

Cancer Risk and Subsequent Survival after Hospitalization for Intermittent Claudication

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Abstract

Background: Intermittent claudication, muscle ischemia due to reduced arterial circulation, may be associated with an increased risk of cancer risk and death due to neoplasm-induced hypercoagulability and angiogenesis, or to shared risk factors, but the relation is not well understood.

Methods: We conducted a population-based cohort study using the Danish National Registry of Patients to identify patients with intermittent claudication from 1980 to 2011 and no history of cancer. We followed these patients for incident cancers using the Danish Cancer Registry and compared cancer incidence among patients with intermittent claudication to that expected in the general population. We also compared the survival of patients with cancer with and without claudication, matched for sex, cancer site, stage, age at diagnosis, and diagnosis year.

Results: A total of 53,762 patients with intermittent claudication were identified. We observed 6,270 incident cancers over a

total 269,430 years of follow-up (mean, 5.0), compared with 4,306 cancer cases expected [standardized incidence ratio = 1.46; 95% confidence interval (CI), 1.42–1.49]. Cancer risk also increased after the exclusion of patients with a prior diagnosis of cerebrovascular disease, myocardial infarction, or diabetes, particularly for tobacco-related cancers. The elevated cancer risk persisted over 10 years of follow-up. For patients with cancer, diagnosis of intermittent claudication within 3 months preceding the cancer diagnosis did not influence survival, but before 3 months, was associated with modestly worse survival (mortality rate ratio = 1.19; 95% CI, 1.14–1.25).

Conclusions: Intermittent claudication is associated with an increased risk of cancer and poorer subsequent survival.

Impact: Clinical attention following intermittent claudication diagnosis may reveal incident cancers. *Cancer Epidemiol Biomarkers Prev*, 24(4); 744–8. ©2015 AACR.

Introduction

Intermittent claudication is a common condition in which reduced arterial flow during activity results in calf pain due to muscle ischemia (1). The prevalence of intermittent claudication increases with age, and is found in an estimated 10% of the population age 70 and older (1). Smoking is the strongest risk factor for peripheral arterial disease and intermittent claudication, but other risk factors include increased age, diabetes, hypertension, and dyslipidemia (1–3). Typically, intermittent claudication is the first clinical manifestation of peripheral arterial disease, and usually signifies atherosclerotic processes and risk of major cardiovascular events. (1–3).

Intermittent claudication shares an atherosclerotic pathology with myocardial infarction and cerebrovascular disease, both of

which have been shown to be associated with an increased risk of cancer (4–10). Myocardial infarction and cerebrovascular disease are strongly associated with cigarette smoking, which is also associated with cancer risk (9–11). Consequently, one explanation for the cancer associations of these vascular diseases is the shared risk factor of smoking. Indeed, the excess cancer risk in individuals with myocardial infarction and cerebrovascular disease is largely limited to smoking-related cancers (4–10). An association between intermittent claudication and cancer risk has been shown in multiple studies, but with inconclusive results regarding whether the increased risk is limited to smoking-related malignancies (9–11). Also unknown is the mortality risk for patients with intermittent claudication who develop cancer in comparison with the prognosis for patients with cancer without an intermittent claudication history. Understanding the relation between intermittent claudication and cancer is important, as intermittent claudication is readily detected clinically; thus, an increased risk of cancer may warrant heightened clinical suspicion.

There are plausible mechanisms for an association between intermittent claudication and cancer risk that is independent of smoking. Paraneoplastic hypercoagulability from an occult tumor may precipitate intermittent claudication, which may then be a symptom of an occult malignancy (6). Shared risk factors other than smoking, such as obesity, high intake of dietary fat, low physical activity, metabolic syndrome, or type II diabetes may contribute to a long-term positive association between intermittent claudication and cancer (8). Finally, increased medical attention after a new diagnosis of intermittent claudication may result in the detection of asymptomatic cancers.

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Understanding of intermittent claudication and cancer risk requires a large, longitudinal, population-based study to adequately examine site-specific cancer risk over time in patients with intermittent claudication, and to examine survival among patients with intermittent claudication with cancer. To clarify these issues, we examined the relation between intermittent claudication and cancer risk and survival in the Danish population using longitudinal data, to determine whether intermittent claudication only confers increased risk of smoking-related cancers, to assess the nature of the intermittent claudication/cancer relation and to investigate the association of intermittent claudication with survival among patients with cancer.

Materials and Methods

Study population and data

This nation-wide cohort study was conducted in Denmark. We obtained data from the Danish National Registry of Patients, which has recorded information from 99.4% of all nonpsychiatric hospitalizations since 1977, and all hospital outpatient and emergency room visits since 1995 (12–16). The information includes, among other elements, dates of admission and discharge or dates of service, and up to 20 diagnoses, classified according to the International Classification of Diseases, 8th revision (ICD-8) until December 31, 1993, and to the 10th revision thereafter. The inclusion of the outpatient hospital visits encompasses essentially all the specialist medical care in the country. All diagnosis coding is done by the treating physicians at the time of discharge. We also obtained data from the Danish Cancer Registry, which has been in existence since 1943 and records all incident cancer cases, with date of diagnosis, using ICD-10. Details of the Danish Cancer Registry protocols and practices are found elsewhere. Briefly, data include civil registration number, diagnosis and date, verification method, extent of disease, first course of treatment, and date and cause of death (17–19). Comprehensive validation has shown that the registry is 95% to 98% complete and valid (12). The Danish Civil Registration System contains a unique identifier for inhabitants, which records date of birth, residency status, and dates of emigration and death (12). The unique identifier links across all public Danish registries to establish nearly complete information on health care utilization, elements of clinical information, and vital status for the entire population.

Patients with intermittent claudication

We established a cohort of individuals with an incident hospital diagnosis of intermittent claudication (Supplementary Table S1) between January 1, 1980, and December 31, 2011, and no prior cancer diagnosis, as determined by the Danish National Registry of Patients and the Danish Cancer Registry, respectively. We eliminated potential prevalent intermittent claudication cases by omitting from analysis subjects with a diagnosis of intermittent claudication during 1977 to 1979. The cohort was followed until a first cancer was reported, or emigration or death occurred. For cancers identified, we collected date of diagnosis, site of the primary cancer, and whether the cancer was metastatic at the time of diagnosis. Because of the clinical association of intermittent claudication with other forms of atherosclerotic vascular disease, we identified individuals diagnosed with intermittent claudication who had previously been diagnosed with stroke, myocardial infarction, or diabetes mellitus (Supplementary Table S1). Date of death, if applicable, was taken from the Danish Civil

Registration System, which is updated daily. Follow-up of individuals with intermittent claudication was through January 1 2013 or date of death if prior.

Cancer comparison cohort and comorbidities

To assess differences in survival between patients with cancer with and without an intermittent claudication diagnosis, we established a cancer comparison cohort using the Danish Cancer Registry. This cohort was created by matching each patient with intermittent claudication with subsequent cancer to 5 patients with cancer with no prior history of intermittent claudication. Comparison cohort members were matched on age (within 5 years), sex, year of cancer diagnosis (within 5 years), stage at diagnosis, and cancer site. For each individual in the study, we computed a comorbidity index score based on all diagnoses recorded in the National Registry of Patients before the date of hospitalization for cancer. Three levels of comorbidity were defined, using the Charlson Index for one-year inpatient mortality based on 15 conditions, excluding cancers (Supplementary Table S1; refs. 20, 21): low (for patients with no recorded underlying comorbid disease); moderate (index score of 1–2); and high (index score of 3+). Diagnoses of intermittent claudication or peripheral vascular disease and cancer were excluded from the index as they, respectively, defined our study cohort and exposure variable. The study was approved by the Danish Data Protection Board (record no: 1-16-02-1-08).

Statistical analysis

Risk analyses. We compared the incidence of cancer in individuals with a diagnosis of intermittent claudication to that of the general population. We computed the expected number of patients with cancer by multiplying national incidence rates of groups defined by age (5-year intervals), sex, and 5-year calendar intervals by the corresponding person years at risk in the intermittent claudication cohort. The ratio of observed to expected cancers yielded standardized incidence ratios (SIR). For calculation of 95% confidence intervals (CI), we assumed a Poisson distribution of the number of observed cancers. Exact 95% CIs were used when the observed number of cases was less than 10; otherwise Byar approximation was used (22). SIRs and absolute risks, accounting for death as a competing risk, were calculated for all cancers combined and for site-specific cancers. SIRs and Kaplan–Meier estimates of absolute risk were computed for the entire follow-up time, and for 0–<3 months, 3–<6 months, 6–<12 months, 1–<2 years, 2–<5 years, 5–<10 years, and 10+ years of follow-up. We also analyzed the data by calendar time periods, 1980–1994 and 1995–2011, that corresponded to the dates during which only inpatient discharges were recorded (1980–1994) and outpatient visits were additionally captured (1995–2011). Because smoking is a shared risk factor for both intermittent claudication and specific cancers, we also analyzed risk separately for cancers deemed smoking-related (ref. 23; Supplementary Table S2) and other malignancies. We repeated the analyses after excluding patients with known diabetes, prior cerebrovascular disease, or prior myocardial infarction to help account for severity of vascular disease.

Survival analyses. We used Kaplan–Meier analysis to summarize time to death among individuals with intermittent claudication and cancer and the comparison cohort of patients with cancer without claudication. Cox proportional hazards models

Table 1. Patients with intermittent claudication over 269,430 person-years of follow-up for cancer from 1980–2011 in Denmark

	Total (<i>N</i> = 53,762)	Patients with intermittent claudication, <i>n</i> (%)	
		Without prior cerebrovascular disease (<i>n</i> = 45,796)	Without prior myocardial infarction (<i>n</i> = 45,833)
Male	30,692 (57.1)	25,791 (56.3)	25,169 (54.9)
Female	23,070 (42.9)	20,005 (43.7)	20,664 (45.1)
Age, y ^a			
0–29	473 (0.9)	466 (1.0)	471 (1.0)
30–49	4,136 (7.7)	3,922 (8.6)	3,862 (8.4)
50–69	25,554 (47.5)	22,319 (48.7)	22,023 (48.1)
70+	23,599 (43.9)	19,089 (41.7)	19,477 (42.5)
Charlson comorbidity index			
0	27,474 (51.1)	27,374 (59.8)	27,393 (59.8)
1 or 2	20,041 (37.3)	14,895 (32.5)	15,003 (32.7)
≥3	6,247 (11.6)	3,527 (7.7)	3,437 (7.5)

^aAge at first diagnosis of intermittent claudication.

estimated mortality rate ratios (MRR) while accounting for comorbidities assessed with the Charlson Index (20, 21).

Results

Characteristics of study population

We identified 53,762 individuals (23,070 females, 30,692 males) with an incident diagnosis of intermittent claudication during the study period (Table 1). The total person-years of follow-up were 269,430, with an average follow-up duration of 5.0 years. The median age at first diagnosis of intermittent claudication was 68 years. Of the 53,762 patients with IC, 6,270 (11.7%) subsequently were diagnosed with cancer during follow-up.

Cancer risk

Over the entire follow-up, an excess of 1,964 total cancers was observed among the patients with intermittent claudication compared with the expected number in the population (Table 2; SIR = 1.46; 95% CI, 1.42–1.49). The intermittent claudication population showed a clear increase in the risk of tobacco-related cancers (SIR = 2.30; 95% CI, 2.22–2.38), but no overall increase in risk of cancers that are not tobacco-related (SIR = 1.03, 95% CI, 0.99–1.07). Hodgkin lymphoma was the only non-tobacco-related malignancy associated with intermittent claudication (SIR

= 2.05; 95% CI, 1.17–3.32; Table 2). These relations were seen in the total cohort as well as among individuals without prior cerebrovascular disease or myocardial infarction. (Table 2) Similarly, risk of any cancer was significantly elevated for patients with intermittent claudication with and without diabetes mellitus, although more so for latter (diabetes mellitus SIR = 1.29; 95% CI, 1.19–1.39, and no diabetes mellitus SIR = 1.48; 95% CI, 1.44–1.52; Supplementary Table S3). The SIRs for tobacco-related cancers were elevated for both men and women (data not shown).

The association of intermittent claudication and excess cancer risk persisted over time, although attenuation was noted beyond 3 months of follow-up. The SIR during 0–<3 months of follow-up was 2.22 (95% CI, 2.02–2.44); subsequent SIRs ranged between 1.40 and 1.47 (Fig. 1). Nevertheless, it is important to note that after 3–6 months, the patients with intermittent claudication had a consistently increased risk of cancer compared with the general population (Fig. 1). The absolute risk of cancer in patients with intermittent claudication naturally rose over time: from 2.39% (95% CI, 2.26–2.5) over the first year to 9.59% (95% CI, 9.31–9.87) over 5 years, and more than 15% (95% CI, 14.96–15.76) over 10 years (Fig. 2). Increasing absolute risk over time was similar for tobacco and non-tobacco-related cancer incidence (Fig. 2).

Table 2. SIRs for selected cancers among patients (*n* = 53,762) with intermittent claudication in Denmark from 1980–2011

	Total cohort (<i>n</i> = 53,762)		
	O ^a	SIR	95% CI
All malignant neoplasms	6,270	1.46	1.42–1.49
Hematologic cancers			
Non-Hodgkin lymphoma	193	1.10	0.95–1.26
Hodgkin lymphoma	16	2.05	1.17–3.32
Leukemia ^b	117	1.08	0.88–1.27
Tobacco-related cancer			
All combined	3142	2.30	2.22–2.38
Tongue	37	2.64	1.86–3.64
Esophagus	137	2.16	1.81–2.55
Pancreas	178	1.33	1.14–1.54
Larynx	107	2.63	2.16–3.18
Lung	1825	2.82	2.69–2.95
Kidney	129	1.53	1.28–1.82
Bladder	546	1.76	1.62–1.92
All other sites	2802	1.06	1.02–1.10

^aObserved number of cases.

^bLeukemia includes lymphoid, myeloid, monocytic, and other leukemias of specified cell type.

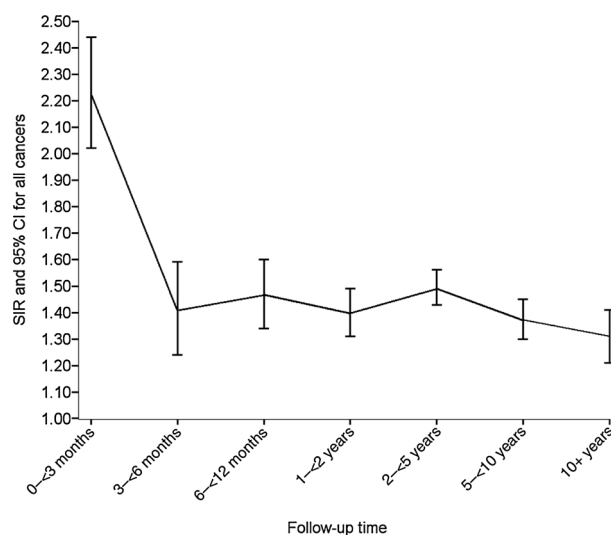


Figure 1. SIRs for all cancers from time since diagnosis of intermittent claudication.

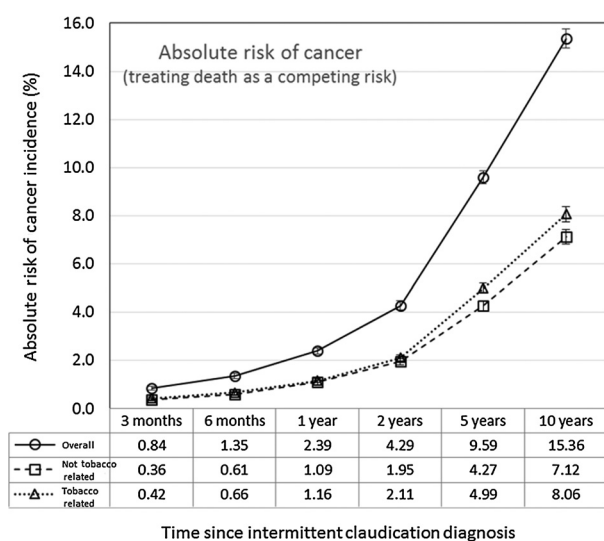


Figure 2.

Absolute risk in percent (95% CI) of cancer incidence from time since diagnosis of intermittent claudication.

Survival with intermittent claudication and cancer

A consistently lower survival was seen in patients with cancer with a prior intermittent claudication diagnosis relative to those without (Fig. 3). Individuals with intermittent claudication diagnosed within 3 months before the cancer diagnosis had a small, nonsignificant increase in mortality compared with those with no intermittent claudication (adjusted MRR = 1.12, 95% CI, 0.96–1.30). Diagnosis of intermittent claudication more than 3 months before cancer diagnosis was associated with a similarly increased and statistically significant increase in mortality (adjusted MRR = 1.19, 95% CI, 1.14–1.25).

Discussion

We found an increased risk of all cancers combined among patients with intermittent claudication, specifically of tobacco-

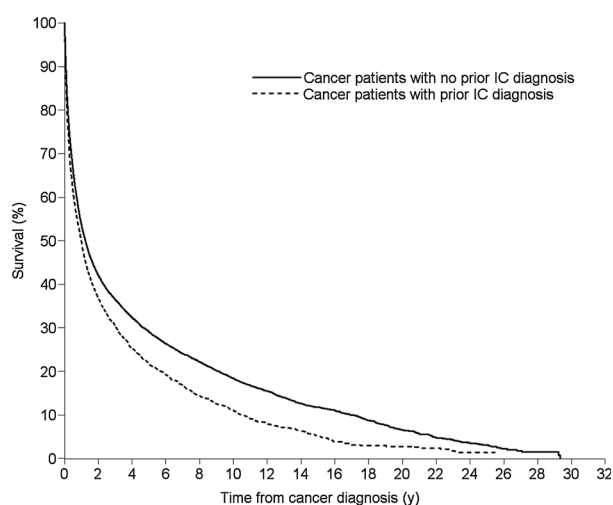


Figure 3.

Survival probability for patients with concurrent intermittent claudication and cancer.

related cancers. The only other cancer that showed an elevated risk after intermittent claudication was Hodgkin lymphoma, which may have been due to detection during the increase medical attention following the intermittent claudication diagnosis. Overall, the excess risk was most pronounced in the 3 months after diagnosis, but remained even after 10 years follow-up. For patients with intermittent claudication who develop cancer, those who had a diagnosis of intermittent claudication within 3 months prior showed mortality comparable with that of similar patients with cancer without intermittent claudication. A more remote intermittent claudication diagnosis before the cancer, however, was associated with a small increase in mortality.

Prior studies linking coronary heart disease and cerebrovascular disease to cancer risk point to an association primarily with smoking-related cancers, with inconsistent findings regarding a few nonsmoking-related cancers (6–11). Previous research regarding the relation of intermittent claudication with risk of cancer is limited to one population-based cohort study from Sweden (9). It found an increased overall risk of cancer in patients with intermittent claudication similar to that which we observed: more than a 40% increased risk of cancer among patients with intermittent claudication, almost entirely attributed to an association with tobacco-related cancers (9).

Because there is a long-term excess of tobacco-related cancers in patients with intermittent claudication, smoking as a shared risk factor probably explains at least part of the intermittent claudication/cancer association. However, biologic mechanisms to explain a relationship have also been proposed, specifically angiogenesis, and hypercoagulability (9). The first of these hypothesized that intermittent claudication is associated with a decreased cancer risk because both intermittent claudication and cancer patients display a decreased capacity for angiogenesis (9). However, our data, and that of the earlier observational study (9) are not consistent with this hypothesis, showing an increased risk of cancer with intermittent claudication.

The second hypothesis posits the opposite association: that cancer may cause intermittent claudication, as a result of prothrombotic neoplastic processes (9). Our finding that the excess cancer risk associated with intermittent claudication declines substantially beyond 3 months is consistent with an occult cancer precipitating intermittent claudication or with the medical attention subsequent to intermittent claudication diagnosis leading to clinical discovery of a completely asymptomatic malignancy.

There are several reasons why patients with cancer with intermittent claudication would have, over the long term, greater mortality than patients with cancer without intermittent claudication. The serious vascular disease the claudicants may have interfered with surgical or chemotherapeutic cancer therapies. Also, the vascular disease in patients with intermittent claudication could impose a mortality burden in its own right.

Because the Danish registry data are virtually complete across the population, referral or selection bias is very unlikely. Similarly, for cancers and survival, complete ascertainment reduces the possibility of selection bias due to being lost at follow-up. Longitudinal data over 30 years for the entire Danish population allowed for subanalyses by cancer site, tobacco-relation, gender, comorbidities, and time.

However, this study also has limitations. The lack of behavioral risk factor data, particularly smoking status, prevented us from adjusting our analyses for that important common risk factor.

Also, we could not capture data about the diagnostic process or severity of intermittent claudication, particularly in relation to the time of cancer diagnosis, and only ascertained those cases identified through hospitalization. Having full information would help our understanding of whether a precipitous worsening of intermittent claudication is likely to herald a neoplasm.

The absolute risk of cancer after a diagnosis of intermittent claudication, about 2.4% over the first year and almost 10% at 5 years, is not large, and modest in relative terms. Consequently, special workup for neoplasms in patients with a new diagnosis of intermittent claudication may not be generally warranted, especially because the excess risk is not concentrated in any one cancer site. Nonetheless, the possibility that a precipitous decline in vascular function among individuals with stable intermittent claudication may herald a malignancy could be a valuable clinical clue.

In summary, intermittent claudication appears to be related to cancer risk at least in part because of the shared risk factor of cigarette smoking. The particularly high relative risk of cancer in the months immediately after the diagnosis suggests that increased medical attention after intermittent claudication diagnosis may have disclosed an asymptomatic cancer or that the onset of intermittent claudication is part of a paraneoplastic syndrome heralding a cancer diagnosis.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Writing, review, and/or revision of the manuscript: T. Onega, J.A. Baron, S.P. Johnsen, D.K. Farkas, H.T. Sørensen
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T. Onega, H.T. Sørensen
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