Incidence and prevalence of comorbidity after cancer diagnosis in Flemish general practice: a registry-based study

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Abstract

Objectives To compare the occurrence of comorbidity at the time of diagnosis and within 5 years after cancer diagnosis, versus an age-matched control group of patients without cancer diagnosis, in two 10-year time periods.

Methods Data for this registry-based study were extracted from Intego, a morbidity registration network gathering data from more than 100 practices in Flanders, Belgium. Cases were identified using ICPC-2 codes representing breast cancer (X76), colon cancer (D75), prostate cancer (Y77) and lung cancer (R84). Controls were matched on age, gender, GP practice, follow-up time and year of contact with the GP. Comorbidity occurrence was analyzed for a period of 5 years after cancer diagnosis or index date for controls. Forest plots per cancer subtype were used to represent the relative risk (RR) and confidence interval (CI) to comorbidity compared to the control group.

Results The study population between 2001 and 2020 comprised more than 700 000 different patients, of which 11.437 patients were diagnosed with either breast, colon, prostate, or lung cancer. Comorbidity at time of diagnosis was significantly higher in cancer patients for all four examined cancer types ($p < 0.05$). In all cancer patients and time periods an elevated risk was found to develop a second malignancy, peripheral vascular disease, and pulmonary embolism. In breast cancer patients a higher risk of depression and osteoporosis was found. In lung cancer patients the risk of COPD was higher. The risk of heart disease was elevated, for both prostate and colon cancer patients. In colon cancer patients, also a higher risk of asthma was found. A higher risk of developing comorbidities was found in patients diagnosed between 2011 and 2020, compared to patients diagnosed between 2000 and 2010. This trend was especially clear for peripheral vascular disease and pulmonary embolism, but also for osteoporosis in breast cancer patients, heart disease in prostate cancer patients and COPD in lung cancer patients.

Conclusion Comorbidity burden in cancer patients is rising both at time of diagnosis and within the first 5 years after diagnosis. With improving cancer survival rates, the burden of comorbidity is expected to increase.

Introduction

Cancer constitutes a huge threat to public health with rising incidence and prevalence worldwide. (1) (2) In many high-income countries malignancies remain the leading cause of death, outnumbering mortality rates due to cardiovascular disease. (3) (4) (5) Overall, early diagnosis and effective treatment have improved cancer survival rates for some cancer types. (6) However, more comorbidity at time of diagnosis and after treatment results in increased disability and lower survival of cancer patients. (7) (8)

Cancer is often associated with comorbidities. (7) (9) (10) Recent studies have shown that 55% of patients diagnosed with cancer have at least one comorbidity and 27% have at least two comorbidities, at the time of cancer diagnosis. (11) (12) Also after cancer diagnosis a more frequent occurrence of comorbidity is seen in cancer patients compared to an age- and gender matched control group. (13) Comorbidities noted frequently in cancer survivors are congestive heart failure, hypertension, chronic obstructive pulmonary disease, and diabetes mellitus. (8) (9) (12) This high level of comorbidity can possibly be explained by shared risk factors, like smoking, poor diet, alcohol consumption, obesity, or physical inactivity. Another explanation may be treatment-related toxicity or comorbidity caused by the cancer treatment. Also, enhanced monitoring and use of healthcare can be a reason of the higher perceived level of comorbidity. Finally, pre-existing comorbidity, for example diabetes mellitus, may lead to an elevated cancer risk. (13)

While cancer incidence is declining slightly in men, and the risk of developing cancer increases in women according to the Belgian Cancer Registry, (14) (15) populations are growing and ageing, causing an overall increase in the number of cancer diagnoses. (1) (14) (16) Although multiple studies have shown a high prevalence of comorbidity among cancer survivors, only a few studies have compared the prevalence of comorbidity in people with and without cancer. (8) Also, results were conflicting; some studies reported an association between cancer diagnosis and increasing comorbidity, whereas others did not. (17) (18) (19) However, little data on the prevalence and incidence of comorbidity in cancer patients are available in the Belgian Cancer Registry. International research concerning this subject is also limited despite the growing importance of comorbidity in cancer patients.

As oncologists may focus on the cancer but largely ignore other medical issues, general practitioners (GPs) could be of great value in the management of the multimorbid cancer patient. (7) (14) (20) Since cancer therapies are rapidly changing and there is only a limited amount of cancer patients per GP practice, it is impossible for GPs to stay up to date about the existing and developing comorbidities in cancer patients. Therefore, it would be useful to know which comorbidities occur after cancer diagnosis and when the comorbidity incidence starts to rise.

In this study, we investigated which chronic diseases occurred within 5 years after breast, colon, prostate, or lung cancer diagnosis in a general practice morbidity registry. Two 10-year time intervals (2001-2010 and 2011-2020) were compared to evaluate trends in patient complexity over time.

Methods

Study design

The present study is a retrospective registry-based study.

Data collection

Data for this study were obtained from Intego, a Belgian general practice-based morbidity registration network at the Department of Public Health and Primary Care of the KU Leuven, operational since 1994. (21) All data were obtained from the electronic health records of over 100 GP practices. (22) Currently, new data are collected on a weekly basis and are entered into a central database. GP practices applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using algorithms to compare their results with those of all other applicants. Only data from practices with optimal registration performance were included in the epidemiological database. Additionally, Intego data have been externally validated by means of national and international comparisons.

Intego GPs prospectively and routinely register all new diagnoses and new drug prescriptions, as well as laboratory test results and patient information, using computer-generated keywords internally linked to codes. New diagnoses were classified according to a very detailed thesaurus automatically linked to the International Classification of Primary Care (ICPC-2). In 2021, the Intego database included historically accumulated data from over 700.000 different patients. The denominator was the yearly contact group (YCG). These are the patients that visited the practice at least once each year. (21) (23) Research demonstrated that the YCG represents approximately 80% of the practice population (22). Furthermore, the YCG is representative according to age and gender for the Flemish population. The 2021 YCG reflected 4.76% of the Flemish population.

The present study used Intego data of a 20-year time interval from 1 January 2001 to 31 December 2020. The ethical review board of the KU Leuven Faculty of Medicine (ML 1723) and the Belgian Privacy Commission (SCSZG/13/079) approved the Intego procedures.

Patient involvement

No patients were involved in the development of the research question, study design or interpretation of the data.

Definition of cancer and cancer subtypes

For this study we included patients with lung, colon, breast, or prostate cancer because these are the most common cancer types (24). Cancer patients were identified based on an ICPC-2 coded diagnosis in their Electronic Medical Record (lung cancer (R84), colon cancer (D75), breast cancer (X76) and prostate cancer (Y77)). (25).

Comorbidity

Comorbidity was defined as a medical condition that exists along with an index condition (in this case cancer). (26) Medical history before the date of cancer diagnosis was registered for all incident cancer cases between 2001 and 2020, as well as for an age-and-gender-matched control group of patients without cancer diagnosis, and a disease count was calculated. Furthermore, the development of comorbidity within 5 years after cancer diagnosis was calculated and compared to the control group. In addendum I, a list of the examined comorbidities can be found. (27)

Data analysis

Incident cases for the different cancer subgroups were identified. Incident cases were defined as patients in the YCG getting a new cancer diagnosis between the 1st of January and the 31st of December that year and without an earlier diagnosis of the investigated cancer. The date of cancer diagnosis was used as the index date.

Patients were matched to a control group on age, gender, GP practice, follow-up time and YCG (1:3 matching ratio). Per cancer subtype we defined a matched control group of patients without the examined cancer diagnosis before the index date or during follow-up time. The R version 4.0.3 and the ccoptimalmatch R package were used to define the most optimal control group.

Trends in disease count were explored in incident cancer cases and matched controls at the moment of diagnosis, and at 1, 3 and 5 years after diagnosis with χ^2-test over two time intervals (2001–2010, 2011-2020).

Prevalence rates of the following diseases were calculated: malignancies, lung disease (asthma, COPD, pulmonary embolism), digestive disease (including ulcers), cardiovascular disease (including myocardial infarction, stroke, hypertension), diabetes mellitus, osteoporosis and depression. According to previous research, these comorbidities were noted frequently amongst cancer patients. (8) (9) (12) ~~(1)~~ In addendum I a complete list of the examined comorbidities can be found. The

prevalence of selected comorbidities was compared between patients diagnosed with cancer and their controls at baseline and after 1, 3 and 5 years, using log-binominal model. With multivariable logistic regression odds rations are computed. The aim in our study was to compute relative risks, using a log-binominal model. The main difference between log-binominal models and multivariable logistic regression is the link function: the log function is used in the log-binominal model; the logit function is used in het multivariable logistic regression. (28)

Forest plots were used to represent the relative risk (RR) and confidence interval (CI) of developing a comorbidity when diagnosed with one of the cancer subtypes, compared to the control group. This was carried out for both time intervals, 2001-2010 and 2010-2020. This analysis was carried out with R version 4.0.3.

Results

Trends in comorbidities in patients with cancer at baseline

Between 1st of January 2001 and 31st of December 2020 a total of 11.437 patients were diagnosed with either breast, colon, prostate or lung cancer.

For **breast cancer** the mean age at time of diagnosis was 54.8 years. Disease count at baseline was 1.2 for cancer patients vs 0.9 for controls ($p < 0.05$). *(Table 1)*

For patients diagnosed with breast cancer between 2011 and 2020, at baseline the most common comorbidities were previous malignancies (23.6%), hypertension (20.9%), diabetes (11%), depression (16.4%), and asthma (11%). *(Table 2)* For previous malignancies, ischemic heart disease, structural heart disease, cerebrovascular disease, diabetes, and depression a significant difference was seen between patients and controls in both time periods. For arrhythmias, hypertension, peripheral vascular disease, COPD, asthma, and digestive disease this difference was only found in the second time interval. *(Table 2)*

Concerning **lung cancer,** patients averaged 62.8 years at the time of diagnosis. Of all the lung cancer patients 36.4% were female. *(Table 1)* A declining trend in male predominance was seen (30.9 vs 39.9% for both time periods). *(Table 2)* Disease count for patients with lung cancer was 2.1, vs 1.3 for controls ($p < 0.05$). Most common comorbidities at baseline were previous malignancies (44.4%), hypertension (26.1%), COPD (20.2%), ischemic heart disease (15%) and peripheral vascular disease (12.8%). In both time intervals a significant difference was found between patients and controls for other previous malignancies, ischemic heart disease, peripheral vascular disease, COPD, and digestive disease.

Cerebrovascular disease, diabetes and depression were also more prevalent in patients with lung cancer diagnosed between 2011 and 2020. *(Table 2)*

Prostate cancer patients averaged 67.7 years old when the diagnosis was registered. Disease count was 1.5 on average vs 1.2 for controls (p <0.05). *(Table 1, 2)* Most common comorbidities at baseline were other malignancies (25.7%), hypertension (33%), ischemic heart disease (13.4%), diabetes (17%) and asthma (12.1%). For other malignancies, arrhythmias, hypertension, cerebrovascular disease, peripheral vascular disease, and asthma this was significantly different between patients and controls, but only in the second time interval. In the first time interval a significant difference was found for other malignancies and diabetes. *(Table 2)*

C**olon cancer** patients were on average 61.5 years old at the time of diagnosis. In total, 52.3% of the patients were female. *(Table 1)* Mean disease count at the time of diagnosis was 1.6 for patients vs 1.1 for controls (p <0.05). Most frequent comorbidities were other malignancies (29.2%), hypertension (29.1%), diabetes (21.7%), depression (12.4%) and asthma (12.1%). In the second time interval, a significant difference was found in all comorbidities between patients and controls, except for pulmonary embolism and digestive disease. In the first time interval, a significant difference was only found for other malignancies and asthma. *(Table 2)*

Trends in comorbidities after cancer diagnosis

Higher risk of second malignancy

For all cancer types and time periods an elevated risk was found to develop a second malignancy.

For **breast cancer patients** a significant difference was seen between patients and controls in both time periods (2001-2010 and 2011-2020) after 1 year (RR 1.17 and RR 2.16, respectively), after 3 years (RR 2.16 vs RR 2.37) and after 5 years (RR 2.19 vs RR 1.99) *(Table 3 and figure 1)*.

This trend was also seen in **lung cancer patients** diagnosed between 2001 and 2010 after 1 year (RR 9.61), after 3 years (RR 2.22) and after 5 years (RR 2.19). Although the relative risk rose more clearly in patients diagnosed between 2011 and 2020 after 1 year (RR 3.78), after 3 years (RR 3.32) and after 5 years (RR 2.8). *(Table 3 and figure 2)*

For **prostate cancer patients** diagnosed between 2001 and 2010 the risk rose within 1 year (RR 2.89), within 3 years (RR 2.05) and within 5 years (RR 1.81). The relative risk was also higher for patients diagnosed between 2011 and 2020 after 1 year (RR 3.47), after 3 years (RR 2.64) and after 5 years (RR 1.95). *(Table 3 and figure 3)*

Also, patients diagnosed with **colon cancer** had a high relative risk to develop another malignancy**.** This counted for patients diagnosed between 2001 and 2010 within 1 year (RR 4.18), within 3 years (RR 3.09) and within 5 years (RR 2.57), as well as for patient diagnosed between 2011 and 2020 within 1 year (RR 2.28), within 3 years (RR 2.94) and within 5 years (RR 2.34). *(Table 3 and figure 4)*

Higher risk of peripheral vascular disease and pulmonary embolism

In the second time interval (2011-2020), a higher risk of peripheral vascular disease and pulmonary embolism was found after cancer diagnosis.

This higher incidence of peripheral vascular disease was found in **breast cancer** patients within 1 year (RR 3.27), within 3 years (RR 2.04) and within 5 years (RR 1.59) after diagnosis. In this time interval also the risk of pulmonary embolism was risen after 3 years (RR 4.66) and after 5 years (RR 2.82). *(Table 3 and figure 1)*

A higher risk of peripheral vascular disease was found in patients who got diagnosed with **lung cancer** between 2011 and 2020, both within 3 years (RR 3.16) and within 5 years (RR 3.16). Also the risk of pulmonary embolism rose in these patients within 1 year (RR 18), within 3 years (RR 15) and within 5 years (RR 19.5). *(Table 3 and figure 2)*

In **prostate cancer patients** an elevated risk of peripheral vascular disease (RR 2.07) was found within 3 years after diagnosis. Within 5 years after diagnosis a higher risk of peripheral vascular disease (RR 1.75) and pulmonary embolism (RR 2.44) was found. *(Table 3 and figure 3)*

For **colon cancer** patients a significant higher risk of pulmonary embolism was found after 1 year (RR 14.94), after 3 years (RR 4.85) and after 5 years (RR 3.78). Also, a higher risk of peripheral vascular disease was found within 3 years (RR 2.05) and within 5 years (RR 1.95). *(Table 3 and figure 4)*

Higher risk of depression in breast cancer patients

Only in patients diagnosed with breast cancer between 2001 and 2010 a higher **depression** rate was found compared to controls, after 1 year (RR 6.12), after 3 years (RR 2.37) and after 5 years (RR 2.23). For patients diagnosed between 2011 and 2020 this rising risk was only found during the first year after diagnosis (RR 2.37). *(Table 3 and figure 1)*

Higher risk of osteoporosis in breast cancer patients

O**steoporosis** was diagnosed more frequently after breast cancer. For patients diagnosed between 2011 and 2020 the relative risk was higher after 1 year (RR 3.01), after 3 years (RR 2.35) and after 5

years (RR 1.92). For patients diagnosed between 2001 and 2010 we only found this trend 5 years after diagnosis (RR 1.87). *(Table 3 and figure 1)*

Higher risk of COPD in lung cancer patients

COPD was diagnosed more frequently in patients who got diagnosed with lung cancer between 2011 and 2020. The relative risk was more increased within 1 year after diagnosis (RR 9.26) compared to 3 years or 5 years after diagnosis (RR 3.86 and RR 2.99, respectively). *(Table 3 and figure 2)*

Higher risk of heart disease in cancer patients

In patients diagnosed with prostate cancer between 2011 and 2020 a higher risk of developing **structural heart disease** (RR 2.79) and **heart failure** (RR 1.93) was found. *(Table 3 and figure 3)*

Within 1 year after diagnosis the risk of **heart failure** rose (RR 4.51) in colon cancer patients. *(Table 3 and figure 4)*

Higher risk of asthma in colon cancer

In the second time interval, a slightly increased risk was found to develop **asthma** in colon cancer patients within 1 year (RR 2.22), within 3 years (RR 1.68) and within 5 years (RR 1.54). *(Table 3 and figure 4)*

Discussion

Trends in comorbidities in patients with cancer at baseline

Our study showed that cancer patients tend to have more comorbidities at the time of diagnosis compared to controls. This was the case for each of the four examined cancer types, and in both time intervals (*Figure 1-4*). This is an important finding since cancer survival rates are improving and more patients are living longer with their cancer, and thus with their comorbidities. (7) (9) (10) (20) Former research showed that cancer survivors suffered on average from five chronic diseases, of which two occurred after cancer diagnosis. (10)(11)(12) This partly supports the results in our study, although the disease count at the time of diagnosis in our study varied between 1 and 2. Our study only investigated the comorbidities listed in Appendix 1, which can explain this difference in disease count.

Most prevalent comorbidities at the time of diagnosis were hypertension, diabetes, and ischemic heart disease, and COPD for lung cancer patients. This is in line with formerly conducted research. (11) The highest comorbidity prevalence was seen in lung cancer patients. This also supports the results of former studies. (9) Multimorbidity is independently associated with both older age and cancer,

although the comorbidity prevalence in cancer patients is more strongly related to age than to cancer. (5) (9) (20) The correlation between comorbidities and cancer can partly be explained by mutual risk factors, e.g. smoking, obesity, physical inactivity. These risk factors are known to be related to cancer, as well as to other diseases, such as diabetes, COPD, stroke, and heart disease. (7) (10) (20) Also, patients with certain comorbidities tend to visit the general practitioner more often and undergo more investigations, e.g. CT scans, participation to screening programs. (13)

Trends in comorbidities after cancer diagnosis

Our study showed an overall higher risk of developing different comorbidities in the first 5 years after cancer diagnosis. Due to the ageing population, comorbidity count is rising in general.

Higher comorbidity burden in time interval 2011-2020

A trend towards higher comorbidity incidence was seen in patients diagnosed with cancer between 2011 and 2020, compared to patients diagnosed between 2001 and 2010. This was seen for heart failure and structural heart disease within 3 years after prostate cancer and asthma within 1, 3 and 5 years after colon cancer. It is unlikely that this could be allocated to a registration effect, because we would expect to see a registration effect in control patients too. A possible explanation is that patients survive longer with their cancer and receive more therapy, which can cause a higher comorbidity incidence.

Higher risk of malignancies after cancer diagnosis

A significantly higher risk was seen in breast, colon, prostate and lung cancer patients to develop a second malignancy within 5 years after diagnosis, compared to controls.

A possible explanation is that cancer patients must undergo a lot of examinations, to define the cancer stadium at the time of diagnosis and that other cancers are found during these investigations. (29) However, the elevated relative risk of another malignancy was also seen within 3 and 5 years and cannot be explained by the initial investigations. Another possible explanation is that metastases occur during or after cancer treatment and are registered as a second cancer diagnosis.

Some cancer types share risk factors, e.g. smoking for both lung and breast cancer. (30) This can partly explain the elevated relative risk of developing a second malignancy. Also, cancer therapy, such as radiation, can cause a higher risk of subsequent malignancy, as was shown by former studies for breast cancer patients and prostate cancer patients after radiotherapy. (30)(31)(32)(33)(34)(35) On the other hand, in patients diagnosed with lung cancer it was shown that surgery, chemotherapy and radiotherapy were not associated with an elevated risk of developing a secondary malignancy. (36)

Elevated risk of peripheral vascular disease and pulmonary embolism

In the four examined cancer types a higher risk of peripheral vascular disease and pulmonary embolism was seen in the second time interval (2011-2020). Both conditions are a major cause of morbidity and mortality in cancer patients. (37) In recent years the greater use of computed tomography in cancer patients has led to a significant increase in diagnosis of incidental venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. (38)(39) Also, an association exists between deep vein thrombosis and occult malignancies, as a result of a paraneoplastic syndrome (Trousseau's syndrome) (40). Malignancies have an impact on all the components of the Virchow's triad. Cancer can cause blood vessel alterations and circulation stasis, due to effects on tissue architecture and volume occupation, but is can also affect hypercoagulability in different ways. (41)(42) Patients treated with chemotherapy have a 6 times higher risk of developing VTE. (42) Especially platinum-based therapies lead to an elevated risk, which explains the lower relative risk in prostate and breast cancer patients as this type of chemotherapy is used more as a treatment for colorectal and lung cancer (43)(44)(45). Also, surgery and subsequent immobility increase the risk of peripheral vascular disease and pulmonary embolism. (42)

Immobilization, associated with surgery and deterioration of the general condition of cancer patient, may also induce arterial insufficiency. (46)

Osteoporosis and depression after breast cancer

In breast cancer patients a higher incidence of both depression and osteoporosis was found in both time periods.

Most treatments in early breast cancer patients cause a profound and rapid suppression of estrogen levels, which increases the rate of bone loss. Still, the relationship between breast cancer and risk of osteoporotic fractures remains unclear. Recent cohort data did not show a significantly elevated risk of fractures in breast cancer patients. The fact that osteoporosis was seen more in the second time interval can be explained by the increased use of Aromatase Inhibitors in breast cancer treatment. (47)(48)

In both time intervals a higher rate of depression was seen in breast cancer patients, which is consistent with previous research. Breast cancer patients often undergo a mastectomy, with leads to postoperative scarring and changes in body image, which can cause long-term stress. Also, menopause and decreased estrogen due to cancer therapy are causes of depression. (49) Other interfering factors may be adverse reactions to chemo- or radiotherapy, changes in social roles and negative emotions. (50.

Strengths and limitations

A major strength of our study is the large real-world population, which is representative for the general Flemish population. Also, the follow-up period of 5 years is a major strength. Our study is one of the first to consider comorbidity both at time of cancer diagnosis and in the first years after diagnosis.

A first limitation concerns the use of the yearly contact group as the denominator. According to former research the YCG only accounts for 80% of the total practice population. (23)

A second limitation is that mortality data were lacking until 2017, since (pseudonymized) social security numbers were not used as identifiers until that time. For patients without a social security number it was not possible to receive mortality data, after linking with the National Registry. This may cause an overestimation of the disease-free time interval in patients that were deceased.

Furthermore, the Intego database can only consider data registered in the medical records by coded diagnoses. Results can therefore be influenced by the quality of registration and changes in coding practices. Only practices that coded more than 80% of their registered diagnoses every year were included in the Intego database. Also, the date of registration could differ from the date of diagnosis in an electronic health record, which can also affect study results.

Finally, for years 2018-2020 the 5-year follow-up was incomplete, since only data until December 31 2022 were available.

Conclusion

This large registry-based study in Flemish general practice, covering a 20-year period showed a significant increase in cancer patient complexity at time of diagnosis.

With improving cancer survival and therapies, a trend towards a higher risk of developing comorbidities was found in patients diagnosed between 2011 and 2020, compared to patients diagnosed between 2000 and 2010. This trend was especially clear for peripheral vascular disease and pulmonary embolism, but also for osteoporosis in breast cancer patients, heart disease in prostate cancer patients and COPD in lung cancer patients.

With improving cancer survival rates, the burden of comorbidity is expected to increase. Therefore, it will become more important to involve general practitioners in a shared cancer care system. This way, the management and quality of life of the multimorbid cancer patient can be optimized.

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Addendum

1. List of examined comorbidities

Malignancies
- A79 Malignant neoplasm not otherwise specified
- B72 Hodgkin's disease/lymphoma
- B73 Leukaemia
- B74 Malignant neoplasm blood other
- D74 Malignant neoplasm stomach
- D75 Malignant neoplasm colon/rectum
- D76 Malignant neoplasm pancreas
- D77 Malignant neoplasm digestive other/NOS
- K72 Malignant neoplasm cardiovascular system
- L71 Malignant neoplasm musculoskeletal
- N74 Malignant neoplasm nervous system
- R84 Malignant neoplasm bronchus/lung
- R85 Malignant neoplasm respiratory, other
- S77 Malignant neoplasm of skin
- T71 Malignant neoplasm thyroid
- U75 Malignant neoplasm of kidney
- U76 Malignant neoplasm of bladder
- U77 Malignant neoplasm urinary other
- X75 Malignant neoplasm cervix
- X76 Malignant neoplasm breast female
- X77 Malignant neoplasm genital other
- Y77 Malignant neoplasm prostate
- Y78 Malignant neoplasm male genital other

Ischemic heart disease
- K74 Ischemic heart disease with angina – ever
- K75 Acute myocardial infarction – ever
- K76 Ischemic heart disease without angina – ever

Structural heart disease
- K83 Heart valve disease nos

Heart failure
- K77 Congestive heart failure

Arrhythmyias
- K78 Atrial fibrillation/flutter
- K79 Paroxysmal tachycardia

Hypertension
- K86 Hypertension uncomplicated
- K87 Hypertension complicated

Cerebrovascular disease
- K90 Stroke/cerebrovascular accident
- K91 Cerebrovascular disease

Peripheral vascular disease
- K92 Atherosclerosis/peripheral vascular disease
- K94 Phlebitis/thrombophlebitis

Lung disease
- Pulmonary embolism
    - K93 Pulmonary embolism
- COPD
    - R79 Chronic bronchitis
    - R95 Chronic obstructive pulmonary disease
- Asthma
    - R96 Asthma

Digestive disease
- D85 Duodenal ulcer
- D86 Peptic ulcer other

Diabetes mellitus
- T89 Diabetes insulin dependent
- T90 Diabetes non-insulin dependent

Depression
- P76 Depressive disorder

Osteoporosis
- L95 Osteoporosis

2. *Tables and figures*

Table 1 *– Characteristics of cases and controls (2001-2020)*

Variables	***BREAST CANCER***		***LUNG CANCER***		***PROSTATE CANCER***		***COLON CANCER***	
	Patients	***Controls***	***Patients***	***Controls***	***Patients***	***Controls***	***Patients***	***Control***
NO. OF PATIENTS	4329	12926	1528	4507	2187	6498	3393	10130
DEMOGRAPHIC VARIABLES								
- *Mean age (SD)*	54.8(16.1)	54.8(16.1)	62.8(15.8)	62.6(15.8)	67.7(12.7)	67.6(12.7)	61.5(14.6)	61.5(14.6)
- *Women N (%)*	4061(93.8%)	12127(93.8%)	556(36.4%)	1658(36.8%)	86(3.9%)	256(3.9%)	1776(52.3%)	5306(52.4%)
- *Disease count, mean (SD)*	1.2(1.4)	0.8(1.2)	2(1.7)	1.3(1.6)	1.5(1.5)	1.2(1.5)	1.5(1.5)	1.1(1.4)
- *Disease count, median (IQR)*	1(2)	0(1)	2(2)	1(2)	1(2)	1(2)	1(2)	1(2)
- *Mean follow-up time (SD)*	6(4.4)	5.8(4.5)	3.9(4)	4.1(4)	5.4(4.4)	5.2(4.5)	5.6(4.2)	5.5(4.2)

Table 2 *– Characteristics of cases and controls + prevalence of comorbidity at time of diagnosis for the two time periods (2001-2010 and 2011-2020)*

Variables	Time period	BREAST CANCER		LUNG CANCER		PROSTATE CANCER		COLON CANCER	
		Patients	**Controls**	**Patients**	**Controls**	**Patients**	**Controls**	**Patients**	**Controls**
NO OF PATIENTS	2001-2010	1184	3516	596	1726	825	2428	822	2440
	2011-2020	3145	9410	932	2781	1362	4070	2571	7690
DEMOGRAPHIC VARIABLES									
Mean age (SD)	2001-2010	55.2(15.9)	55(15.8)	63(15.2)	62.7(15.3)	67.8(11.5)	67.6(11.5)	62.2(15.3)	62.1(15.2)
	2011-2020	54.7(16.2)	54.6(16.2)	62.6(16.1)	62.6(16.1)	67.7(13.4)	67.6(13.3)	61.3(14.4)	61.3(14.4)
Women N (%)	2001-2010	1140(96.3%)	3386(96.3%)	184(30.9%)	544(31.5%)	0 (0%)	0 (0%)	426(51.8%)	1265(51.8%)
	2011-2020	2921(92.9%)	8741(92.9%)	372(39.9%)	1114(40.1%)	0 (0%)	0 (0%)	1350(52.5%)	4041(52.5%)
Disease count, mean (SD)	2001-2010	**1.2(1.3)**	**0.9(1.2)**	**2.1(1.7)**	**1.3(1.6)**	**1.5(1.5)**	**1.3(1.4)**	**1.4(1.4)**	**1.2(1.5)**
	2011-2020	**1.2(1.4)**	**0.8(1.2)**	**2(1.8)**	**1.3(1.6)**	**1.6(1.5)**	**1.2(1.5)**	**1.6(1.5)**	**1.1(1.4)**
Disease count, median (IQR)	2001-2010	**1(2)**	**0(1)**	**2(2)**	**1(2)**	**1(2)**	**1(2)**	**1(2)**	**1(2)**
	2011-2020	**1(2)**	**0(1)**	**2(2)**	**1(2)**	**1(2)**	**1(2)**	**1(2)**	**1(2)**
Mean follow-up time	2001-2010	9.5(5.3)	9.3(5.4)	5.4(4.9)	5.6(4.8)	8.3(5.2)	8.2(5.3)	8.3(5.2)	8.3(5.2)
	2011-2020	**4.7(3.2)**	**4.4(3.3)**	3(3)	3.1(3)	**3.6(2.6)**	**3.4(2.7)**	**4.8(3.3)**	**4.6(3.4)**
COMORBIDITY TYPES									
Malignancies N (%)	2001-2010	**232 (19.6%)**	**204 (5.8%)**	**280 (47%)**	**254 (14.7%)**	**153 (18.5%)**	**243 (10%)**	**199 (24.2%)**	**299 (12.3%)**
	2011-2020	**742 (23.6%)**	**698 (7.4%)**	**414 (44.4%)**	**476 (17.1%)**	**350 (25.7%)**	**509 (12.5%)**	**750 (29.2%)**	**1021 (13.3%)**

Ischemic heart disease N (%)	2001-2010 2011-2020	**82(6.9%)** **173(5.5%)**	**169(4.8%)** **378(4%)**	**106(17.8%)** **140(15%)**	**226(13.1%)** **234(8.4%)**	127(15.4%) 182(13.4%)	330(13.6%) 486(11.9%)	92(11.2%) **255(9.9%)**	215(8.8%) **554(7.2%)**
Structural heart disease N (%)	2001-2010 2011-2020	**28(2.4%)** **74(2.4%)**	**50(1.4%)** **150(1.6%)**	18(3%) 36(3.9%)	58(3.4%) 81(2.9%)	25(3%) 59(4.3%)	81(3.3%) 131(3.2%)	31(3.8%) **85(3.3%)**	60(2.5%) **175(2.3%)**
Heart failure N (%)	2001-2010 2011-2020	10(0.8%) 41(1.3%)	32(0.9%) 90(1%)	28(4.7%) 30(3.2%)	61(3.5%) 57(2%)	20(2.4%) 32(2.3%)	92(3.8%) 107(2.6%)	17(2.1%) **56(2.2%)**	53(2.2%) **120(1.6%)**
Arrhythmias N (%)	2001-2010 2011-2020	48(4.1%) **137(4.4%)**	106(3%) **314(3.3%)**	47(7.9%) 67(7.2%)	132(7.6%) 196(7%)	69(8.4%) **145(10.6%)**	183(7.5%) **352(8.6%)**	51(6.2%) **186(7.2%)**	137(5.6%) **422(5.5%)**
Hypertension N (%)	2001-2010 2011-2020	248(20.9%) **685(21.8%)**	671(19.1%) **1592(16.9%)**	**151(25.3%)** 243(26.1%)	**352(20.4%)** 711(25.6%)	224(27.2%) **449(33%)**	602(24.8%) **1104(27.1%)**	198(24.1%) **748(29.1%)**	622(25.5%) **1782(23.2%)**
Cerebrovascular disease N(%)	2001-2010 2011-2020	**44(3.7%)** **115(3.7%)**	**83(2.4%)** **240(2.6%)**	41(6.9%) **72(7.7%)**	95(5.5%) **123(4.4%)**	49(5.9%) **107(7.9%)**	109(4.5%) **210(5.2%)**	33(4%) **138(5.4%)**	87(3.6%) **271(3.5%)**
Periferal vascular disease N (%)	2001-2010 2011-2020	95(8%) **203(6.5%)**	226(6.4%) **483(5.1%)**	**105(17.6%)** **119(12.8%)**	**164(9.5%)** **209(7.5%)**	77(9.3%) **122(9%)**	215(8.9%) **272(6.7%)**	86(10.5%) **208(8.1%)**	210(8.6%) **511(6.6%)**
Lung disease N (%)									
- **Pulmonary embolism N(%)**	2001-2010 2011-2020	9(0.8%) 26(0.8%)	25(0.7%) 68(0.7%)	8(1.3%) 17(1.8%)	12(0.7%) 36(1.3%)	7(0.8%) 19(1.4%)	22(0.9%) 40(1%)	8(1%) 21(0.8%)	28(1.1%) 72(0.9%)
- **COPD N (%)**	2001-2010 2011-2020	57(4.8%) **132(4.2%)**	142(4%) **283(3%)**	**130(21.8%)** **188(20.2%)**	**157(9.1%)** **197(7.1%)**	84(10.2%) 108(7.9%)	269(11.1%) 316(7.8%)	56(6.8%) **178(6.9%)**	164(6.7%) **409(5.3%)**

- **Asthma N (%)**	2001-2010	130(11%)	320(9.1%)	**88(14.8%)**	**160(9.3%)**	92(11.2%)	236(9.7%)	**102(12.4%)**	**225(9.2%)**
	2011-2020	**380(12.1%)**	**827(8.8%)**	110(11.8%)	294(10.6%)	**165(12.1%)**	**353(8.7%)**	**310(12.1%)**	**742(9.6%)**
Digestive disease N (%)	2001-2010	50(4.2%)	145(4.1%)	**67(11.2%)**	**112(6.5%)**	55(6.7%)	163(6.7%)	44(5.4%)	145(5.9%)
	2011-2020	**103(3.3%)**	**230(2.4%)**	**66(7.1%)**	**101(3.6%)**	70(5.1%)	181(4.4%)	112(4.4%)	289(3.8%)
Diabetes mellitus N (%)	2001-2010	**130(11%)**	**302(8.6%)**	84(14.1%)	200(11.6%)	**121(14.7%)**	**271(11.2%)**	103(12.5%)	266(10.9%)
	2011-2020	**529(16.8%)**	**922(9.8%)**	**177(19%)**	**414(14.9%)**	232(17%)	632(15.5%)	**557(21.7%)**	**930(12.1%)**
Depression N (%)	2001-2010	**194(16.4%)**	**486(13.8%)**	74(12.4%)	166(9.6%)	78(9.5%)	201(8.3%)	104(12.7%)	255(10.5%)
	2011-2020	**443(14.1%)**	**1073(11.4%)**	**133(14.3%)**	**297(10.7%)**	105(7.7%)	264(6.5%)	**320(12.4%)**	**819(10.7%)**
Osteoporosis N (%)	2001-2010	58(4.9%)	173(4.9%)	24(4%)	46(2.7%)	19(2.3%)	39(1.6%)	35(4.3%)	122(5%)
	2011-2020	139(4.4%)	376(4%)	43(4.6%)	111(4%)	28(2.1%)	59(1.4%)	**130(5.1%)**	**295(3.8%)**

Statistically significant values are indicated in bold

N, number; SD, standard deviation; IQR, interquartile range

Table 3 – Patients at risk 1,3 and 5-year prevalence of the considered comorbidity types in patients with cancer diagnosis and controls (diagnosis 2011-2020)

	PATIENTS AT RISK		**INDIDENCE AFTER 1 YEAR**			**INCIDENCE AFTER 3 YEARS**			**INCIDENCE AFTER 5 YEARS**		
TYPE OF COMORBIDITY	PATIENTS	CONTROLS	PATIENTS	CONTROLS	RR [CI]	PATIENTS	CONTROLS	RR [CI]	PATIENTS	CONTROLS	RR [CI]
BREAST CANCER											
Malignancies N (%)	2562	8871	30	48	2.16 [1.37, 3.41]	98	143	2.37 [1.84, 3.06]	873	294	10.28 [9.08, 11.65]
Ischemic heart disease N (%)	2972	9032	2	21	0.29 [0.07, 1.23]	14	65	0.65 [0.37, 1.16]	26	108	0.73 [0.48, 1.12]
Structural heart disease N (%)	3071	9260	1	5	0.6 [0.07, 5.16]	5	21	0.72 [0.27, 1.9]	14	39	1.08 [0.59, 1.99]
Heart failure N (%)	3104	9320	6	9	2 [0.71, 5.62]	17	41	1.24 [0.71, 2.19]	26	71	1.1 [0.7, 1.72]
Arrhythmias N (%)	3008	9096	5	14	1.08 [0.39, 3]	23	55	1.26 [0.78, 2.05]	50	98	1.54 [1.1, 2.16]
Hypertension N (%)	2460	7818	21	60	1.11 [0.68, 1.82]	87	220	1.26 [0.98, 1.6]	125	388	1.02 [0.84, 1.25]
Cerebrovascular disease N (%)	3030	9170	2	9	0.67 [0.15, 3.11]	14	40	1.06 [0.58, 1.94]	19	69	0.83 [0.5, 1.38]
Peripheral vascular disease N (%)	2942	8927	14	13	3.27 [1.54, 6.94]	41	61	2.04 [1.38, 3.02]	57	109	1.59 [1.15, 2.18]
Lung disease N (%)											
- Pulmonary embolism N (%)	3119	9342	2	2	3 [0.42, 21.25]	14	9	4.66 [2.02, 10.75]	16	17	2.82 [1.43, 5.57]
- COPD N (%)	3013	9127	7	8	2.65 [0.96, 7.3]	15	42	1.08 [0.6, 1.95]	25	79	0.96 [0.61, 1.5]
- Asthma N (%)	2765	8583	14	34	1.28 [0.69, 2.38]	39	117	1.03 [0.72, 1.48]	69	212	1.01 [0.77, 1.32]

Digestive disease N(%)	3042	9180	2	5	1.21 [0.23, 6.22]	9	17	1.6 [0.71, 3.58]	11	31	1.07 [0.54, 2.13]
Diabetes mellitus N (%)	2616	8488	12	69	0.56 [0.31, 1.04]	42	151	0.9 [0.64, 1.26]	64	224	0.93 [0.7, 1.22]
Depression N (%)	2702	8337	20	26	2.37 [1.33, 4.24]	49	108	1.4 [1, 1.96]	72	185	1.2 [0.92, 1.57]
Osteoporosis N (%)	3006	9034	17	17	3.01 [1.54, 5.88]	36	46	2.35 [1.52, 3.63]	55	86	1.92 [1.37, 2.69]
LUNG CANCER											
Malignancies N (%)	645	2437	31	31	3.78 [2.31, 6.17]	72	82	3.32 [2.45, 4.5]	91	123	2.8 [2.16, 3.61]
Ischemic heart disease N (%)	792	2547	2	9	0.71 [0.15, 3.3]	7	22	1.02 [0.44, 2.39]	12	36	1.07 [0.56, 2.05]
Structural heart disease N (%)	896	2700	1	1	3.01 [0.19, 48.11]	5	8	1.88 [0.62, 5.74]	6	16	1.13 [0.44, 2.88]
Heart failure N (%)	902	2724	2	4	1.51 [0.28, 8.23]	5	21	0.72 [0.27, 1.9]	6	30	0.6 [0.25, 1.45]
Arrhythmias N (%)	865	2585	4	11	1.09 [0.35, 3.4]	14	39	1.07 [0.59, 1.97]	19	55	1.03 [0.62, 1.73]
Hypertension N (%)	689	2070	11	25	1.32 [0.65, 2.67]	28	89	0.95 [0.62, 1.43]	39	119	0.98 [0.69, 1.4]
Cerebrovascular disease N (%)	860	2658	3	8	1.16 [0.31, 4.36]	11	20	1.7 [0.82, 3.53]	12	31	1.2 [0.62, 2.32]
Peripheral vascular disease N (%)	813	2572	3	4	2.37 [0.53, 10.58]	15	15	3.16 [1.55, 6.44]	23	23	3.16 [1.78, 5.61]
Lung disease N (%)											
- Pulmonary embolism N (%)	915	2745	6	1	18 [2.17, 149.23]	10	2	15 [3.29, 68.33]	13	2	19.5 [4.41, 86.25]
- COPD N (%)	744	2584	8	3	9.26 [2.46, 34.82]	20	18	3.86 [2.05, 7.26]	25	29	2.99 [1.76, 5.08]

- Asthma N (%)	822	2487	3	9	1.01 [0.27, 3.72]	7	28	0.76 [0.33, 1.72]	15	46	0.99 [0.55, 1.76]
Digestive disease N(%)	866	2680	1	1	3.09 [0.19, 49.41]	3	5	1.86 [0.44, 7.75]	4	8	1.55 [0.47, 5.13]
Diabetes mellitus N (%)	755	2367	4	28	0.45 [0.16, 1.27]	14	60	0.73 [0.41, 1.3]	19	77	0.77 [0.47, 1.27]
Depression N (%)	799	2484	1	3	1.04 [0.11, 9.95]	10	13	2.39 [1.05, 5.43]	13	19	2.13 [1.06, 4.29]
Osteoporosis N (%)	889	2670	2	8	0.75 [0.16, 3.53]	5	13	1.16 [0.41, 3.23]	11	20	1.65 [0.79, 3.43]
COLON CANCER											
Malignancies N (%)	2039	6908	35	52	2.28 [1.49, 3.49]	118	136	2.94 [2.31, 3.74]	163	236	2.34 [1.93, 2.84]
Ischemic heart disease N (%)	2316	7136	2	17	0.36 [0.08, 1.57]	21	62	1.04 [0.64, 1.71]	38	106	1.1 [0.76, 1.6]
Structural heart disease N (%)	2486	7515	1	6	0.5 [0.06, 4.18]	10	25	1.21 [0.58, 2.51]	13	48	0.82 [0.44, 1.51]
Heart failure N (%)	2515	7570	9	6	4.51 [1.61, 12.67]	24	45	1.61 [0.98, 2.63]	35	88	1.2 [0.81, 1.77]
Arrhythmias N (%)	2385	7268	5	27	0.56 [0.22, 1.46]	18	70	0.78 [0.47, 1.31]	40	116	1.05 [0.74, 1.5]
Hypertension N (%)	1823	5908	16	49	1.06 [0.6, 1.86]	58	192	0.98 [0.73, 1.31]	92	335	0.89 [0.71, 1.11]
Cerebrovascular disease N (%)	2433	7419	5	9	1.69 [0.57, 5.05]	14	38	1.12 [0.61, 2.07]	20	67	0.91 [0.55, 1.5]
Peripheral vascular disease N (%)	2363	7179	6	14	1.3 [0.5, 3.38]	31	46	2.05 [1.3, 3.22]	54	84	1.95 [1.39, 2.74]
Lung disease N (%)											
- Pulmonary embolism N (%)	2550	7618	5	1	14.94 [1.75, 127.72]	13	8	4.85 [2.01, 11.7]	19	15	3.78 [1.93, 7.44]

- COPD N (%)	2393	7281	6	12	1.52 [0.57, 4.05]	17	41	1.26 [0.72, 2.22]	28	76	1.12 [0.73, 1.72]
- Asthma N (%)	2261	6948	13	18	2.22 [1.09, 4.52]	35	64	1.68 [1.12, 2.53]	54	108	1.54 [1.11, 2.12]
Digestive disease N(%)	2459	7401	4	1	12.04 [1.35, 107.61]	5	9	1.67 [0.56, 4.98]	9	21	1.29 [0.59, 2.81]
Diabetes mellitus N (%)	2014	6760	9	58	1.29 [0.59, 2.81]	33	145	0.76 [0.53, 1.11]	56	216	0.87 [0.65, 1.16]
Depression N (%)	2251	6871	8	19	1.29 [0.56, 2.93]	27	66	1.25 [0.8, 1.95]	42	106	1.21 [0.85, 1.72]
Osteoporosis N (%)	2441	7395	3	7	1.3 [0.34, 5.02]	15	31	1.47 [0.79, 2.71]	24	56	1.3 [0.81, 2.09]
PROSTATE CANCER											
Malignancies N (%)	1110	3680	22	21	3.47 [1.92, 6.29]	67	84	2.64 [1.93, 3.62]	93	158	1.95 [1.52, 2.5]
Ischemic heart disease N (%)	1180	3584	6	13	1.4 [0.53, 3.68]	25	52	1.46 [0.91, 2.34]	34	84	1.23 [0.83, 1.82]
Structural heart disease N (%)	1303	3939	2	1	6.05 [0.55, 66.62]	12	13	2.79 [1.28, 6.1]	18	32	1.7 [0.96, 3.02]
Heart failure N (%)	1330	3963	5	4	3.72 [1, 13.85]	24	37	1.93 [1.16, 3.22]	34	76	1.33 [0.89, 1.99]
Arrhythmias N (%)	1217	3718	3	12	0.76 [0.22, 2.7]	24	71	1.03 [0.65, 1.63]	44	121	1.11 [0.79, 1.56]
Hypertension N (%)	913	2966	13	39	1.08 [0.58, 2.02]	63	181	1.13 [0.86, 1.49]	101	284	1.16 [0.93, 1.43]
Cerebrovascular disease N (%)	1255	3860	4	5	2.46 [0.66, 9.15]	13	36	1.11 [0.59, 2.09]	21	58	1.11 [0.68, 1.83]
Peripheral vascular disease N (%)	1240	3798	6	7	2.63 [0.88, 7.8]	25	37	2.07 [1.25, 3.42]	36	63	1.75 [1.17, 2.62]

Lung disease N (%)											
- Pulmonary embolism N (%)	1343	4030	0	3	0 [0, Inf]	8	10	2.4 [0.95, 6.07]	13	16	2.44 [1.18, 5.06]
- COPD N (%)	1254	3754	4	11	1.09 [0.35, 3.41]	14	43	0.97 [0.54, 1.78]	24	79	0.91 [0.58, 1.43]
- Asthma N (%)	1197	3717	8	18	1.38 [0.6, 3.17]	17	50	1.06 [0.61, 1.82]	30	83	1.12 [0.74, 1.7]
Digestive disease N(%)	1292	3889	2	2	3.01 [0.42, 21.35]	5	10	1.51 [0.52, 4.4]	8	20	1.2 [0.53, 2.73]
Diabetes mellitus N (%)	1130	3438	7	19	1.12 [0.47, 2.66]	30	78	1.17 [0.77, 1.77]	49	126	1.18 [0.86, 1.63]
Depression N (%)	1257	3806	5	7	2.16 [0.69, 6.8]	20	44	1.27 [0.73, 2.19]	28	64	1.32 [0.85, 2.06]
Osteoporosis N (%)	1334	4011	1	3	1 [0.1, 9.63]	7	10	2.1 [0.8, 5.52]	9	17	1.59 [0.71, 3.56]

Figure 1 *– Relative risk of the considered comorbidity types in breast cancer patients, after 3 and 5 years, for time period 2001-2010 and 2011-2020*

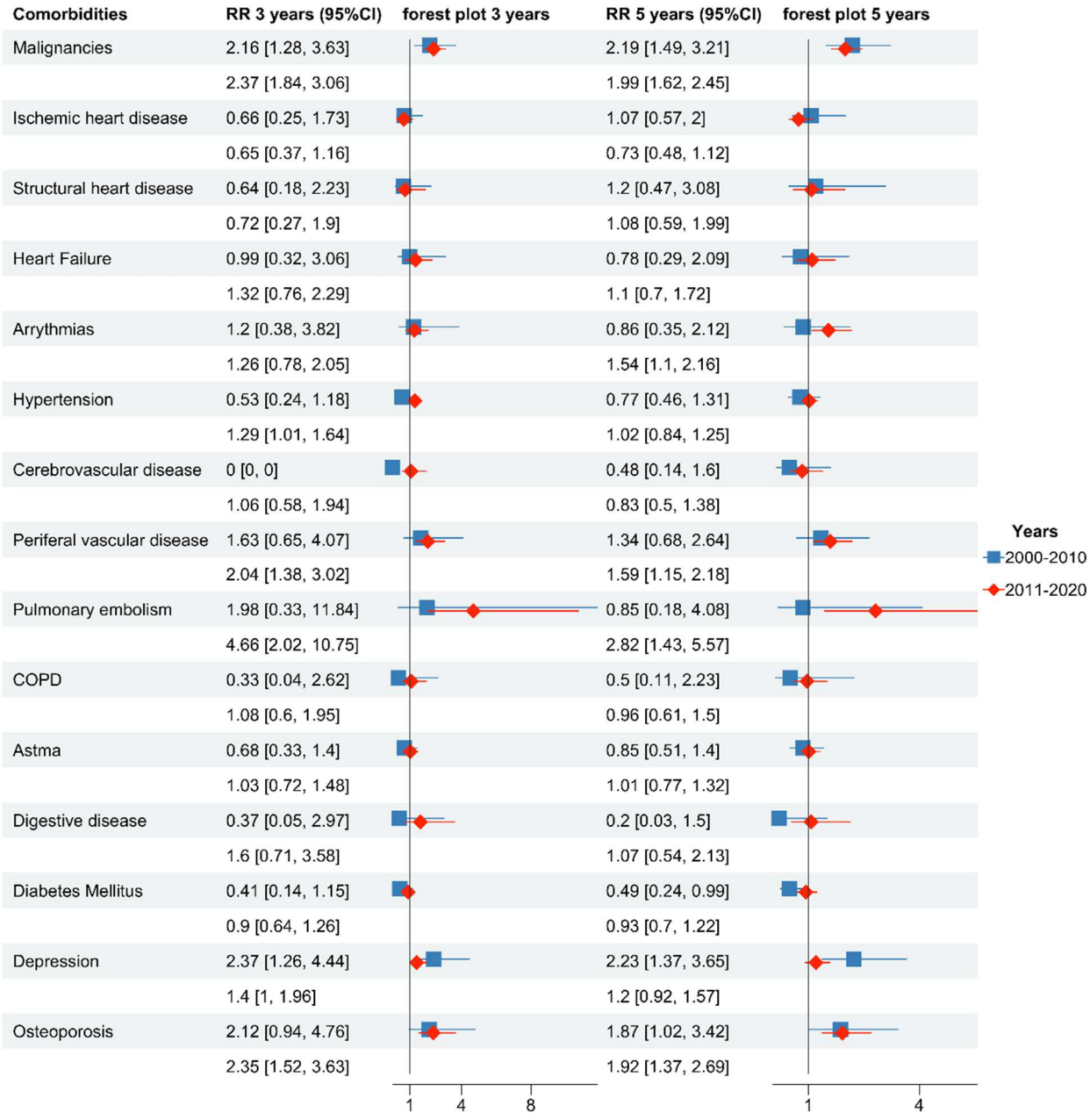

Figure 2 *– Relative risk of the considered comorbidity types in lung cancer patients, after 3 and 5 years, for time period 2001-2010 and 2011-2020*

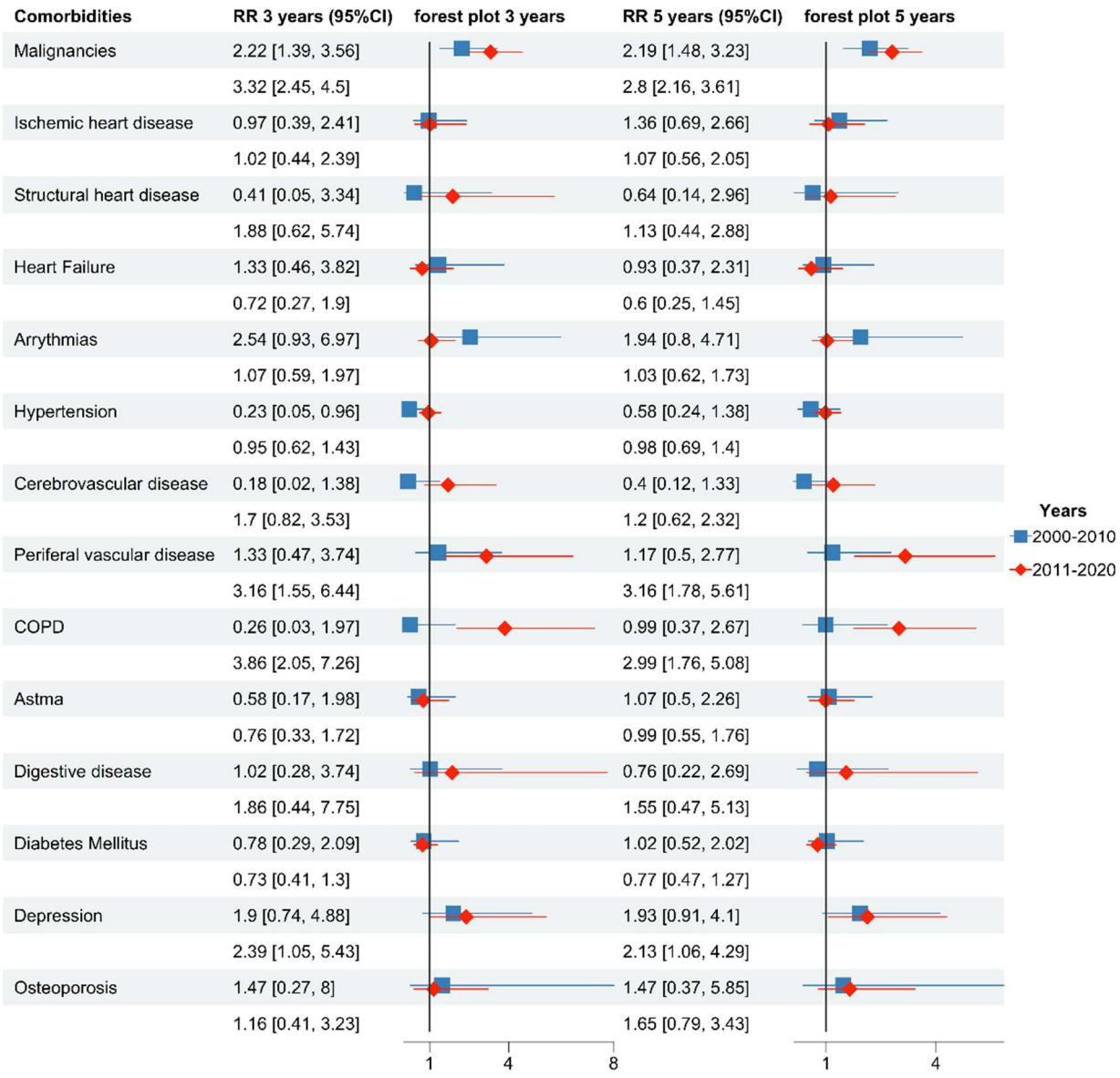

Figure 3 *– Relative risk of the considered comorbidity types in prostate cancer patients, after 3 and 5 years, for time period 2001-2010 and 2011-2020*

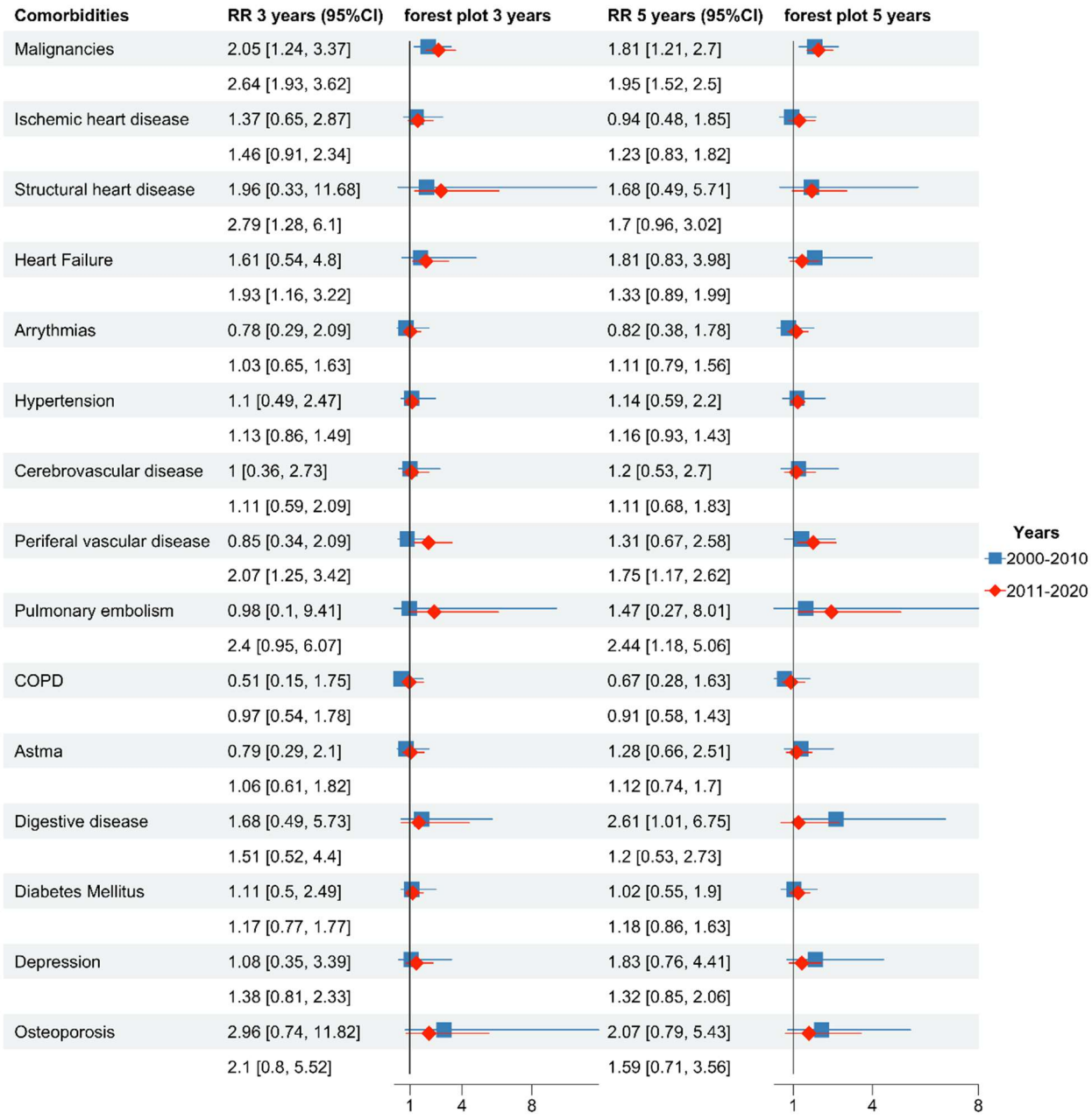

Figure 4 *– Relative risk of the considered comorbidity types in colon cancer patients, after 3 and 5 years, for time period 2001-2010 and 2011-2020*

