# Risk for Non-smoking-related Cancer in Atherosclerotic Patients[1]

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## Abstract

**Some studies have suggested that the pathogenesis of atherosclerosis and that of cancer have common features, and in addition to tobacco smoking, oxidative stress, diet, and sex hormones have been considered as common etiological factors. To investigate whether there is an association between atherosclerosis and cancer, we evaluated the cancer pattern of patients with atherosclerosis of the aorta and of peripheral and cerebral vessels. A total of 69,485 patients with atherosclerosis were identified through the Danish National Registry of Patients between 1977 and 1989, and the incidence of cancer in this group was calculated by linkage to the Danish Cancer Registry for the period 1977–1993. No consistent excesses over the expected figures were seen for cancer at any site unrelated to tobacco smoking in either the total cohort or in subgroups. Specifically, we found no association at the individual level between atherosclerosis and colorectal cancers or hormone-related cancers, except from a decreased standardized incidence ratio of 0.7 (95% confidence interval, 0.5–0.9) for endometrial cancer. The standardized incidence ratio for cancers of the brain and nervous system was 1.1 (95% confidence interval, 0.9–1.3) for all patients combined, whereas patients with atherosclerosis of precerebral or cerebral arteries had a slightly increased risk (40%) for cancers of the brain and nervous system. The excess was seen only during the initial 3 years after discharge from hospital, and the likely explanation was a missed diagnosis. The study does not support the view that patients with atherosclerotic diseases represent a high-risk group for prostate cancer and potential future targets for prostate cancer screening interventions.**

## Introduction

Experimental studies (1, 2) suggest common features in the pathogenesis of atherosclerosis and cancer, and a large number of common risk factors for the two disease entities has been suggested, besides the well-known atherogenic and carcinogenic effect of tobacco smoking (3). The proposed risk factors that they have in common include oxidative stress (4, 5), diet (6, 7), obesity (8, 9), low physical activity (8, 10, 11), and endogenously as well as exogenously derived sex hormones (9, 12, 13). A cross-sectional study (14) and a recent case-control study (15) reported an association between a history of coronary heart disease and prostate cancer, whereas no association was reported in two earlier case-control studies (16, 17). Three case-control studies have studied the association with self-reported ischemic heart disease and stroke and colorectal cancer, but the findings were contradictory (15, 18, 19). In a previous cohort study of the risk for cancer among patients who had an acute myocardial infarct, we find no association with any specific cancer site unrelated to tobacco smoking (20). A large subset of the patients with acute myocardial infarct is not eligible for analyses of risk for subsequent cancer because of a very high initial mortality rate (21). Furthermore, the risk factors for different clinical manifestations of atherosclerosis seem to vary (22). Two small cohort studies of patients with peripheral artery disease (23, 24) have been reported, but none had the statistical power to evaluate the risk for specific non-smoking-related cancers in these patients. Therefore, we considered it interesting to evaluate the cancer pattern of patients with extracoronary manifestations of atherosclerosis in the peripheral arteries, brain, and aorta and also to determine whether occlusion of precerebral arteries or atherosclerosis of the cerebral arteries is accompanied by an increased risk for brain cancer.

In this nationwide study from Denmark, the incidence of specific non-smoking-related cancers was assessed in large cohorts of patients with extracoronary manifestations of atherosclerosis on the basis of information from population-based hospital discharge and cancer registers.

## Patients and Methods

The Danish National Registry of Patients was used to identify 99,859 individuals who had been discharged with a record of extracoronary manifestations of atherosclerosis between 1977 and 1989. Each record includes the personal identification number unique to every Danish citizen (encoding sex and date of birth), dates of admission and discharge, the hospital department attended, and up to 20 discharge diagnoses on patients admitted to nonpsychiatric hospitals in Denmark since 1977. The discharge diagnoses are coded according to a modified Danish version of ICD-8[3] (25). All patients discharged with a diagnosis of atherosclerosis of the cerebral arteries (ICD-8 code 437), occlusion of the precerebral arteries (ICD-8 code 432), or atherosclerosis of the aorta (ICD-8 440.09), renal arteries (ICD-8 440.19), iliac arteries (ICD-8 440.30), peripheral arteries (ICD-8 440.20, 440.21, 440.28, and 440.29) and other

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[3] The abbreviations used are: ICD-8, International Classification of Diseases, Eighth Revision; SIR, standardized incidence ratio; CI, confidence interval.

specified arteries (ICD-8 440.39), or general or unspecified atherosclerosis (ICD-8 440.99) were included in the cohort. The term precerebral arteries comprises the carotid, basilar, and vertebral arteries. A diagnosis was included no matter whether it was the main hospital discharge diagnosis or a secondary one. For patients who had been discharged more than once for the same condition or for various of the selected diagnoses, only the first record was retained, and this was taken as the date of entry into the study. To analyze the cancer risk in specified subcohorts, the date of the first known discharge with the diagnosis of interest was used as the time of entry into the study.

Cohort members were linked to the Central Population Register for verification of the personal identification number and for information on vital status and migration. Of the 99,859 people initially identified in the Danish National Registry of Patients, 297 (0.3%) were excluded from the cohort because they were not Denmark residents or because their identification number was invalid. Another 30,077 patients (30%) were excluded because they had died during the first year of follow-up after a diagnosis of atherosclerosis.

The records of the remaining 69,485 patients (34,136 men and 35,349 women) were linked to the files of the Danish Cancer Register, which collects information on all patients in Denmark with cancer, including benign brain tumors and urinary bladder papillomas. Cancers were classified according to a modified Danish version of ICD-7 (26). Follow-up for cancer occurrence was begun 1 year after a hospital discharge for atherosclerosis and ended at the date of emigration ($n = 40$), date of death ($n = 50{,}208$), or December 1993 ($n = 19{,}237$), whichever occurred first. The first year of follow-up was excluded to minimize any selection bias that might be introduced by the entry of patients with atherosclerosis induced by subclinical cancer (27, 28).

The person-years under observation were multiplied by sex-, age-, and calendar-specific incidence rates for the Danish population to estimate the expected number of cancers. SIRs, as a measure of the relative risk, and 95% CIs were calculated assuming a Poisson distribution of the observed cancers.

Because tobacco smoking is a risk factor for atherosclerosis, the risk estimates are given separately for smoking-related and non-smoking-related cancer sites. The confirmed smoking-related cancers include cancers of the lung, larynx, oral cavity, tongue, pharynx, esophagus, pancreas, kidney, and urinary bladder. The suspected sites are lip, liver, cervix, and stomach; leukemia is also a suspected type (9). The cancer sites denoted as non-smoking-related included cancer sites not associated with tobacco smoking and endometrial cancer, which is probably inversely associated with tobacco smoking (29).

## Results

The 69,485 cohort members were followed-up for an average of 4.7 years (range, 1–17 years). The median age at the start of follow-up was 69 years for men and 74 years for women. The total number of person-years experienced by the cohort was 329,952.

Overall, 7391 cancers were observed in atherosclerotic patients, and 6295 were expected, yielding a SIR of 1.17 (95% CI, 1.15–1.20). The SIR was 1.25 (1.21–1.28) for men and 1.09 (1.05–1.13) for women. As expected, the risk of smoking-related cancer was significantly increased in atherosclerotic patients. The overall risk for cancers at these sites was 1.52 (95% CI, 1.46–1.58) in men and 1.45 (95% CI, 1.37–1.54) in women, with a total of 3438 observed cases (data not shown).

*Table 1* Observed numbers of cancers unrelated to tobacco smoking and SIRs

Shown are the results for 69,485 patients discharged from hospital with a diagnosis of atherosclerosis; cancers observed during the first year of follow-up were excluded.

| Cancer site | No. observed | SIR | 95% CI |
|---|---|---|---|
| Digestive tract | | | |
| Colon | 545 | 0.9 | 0.8–1.0 |
| Rectum | 273 | 0.9 | 0.8–1.0 |
| Gall bladder and bile ducts | 75 | 1.1 | 0.8–1.3 |
| Hormone-related cancers | | | |
| Breast | 461 | 1.0 | 0.9–1.0 |
| Endometrium | 72 | 0.7 | 0.5–0.9 |
| Ovary | 83 | 0.8 | 0.7–1.0 |
| Prostate | 449 | 0.9 | 0.8–1.0 |
| Testis | 6 | 0.9 | 0.3–2.0 |
| Skin | | | |
| Melanoma | 75 | 0.8 | 0.7–1.1 |
| Nonmelanoma | 996 | 1.1 | 1.0–1.1 |
| Lymphomas | | | |
| Non-Hodgkin's lymphoma | 128 | 1.0 | 0.9–1.2 |
| Hodgkin's disease | 14 | 1.2 | 0.6–2.0 |
| Brain and nervous tissue | 100 | 1.1 | 0.9–1.3 |
| Other specified organs | 368 | 1.2 | 1.0–1.3 |
| Secondary and unspecified | 308 | 1.5 | 1.4–1.7 |
| All sites unrelated to smoking | 3953 | 0.99 | 0.96–1.02 |

*Table 2* Observed numbers of cancers of the prostate and SIRs among 34,136 male patients discharged from hospital with a diagnosis of atherosclerosis

| Years | No. observed | SIR | 95% CI |
|---|---|---|---|
| Total (1–17 years of follow-up) | 449 | 0.9 | 0.8–1.0 |
| Age at discharge | | | |
| <50 | 3 | 1.3 | 0.3–3.8 |
| 50–59 | 47 | 1.3 | 1.0–1.7 |
| 60–69 | 141 | 1.0 | 0.8–1.1 |
| ≥70 | 258 | 0.8 | 0.7–0.9 |

Table 1 gives the risks for cancer types unrelated to tobacco smoking. The overall risk for these cancers was not increased in comparison with the general population, with a SIR of 0.99 (0.96–1.02), 1.03 for men and 0.95 for women. With the exception of a statistically significant decrease in risk for endometrial cancer of 30% and an increase for secondary and unspecified cancers, the cancer pattern was similar to that of the general population for all types of cancer.

Table 2 gives the SIR for prostate cancers in male atherosclerotic patients. The overall risk for prostate cancer was 0.9 (95% CI, 0.8–1.0), with a total of 449 observed cases. Analyses stratified by age did not reveal an increased risk for prostate cancer in any age group, but for patients with onset of disease at 70 years or older, a significantly decreased SIR of 0.8 (95% CI, 0.7–0.9) was observed.

Additional analyses by age at discharge did not reveal increased risks in younger patients; specifically, the incidence of colorectal cancer was as expected. Fewer cases of endometrial cancer were observed than were expected among women who had been discharged after the age of 60 years, at which point, most women have passed menopause (SIR = 0.7; 95% CI, 0.5–0.9). Women discharged with an atherosclerotic diagnosis before the age of 52, which is the mean age of menopause of Danish women (30), had a SIR of 1.0 (95% CI, 0.7–1.4), based on 32 cases. The risk for breast cancer among women was not decreased in any age group (data not shown).

*Table 3* Observed numbers of cancers of the brain and nervous system and SIRs among 33,306 patients discharged from hospital with a diagnosis of occlusion of the precerebral arteries or atherosclerosis of the cerebral arteries

| | No. observed | SIR | 95% CI |
|---|---|---|---|
| Total (1–17 yr of follow-up) | 49 | 1.4 | 1.0–1.8 |
| Age at discharge | | | |
| <50 | 3 | 4.0 | 0.8–11.6 |
| 50–59 | 9 | 2.3 | 1.1–4.5 |
| 60–69 | 11 | 1.1 | 0.6–2.0 |
| ≥70 | 26 | 1.2 | 0.8–1.7 |
| Time since discharge (yr) | | | |
| 1–2 | 23 | 1.8 | 1.1–2.6 |
| 3–5 | 14 | 1.1 | 0.6–1.8 |
| 6–17 | 12 | 1.1 | 0.6–2.0 |

Other analyses were conducted to evaluate the risks for cancer by primary site of atherosclerosis. There were no significant findings for non-smoking-related cancers in any of the specified subcohort analyses.

Table 3 shows the occurrence of cancers of the brain and nervous system, specifically, in patients discharged with occlusion of the precerebral arteries or atherosclerosis of the cerebral arteries. The overall risk for these cancers was slightly increased (40%), but the excess was restricted to the initial 1–3 years of follow-up from discharge. In age groups over 60 at discharge, however, the incidence of these tumor types was close to that expected. The risk for cancers of the brain and nervous system were particularly high during the first year after discharge (SIR = 7.3; 95% CI, 5.5–9.4), on the basis of 59 cases (data not shown).

## Discussion

If atherosclerosis and cancer are linked by a major common risk factor, a person with either condition should be at elevated risk for the other, as illustrated by the increased risk for smoking-related cancers. In patients with extracoronary manifestations of atherosclerosis the overall occurrence of cancers at sites unrelated to tobacco smoking was not higher than that expected from the incidence rates of the general population, and no increased risk was observed for cancer at any specific sites. Specifically, the present population-based cohort study did not confirm the observed association between prostate cancer and atherosclerotic heart disease observed in a recent hospital based case-control study (15), in accordance with the results of our previous study of the occurrence of acute myocardial infarct and subsequent development of cancer (20). We found no association at the individual level between atherosclerosis and cancers of the colon, rectum, or breast.

The validity of the discharge diagnosis of extracoronary atherosclerosis in the Danish National Registry of Patients is unknown, but in a previous study, the validity of diagnoses of cardiovascular diseases in general was 80% on a 5-digit level (31). We presume that the validity of diagnoses of aortic atherosclerosis, atherosclerosis of the renal artery, and atherosclerosis of the iliac arteries is high, because the site of atherosclerosis is specifically given. If some of the atherosclerotic diagnoses were erroneous, such random misclassification of individuals would tend to reduce the observed relative risk for cancer toward the null. The size of the present study, however, should allow room for such misclassification.

Lifestyle factors, such as smoking and presumably unhealthy dietary habits, may be changed because of a hospitalization for atherosclerosis, which in turn could decrease the risk for subsequent cancer. The risk for smoking-related cancers, however, was higher in long- than short-term follow-up periods, indicating that a probably healthier lifestyle after discharge may not have reduced smoking-related cancers to expected levels among atherosclerotic patients during the maximal 17 years of follow-up in our study.

Some 30,000 atherosclerotic patients did not survive at least 1 year after discharge from hospital and, consequently, were not included in the risk analysis for subsequent cancer. Clearly, the large subset of patients lost differs from the subset of patients surviving 1 year, with respect to the severity of the atherosclerotic disease and/or the distribution of risk factors to atherosclerosis. Unfortunately, the distribution of risk factors for extracoronary manifestations of atherosclerosis among fatal and nonfatal cases in the Danish population is, to our knowledge, largely unknown.

Surveillance bias is often mentioned in connection with hospitalized patients, because the clinical examination, blood tests, and X-rays performed during hospital admission may reveal yet unrecognized malignant tumors. On the other hand, the presence of atherosclerotic diseases might have caused underascertainment of cancer in the study if the patients were so elderly or ill that a diagnostic workup for cancer did not seem appropriate. The exclusion of cancers and follow-up time for the first year after discharge probably eliminates the effect of overascertainment or underascertainment of cancer, if present.

The incidence rate of atherosclerotic diseases is higher in men than in women, especially in younger age groups; it has been proposed that higher estrogen levels in women, especially in the premenopausal period, may protect against atherosclerosis (13). The decreased risk for endometrial cancer observed in the present study supports the idea of antiatherogenic effects of estrogens in both pre- and postmenopausal women; however, the decreased risk for endometrial cancer associated with tobacco smoking reported in some studies is another likely explanation (29). It is surprising that the risk for breast cancer, which is also related to estrogens, was not decreased in any age group.

The overall risk for cancers of the brain and nervous system in patients discharged with occlusion of precerebral arteries or atherosclerosis of the cerebral arteries appeared to be slightly increased (40%), but the excess was restricted to the initial 1–3 years from date of discharge. The most likely explanation is that the symptoms of preclinical brain cancers were misinterpreted. Similar findings have been reported from a Danish cohort study of stroke patients (32).

Patients with atherosclerotic diseases have increased concentrations of cholesterol (33, 34), and some studies have reported higher serum cholesterol concentrations in patients with brain tumors than in controls (35, 36). The normal risk for brain cancer observed among our atherosclerotic patients gives no support to the hypothesis of an association between high cholesterol concentration and subsequent brain tumors.

In conclusion, our study of nearly 70,000 patients discharged with extracoronary manifestations of atherosclerosis and followed for a maximum of 17 years gives no support to the hypothesis that atherosclerosis is associated with any specific cancer site unrelated to tobacco smoking. The study does not support the view (15) that survivors of atherosclerotic diseases may represent a high-risk group for future prostate cancer screening interventions.

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