of the personal identification number, which is assigned to all citizens shortly after birth by the Central Population Register (CPR), ensures that a complete prescription history can be established for each participant from January 1, 1991 forward. The prescriptions included in the present study cover the group of high-mobility-group-coenzyme A reductase inhibitors (the "statins"), simvastatin (ATC code B04A B01), lovastatin (B04A B02), and pravastatin (B04A B03); fibrates, clofibrate (B04A C01), benzafibrate (B04A C02), and gemfibrozil (B04A C04); acid-binding resins, colestipol (B04A D02) and colestyramine (B04A D01); and nicotinic acids, acipomox (B04A X03) and nicotinic alcohol (B04A E05).

Following previously established procedures [14] the study cohort was linked to the files of the Danish Cancer Registry, which collects information on all individuals in Denmark with cancer [15], and to the National Mortality

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Files which include information on date of death. Follow-up for cancer occurrence was begun at the date of first known prescription of a lipid-lowering drug and was ended on the date of death ($n = 91$) or December 31, 1994 ($n = 1791$), whichever occurred first. No patients were lost to follow-up.

The expected numbers of cancers were calculated by multiplying the number of person-years of the cohort members by the age-, sex-, and calendar year-specific incidence rates of the population of North Jutland. The standardized incidence ratio (SIR)—the ratio of the observed to the expected number of cancers—served as a measure of the relative risk, and 95% confidence intervals (CIs) were calculated, assuming a Poisson distribution of the observed cancers [16].

RESULTS

For the 1882 patients included in the study, 4580 person-years of follow-up were accrued (average, 2.4 years; range, >0 to 4 years), and the median age at entry was 52 years. Most patients used a single group of drugs—statins (52%), fibrates (22%), bile acid-binding resins (13%), or nicotinic acids (1%)—throughout the registration period; some 12% used drugs from more than one group. Approximately 400 of the 550 patients recorded in the prescription database during the first 5 months of 1991 are thought to have been prevalent users at the start-up of the database, and thus are potential long-term users.

Overall, 41 cancers were diagnosed, with 42.9 expected (Table 1), yielding a SIR of 1.0 (95% CI, 0.7–1.3), with SIRs of 1.1 (0.7–1.7) for men and 0.8 (0.4–1.2) for women.

The SIR was 0.8 (0.5–1.3) for users of statins and 1.2 (0.6–2.0) for users of fibrates. Other use or mixed use was

associated with a relative risk of 1.0 (0.6–1.8). No excess risk for all cancer types combined was seen among patients who had potential long-term use (SIR, 0.8; 95% CI, 0.4–1.2).

No significant increase in risk was observed for any specific form of cancer (Table 1), including cancer of the breast, with six cases observed and 4.2 expected (SIR, 1.4). In the subgroup of patients who received statins exclusively, three cases of breast cancer were observed with 2.1 expected (SIR, 1.5; 95% CI, 0.3–4.3).

DISCUSSION

The overall occurrence of cancer in individuals taking lipid-lowering drugs was close to that expected from incidence rates for the general population of the study area. In previously reported surveys of the general population, low or declining levels of total serum cholesterol have been linked with increased risks of death from cancer [5–7,17,18], perhaps via metabolic disturbances of transmembranous processes or other cell properties [19]. However, as the strength of this inverse association seems to increase with decreasing time between data of blood testing and date of death, the decline in serum cholesterol is generally considered to be the result, rather than the cause, of cancer [6,19].

There is also some [8–10,20], albeit inconsistent [2,21,22], evidence that intentional lowering of serum cholesterol by adjustment of dietary habits or by drug intervention may be associated with elevated mortality from cancer. Meta-analyses conducted in the early 1990s [8,9] suggested a relation between cholesterol-lowering regimens and increased cancer mortality, due mainly to excess deaths from cancers of the colon and lung in men and hematological cancers in men and women [9]. Our findings do not support those observa-

TABLE 1. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) for cancers at selected sites among 1882 patients taking lipid-lowering drugs

| Site of cancer (ICD-7 code) | Number observed | Number expected | SIR | 95% CI |
|---|-----------------|-----------------|-----|---------|
| All malignant neoplasms (140–205) | 41 | 42.9 | 1.0 | 0.7–1.3 |
| Digestive organs (150–159) | 7 | 8.9 | 0.8 | 0.3–1.6 |
| Esophagus | 1 | 0.4 | 2.8 | 0.1–1.5 |
| Stomach (151) | 1 | 1.2 | 0.9 | 0.0–4.8 |
| Colon (153) | 1 | 3.0 | 0.3 | 0.0–1.8 |
| Rectum (154) | 1 | 1.9 | 0.5 | 0.0–2.9 |
| Liver (155) | 1 | 0.3 | 3.7 | 0.1–21 |
| Pancreas (157) | 2 | 1.2 | 1.6 | 0.2–5.8 |
| Lung (162) | 7 | 6.1 | 1.2 | 0.5–2.4 |
| Breast (170) | 6 | 4.2 | 1.4 | 0.5–3.1 |
| Female genital organs (171–176) | 2 | 3.1 | 0.6 | 0.1–2.3 |
| Male genital organs (177–179) | 1 | 2.3 | 0.4 | 0.0–2.4 |
| Urinary system (180–181) | 4 | 3.9 | 1.0 | 0.3–2.6 |
| Skin (190–191) | 8 | 7.3 | 1.1 | 0.5–2.2 |
| Lymphatic and hematopoietic tissues (200–205) | 0 | 2.7 | 0 | 0.0–1.4 |
| Other and unspecified sites | 6 | 4.4 | 1.4 | 0.5–3.0 |

tions and are more in line with those of a recent meta-analysis of 20 lipid-lowering trials [21], which reported no evidence of increased mortality from total cancer or any of the major types of cancer. While we could not confirm the excess breast cancer risk reported in a recent trial of pravastatin in the United States [23], the power of the present study to test this specific association was limited by small numbers.

Although we had the advantage of being able to collect information on drug use from a computerized pharmacoepidemiological prescription database [11,24] with virtually 100% follow-up of study subjects for cancer using the national cancer registry, the study was constrained by a follow-up period for prevalent users of only 4 years. This latency period may be too brief to measure a carcinogenic effect, even if the drugs act as tumor promoters. Although we attempted to address this problem in part by stratifying the cohort members into prevalent users by January 1, 1991 and users starting their treatment after that point in time, we found no indication of increased cancer risk among the prevalent users with longer periods of treatment.

In summary, our study of lipid-lowering medications revealed no evidence of a cancer-causing effect. However, studies with larger numbers and longer follow-up for cancer incidence are needed to fully evaluate any potential carcinogenic risk associated with use of these drugs or with other methods of lowering serum cholesterol.

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