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# Risk of coronary heart disease in patients with cancer: A nationwide follow-up study from Sweden

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ABSTRACT

*Background:* Risk of coronary heart disease (CHD) in cancer patients has not been thoroughly investigated. The aim of the present study was to examine whether there is an association between cancer and first hospitalisation for CHD.

*Methods:* All individuals in Sweden with a diagnosis of cancer between 1st January 1987 and 31st December 2008 were followed for first hospitalisation for CHD. The reference population was the total population of Sweden without cancer. Standardised incidence ratios (SIRs) for CHD were calculated.

*Results:* The overall CHD risk during the first 6 months after diagnosis of cancer was 1.70 (95% confidence interval (95% CI) 1.66–1.75). For 26 of the 34 cancers studied, the risk of CHD was increased during the first 6 months after diagnosis of cancer. The overall CHD risk decreased rapidly, but remained slightly elevated, even 10+ years after diagnosis of cancer (SIR 1.07; 95% CI 1.04–1.11). The cancer sites/types for which risk of CHD was highest during the first 6 months were small intestine (SIR 2.88; 95% CI 2.02–3.99), leukaemia (SIR 2.84; 95% CI 2.37–3.37), kidney (SIR 2.65; 95% CI 2.30–3.04), lung (SIR 2.56; 95% CI 2.35–2.80) and liver (SIR 2.28; 95% CI 1.91–2.71). Metastases were associated with an increased risk of CHD (SIR 1.46; 95% CI 1.28–1.65).

*Interpretation:* Most cancers were associated with an increased risk of CHD during the first 6 months after diagnosis. CHD risk was related to the presence of metastates. Cancer patients may need a more aggressive treatment of classical CHD risk factors.



## 1. Introduction

Coronary heart disease (CHD) and myocardial infarction are the major causes of morbidity and mortality worldwide.[1] An association between cancer and venous thromboembolism (VTE) has been recognised since at least 1865.[2] Cancer increases the risk of VTE 4- to 6-fold.[2] Patients with cancer frequently have laboratory evidence of haemostatic activation.[3] Tumour cells produce various cytokines and chemokines that attract leucocytes, which result in an inflammatory response.[4] This may in turn have prothrombotic and atherosclerotic effects.[5–7]

An increased risk of CHD has been reported in patients with lung cancer,[8] breast cancer,[9] Hodgkin's lymphoma[10,11] and non-Hodgkin's[12] lymphoma who were treated with radiation. However, two studies of breast cancer patients treated with radiation did not find an increased CHD risk.[13,14] Mediastinal radiation therapy is an established risk factor for CHD

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among cancer patients.[15] However, there are many other potential prothrombotic mechanisms in cancer patients such as increased platelet activation and aggregability, damaged or dysfunctional endothelium, increased number of circulating microparticles, procoagulants changed due to chemotherapy and angiogenesis (reviewed by Blann and Dunmore).[16] Moreover, cancer and CHD share a common risk factor (tobacco smoke), and an increased risk of CHD would be expected among patients with smoking-related cancers (i.e. cancers of the lung, larynx, oesophagus, mouth and tongue, pharynx, urinary bladder, pancreas and kidney).[17–20] Other suspected smoking-related cancers sites include lip, liver, cervix, stomach, leukaemia and salivary gland. Thus, cancer and CHD share a number of risk factors and an increased risk of CHD among cancer patients would be expected. However, the CHD risk in cancer patients has been much less thoroughly investigated than the VTE risk.[1,2]

We hypothesised that haemostatic activation and inflammation associated with cancer may affect risk of CHD. In a nationwide follow-up study of data from 1987 to 2008 we estimated risk of hospitalisation for CHD in all Swedish patients diagnosed with cancer.

## 2. Methods

### 2.1. MigMed 2 Database

This study was approved by the Ethics Committee of Lund University, Sweden. Data used in this study were retrieved from the MigMed 2 Database (an updated version of the original MigMed database), maintained at the Center for Primary Health Care Research, Lund University/Region Skåne, Malmö. MigMed 2 contains data on all individuals registered as residents of Sweden. It contains individual-level information on age, sex, occupation, geographic region of residence, hospital diagnoses and dates of hospital admissions in Sweden (1964–2008), as well as country of birth, parents' country of birth, date of emigration and date and cause of death. The database was constructed using several national Swedish data registers (reviewed by Rosen and Hakulinen),[21] including, but not limited to, the Swedish Cancer Registry,[22] the Swedish National Population and Housing Census (1960–1990),[23] the Total Population Register, the Multi-Generation Register,[24] and the Swedish Hospital Discharge Register (1964–2008).[25]

Information retrieved from the various registers in the MigMed 2 Database is linked, at the individual level, via the 10-digit personal identification number assigned to each resident of Sweden for his or her lifetime. Registration numbers were replaced by serial numbers to preserve anonymity. As well as being used to track all records in the database at the individual level, these serial numbers were used to check that individuals with hospital diagnoses of CHD appeared only once in the dataset (for the first hospital diagnosis of CHD during the study period).

The follow-up period for analysis of data in the present study started on 1st January 1987 and continued until hospitalisation for CHD, death, emigration or the end of the study period (31st December 2008). Data for first hospitalisation for CHD during the study period were retrieved from the Hospital Discharge Register (1987–2008). This register does not include data for hospital outpatients or patients treated at primary health care centres.

### 2.2. Predictor variable

The predictor variable was diagnosis of cancer in the Swedish Cancer Registry. Cancer site/type was identified according to the 7th revision of the International Classification of Diseases (ICD-7) (Supplementary Table 1). The Swedish Cancer Registry records all new cases of cancer. Close to 100% of all cases nationwide have been histologically or cytologically confirmed.[22] Information on metastasis has been included in the Swedish Cancer Registry since 2002.

### 2.3. Outcome variable

Diagnosis of CHD was based on the 9th and 10th revisions of the International Classification of Diseases (ICD-9 and ICD-10). Cases of CHD were identified using the following ICD codes: 410-414 (ICD-9) and I20–I25 (ICD-10).

ICD 9
- 410: acute cardiac infarction
- 411: other acute and subacute forms of CHD
- 412: old cardiac infarction
- 413: angina pectoris
- 414: other forms of chronic CHD

ICD 10
- I20: angina pectoris
- I21: acute cardiac infarction
- I22: reinfarction (within 4 weeks)
- I23: complications due to acute cardiac infarction

**Table 1 – Basic characteristics of patients diagnosed with CHD between 1987 and 2008.**

| | With cancer | | Without cancer | |
|---|---|---|---|---|
| | Number | % | Number | % |
| *Age (years)* | | | | |
| <60 | 1582 | 4.6 | 96,171 | 16.8 |
| 60–69 | 4971 | 14.3 | 126,609 | 22.1 |
| 70–79 | 12,821 | 37.0 | 183,910 | 32.1 |
| ⩾80 | 15,292 | 44.1 | 166,804 | 29.1 |
| *Sex* | | | | |
| Male | 22,152 | 63.9 | 343,957 | 60.0 |
| Female | 12,514 | 36.1 | 229,539 | 40.0 |
| *Time period* | | | | |
| 1987–1990 | 2128 | 6.1 | 124,730 | 21.7 |
| 1990–1994 | 7645 | 22.1 | 173,255 | 30.2 |
| 1995–1999 | 8143 | 23.5 | 118,333 | 20.6 |
| 2000–2004 | 9862 | 28.4 | 98,792 | 17.2 |
| 2005–2008 | 6888 | 19.9 | 58,384 | 10.2 |
| *Region of residence* | | | | |
| Large city | 11,289 | 32.6 | 166,458 | 29.0 |
| Southern Sweden | 14,933 | 43.1 | 228,369 | 39.8 |
| Northern Sweden | 6702 | 19.3 | 124,397 | 21.7 |
| Other | 1742 | 5.0 | 54,270 | 9.5 |
| All | 34,666 | 100.0 | 573,494 | 100.0 |

**Table 2 – SIRs for subsequent CHD in cancer patients by follow-up interval.**

| Cancer site/type | Follow-up interval | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <6 months | | | | 6–12 months | | | | 1–5 years | | | | 5–10 years | | | | 10+ years | | | | All | | | | 1+ years | | | |
| | O | SIR | 95% CI | | O | SIR | 95% CI | | O | SIR | 95% CI | | O | SIR | 95% CI | | O | SIR | 95% CI | | O | SIR | 95% CI | | O | SIR | 95% CI | |
| Upper aerodigestive tract | 95 | **1.29** | 1.04 | 1.57 | 66 | 1.06 | 0.82 | 1.35 | 315 | 1.00 | 0.89 | 1.12 | 227 | **1.15** | 1.01 | 1.31 | 106 | 1.03 | 0.84 | 1.24 | 809 | **1.08** | 1.01 | 1.15 | 648 | 1.05 | 0.98 | 1.14 |
| Salivary gland | 12 | **1.97** | 1.01 | 3.45 | 5 | 0.95 | 0.3 | 2.24 | 27 | 1 | 0.66 | 1.46 | 24 | 1.37 | 0.87 | 2.04 | 13 | 1.2 | 0.64 | 2.06 | 81 | 1.21 | 0.96 | 1.51 | 64 | 1.16 | 0.89 | 1.48 |
| Oesophagus | 40 | 1.4 | 1 | 1.91 | 19 | 1.33 | 0.8 | 2.08 | 26 | 0.81 | 0.53 | 1.19 | 14 | 1.04 | 0.57 | 1.75 | 3 | 0.56 | 0.11 | 1.65 | 102 | 1.09 | 0.89 | 1.32 | 43 | 0.85 | 0.61 | 1.14 |
| Stomach | 203 | **2.1** | 1.82 | 2.41 | 46 | 0.85 | 0.62 | 1.13 | 162 | 0.91 | 0.78 | 1.07 | 60 | 0.65 | 0.5 | 0.84 | 46 | 0.9 | 0.66 | 1.2 | 517 | **1.1** | 1 | 1.19 | 268 | 0.84 | 0.74 | 0.94 |
| **Small intestine** | 36 | **2.88** | 2.02 | 3.99 | 7 | 0.74 | 0.29 | 1.52 | 39 | 0.83 | 0.59 | 1.14 | 33 | 1.21 | 0.84 | 1.71 | 19 | 1.38 | 0.83 | 2.16 | 134 | **1.22** | 1.02 | 1.45 | 91 | 1.04 | 0.84 | 1.28 |
| **Colon** | 482 | **1.82** | 1.66 | 1.99 | 157 | 0.72 | 0.61 | 0.85 | 1104 | 1.04 | 0.98 | 1.1 | 669 | **1.1** | 1.02 | 1.19 | 336 | 1.08 | 0.96 | 1.2 | 2748 | **1.11** | 1.07 | 1.16 | 2109 | **1.06** | 1.02 | 1.11 |
| **Rectum** | 262 | **1.66** | 1.46 | 1.87 | 107 | 0.81 | 0.66 | 0.98 | 635 | 0.99 | 0.91 | 1.07 | 371 | 1.04 | 0.94 | 1.15 | 209 | **1.17** | 1.01 | 1.34 | 1584 | **1.08** | 1.03 | 1.13 | 1215 | 1.03 | 0.97 | 1.09 |
| **Anus** | 14 | **2.12** | 1.15 | 3.56 | 2 | 0.35 | 0.03 | 1.29 | 27 | 1 | 0.66 | 1.46 | 16 | 0.99 | 0.56 | 1.61 | 7 | 0.72 | 0.29 | 1.5 | 66 | 1.01 | 0.78 | 1.29 | 50 | 0.95 | 0.7 | 1.25 |
| Liver | 131 | **2.28** | 1.91 | 2.71 | 24 | 1.12 | 0.72 | 1.67 | 57 | 1.05 | 0.79 | 1.36 | 13 | 0.58 | 0.31 | 0.99 | 17 | 1.38 | 0.8 | 2.22 | 242 | **1.44** | 1.26 | 1.63 | 87 | 0.97 | 0..78 | 1.2 |
| Pancreas | 112 | **2** | 1.64 | 2.4 | 15 | 0.82 | 0.46 | 1.36 | 18 | 0.7 | 0.41 | 1.1 | 5 | 0.64 | 0.2 | 1.5 | 3 | 0.79 | 0.15 | 2.34 | 153 | **1.37** | 1.16 | 1.61 | 26 | 0.69 | 0.45 | 1.02 |
| Nose | 7 | 1.28 | 0.51 | 2.65 | 1 | 0.22 | 0 | 1.28 | 18 | 0.83 | 0.49 | 1.31 | 11 | 0.8 | 0.4 | 1.44 | 12 | 1.63 | 0.84 | 2.85 | 49 | 0.93 | 0.69 | 1.23 | 41 | 0.96 | 0.69 | 1.3 |
| Lung | 516 | **2.56** | 2.35 | 2.8 | 145 | **1.38** | 1.17 | 1.63 | 291 | **1.16** | 1.03 | 1.3 | 136 | **1.29** | 1.08 | 1.52 | 55 | 1.12 | 0.85 | 1.46 | 1143 | **1.6** | 1.51 | 1.7 | 482 | **1.19** | 1.08 | 1.3 |
| **Breast** | 349 | **1.27** | 1.14 | 1.41 | 270 | 1.04 | 0.92 | 1.18 | 1351 | 0.85 | 0.81 | 0.9 | 1059 | 0.91 | 0.86 | 0.97 | 799 | 1.02 | 0.95 | 1.09 | 3828 | 0.94 | 0.91 | 0.97 | 3209 | 0.91 | 0.88 | 0.94 |
| Cervix | 26 | **1.67** | 1.09 | 2.44 | 14 | 1.06 | 0.58 | 1.79 | 66 | 1 | 0.78 | 1.28 | 60 | 1.25 | 0.95 | 1.61 | 40 | 1.01 | 0.72 | 1.37 | 206 | 1.13 | 0.98 | 1.3 | 166 | 1.08 | 0.92 | 1.26 |
| **Endometrium** | 96 | **1.35** | 1.1 | 1.65 | 60 | 0.92 | 0.7 | 1.18 | 373 | 0.94 | 0.84 | 1.04 | 263 | 0.86 | 0.76 | 0.97 | 190 | 0.89 | 0.77 | 1.03 | 982 | 0.93 | 0.87 | 0.99 | 826 | 0.9 | 0.84 | 0.96 |
| **Ovary** | 70 | **1.77** | 1.38 | 2.24 | 23 | 0.72 | 0.45 | 1.08 | 145 | 0.99 | 0.83 | 1.16 | 85 | 0.93 | 0.74 | 1.15 | 57 | 0.84 | 0.63 | 1.08 | 380 | 1 | 0.91 | 1.11 | 287 | 0.94 | 0.83 | 1.05 |
| **Other female genital** | 25 | **1.96** | 1.27 | 2.9 | 13 | 1.26 | 0.67 | 2.15 | 59 | 1.25 | 0.95 | 1.61 | 37 | 1.3 | 0.91 | 1.79 | 22 | 1.44 | 0.9 | 2.19 | 156 | **1.37** | 1.16 | 1.6 | 118 | **1.3** | 1.07 | 1.55 |
| **Prostate** | 1136 | **1.41** | 1.33 | 1.49 | 866 | **1.17** | 1.09 | 1.25 | 4411 | **1.14** | 1.11 | 1.17 | 1988 | **1.1** | 1.06 | 1.15 | 607 | **1.14** | 1.05 | 1.24 | 9008 | **1.16** | 1.14 | 1.19 | 7006 | **1.13** | 1.1 | 1.16 |
| **Testis** | 6 | 1.94 | 0.7 | 4.25 | 1 | 0.34 | 0 | 1.97 | 17 | 0.8 | 0.46 | 1.28 | 29 | 1.25 | 0.84 | 1.8 | 25 | 0.98 | 0.63 | 1.45 | 78 | 1.03 | 0.81 | 1.28 | 71 | 1.01 | 0.79 | 1.28 |
| **Other male genital** | 7 | 0.94 | 0.37 | 1.96 | 13 | **2.06** | 1.09 | 3.53 | 23 | 0.72 | 0.46 | 1.08 | 17 | 0.86 | 0.5 | 1.39 | 8 | 0.84 | 0.36 | 1.66 | 68 | 0.91 | 0.71 | 1.15 | 48 | 0.79 | 0.58 | 1.04 |
| Kidney | 204 | **2.65** | 2.3 | 3.04 | 90 | **1.52** | 1.22 | 1.87 | 374 | **1.25** | 1.12 | 1.38 | 222 | **1.17** | 1.02 | 1.33 | 133 | **1.24** | 1.04 | 1.48 | 1023 | **1.4** | 1.31 | 1.48 | 729 | **1.22** | 1.14 | 1.31 |
| Urinary bladder | 355 | **1.74** | 1.56 | 1.93 | 260 | **1.47** | 1.3 | 1.66 | 1155 | **1.24** | 1.16 | 1.31 | 725 | **1.23** | 1.15 | 1.33 | 402 | **1.32** | 1.19 | 1.46 | 2897 | **1.31** | 1.26 | 1.36 | 2282 | **1.25** | 1.2 | 1.3 |
| **Melanoma** | 103 | 1.11 | 0.91 | 1.35 | 75 | 0.87 | 0.68 | 1.09 | 524 | 1.03 | 0.94 | 1.12 | 338 | 0.95 | 0.85 | 1.05 | 205 | 0.86 | 0.75 | 0.99 | 1245 | 0.97 | 0.92 | 1.03 | 1067 | 0.97 | 0.91 | 1.03 |
| **Skin, squamous cell** | 265 | **1.29** | 1.14 | 1.46 | 235 | **1.25** | 1.1 | 1.43 | 1290 | **1.28** | 1.21 | 1.35 | 683 | **1.22** | 1.13 | 1.31 | 292 | **1.19** | 1.05 | 1.33 | 2765 | **1.25** | 1.2 | 1.3 | 2265 | **1.25** | 1.19 | 1.3 |
| **Eye** | 6 | 0.81 | 0.29 | 1.78 | 5 | 0.72 | 0.23 | 1.68 | 42 | 1.09 | 0.79 | 1.48 | 21 | 0.92 | 0.57 | 1.41 | 18 | 1.35 | 0.8 | 2.14 | 92 | 1.04 | 0.83 | 1.27 | 81 | 1.09 | 0.86 | 1.35 |
| **Nervous system** | 111 | **2.13** | 1.75 | 2.57 | 30 | 0.85 | 0.57 | 1.21 | 172 | 0.92 | 0.79 | 1.07 | 138 | 0.9 | 0.76 | 1.07 | 91 | 0.81 | 0.65 | 1 | 542 | 1 | 0.92 | 1.09 | 401 | 0.89 | 0.8 | 0.98 |
| **Thyroid gland** | 23 | **1.81** | 1.15 | 2.72 | 5 | 0.49 | 0.15 | 1.14 | 54 | 0.86 | 0.64 | 1.12 | 47 | 0.93 | 0.68 | 1.24 | 34 | 0.84 | 0.58 | 1.17 | 163 | 0.92 | 0.78 | 1.07 | 135 | 0.88 | 0.73 | 1.04 |
| **Endocrine glands** | 89 | **2.2** | 1.77 | 2.71 | 55 | **1.44** | 1.09 | 1.88 | 308 | **1.19** | 1.06 | 1.33 | 265 | **1.24** | 1.09 | 1.39 | 172 | 1.12 | 0.95 | 1.3 | 889 | **1.26** | 1.18 | 1.34 | 745 | **1.19** | 1.1 | 1.28 |
| **Bone** | 2 | 0.78 | 0.07 | 2.88 | 1 | 0.47 | 0 | 2.69 | 16 | 1.45 | 0.83 | 2.36 | 5 | 0.61 | 0.19 | 1.43 | 3 | 0.49 | 0.09 | 1.44 | 27 | 0.9 | 0.59 | 1.31 | 24 | 0.94 | 0.6 | 1.41 |
| **Connective tissue** | 29 | **1.64** | 1.1 | 2.36 | 12 | 0.85 | 0.44 | 1.49 | 71 | 1.02 | 0.8 | 1.29 | 36 | 0.86 | 0.6 | 1.19 | 24 | 0.93 | 0.59 | 1.38 | 172 | 1.02 | 0.87 | 1.18 | 131 | 0.95 | 0.8 | 1.13 |
| **Non-Hodgkin lymphoma** | 305 | **2.2** | 1.96 | 2.46 | 109 | 0.96 | 0.79 | 1.15 | 602 | 1.04 | 0.96 | 1.13 | 301 | 0.97 | 0.86 | 1.08 | 135 | 0.96 | 0.81 | 1.14 | 1452 | **1.13** | 1.08 | 1.19 | 1038 | 1.01 | 0.95 | 1.07 |
| **Hodgkin's lymphoma** | 11 | 1.86 | 0.92 | 3.34 | 4 | 0.86 | 0.22 | 2.23 | 32 | 1.25 | 0.85 | 1.76 | 28 | **1.51** | 1 | 2.18 | 38 | **2.79** | 1.97 | 3.83 | 113 | **1.65** | 1.36 | 1.99 | 98 | **1.7** | 1.38 | 2.07 |
| **Myeloma** | 104 | **2.17** | 1.77 | 2.63 | 54 | **1.37** | 1.03 | 1.79 | 232 | **1.42** | 1.24 | 1.61 | 61 | 1.22 | 0.93 | 1.57 | 23 | **1.62** | 1.02 | 2.43 | 474 | **1.5** | 1.37 | 1.64 | 316 | **1.39** | 1.24 | 1.55 |
| Leukaemia | 130 | **2.84** | 2.37 | 3.37 | 54 | **1.67** | 1.25 | 2.18 | 161 | **1.18** | 1 | 1.37 | 94 | **1.41** | 1.14 | 1.73 | 39 | 1.37 | 0.98 | 1.88 | 478 | **1.54** | 1.41 | 1.69 | 294 | **1.27** | 1.13 | 1.42 |
| All | 5362 | **1.7** | 1.66 | 1.75 | 2843 | **1.1** | 1.06 | 1.14 | 14,197 | **1.08** | 1.06 | 1.1 | 8081 | **1.06** | 1.04 | 1.09 | 4183 | **1.07** | 1.04 | 1.11 | 34,666 | **1.14** | 1.13 | 1.15 | 26,461 | **1.07** | 1.06 | 1.09 |

Bold type, 95% CI does not include 1.

Cancer sites/types highlighted in bold: not linked to tobacco smoking.[15–18]

O, observed number of cases; SIR, standardised incidence ratio; CI, confidence interval.

**Table 3 – SIRs for subsequent CHD between 2002 and 2008 in cancer patients with and without metastasis.**

| Cancer site/type | No metastasis | | | | With metastasis | | | |
|---|---|---|---|---|---|---|---|---|
| | O | SIR | 95% CI | | O | SIR | 95% CI | |
| Upper aerodigestive tract | 35 | 0.9 | 0.63 | 1.25 | 1 | 2.16 | 0 | 12.36 |
| Oesophagus | 10 | 1.84 | 0.88 | 3.4 | 3 | 2.08 | 0.39 | 6.16 |
| Stomach | 16 | 1.21 | 0.69 | 1.96 | 6 | 1.93 | 0.69 | 4.22 |
| Colon | 124 | 0.88 | 0.73 | 1.05 | 21 | 1.16 | 0.72 | 1.78 |
| Rectum | 68 | 0.9 | 0.7 | 1.14 | 13 | 1.34 | 0.71 | 2.3 |
| Liver | 8 | 1.37 | 0.58 | 2.71 | 5 | **3.43** | 1.08 | 8.08 |
| Pancreas | 7 | 1.44 | 0.57 | 2.98 | 4 | 1.44 | 0.38 | 3.73 |
| Nose | 3 | 1.46 | 0.28 | 4.33 | 0 | | | |
| Lung | 135 | **1.7** | 1.43 | 2.02 | 64 | **2.18** | 1.68 | 2.78 |
| Breast | 177 | 0.79 | 0.68 | 0.92 | 9 | 1.53 | 0.69 | 2.91 |
| Prostate | 277 | 0.88 | 0.78 | 0.99 | 106 | 1.22 | 1 | 1.48 |
| Other male genital | 4 | 1.01 | 0.26 | 2.62 | 0 | | | |
| Kidney | 28 | 1.23 | 0.82 | 1.78 | 5 | 1.16 | 0.36 | 2.72 |
| Urinary bladder | 77 | **1.74** | 1.37 | 2.18 | 4 | 2.34 | 0.61 | 6.06 |
| Melanoma | 35 | 0.87 | 0.61 | 1.21 | 0 | | | |
| Skin, squamous cell | 117 | 1.01 | 0.83 | 1.21 | 0 | | | |
| Thyroid gland | 3 | 0.53 | 0.1 | 1.57 | 2 | 3.5 | 0.33 | 12.87 |
| Endocrine glands | 3 | 2.59 | 0.49 | 7.66 | 1 | 3.5 | 0 | 20.08 |
| Connective tissue | 4 | 0.85 | 0.22 | 2.2 | 1 | 4.38 | 0 | 25.11 |
| All | 1142 | 0.99 | 0.93 | 1.05 | 246 | **1.46** | 1.28 | 1.65 |

Bold type, 95% CI does not include 1.
O, observed number of cases; SIR, standardised incidence ratio; CI, confidence interval.

I24: other acute forms of CHD
I25: chronic CHD

### 2.4. *Individual-level variables*

The individual-level variables were sex, age, time-period, geographic region of residence, socioeconomic status (SES) and comorbidity.

Sex: male or female.

Age was divided into 5-year categories. Subjects of all ages were included in the study.

Time period: Time was divided into four periods: 1987–1990, 1991–1994, 1995–1999, 2000–2004, 2005–2008.

Geographic region of residence was included as an individual-level variable to adjust for possible differences in hospital admissions for CHD between different geographic regions in Sweden. It was categorised as (1) large city (city with a population of >200,000 (i.e. Stockholm, Gothenburg or Malmo), (2) Southern Sweden (both rural and urban), (3) Northern Sweden (both rural and urban) and (4) Others (if geographic region was not possible to determine).

Occupation was used as a proxy for SES. Occupational data were retrieved from national census records in the MigMed 2 Database. We classified each individual's occupation into one of the six categories: (1) blue-collar worker, (2) white-collar worker, (3) professional, (4) self-employed, (5) farmer and (6) non-employed (Individuals without paid employment). Students without an occupation were categorised on the basis of their father's or mother's occupation. If that was not possible, they were included in the 'non-employed' category. For individuals aged <20 years, parental occupation was used.

Comorbidity was defined as first hospital diagnosis at follow-up (1987–2008) for the following: (1) chronic obstructive pulmonary disease (COPD) (490–496 (ICD-9) and J40–J49 (ICD-10)); (2) obesity (278A (ICD-9) and E65–E68 (ICD-10)); (3) alcoholism (291 and 303 (ICD-9) and F10 (ICD-10)); (4) diabetes mellitus (250 (ICD-9) and E10-E14 (ICD-10)); and (5) hypertension (401–405 (ICD-9) and I10–I15 (ICD-10)).

### 2.5. *Statistical analysis*

Person-years of risk (i.e. number of persons at risk multiplied by time at risk) were calculated from the time at which subjects were included in the study (1987 or later) until first hospitalisation for CHD, death, emigration or the end of the study period. The expected number of cases was based on the number of cases in the reference group. Standardised incidence ratios (SIRs) were calculated as the ratio of observed (*O*) and expected (*E*) number of CHD cases using the indirect standardisation method[26]:

$$\mathrm{SIR} = \frac{\sum_{j=1}^{J} o_j}{\sum_{j=1}^{J} n_j \lambda_j^*} = \frac{O}{E^*},$$

where $O = \sum o_j$ denotes the total observed number of cases in the study group; $E^*$ (expected number of cases) is calculated by applying stratum-specific standard incidence rates ($\lambda_j^*$) obtained from the reference group to the stratum-specific person-years ($n_j$) of risk for the study group; $o_j$ represents the observed number of cases that the cohort subjects contribute to the *j*th stratum; and *J* represents the strata defined by cross-classification of the different adjustment variables (age, sex, time period, SES, geographic region of residence and comorbidity).[26] 95% confidence intervals (95% CIs) were

**Table 4 – SIR for subsequent CHD in cancer patients by period of diagnosis.**

| Cancer site | 1987–1997 | | | | 1998–2008 | | | |
|---|---|---|---|---|---|---|---|---|
| | O | SIR | 95% CI | | O | SIR | 95% CI | |
| Upper aerodigestive tract | 597 | 1.04 | 0.96 | 1.12 | 212 | **1.21** | 1.06 | 1.39 |
| Salivary gland | 61 | 1.22 | 0.94 | 1.57 | 20 | 1.18 | 0.72 | 1.83 |
| Oesophagus | 68 | 1.12 | 0.87 | 1.42 | 34 | 1.03 | 0.72 | 1.45 |
| Stomach | 384 | 1.04 | 0.94 | 1.15 | 133 | **1.30** | 1.09 | 1.54 |
| Small intestine | 107 | **1.34** | 1.10 | 1.62 | 27 | 0.90 | 0.59 | 1.31 |
| Colon | 1965 | **1.11** | 1.07 | 1.16 | 783 | **1.11** | 1.04 | 1.19 |
| Rectum | 1177 | **1.10** | 1.04 | 1.16 | 407 | 1.02 | 0.92 | 1.12 |
| Anus | 44 | 0.95 | 0.69 | 1.28 | 22 | 1.17 | 0.73 | 1.78 |
| Liver | 162 | **1.36** | 1.16 | 1.58 | 80 | **1.64** | 1.30 | 2.05 |
| Pancreas | 100 | **1.32** | 1.08 | 1.61 | 53 | **1.47** | 1.10 | 1.92 |
| Nose | 42 | 1.01 | 0.73 | 1.37 | 7 | 0.62 | 0.25 | 1.28 |
| Lung | 710 | **1.50** | 1.40 | 1.62 | 433 | **1.80** | 1.63 | 1.98 |
| Breast | 3004 | 0.97 | 0.94 | 1.01 | 824 | 0.84 | 0.79 | 0.90 |
| Cervix | 163 | 1.10 | 0.94 | 1.29 | 43 | 1.24 | 0.89 | 1.67 |
| Endometrium | 715 | 0.91 | 0.85 | 0.98 | 267 | 0.99 | 0.87 | 1.11 |
| Ovary | 291 | 0.99 | 0.88 | 1.11 | 89 | 1.07 | 0.86 | 1.31 |
| Other female genital | 108 | **1.29** | 1.06 | 1.56 | 48 | **1.57** | 1.16 | 2.08 |
| Prostate | 6001 | **1.22** | 1.19 | 1.25 | 3007 | **1.07** | 1.03 | 1.10 |
| Testis | 68 | 1.08 | 0.84 | 1.37 | 10 | 0.77 | 0.37 | 1.43 |
| Other male genital | 47 | 0.88 | 0.65 | 1.17 | 21 | 0.98 | 0.61 | 1.50 |
| Kidney | 786 | **1.40** | 1.30 | 1.50 | 237 | **1.40** | 1.23 | 1.59 |
| Urinary bladder | 2166 | **1.30** | 1.24 | 1.35 | 731 | **1.35** | 1.26 | 1.45 |
| Melanoma | 920 | 0.97 | 0.91 | 1.03 | 325 | 0.97 | 0.87 | 1.09 |
| Skin, squamous cell | 1872 | **1.24** | 1.18 | 1.30 | 893 | **1.27** | 1.19 | 1.36 |
| Eye | 69 | 1.04 | 0.81 | 1.32 | 23 | 1.02 | 0.65 | 1.54 |
| Nervous system | 412 | 0.99 | 0.89 | 1.09 | 130 | 1.07 | 0.89 | 1.27 |
| Thyroid gland | 127 | 0.88 | 0.73 | 1.04 | 36 | 1.11 | 0.78 | 1.54 |
| Endocrine glands | 754 | **1.30** | 1.21 | 1.40 | 135 | 1.06 | 0.89 | 1.26 |
| Bone | 22 | 0.90 | 0.56 | 1.36 | 5 | 0.90 | 0.28 | 2.12 |
| Connective tissue | 124 | 0.99 | 0.82 | 1.18 | 48 | 1.10 | 0.81 | 1.47 |
| Non-Hodgkin lymphoma | 1031 | **1.14** | 1.07 | 1.21 | 421 | **1.12** | 1.01 | 1.23 |
| Hodgkin's disease | 93 | **1.72** | 1.39 | 2.11 | 20 | 1.39 | 0.85 | 2.15 |
| Myeloma | 322 | **1.44** | 1.28 | 1.60 | 152 | **1.67** | 1.41 | 1.95 |
| Leukaemia | 325 | **1.54** | 1.38 | 1.72 | 153 | **1.54** | 1.30 | 1.80 |
| All | 24,837 | **1.15** | 1.13 | 1.16 | 9829 | **1.12** | 1.10 | 1.15 |

Bold type, 95% CI does not include 1.00.

calculated assuming a Poisson distribution.[26] All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, United States of America).

## 3. Results

Table 1 shows the basic characteristics of patients with and without cancer who were hospitalised with CHD during the study period. A total of 573,494 individuals without cancer were hospitalised with a main diagnosis of CHD (Table 1), while 34,666 individuals with cancer were subsequently hospitalised for CHD (Table 1). The four most common cancers were prostate cancer (139,510 cases), breast cancer (116,358), colon cancer (61,802) and lung cancer (59,644) (Supplementary Table 1).

The risk of CHD was increased during the first 6 months after diagnosis of cancer for 26 of the 34 cancers studied (Table 2). The overall risk of CHD during the first 6 months after diagnosis of cancer was 1.70 (95% CI 1.66–1.75). The overall CHD risk decreased over time, from 1.10 after 6–12 months (95% CI 1.06 –1.14), to 1.08 after 1–4 years (95% CI 1.06–1.10), 1.06 after 5–10 years (95% CI 1.04–1.09), and 1.07 after 10+ years (95% CI 1.04–1.11).

### 3.1. CHD risk in cancer patients

The overall incidence rate of CHD was 152 per 100,000 person year in cancer patients, compared to 143 in the general population. The risk of CHD was $\geqslant 2$ during the first 6 months after diagnosis of cancer of 12 sites/types: stomach, small intestine, anus, liver, pancreas, lung, kidney, nervous system, endocrine glands, non-Hodgkin lymphoma, myeloma and leukaemia (Table 2). For seven cancer sites/types—rectum, prostate, kidney, urinary bladder, skin (squamous cell), Hodgkin's lymphoma and myeloma—the risk of CHD was increased 10+ years after diagnosis of cancer (Table 2). Notably, the risk of CHD was not increased during the first 5 years after diagnosis of Hodgkin's lymphoma. In contrast to other cancer sites/types, the risk of CHD was highest after 10+ years in Hodgkin's lymphoma patients (SIR 2.79; 95% CI 1.97–3.83) (Table 2).

### 3.2. *Cancer sites unrelated to tobacco smoking*

Several cancer sites/types unrelated to tobacco smoking—small intestine, colon, rectum, anus, breast, endometrium, ovary, other female genital cancers, prostate, skin, squamous cell, nervous system, thyroid gland, endocrine glands, connective tissue, non-Hodgkin lymphoma and myeloma—were associated with increased CHD risk during the first six months after cancer diagnosis (Table 2).

### 3.3. *Metastases and CHD risk*

The Swedish Cancer Registry only contains data on metastases since 2002. In patients with metastases, the overall CHD risk between 2002 and 2008 was significantly increased (SIR 1.46; 95% CI 1.28–1.85) (Table 3). The overall risk of CHD was not increased among cancer patients without metastasis (SIR 0.99; 95% CI 0.93–1.05) (Table 3).

### 3.4. *Stratified analysis of CHD risk from 1987–1997 and 1998–2008*

Stratified analyses of CHD risk from 1987–1997 and 1998–2008 were performed in order to partly account for possible changes in risk due to changes in treatment (Table 4). However, no major differences in CHD risks were observed between these periods.

### 3.5. *Subsequent risk of myocardial infarction in cancer patients*

Subanalysis was performed regarding myocardial infarction. The overall risk of myocardial infarction (Table 5) was similar in size to the overall risk of CHD (Table 2).

### 3.6. *SIR for subsequent CHD in cancer patients by comorbidities/risk factors*

Among cancer patients stratified analysis was performed for risk factors comparing cancer patients with and without comorbidities/risk factors. Cancer patients with COPD, obesity, diabetes mellitus or hypertension had increased risks of CHD.

**Table 5 – SIR for subsequent myocardial infarction in cancer patients.**

| Cancer site | O | SIR | 95% CI | |
|---|---|---|---|---|
| Upper aerodigestive tract | 701 | **1.11** | 1.03 | 1.20 |
| Salivary gland | 74 | **1.30** | 1.02 | 1.64 |
| Oesophagus | 88 | 1.14 | 0.91 | 1.40 |
| Stomach | 458 | **1.18** | 1.08 | 1.30 |
| Small intestine | 114 | **1.22** | 1.00 | 1.46 |
| Colon | 2390 | **1.13** | 1.08 | 1.17 |
| Rectum | 1403 | **1.12** | 1.07 | 1.18 |
| Anus | 56 | 0.99 | 0.75 | 1.29 |
| Liver | 225 | **1.64** | 1.43 | 1.87 |
| Pancreas | 134 | **1.53** | 1.28 | 1.81 |
| Nose | 45 | 1.04 | 0.76 | 1.39 |
| Lung | 1022 | **1.72** | 1.61 | 1.83 |
| Breast | 3239 | 0.95 | 0.92 | 0.98 |
| Cervix | 188 | **1.29** | 1.11 | 1.48 |
| Endometrium | 855 | 0.95 | 0.89 | 1.02 |
| Ovary | 315 | 1.03 | 0.92 | 1.15 |
| Other female genital | 138 | **1.46** | 1.22 | 1.72 |
| Prostate | 8010 | **1.18** | 1.15 | 1.20 |
| Testis | 65 | 1.03 | 0.79 | 1.31 |
| Other male genital | 59 | 0.91 | 0.69 | 1.18 |
| Kidney | 929 | **1.50** | 1.40 | 1.59 |
| Urinary bladder | 2616 | **1.37** | 1.32 | 1.42 |
| Melanoma | 1068 | 0.97 | 0.91 | 1.03 |
| Skin, squamous cell | 2526 | **1.30** | 1.25 | 1.36 |
| Eye | 77 | 1.02 | 0.80 | 1.27 |
| Nervous system | 469 | 1.04 | 0.95 | 1.14 |
| Thyroid gland | 134 | 0.92 | 0.77 | 1.09 |
| Endocrine glands | 750 | **1.24** | 1.15 | 1.33 |
| Bone | 25 | 1.00 | 0.64 | 1.47 |
| Connective tissue | 156 | 1.10 | 0.94 | 1.29 |
| Non-Hodgkin lymphoma | 1220 | **1.13** | 1.07 | 1.20 |
| Hodgkin's disease | 94 | **1.67** | 1.35 | 2.04 |
| Myeloma | 410 | **1.61** | 1.46 | 1.77 |
| Leukaemia | 397 | **1.51** | 1.36 | 1.66 |
| All | 30,450 | **1.17** | 1.16 | 1.19 |

Bold type, 95% CI does not include 1.00.

## 4. Discussion

The present study is the first nationwide study that shows that cancer is associated with an increased risk of CHD. The causes behind our findings are, however, not clear and may be related to many factors such as common risk factors, treatment, cancer related inflammation and haemostatic activation. Moreover, this effect is not limited to smoking-related cancers. Several non-smoking related cancers were also associated with increased risk of CHD (Table 2). The risk of CHD during the first 6 months after diagnosis of cancer was similar in magnitude to those for traditional risk factors for CHD.[1] Although, the risk declined rapidly thereafter, the overall risk of CHD remained slightly raised for 10 or more years after cancer diagnosis. The overall risk for CHD was related to the presence of metastases (Table 3). The risk for CHD in cancer patients was also related to comorbidities/risk factors as COPD (an indicator of smoking), obesity, diabetes mellitus and hypertension, which should be considered in the clinical evaluation of CHD risk in cancer patients (Table 6).[27] Our findings are important because cardiovascular disease especially in combination with diabetes and COPD has been reported to be associated with treatment intensity, treatment outcome and prognosis.[27]

The increased risk of CHD may have different underlying causes for different cancer sites/types. Since inflammation has been linked to both atherosclerosis and haemostatic activation, a general link between cancer-associated inflammation/haemostatic activation and CHD is possible.[4–7] The observed association of tumour metastasis with CHD risk indicates that this hypothesis is possible, i.e. increased inflammation and haemostatic activation due to presence of metastases (Table 3). However, many other explanations may exist. It is possible that efficient cancer treatment might reduce tumour size, associated inflammation, haemostatic activation and, thus, risk of CHD. The fact that the risk of CHD decreases rapidly suggests that CHD risk could be linked to tumour size,

**Table 6 – SIR for subsequent coronary heart disease in cancer patients by comorbidities/risk factors.**

| Comorbidity/risk factor | With comorbidity/risk factor | | | | Without comorbidity/risk factor | | |
|---|---|---|---|---|---|---|---|
| | O | SIR | 95% CI | | O | SIR | 95% CI |
| COPD | 2390 | **1.38** | 1.33 | 1.44 | 32,276 | 1.00 | |
| Obesity | 96 | **1.39** | 1.12 | 1.69 | 34,570 | 1.00 | |
| Alcoholism | 795 | 1.05 | 0.98 | 1.13 | 33,871 | 1.00 | |
| Diabetes mellitus | 2392 | **1.95** | 1.87 | 2.03 | 32,274 | 1.00 | |
| Hypertension | 1160 | **1.67** | 1.57 | 1.77 | 33,506 | 1.00 | |

Bold type, 95% CI does not include 1.00.

which is likely to decrease over time due to treatment. However, as we lack treatment data, we cannot prove this hypothesis. In fact, the rapid decrease in risk could also be due to cessation of chemotherapy or reduction of cancer related stress. Moreover, smoking cessation—a confounder that we cannot adjust for—may also contribute to the rapidly decreasing incidence of CHD after cancer diagnosis.

In smoking-related cancers, the increased CHD risk may be due to tobacco smoking.[17–20] The effects of treatment (mediastinal radiation)[10–12,15] may also contribute to the identified associations, especially in the case of Hodgkin's lymphoma. However, CHD risk was only slightly and briefly increased among breast cancer patients, arguing against the notion that radiation has an important effect on CHD risk in breast cancer patients.[13] Another explanation for the increased CHD risk is that not only radiation, but also cytostatics, may be harmful for the heart and increase the risk of CHD.[28] Another potential confounder that could contribute to the increased CHD risk during the first 6 months after diagnosis is the psychological trauma and stress of having cancer. Although we were unable to evaluate the impact of psychosocial stress, psychosocial factors are suggested to be risk factors for CHD.[29]

The present study has certain limitations. For example, we had no data on general cardiovascular risk factors such as weight, smoking and diet. It is unrealistic to gather such data for an entire national population. However, we did adjust for socioeconomic status, which is associated with several common risk factors such as smoking. Adjustment was also made for comorbidities/risk factors (i.e. COPD, obesity, alcoholism, hypertension and diabetes mellitus). A further limitation is that we had no access to outpatient data, which means that only the most severe cases of CHD (i.e. those requiring hospitalisation) were included in the analyses. However, all cases of acute coronary syndrome should, according to official guidelines, be treated at hospitals in Sweden.[30] Moreover, incidence rates were calculated for the whole follow-up period, divided into five time periods, and adjustments were made for possible changes in incidence rates over time.

The study also had a number of strengths. For instance, the study population included all patients diagnosed with cancer and hospitalised with CHD in Sweden during the study period. Because of the personal identification number assigned to each resident in Sweden, it was possible to trace every subject for the whole follow-up period. Data on occupation were 99.2% complete (1980 and 1990 censuses), which enabled us to adjust our models for socioeconomic status. Moreover, the Cancer Registry records all new cases of cancer, and close to 100% of the cases are histologically or cytologically confirmed. A further strength of the present study was the use of validated hospital discharge data. The Hospital Discharge Register has high validity,[21,31] especially for cardiovascular disorders such as myocardial infarction, for which approximately 95% of diagnoses have been shown to be correct.[31–33] Another advantage was that the exclusive use of hospital diagnoses eliminated recall bias.

In summary, risk of hospitalisation for CHD was, for most cancer sites/types, found to be significantly increased during the first 6 months after diagnosis of cancer. The risk of CHD decreased rapidly thereafter, but for many cancer sites was elevated for more than 10 years. Overall risk of CHD was related to the presence of metastasis and cardiovascular risk factors. The findings of the present study indicate that newly diagnosed cancers in general are associated with and increased risk for coronary atherosclerotic disorders. Cancer patients may need a more aggressive treatment of classical CHD risk factors.

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None.

## Contributors

All authors contributed to the conception and design of the study; J.S and K.S. contributed to the acquisition of data; all authors contributed to the analysis and interpretation of data; B.Z. drafted the manuscript; and all authors revised it critically and approved the final version. All authors had full access to all of the data (including statistical reports and tables) and take responsibility for the integrity of the data and the accuracy of its analysis.

## Conflict of interest statement

None declared.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.09.015.

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