Myocardial infarction and future risk of cancer in the general population – The Tromsø Study

Ludvig B. Rinde[1], Birgit Småbrekke[1], Erin M. Hald[1,2], Ellen E. Brodin[1,2], Inger Njølstad[1,3], Ellisiv B. Mathiesen[1,4], Maja-Lisa Løchen[3], Tom Wilsgaard[3], Sigrid K. Brækkan[1,2], Anders Vik[1,2], John-Bjarne Hansen[1,2]

[1]K. G. Jebsen -Thrombosis Research and Expertise Center (TREC), Department of Clinical Medicine, UiT The Arctic University of Norway,

[2]University Hospital of North Norway, Division of Internal Medicine, Tromsø, Norway,

[3]Epidemiology of Chronic Diseases Research Group, Department of Community Medicine, UiT The Arctic University of Norway, Tromsø. Norway,

[4]Brain and Circulation Research Group, Department of Clinical Medicine, UiT The Arctic University of Norway.

Running title: Myocardial infarction and cancer

Correspondence to: Ludvig B. Rinde, K. G. Jebsen - Thrombosis Research and Expertise Center (TREC), Department of Clinical Medicine, University of Tromsø, The Arctic University of Norway, N-9037, Norway.

E-mail ludvig.b.rinde@uit.no, telephone: +47 97 13 47 60

Word count abstract: 244
Word Count: 3312
Number of tables: 4
Number of figures: 1
Supplementary tables: 1

Abstract

The association between myocardial infarction (MI) and future risk of incident cancer is scarcely investigated. Therefore, we aimed to study the risk of cancer after a first time MI in a large cohort recruited from a general population. Participants in a large population-based study without a previous history of MI or cancer (n=28763) were included and followed from baseline to date of cancer, death, migration or study end. Crude incidence rates (IRs) and hazard ratios (HRs) for cancer after MI were calculated. During a median follow-up of 15.7 years, 1747 subjects developed incident MI, and of these, 146 suffered from a subsequent cancer. In the multivariable-adjusted model (adjusted for age, sex, BMI, systolic blood pressure, diabetes mellitus, HDL cholesterol, smoking, physical activity and education level), MI patients had 46% (HR 1.46; 95% CI: 1.21-1.77) higher hazard ratio of cancer compared to those without MI. The increased cancer incidence was highest during the first 6 months after the MI, with a 2.2-fold higher HR (2.15; 95% CI: 1.29-3.58) compared with subjects without MI. After a 2-year period without higher incidence rate, MI patients displayed 60% (HR 1.60; 95% CI: 1.27-2.03) higher HR of future cancer more than 3 years after the event. The increased incidence rates were higher in women than men. Patients with MI had a higher short- and long-term incidence rate of cancer compared to subjects without MI. Our findings suggest that occult cancer and shared risk factors of MI and cancer may partly explain the association.

Introduction

Myocardial infarction (MI) and cancer are major causes of morbidity and mortality worldwide [1]. While there is limited knowledge regarding the relation between MI and cancer, previous registry-based cohorts of MI patients suggest that these patients are at a modest 5-8 % increased risk of cancer [2, 3]. Occult cancer may induce a prothrombotic phenotype [4] of which MI may be the first sign [5]. An association between MI and subsequent cancer risk may be due to shared risk factors (e.g. smoking [6], obesity [7, 8], and low physical activity [9]), a consequence of MI diagnosis and treatment (e.g. surveillance bias), or an MI-related (e.g. chronic inflammation) impact on cancer risk. Growing evidence suggests that MI and cancer share the same molecular pathways of disease development and progression [10, 11] and that chronic inflammation plays a pivotal role in both carcinogenesis and atherosclerosis [12, 13].

The risk of cancer after MI has been scarcely investigated, and information on this topic is mainly derived from registry-based case-cohort studies. Due to lack of information about possible confounders like body mass index (BMI) and smoking [3, 2], exclusion of patients that died during the first year after MI [3], and limited validation of exposures and outcomes [3, 2], the results of these studies should be interpreted with caution. Moreover, the time since the MI diagnosis may influence the cancer risk. Therefore, we aimed to investigate the risk of cancer after a first episode of MI using a large population-based cohort with validated information about MI, cancer, and potential confounders.

Methods

Study population

We recruited study participants from the fourth, fifth and sixth survey of the Tromsø Study,

conducted in 1994-95, 2001 and 2007-08, respectively. The Tromsø Study is a single-center,

prospective, population-based study, with repeated health surveys of the inhabitants in Tromsø,

Norway. The overall attendance proportion was high; 77 % in the fourth, 78 % in the fifth and 66

% in the sixth survey. In total, 30 586 unique subjects aged 25 to 97 years participated in at least

one of the three surveys. A detailed description of the Tromsø Study has previously been

published elsewhere [14]. The regional committee for research ethics in Northern-Norway

approved the study, and all subjects gave their informed written consent. Subjects who did not

consent to medical research (n = 225), and subjects not officially registered as inhabitants of the

municipality of Tromsø at the date of study enrollment (n = 49) were excluded. Furthermore,

subjects with a history of cancer (n = 815) or MI (n = 734) before baseline were excluded.

Consequently, 28 763 subjects were included in the study, and followed from the date of

enrollment to the end of follow up, the 31st of December 2010 (Fig. 1).

Baseline measurements

Baseline information about study participants was collected by physical examination, blood

samples and self-administrated questionnaires. Systolic and diastolic blood pressure were

measured three times with 1-minute intervals with an automatic device (Dinamap Vital Signs

Monitor, 1846; Critikon Inc., Tampa, FL, USA) in a sitting position after 2 minutes of rest, and

defined as the mean of the last two readings. Non-fasting blood samples were collected from an

antecubital vein, serum prepared by centrifugation after 1-hour respite at room temperature and

analyzed at the Department of Clinical Chemistry, University Hospital of North Norway, Tromsø, Norway. Serum total cholesterol was analyzed by an enzymatic colorimetric method using a commercially available kit (CHOD-PAP, Boehringer-Mannheim, Mannheim, Germany). Serum HDL-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. Height and weight were measured with subjects wearing light clothes and no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Subjects were classified as obese (BMI $\geq$ 30 kg/m^2) according to the World Health Organization definition [15]. Hypertension was defined as mean systolic blood pressure $\geq$ 140 mm Hg, mean diastolic blood pressure $\geq$ 90 mm Hg, or self-reported use of blood pressure-lowering drugs. Hypercholesterolemia was classified as total serum cholesterol $\geq$ 6.5 mmol/L or self-reported use of lipid lowering drugs. Information on smoking status, family history of MI, diabetes mellitus, physical activity and education level was collected from a self-administrated questionnaire. Smoking status was assessed as self-reported daily smoking of cigarettes cigar or pipe (yes/no). Physical activity was classified as more than 1 hour of moderate or hard physical activity per week (yes/no), and education was dichotomized into a variable stating less or more than 10 years of education (yes/no). The proportion of missing data in our study was low (<3 %), and subjects with missing values were found to be similar to subjects included in the analysis with regards to clinically relevant parameters.

Assessment of myocardial infarction events

Based on data from hospital and out-of hospital medical records, autopsy records, and death certificates, an independent end-point committee validated hospitalized and out-of-hospital events of myocardial infarction. Further, the Norwegian national 11-digit identification number allowed linkage to national and local diagnosis registries. Cases of possible incident myocardial

infarction were identified by linkage to the hospital discharge diagnosis registry at the University Hospital of North Norway with a broad search for the International Classification of Diseases (ICD), ICD 8 codes 410–414, 427, 795–796 in the period 1969–1979 (in order to exclude prevalent MIs before inclusion), ICD 9 codes 410–414, 427.5, 798 and 799 in the period 1980–98, and thereafter ICD 10 codes I20–I25, I46, R96, R98 and R99. The hospital medical records were retrieved for case validation. Modified World Health Organization MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease)/MORGAM (MONICA Risk, Genetics, Archiving and Monograph Project) criteria for MI were used. MI was defined by one of the following sets of conditions: a) typical, atypical or inadequately described symptoms + a definite new infarction in ECG recordings, b) typical symptoms + significantly higher myocardial enzyme and/or troponin levels, c) atypical or inadequately described symptoms + significantly higher myocardial enzyme and/or troponin levels + a probable new infarction in ECG recordings, and d) post-mortem evidence of recent MI or thrombosis.[16]. Further, linkage to the National Causes of Death Registry at Statistics Norway allowed identification of fatal incident cases of MI that occurred as out-of-hospital deaths, including deaths that occurred outside of Tromsø. Information from the death certificates was used to collect relevant information on the MI events from additional sources such as autopsy reports and records from nursing homes, ambulance services, and general practitioners.

Registry of cancer events

Cancer events were identified by linkage to the Cancer Registry of Norway by use of the unique national civil registration numbers of the study participants. Identification of events in the Cancer Registry were obtained with the International Classification of Disease, Revision 7 (ICD

7) codes 140-205. Subjects with non-melanoma skin tumors (ICD 7 191.0-191.9) were classified as cancer-free. Cancer registration is mandatory by law in Norway and the Cancer Registry is considered complete and valid. The Cancer Registry provides information about date of cancer diagnosis, location of the disease, cancer stage (localized, regional, distant or unknown) histological grade and initial treatment. Evaluation of the registry data quality showed 98.8 % completeness. For all sites combined, 93.8% of the cases were morphologically verified, 0.9% were registered on the basis of a death certificate only, and 2.2% were registered with primary site unknown. [17].

Statistical Analysis

Statistical analyses were performed using STATA version 14.0 (Stata corporation, College Station, TX, USA). Crude incidence rates (IRs) of cancer were calculated and expressed as number of events per 1 000 person-years at risk. For each participant, non-exposed and exposed person-years of follow-up were counted from the date of enrollment to the date of an incident diagnosis of cancer, the date the participant died or moved from the municipality, or until the end of the study period, 31st of December 2010, whichever came first. Subjects who died (2938) or moved (4566) from the municipality during follow-up were censored at the date of death or migration, respectively. MI was treated as a time-varying co-variate. Subjects who developed MI during the study period contributed with non-exposed person-time from the inclusion date to the date of a diagnosis of MI, and then with exposed person-time from the date of MI onward. Consequently, subjects developing cancer before MI contributed with cancer events in the non-exposed category.

Cox proportional hazard regression models were used to estimate age- and sex-adjusted

and multivariable adjusted hazard ratios (HRs) with 95 % confidence intervals (CI) for cancer after MI. MI was entered as a time-varying exposure in the Cox-model. Thus, 28 740 subjects contributed with 346 684 observation periods. Age was used as a time-scale in the Cox model, with the age of the participants at study enrollment defined as entry time and age at cancer-event or censoring event (i.e. death, migration, or the date of study end) as exit-time. The HRs were estimated according to different time intervals after the MI using the stsplit function in Stata (<6 months, 6 months-<1 year, 1-3 years, and more than 3 years), and adjusted for potential confounders in three different models. Model 1 was adjusted for sex and age (as time scale), while Model 2 was additionally adjusted for BMI. Model 3 was adjusted for age (as time scale), sex, BMI (as a continuous variable), diabetes mellitus, current smoking (yes/no), systolic blood pressure, HDL-cholesterol, physical activity and education level. Since the median age of first MI is known to be approximately 10 years higher in women than in men [18], sex-specific analyses were conducted. Missing data were handled using available-case analyses. The proportional hazards assumption was tested using Schoenfeld residuals and was not violated.

Results

In total, 1 747 (6.1 %) subjects experienced a first-time MI, and of these 146 (8.4 %) developed subsequent cancer during a median follow up of 15.7 years. Baseline characteristics of the study participants with and without MI are shown in Table 1. Subjects who developed MI had higher mean age and BMI, and included higher proportions of men, smokers, and subjects with hypertension, hypercholesterolemia and diabetes mellitus. The proportions of physically active subjects and subjects with more than 10 years of education were lower among those who developed MI during follow up (Table 1).

The distributions of different cancer sites among patients with MI are shown in table 2. The most frequent types of cancers were colorectal cancer (22 %), prostate cancer (22 %) and lung cancer (16 %) (Table 2).

The incidence rates and HRs for cancer are shown in table 3. In subjects without MI, 2 470 cancer events were identified during 340 216 person-years (IR 7.3 per 1 000 person-years) of follow up, whereas there were 146 cancer events during 6 468 person-years of follow-up in subjects diagnosed with MI (IR 22.6 per 1 000 person-years). Overall, MI was associated with a 46 % (multivariable adjusted HR 1.46; 95% CI: 1.21-1.77) increased hazard ratio of cancer. In sex specific analyses, women had higher incidence rate estimates for cancer by MI than men, but the confidence intervals overlapped (Table 3). In sub group-analyses by tobacco-associated cancers, the incidence rate estimates for tobacco-associated and not-tobacco-associated cancers were similar for both groups (Supplementary Table 1). Other risk factors such as male sex, high BMI, increased systolic blood pressure, diabetes mellitus and current smoking were all associated with increased risk of cancer in our study population. Contrary, higher education and physical activity had a protective effect on the risk of cancer (Supplementary Table 2).

The incidence of cancer in subjects with MI changed over time after the MI event (Table 4). The highest incidence was found for the first 6 months after the MI diagnosis (IR 29.0 per 1 000 person-years). The absolute risk increase was 21.7 additional events of cancer per 1 000 persons the first 6 months after diagnosis compared with subjects without MI (Table 4). The hazard ratio of cancer was 2.2-fold higher the first six months after MI (HR 2.15; 95% CI: 1.29-3.58) compared to subjects without MI, followed by a time period from 6 months to 3 years after MI without any increased cancer incidence rate (Table 4). In the period more than 3 years after MI, the hazard ratio of cancer was 60 % (HR 1.60; 95% CI: 1.27-2.03) higher compared to

subjects without MI. The short- and long-term incidence rate estimates for cancer by MI were

higher for women than for men (Table 4).

Discussion

In our prospective cohort of almost 29 000 subjects followed for 16 years, subjects who developed MI had 46 % higher hazard ratio of cancer compared to subjects without MI. The risk of incident cancer by MI displayed a biphasic risk pattern. During the first 6 months after the MI diagnosis, a transient 2.2-fold increased hazard ratio of cancer was accompanied by a time-period from 6 months to 3 years after MI without any association between MI and cancer. A secondary phase with a 60 % increased incident rate of incident cancer was observed more than 3 years after the MI diagnosis. The hazard ratio of cancer by MI was higher in women than in men.

Few studies have investigated the association between MI and future risk of cancer. Two independent registry-based cohorts of coronary heart disease (CHD) patients have suggested that MI patients are at modest increased risk of cancer, particularly of smoking-related cancers [3, 2]. Patients with ischemic syndromes in Stockholm county (n = 63 921) had an 8 % higher risk of cancer, particularly of smoking-related cancer in which the risk was 16 %, and 62 % increased in men and women, respectively [2]. Similarly, a Danish registry-based cohort of one-year survivors of MI (n = 96 891) showed an overall 5% increased risk of cancer, and an 8% and 36% increased risk of smoking-related cancer in men and women, respectively [3]. In accordance with these studies, we observed that women had an apparently higher short- and long-term incidence rate of cancer after MI compared to men. Although sex-dependent mechanisms could possibly explain the association, it is likely that the apparently increased hazard ratio in women is partly explained by the lower baseline risk of MI in women compared to men, as the absolute risk increase (difference in incidence rates) of cancer by MI was similar in men and women (Table 3 and Table 4).

In our study, the hazard ratio of cancer was particularly high during the first six months after the MI diagnosis. Surveillance bias may to some extent explain the immediate transient increase in incidence rate of cancer after MI. First, patients hospitalized for MI are subjected to in-depth examination and testing that may lead to earlier detection of cancer. Second, aggressive antithrombotic therapy in the initial phase of MI may cause an asymptomatic tumor to present with bleeding with subsequent detection. Third, surveillance bias is expected to be accompanied by an apparent lowering of the cancer incidence after the initial period due to earlier diagnosis of cancer in subjects that are surveilled and treated for MI. Another possible explanation could be the presence of occult cancer at the time of MI. Occult cancer may provide a prothrombotic phenotype [4] of which MI may be the first sign. Occult cancer is associated with increased MI risk [5], and the risk of MI is particularly high the first 6 months after cancer diagnosis [19].

The observed 60% increased hazard ratio of cancer occurring more than 3 years after the MI event suggests that other mechanisms than surveillance bias and occult cancer are involved for the long-term risk. For instance, MI and cancer share common risk factors such as smoking [6], obesity [8, 7], and low physical activity [9]. Both environmental and behavioral risk factors have atherogenic and carcinogenic effects, which may give rise to an increased risk of cancer in individuals with atherosclerotic diseases [20]. The most apparent risk factor is smoking, which increases the risk of several types of cancer and MI [21, 22, 6]. Some previous studies have attributed the observed increased incidence of cancer after MI to tobacco-related cancers [2, 3], and in a study of almost 100 000 one-year-survivors of MI there was no increased risk of cancers that were not related to smoking [3]. On the other hand, a registry-based follow-up study reported an increased incidence rate of arterial thrombosis in cancer patients, and the incidence rate was not exclusively higher in cancers associated with smoking [19]. In our study, adjustments for

established shared risk factors such as smoking, obesity and physical activity in our multivariable model did not influence the relation between MI and cancer. Furthermore, the hazard ratios were similar for tobacco-associated and not tobacco-associated cancer. Thus, our findings suggest that these factors could not explain the long-term cancer risk.

Even though MI and cancer share some molecular pathways of disease development and progression [10, 11], the distinct mechanisms behind the observed association between MI and cancer are unclear. Cancer patients exhibit a prothrombotic phenotype attributed to the presence of circulating procoagulants (e.g. tissue factor) liberated from cancer cells and macrophages, an increased turnover and activity of platelets, damage to the endothelium, and abnormalities of the blood flow [4, 23]. This implies that occult cancer may contribute to the short-term risk of cancer after MI. A previous case-control study has suggested a link between hypercoagulability in cancer and risk of MI [5], but there is conflicting data, regarding the increased risk of MI in thrombophilia [1, 24-29]. However, it is possible that inflammation could be an important link between cancer and MI. Studies have shown that inflammation may initiate and increase atherosclerosis, evoke MI [13, 30], and be carcinogenic [31, 32, 12]. The hypothesis of inflammation as a link is supported by studies showing an increased risk of MI in cancers associated with inflammation (e.g. colorectal cancer) [5, 33, 2, 34]. However, due to the few studies in this field, the causal mechanism for the association remains unsettled.

Secondary prevention for MI may influence the risk of cancer. Prolonged aspirin treatment have shown reduced mortality of several common cancers [35]. Furthermore, daily treatment with aspirin (six studies, n = 35 535) reduced the risk of incident cancer from 3 years onward [36]. Thus, treatment with aspirin would be expected to weaken the association between MI and long-term cancer [35-37]. Studies on statin treatment and future development of cancer

are inconsistent: Some studies have observed that use of statins may reduce both the risk of developing cancer and the rates of cancer-specific mortality for several cancer types [38-40]. However, other studies indicated that statins might increase the risk of cancer [41-43]. One main objection regarding many statin trials is the short study length with 5 years at most [43], and it may take many years before exposure to carcinogenic substances results in cancer. The prescription of statins started in the middle of the 1990s and quickly became a standard treatment for patients with MI. Thus, most of the patients with MI in the present study have been prescribed statins. Unfortunately, we are not able to adjust for statin or aspirin use due to incomplete registration in the Tromsø Study.

The clinical implications for our findings are uncertain. The socioeconomic cost and individual suffering of a screening program for cancer in patients with MI would probably surpass the benefits of early detection and improved prognosis since a major proportion of cancers in our study was detected within 6 months without a screening program. However, the long-term increased incidence rate of cancer after MI suggests that MI itself, or drugs used for secondary prevention of MI, may convey development of cancer or, even more likely, that the two conditions share genetic or environmental risk factors. Accordingly, the impact of shared risk factors was apparently stronger for cancer risk in MI (60 % increased risk more than 3 years after MI) than in venous thromboembolism (30 % increased risk) [44, 45]. Thus, it is warranted to identify predictors of cancer in MI patients in order to identify subjects at high cancer risk, and to unveil modifiable risk factors susceptible for intervention in order to reduce the incidence of cancer in MI patients.

The main strengths of our study are the prospective design with a long follow-up period, the large number of participants recruited from a general population, thoroughly validated events

of both MI and cancer and the possibility to adjust for lifestyle factors as potential confounders. As most known shared risk factors for MI and cancer are modifiable, the risk profile may change during follow-up. To minimize this possible misclassification, we updated the baseline information with repeated measurements in the two latest Tromsø surveys. Due to a limited number of cancer events, we had limited statistical power to investigate the risk of specific cancer types or the cancer stage at the time of diagnosis. Although our model included several potential confounders, residual confounding could still be present, and a possibility to adjust for medication and inflammatory markers would have strengthened the study.

In conclusion, subjects who developed MI had a higher short- and long-term hazard ratio of cancer compared to those without MI. The long-term increased incidence rate of cancer after MI may be explained by shared genetic or environmental risk factors other than smoking, obesity, and low physical activity. Future studies are warranted to identify predictors and modifiable risk factors of long-term cancer risk in MI-patients.

Acknowledgments

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. White HD, Chew DP. Acute myocardial infarction. Lancet. 2008;372(9638):570-84.

2. Pehrsson SK, Linnersjo A, Hammar N. Cancer risk of patients with ischaemic syndromes. J Intern Med. 2005;258(2):124-32.

3. Dreyer L, Olsen JH. Cancer risk of patients discharged with acute myocardial infarct. Epidemiology. 1998;9(2):178-83.

4. Lip GY, Chin BS, Blann AD. Cancer and the prothrombotic state. Lancet Oncol. 2002;3(1):27-34.

5. Naschitz JE, Yeshurun D, Abrahamson J, Eldar S, Chouri H, Kedar S et al. Ischemic heart disease precipitated by occult cancer. Cancer. 1992;69(11):2712-20.

6. Warren GW, Alberg AJ, Kraft AS, Cummings KM. The 2014 Surgeon General's report: "The health consequences of smoking--50 years of progress": a paradigm shift in cancer care. Cancer. 2014;120(13):1914-6.

7. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 2005;366(9497):1640-9.

8. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. Lancet Oncol. 2002;3(9):565-74.

9. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380(9838):219-29.

10. Morganti M, Carpi A, Nicolini A, Gorini I, Glaviano B, Fini M et al. Atherosclerosis and cancer: common pathways on the vascular endothelium. Biomed Pharmacother. 2002;56(7):317-24.

11. Ross JS, Stagliano NE, Donovan MJ, Breitbart RE, Ginsburg GS. Atherosclerosis and cancer: common molecular pathways of disease development and progression. Ann N Y Acad Sci. 2001;947:271-93.

12. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30(7):1073-81.

13. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352(16):1685-95.

14. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. Int J Epidemiol. 2012;41(4):961-7.

15. The Norwegian Institute of Public Health. Overweight and obesity in Norway: fact sheet. Available from http://www.fhi.no/eway/default.aspx?pid=240&trg=List_6673&Main_6664=6894:0:25,7585:1:0:0:::0:0&MainContent_6894=6671:0:25,7612:1:0:0:::0:0&List_6673=6674:0:25,7616:1:0:0:::0:0. Accessed 26 February, 2015

16. WHO MONICA Project. MONICA Manual. Available from http://www.thl.fi/publications/monica/index.html. Accessed 26 February, 2015

17. Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218-31.

18. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322.

19. Zoller B, Ji J, Sundquist J, Sundquist K. Risk of coronary heart disease in patients with cancer: a nationwide follow-up study from Sweden. Eur J Cancer. 2012;48(1):121-8.

20. Hansen ES. International Commission for Protection Against Environmental Mutagens and Carcinogens. ICPEMC Working Paper 7/1/2. Shared risk factors for cancer and atherosclerosis--a review of the epidemiological evidence. Mutat Res. 1990;239(3):163-79.

21. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004;328(7455):1519.

22. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.

23. Caine GJ, Stonelake PS, Lip GY, Kehoe ST. The hypercoagulable state of malignancy: pathogenesis and current debate. Neoplasia. 2002;4(6):465-73.

24. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med. 1995;332(14):912-7.

25. Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. N Engl J Med. 1995;332(10):635-41.

26. Girolami A, Simioni P, Scarano L, Girolami B. Venous and arterial thrombophilia. Haematologica. 1997;82(1):96-100.

27. Heit JA. Thrombophilia: common questions on laboratory assessment and management. Hematology Am Soc Hematol Educ Program. 2007;2007(1):127-35.

28. Middeldorp S, van Hylckama Vlieg A. Does thrombophilia testing help in the clinical management of patients? Br J Haematol. 2008;143(3):321-35.

29. de Moerloose P, Boehlen F. Inherited thrombophilia in arterial disease: a selective review. Semin Hematol. 2007;44(2):106-13.

30. Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868-74.

31. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454(7203):436-44.

32. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-7.

33. Erichsen R, Svaerke C, Sorensen HT, Sandler RS, Baron JA. Risk of colorectal cancer in patients with acute myocardial infarction and stroke: a nationwide cohort study. Cancer Epidemiol Biomarkers Prev. 2013;22(11):1994-9.

34. Reicher-Reiss H, Jonas M, Goldbourt U, Boyko V, Modan B. Selectively increased risk of cancer in men with coronary heart disease. Am J Cardiol. 2001;87(4):459-62.

35. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011;377(9759):31-41.

36. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet. 2012;379(9826):1602-12.

37. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet. 2012;379(9826):1591-601.

38. Cardwell CR, Hicks BM, Hughes C, Murray LJ. Statin use after colorectal cancer diagnosis and survival: a population-based cohort study. J Clin Oncol. 2014;32(28):3177-83.

39. Cardwell CR, Mc Menamin U, Hughes CM, Murray LJ. Statin use and survival from lung cancer: a population-based cohort study. Cancer Epidemiol Biomarkers Prev. 2015;24(5):833-41.

40. Graaf MR, Beiderbeck AB, Egberts AC, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. J Clin Oncol. 2004;22(12):2388-94.

41. Chang CC, Ho SC, Chiu HF, Yang CY. Statins increase the risk of prostate cancer: a population-based case-control study. Prostate. 2011;71(16):1818-24.

42. Goldstein MR, Mascitelli L, Pezzetta F. Do statins prevent or promote cancer? Curr Oncol. 2008;15(2):76-7.

43. Ravnskov U, Rosch PJ, McCully KS. Statins do not protect against cancer: quite the opposite. J Clin Oncol. 2015;33(7):810-1.

44. Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer. Lancet. 1998;351(9109):1077-80.

45. Sorensen HT, Mellemkjaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. N Engl J Med. 1998;338(17):1169-73.

Figure legends

Figure 1 Inclusion of study participants from the fourth (1994–1995), fifth (2001–2002) and sixth (2007–2008) surveys of the Tromsø study

Tables

Table 1. Baseline Characteristics of Participants without and with Myocardial Infarction (n=28763). The Tromsø Study 1994-2010

	No MI (n = 27016)	**MI (n = 1747)**
Age, yrs.	45 ± 14	62 ± 13
Sex (male)	46.1 (12 467)	62.0 (1 083)
BMI (kg/m^2)	25.2 ± 3.9	26.6 ± 4.1
Total cholesterol (mmol/L)	5.89 ± 1.27	6.92 ± 1.27
HDL cholesterol (mmol/L)	1.50 ± 0.41	1.41 ± 0.40
Triglycerides (mmol/L)	1.23 (0.86, 1.85)	1.65 (1.17, 2.38)
Systolic blood pressure (mmHg)	132 ± 19	152 ± 24
Diastolic blood pressure (mmHg)	77 ± 12	87 ± 14
Hypertension[a]	31.1 (8 397)	70.4 (1 230)
Hypercholesterolemia[b]	30.1 (8 125)	62.5 (1 092)
Smoking [c]	35.8 (9 666)	42.5 (742)
Physical activity [d]	33.6 (9 082)	20.7 (361)
Education[e]	29.3 (7 918)	12.1 (212)
Self-reported diabetes mellitus	1.4 (378)	6.4 (112)

Values are % (n), mean ± SD or median (25th and 75th percentile) (for triglycerides) . BMI indicates body mass index and MI, myocardial infarction

[a]Mean systolic/diastolic blood pressure ≥140/≥90 mm Hg, use of blood pressure-lowering drugs, or self-reported hypertension.
[b]Total cholesterol ≥ 6.5 mmol/L, use of lipid-lowering drugs, or self-reported hypercholesterolemia
[c]Self-reported daily smoking, yes/no
[d]≥ 1 hours of moderate or hard physical activity per week, yes/no
[e]> 10 years of education

Table 2. Site of Cancer Diagnosis after Myocardial Infarction sorted in descending order of frequency. The Tromsø Study 1994-2010

Cancer sites	% (n)
Colorectal cancer	21.9 (32)
Prostatic cancer	21.9 (32)
Lung cancer	16.4 (24)
Hematological cancer	6.2 (9)
Urinary bladder cancer	5.5 (8)
Gastric cancer	3.4 (5)
Kidney cancer	3.4 (5)
Pancreatic cancer	3.4 (5)
Lymphatic cancer	2.7 (4)
ENT cancer	2.1 (3)
Breast cancer	2.1 (3)
CNS/PNS cancer	1.4 (2)
Liver cancer	1.4 (2)
Esophagus cancer	0.7 (1)
Gynecological cancer	0.7 (1)
Other cancer sites	6.8 (10)
Total cancer events	100 (146)

Values are % (n). CNS/PNS, indicates central nervous system/peripheral nervous system, and

ENT, ear, nose and throat

Table 3 Sex-Stratified Incidence Rates and Hazard Ratios for Cancer after Myocardial Infarction. The Tromsø Study 1994-2010

	Person-years	Cancer events	Crude IR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[bc]	HR (95% CI)[bcd]
Total						
No MI	340216	2470	7.3 (7.0-7.6)	Reference	Reference	Reference
MI	6468	146	22.6 (19.2-26.5)	1.41 (1.19-1.67)	1.43 (1.21-1.70)	1.46 (1.21-1.77)
Women						
No MI	182846	1272	7.0 (6.6-7.3)	Reference	Reference	Reference
MI	2215	46	20.8 (15.6-27.7)	1.48 (1.09-1.99)	1.50 (1.11-2.02)	1.65 (1.19-2.29)
Men						
No MI	157371	1198	7.6 (7.2-8.1)	Reference	Reference	Reference
MI	4253	100	23.5 (19.3-28.6)	1.30 (1.06-1.60)	1.31 (1.07-1.61)	1.29 (1.02-1.62)

CI indicates confidence interval; MI, myocardial infarction; IR, incidence rate and HR, hazard ratio

[a]Per 1000 persons-years

[b]Adjusted for age (as time scale) and sex-adjusted

[c]Adjusted for body mass index.

[d]Adjusted for systolic blood pressure, diabetes mellitus, HDL, smoking, physical activity, and education level

Table 4 Incidence Rates and Hazard Ratios of Cancer according to time after Myocardial Infarction. The Tromsø Study 1994-2010

	Person-years	Cancer events	Crude IR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[bc]	HR (95% CI)[bcd]
Total						
No MI	340216	2470	7.3 (7.0-7.6)	Reference	Reference	Reference
< 6 months after MI	552	16	29.0 (17.8-47.4)	1.94 (1.18-3.17)	1.96 (1.20-3.21)	2.15 (1.29-3.58)
6 months - <1 year after MI	514	8	15.6 (7.8-31.1)	1.04 (0.52-2.09)	1.05 (0.53-2.11)	0.92 (0.41-2.06)
1-3 years after MI	1747	28	16.0 (11.1-23.2)	1.05 (0.72-1.52)	1.06 (0.73-1.54)	1.13 (0.76-1.68)
> 3 years after MI	3655	94	25.7 (21.0-31.5)	1.54 (1.25-1.90)	1.57 (1.27-1.93)	1.60 (1.27-2.03)
Women						
No MI	181846	1272	7.0 (6.6-7.3)	Reference	Reference	Reference
< 6 months after MI	195	7	35.8 (17.1-75.2)	2.66 (1.26-5.6)	2.69 (1.28-5.67)	3.20 (1.52-6.76)
6 months - <1 year after MI	181	2	11.1 (2.8-44.2)	0.81 (0.20-3.23)	0.82 (0.20-3.28)	0.99 (0.25-3.95)
1-3 years after MI	608	8	13.2 (6.6-26.3)	0.95 (0.47-1.90)	0.96 (0.48-1.93)	1.17 (0.58-2.35)
> 3 years after MI	1231	29	23.6 (16.4-33.9)	1.65 (1.14-2.39)	1.67 (1.15-2.43)	1.75 (1.14-2.69)

Table 4 Continued

	Person-years	Cancer events	Crude IR (95% CI)*	HR (95% CI)†	HR (95% CI)†!	HR (95% CI)†!‡
Men						
No MI	157371	1198	7.6 (7.2-8.1)	Reference	Reference	Reference
< 6 months after MI	356	9	25.3 (13.1-48.6)	1.55 (0.80-2.99)	1.56 (0.81-3.00)	1.58 (0.78-3.17)
6 months - <1 year after MI	333	6	18.0 (8.1-40.1)	1.09 (0.49-2.42)	1.09 (0.49-2.44)	0.83 (0.31-2.23)
1-3 years after MI	1139	20	17.6 (11.3-27.2)	1.05 (0.67-1.63)	1.05 (0.68-1.64)	1.04 (0.64-1.68)
> 3 years after MI	2424	65	26.8 (21.0-34.2)	1.41 (1.09-1.81)	1.41 (1.10-1.82)	1.42 (1.07-1.89)

CI indicates confidence interval; MI, myocardial infarction; IR, incidence rate and HR, hazard ratio

[a]Per 1000 persons-years

[b]Adjusted for age (as time scale) and sex-adjusted

[c]Adjusted for body mass index

[d]Adjusted for systolic blood pressure, diabetes mellitus, HDL, smoking, physical activity, and education level