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Double trouble? – The dual impact of cancer and diabetes on patient reported outcomes and mortality

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CHAPTER 1

GENERAL INTRODUCTION

Cancer and diabetes

Nowadays, the mean age of the population and life expectancy are rapidly increasing. The percentage of people aged ≥65 years old is expected to rise from 15% in 2000 to 24% in 2030 in European countries[1]. This trend results in a growing burden of chronic diseases in many countries. A recent study showed for example, that in the Netherlands, 34% of general practice patients had at least 1 chronic disease while 13% was diagnosed with ≥2 chronic diseases[2]. Among the elderly aged ≥75 years this prevalence was even higher, with 84% having at least 1 and 59% having ≥2 chronic diseases[2]. Both cancer and diabetes belong to the most common chronic diseases, and in 2008 they accounted for 7.6 million and 1.3 million deaths worldwide, respectively[3].

Cancer is characterized by abnormal cell growth and division. Instead of dying, cancer cells grow out of control, and form new abnormal cells. These cancer cells have the potential to invade nearby normal tissue and metastasize to other body parts after the cancer cells get into the bloodstream. The most common ways to treat cancer are surgery, chemotherapy, and radiation therapy. Cancer can present itself in over 100 subtypes named after their anatomical origin. In 2014, a total of 104.000 people were diagnosed with cancer, this was an increase of 2% as compared to the year before[4]. The cancer types with the highest incidence include skin cancer, colorectal cancer, breast cancer, lung cancer, and prostate cancer with 15.339, 15.003, 14.631, 11.910, and 9.926 incident cases in 2014, respectively[4]. In this thesis, the main focus will be on colorectal cancer and breast cancer.

Diabetes mellitus, further referred to as diabetes, is a chronic metabolic disorder. Diabetes that is undertreated or untreated is characterized by chronic hyperglycemia (i.e. elevated blood glucose levels)[5]. Hyperglycemia is usually accompanied by symptoms of polyuria, polydipsia, and blurred vision, and can cause more severe complications on the long-term, including loss of vision, renal failure, neuropathy, sexual dysfunction, and cardiovascular disease[5]. Two types of diabetes can be distinguished, type 1 is the least common and accounts for 5-10% of all cases while type 2 diabetes is prevalent in >90% of all cases. Type 1 diabetes generally develops during childhood or adolescence, and is characterized by the damage and destruction of the beta cells as result of an auto-immune response. This leads to absolute insulin deficiency. In type 2 diabetes, there is a relative insulin deficiency as a result of both insulin resistance of bodily tissues and insulin deficiency resulting from beta-cell dysfunction. This type of diabetes often develops at older age, and mainly results from poor lifestyle habits (i.e. overweight/obesity and lack of physical activity)[5]. In the Netherlands, after diabetes is diagnosed, patients are firstly encouraged to improve the quality of their diet, lose weight, and engage more in physical activity. If lifestyle education does not result in improved blood glucose levels, treatment with oral glucose lowering drugs (GLDs) is initiated. Since 2006, metformin is used as a first line treatment, however, if blood glucose levels are poorly controlled metformin is substituted or other agents, such as sulphonylurea derivatives, other GLDs, and eventually insulin, are added[6].

The burden of cancer and diabetes

The number of cancer survivors is increasing due to aging of the population and declining mortality rates as a result of earlier cancer detection and better treatment. In the Netherlands, the 10-year prevalence of cancer patients or survivors (i.e. all people diagnosed with cancer in the past 10 years and still alive at index date) is expected to increase drastically from 420.000 men and women in 2009 to 660.000 men and women in 2020[7]. Similarly, the number of diabetes patients in the Netherlands is expected to nearly double from 740.000 in 2007 to 1.3 million in 2025[8].

Due to the increased prevalence of both cancer and diabetes, these diseases often occur together. Additionally, recent meta-analyses reported that some cancers develop more often among diabetes patients. Diabetes has been strongly associated with a higher risk of developing liver[9], pancreatic[10], and endometrial cancer[11] with hazard ratios ranging between 1.82 and 2.50. Similarly, although less strong, associations between diabetes and a 20-40% increased risk of breast[12], colorectal[13], bladder[14], non-Hodgkin's lymphoma[15], and kidney cancer[16] have been observed. In contrast, prostate cancer risk has been reported to be 15% lower in men with diabetes[17]. As diabetes is associated with increased cancer risk, the number of patients living with both cancer and diabetes is bound to increase. In a report published by the Dutch Cancer Society, the number of cancer patients with diabetes at diagnosis was expected to double from 5.500 patients in 2000 to 10.000 patients in 2015[18]. Other research shows that comorbidity, including the prevalence of diabetes, increases with age, but remains stable or decreases after the age of 80 years[19]. Data from the Netherlands Cancer Registry shows that on January 1, 2015 already 20% of colorectal and breast cancer patients aged between 75 and 85 years had diabetes at cancer diagnosis (Figure 1).

Proposed mechanisms on the association between cancer and diabetes

Although the exact mechanisms underlying the associations between cancer and diabetes are largely unknown, several mechanisms were proposed in literature. Cancer and diabetes share several risk factors that might be common denominators, and thus (partly) explain the association between both diseases. Besides non-modifiable risk factors such as older age and race/ethnicity, cancer and diabetes share several modifiable risk factors including obesity, smoking, physical inactivity, excessive alcohol use, and poor dietary habits[20]. The combination of both these non-modifiable and modifiable risk factors increases the likelihood for an individual with diabetes to develop cancer and vice versa. Also, several biological mechanisms for the association between diabetes and cancer risk have been proposed[20,21]. The leading hypothesis is that hyperinsulinemia (i.e.

elevated blood insulin levels) promotes tumor cell growth through direct and indirect pathways. In an early stage of diabetes, the pancreas increases the secretion of insulin to compensate for the decreased insulin sensitivity in the body tissue, which results in hyperinsulinemia. The majority of tumor cells express insulin and insulin-like growth factor 1 (IGF-1) receptors on their surface. Insulin can bind to insulin receptors on the tumor cells which may result in direct cell growth promotion[22]. In addition, hyperinsulinemia can indirectly promote cell growth as insulin reduces the hepatic production of IGF binding proteins, and thereby increasing active IGF-1 levels[23]. Subsequently, IGF-1 could act, after binding to the IGF-1 receptor, as a growth stimulus for the tumor cells and increase tumor growth, invasion, and metastasis[24].

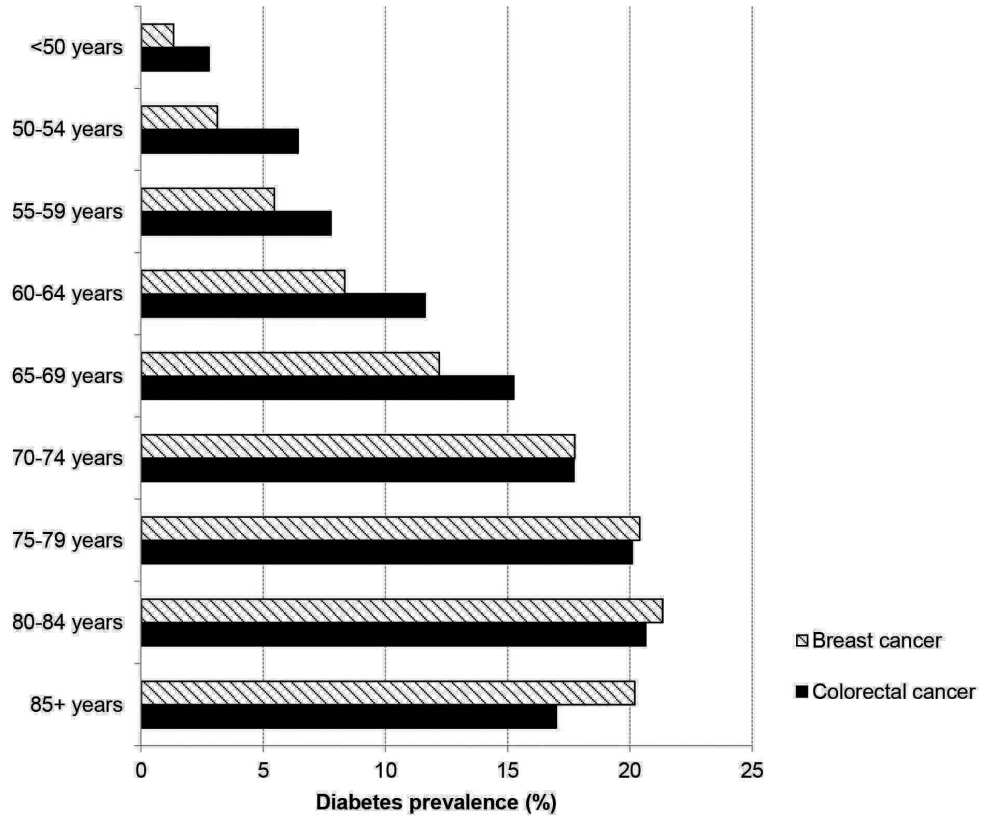

Figure 1 The prevalence of diabetes among colorectal cancer patients and breast cancer patients at January 1, 2015, stratified by age categories.
Datasource: South region of the Netherlands Cancer Registry

The dual impact of cancer and diabetes on patient reported outcomes

Previous research regarding the association between cancer and diabetes mainly focused on the impact of diabetes on cancer incidence and mortality, while less attention has been paid to the impact of having both diseases on Patient Reported Outcomes (PROs). These patient perspectives have become important outcome measures to evaluate the impact of a disease and its treatment on a patient's life, and are increasingly incorporated in guidelines for research and policy[25,26]. PROs is used as an umbrella term and include a wide range of measures, for example Health-Related Quality of Life (HRQoL), symptoms, and satisfaction with health-care.

Up to now, studies that have investigated the dual impact of cancer and diabetes on PROs mainly focused on HRQoL[27-31]. HRQoL is a multidimensional construct, which reflects patient's perceptions of their physical, emotional, social and cognitive function, and disease and treatment-related symptoms. All previous studies[27-30], but one longitudinal study[31], suggest that having both cancer and diabetes results in poorer HRQoL. However, due to the limited evidence, the different study populations (which are mainly confined to prostate cancer patients), the predominantly cross-sectional study designs, and the different HRQoL measurements used, no strong conclusions can be drawn. Moreover, other important outcomes which are highly prevalent among people with both cancer and diabetes, such as neuropathic symptoms[32,33] and sexual dysfunction[34-36], need further attention.

Both cancer and diabetes independently negatively affect PROs, however, it is unclear whether having both diseases results in even worse outcomes than the sum of their individual effects (i.e. 1+1=3). When we know which factors explain the possible worse outcomes among patients with both diseases, this might enhance further research in developing interventions to improve outcomes. Moreover, it might aid clinicians in their decisions regarding treatment types to prevent side-effects, symptoms, and complications that have a significant impact on a person's daily life. Thus, more research is needed to determine the effects of having both cancer and diabetes on PROs. This was recently underlined in a review that described the current evidence on the association between cancer and diabetes[37]. The authors identified gaps in literature and stated that future studies should address the hypothesis that cancer patients with diabetes have reduced HRQoL, and additionally, the influence of lifestyle and PROs on this association need to be elucidated[37].

The dual impact of cancer and diabetes on mortality

A meta-analysis that included 23 studies showed that cancer patients with diabetes at diagnosis have about a 40% higher mortality risk as compared with cancer patients

without diabetes[38]. A higher mortality was mainly found among patients with diabetes and endometrial (HR=1.76; 95%CI:1.34-2.31), breast (HR=1.61; 95%CI: 1.46-1.78) or colorectal (HR=1.32; 95%CI:1.24-1.41) cancer as compared to those without diabetes[38]. The exact mechanism underlying this increased mortality is unknown. However, a review published in 2011 identified several methodological key points that should be taken into account regarding the association between diabetes and mortality in cancer patients[39]. Research, particularly among breast cancer patients, shows that patients with diabetes present with more advanced cancer stage at diagnosis[40]. This might be a consequence of lower screening uptake in cancer patients with versus without diabetes[41]. Another possible explanation for the higher mortality among cancer patients with diabetes lies within the received cancer treatment. A study conducted in the Netherlands showed that esophageal, colon, breast, and ovary cancer patients with diabetes at cancer diagnosis were treated less aggressively as compared to those without diabetes[42].

Besides clinical factors, modifiable lifestyle factors also might play a role in the higher mortality rates observed among patients with both diseases. Physical inactivity, underweight or obesity, smoking, and excessive alcohol use have all been associated with increased mortality among both cancer and diabetes patients[43-50]. However, in a meta-analysis that assessed the association between preexisting diabetes and mortality among colorectal cancer patients only 12 of the 21 included studies adjusted for lifestyle behaviors[51]. Therefore, as cancer patients with diabetes might have an even worse lifestyle than cancer patients without diabetes, the influence of lifestyle on the increased mortality in patients with both diseases needs to be studied further.

Glucose lowering drugs and mortality among cancer patients

Research regarding the link between cancer and diabetes was initiated at least 100 years ago[52] but at that time the topic did not reach mainstream interest. However, major interest for the link between cancer and diabetes was raised in 2005 after a study was published that showed that treatment with metformin, used as primary treatment in diabetes, was associated with lower cancer incidence[53]. Moreover, the simultaneous publication of four studies in a prominent scientific journal raised the question of a possible association between use of insulin glargine, a long-acting insulin analogue, and increased cancer risk[54-57]. These results led to major focus on the potential effects of GLDs, mainly metformin, on cancer incidence as well as on mortality. Several of the studies that followed presented exceptionally strong protective effects of metformin on mortality among cancer patients[58-61]. However, these observational studies had several methodological limitations. Studies that assessed the association between GLD use and mortality among cancer patients, often classified patients as GLD user at time of cancer diagnosis and not from the actual drug initiation onwards. This classification may have induced immortal time bias as patients cannot die in the period prior to drug initiation, introducing a period of immortal time[62]. In addition, several studies mainly focused on metformin use versus non-use, whereas diabetes patients often switch between different

GLDs or use a combination of GLDs. Finally, earlier studies often did not assess dose-response associations. Thus to gain insight in the association between GLD use, including metformin, and mortality among cancer patients there is a need for well-designed large observational studies that account for immortal time bias and test for dose-response associations.

Aims and outline of the thesis

Thus, following the results of previous studies, the association between cancer and diabetes is complex, and several knowledge gaps were identified. Even though 1 in 5 cancer patients presents with diabetes at cancer diagnosis, there is a considerable gap in our knowledge on the impact of both cancer and its treatment, and diabetes on PROs. Moreover, it is still unclear which factors underlie the increased mortality found among cancer patients with as compared to cancer patients without diabetes. Therefore, this thesis aimed to assess the dual impact of cancer and diabetes on PROs (Part I) and mortality (Part II). The main objectives of this thesis were:

- To assess the impact of comorbidity, with a main focus on cancer and diabetes, on PROs, including HRQoL and symptoms (Part I)
- To assess the impact of cancer and diabetes, and the role of lifestyle factors, on mortality (Part II)
- To assess the effect of glucose lowering drug use on mortality among breast cancer patients (Part II)

Based on the current literature, we hypothesize that cancer patients with diabetes have poorer outcomes, both regarding PROs and mortality.

The current literature on the effect of cancer and diabetes on PROs is limited, and therefore, in **Part I** we first systematically reviewed the scientific literature regarding the dual impact of cancer and diabetes on PROs (**Chapter 2**). In this chapter, we additionally identified gaps in current literature and proposed a research agenda for further research. In **Chapter 3-7**, PROs were studied among cancer patients. For these studies, clinical data was retrieved from the Netherlands Cancer Registry (NCR) and linked to longitudinal data on PROs collected by the web-based Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) registry[63]. First, we described the variance in HRQoL explained by comorbidity in comparison with sociodemographic and clinical characteristics among thyroid, colorectal cancer and (non)-Hodgkin's lymphoma patients in **Chapter 3**. Moreover, we assessed the effect of individual comorbidities on HRQoL. Subsequently we studied the individual and combined effect of cancer and diabetes on HRQoL (**Chapter 4**). For this study a sample including colorectal cancer patients with and without diabetes, and a normative sample with and without diabetes was used. As the prevalence of neuropathic symptoms among cancer as well as diabetes patients is high and little is known about the prevalence of these symptoms among patients with both diseases, we assessed the difference in neuropathic symptoms between colorectal cancer patients with and without diabetes in

Chapter 5. As previous studies reported that cancer patients with versus without diabetes might be less aggressively treated, we additionally assessed whether the type of received cancer treatment differed between both groups. Finally, we studied the difference in HRQoL between colorectal cancer patients with and without diabetes prospectively in **Chapter 6**. Moreover, as cancer and diabetes share several lifestyle-related risk factors which are independently associated with worse HRQoL, we additionally assessed the role of lifestyle on HRQoL among both groups.

In **Part II** we assessed the dual impact of cancer and diabetes on mortality. Literature shows that mortality among cancer patients with versus without diabetes is about 40% higher but often lifestyle factors are not taken into account. As lifestyle factors are independently associated with mortality, we aimed to assess whether lifestyle factors could explain the increased mortality found among colorectal cancer patients with versus without diabetes (**Chapter 7**). In the following two chapters of this thesis we focused on the effect of GLDs on the prognosis of breast cancer patients in response to recent literature on the promising protective effect of metformin on mortality among cancer patients. We conducted complex time-varying analyses to account for methodological restrictions in previous studies, and assessed the effect of GLD use on mortality among breast cancer patients with type 2 diabetes using data from the United Kingdom (UK) in **Chapter 8**. As we had no (complete) data regarding breast cancer stage and receptor status in the UK sample, we conducted similar analyses in a Dutch sample where this information was available (**Chapter 9**). For this study, clinical data from the NCR was linked to the PHARMO database network which contains data on drug dispensions from out-patient pharmacies in the Netherlands[64]. Finally, a summary of the main findings, methodological considerations, and implications of the results presentend in this thesis were described in the general discussion (**Chapter 10**).

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PART I

THE IMPACT OF CANCER AND DIABETES ON PATIENT REPORTED OUTCOMES

CHAPTER 2

THE IMPACT OF HAVING BOTH CANCER AND DIABETES ON PATIENT REPORTED OUTCOMES: A SYSTEMATIC REVIEW AND DIRECTIONS FOR FUTURE RESEARCH

Abstract

Purpose
This systematic review aims to summarize the current literature regarding potential effects of having both cancer and diabetes on Patient Reported Outcomes (PROs) and to provide directions for future research.

Methods
MEDLINE, The Cochrane Library, CINAHL and PsycINFO were searched from inception to January 2015. All English, peer-reviewed studies that included patients with both cancer and diabetes and assessed PROs, were included. All included studies were independently assessed on methodological quality by two investigators.

Results
Of the 3,553 identified studies, 10 studies were included and all were considered of high (40%) or adequate (60%) methodological quality. Eight of the 10 studies focused on Health-Related Quality of Life (HRQoL), functioning or symptoms and 2 studies assessed diabetes self-management. Overall, HRQoL and functioning was lower, and symptoms were higher among patients with both cancer and diabetes as compared to having cancer or diabetes alone. Furthermore, one study reported that diabetes self-management was impaired after chemotherapy.

Conclusions
Having both cancer and diabetes resulted in worse PROs compared to having either one of the diseases, however, the considerable heterogeneity of the included studies hampered strong conclusions. Future studies are needed as this research area is largely neglected. As the majority of the included studies focused on HRQoL, future research should address the impact of both diseases on other PROs such as depression, patient empowerment and self-management.

Introduction

Due to the increased aging of the population, early detection, and better treatment of diseases, the number of cancer survivors is increasing[1]. As a result, more and more cancer survivors live with other chronic diseases of which diabetes is one of the most prevalent[2]. The prevalence of concurrent diabetes among cancer patients depends on cancer type, gender, and age at diagnosis, and varies from 8% among prostate cancer patients to approximately 26% among pancreas cancer patients aged 65 years or older[2]. This high prevalence of diabetes among cancer patients results in worse outcomes and increases the burden on health systems worldwide.

The link between cancer and diabetes is extensively studied in recent literature and is mainly focused on the impact of diabetes on cancer incidence and mortality. Recent meta-analyses show that diabetes is strongly associated with the development of pancreatic (OR=1.82, 95%CI:1.66-1.89)[3], liver (OR=2.50, 95%CI:1.80-3.50)[4], and endometrial cancer (RR=2.10, 95%CI:1.75-2.53)[5]. Moderate, positive associations have been reported for diabetes and breast (RR=1.20, 95%CI:1.12-1.28)[6], colorectal (RR=1.26, 95%CI:1.05-1.50)[7] and bladder (RR=1.24, 95%CI:1.08-1.42)[8] cancer incidence, while diabetes has been associated with a decreased incidence of prostate cancer (RR=0.84, 95%CI:0.76-0.93)[9]. Furthermore, previous research shows that having diabetes is associated with a 30-40% increased mortality risk among cancer patients, which was mainly apparent among breast, endometrial, and colorectal cancer patients[10,11].

As the group of patients with both cancer and diabetes is growing, patients' experience of living with both diseases is becoming more important. However, this research area is largely neglected. Patient Reported Outcome (PRO) assessments such as Health-Related Quality of Life (HRQoL), functioning and symptoms are needed as it is plausible that patients with multiple chronic diseases experience more problems. This knowledge is essential to improve clinical practice and care for this growing group of patients.

A significant number of cancer survivors consistently report lower physical functioning, sexual functioning, and more symptoms of distress and fatigue[12,13]. Similarly, diabetes patients are more likely to suffer from depression[14], report a lower quality of life[15] and lower sexual functioning[16]. As both cancer and diabetes patients report deteriorated PROs compared to people without the disease, we hypothesize that having both chronic diseases will result in even more deteriorated PROs. The aim of this systematic literature review is to summarize the current knowledge on the impact of having both cancer and diabetes on PROs. In addition, as we expect that this research area will be largely neglected, we also aim to provide directions for future research.

Methods

Search strategy

LF conducted the systematic literature search on August 2013 and updated the search on January 2015. The following databases were included: MEDLINE, The Cochrane Library, CINAHL and PsycINFO. Subject headings and free text terms for diabetes (i.e. diabet* OR diabetes mellitus) were combined with search terms for cancer (i.e. cancer* OR neoplasm* OR oncolog*). As PROs cover a wide range of different aspects, we did not include any search terms for PROs to avoid missing relevant papers. The full search strategy is shown in Appendix A (page 40). After the search was conducted the cited references of the selected studies were searched using Web of Science and their references lists checked; in addition, PubMed Related Articles were used for the two most recent included studies to identify studies that were not found with the initial literature search.

Selection criteria

All retrieved studies (including abstracts of unpublished studies) were screened and studies that met the following four selection criteria were included: (1) the study is focused on patients with both cancer and diabetes, (2) PRO is primary or secondary outcome measure of the study, (3) is published in a peer-reviewed journal, and (4) is published in English. Studies that assessed the effects of several chronic or comorbid diseases, including diabetes, among cancer patients on PROs were not included as the studies should have a primary focus on both cancer and diabetes. Similarly, studies that aimed to address comorbid or chronic diseases, including cancer, among diabetes patients were excluded.

Quality assessment

Each selected study was independently scored on methodological quality by 2 reviewers (PV and MT) based on a set of 14 quality criteria (Table 1). These quality criteria were based on established criteria lists used in previous studies[17,18]. Disagreements between the reviewers on the quality criteria were resolved during a consensus meeting. All studies received 1 point for each of the 14 quality criteria that was met. If a criterion was not met or described insufficiently, 0 point was assigned. Thus, each study can obtain a maximum score of 14 points. Studies that scored 75% or more of the maximum attainable score (i.e. ≥11 points) were considered as 'high quality study', studies scoring between 50-75% (i.e. 7-10 points) were considered of 'adequate quality', while those scoring <50% (i.e. ≤6 points) were considered of 'low quality'. These criteria were arbitrarily chosen and based on previous research[17].

Table 1 List of criteria for assessing the methodological quality of studies on patient reported outcomes among patients with cancer and diabetes

Positive if with respect to		Number of studies that scored positive
Patient Reported Outcomes		N (%)
	1. Examining PROs was a primary objective of the study	10 (100)
	2. A validated questionnaire to measure PROs was used	10 (100)
Study population		
	3. The patient sampling process is described	10 (100)
	4. A (healthy) normative sample is included for comparison	3 (30)
	5. Patients with both cancer and diabetes are compared to either patients with only cancer or only diabetes on at least two sociodemographic variables	8 (80)
	6. A description is included of at least two clinical variables regarding cancer diagnosis (e.g. cancer stage, treatment, time since cancer diagnosis)	8 (80)
	7. A description is included of at least two clinical variables regarding diabetes diagnosis or severity (e.g. HbA1c levels, treatment, time since diabetes diagnosis)	3 (30)
	8. Inclusion and/or exclusion criteria are described	9 (90)
	9. Participation rates for patient groups are described and these are >75%	4 (40)
	10. Information is given regarding differences in demographic and/or clinical characteristics of respondents versus non-respondents	3 (30)
Study design		
	11. The study sample includes at least 75 patients (arbitrarily chosen)	8 (80)
	12. The process of data collection is described	8 (80)
	13. The difference in the outcome variable between cancer patients with diabetes and patients with only cancer and/or only diabetes is assessed in multivariable models, including at least 2 covariates	8 (80)
Results		
	14. Mean, median, standard deviations or percentages are reported and compared between cancer patients with diabetes and patients with only cancer and/or only diabetes for the most important outcome measures	8 (80)

Results

Description of the included studies

The initial broad search strategy on cancer and diabetes, that did not include a term for 'PROs', yielded 3,553 hits, and after the removal of duplicates and the application of selection criteria a total of 10 studies were included in this study, of which 2 were based on the same data[19,20] (Figure 1). Eight of the included studies had a sample size of at least 590 participants while 2 studies, based on the same data, included 43 patients[19,20] (Table 2). The number of patients with both cancer and diabetes was rather low; 5 studies included less than 100 patients with both diseases[19 -23]. Moreover, only 4, of which 3 unique, studies had a longitudinal design[19,20,24,25], while the other 6 studies addressed the associations between cancer and diabetes and PROs cross-sectionally[21-23,26-28]. Most

studies focused on patients with specific cancer types including patients with diabetes and prostate [22-25], colorectal [27,28], or breast cancer[23]. Five studies included cancer patients with diabetes (CA+DM+) and made a comparison with cancer patients without diabetes (CA+DM-)[21,22,24,25,28], one study compared CA+DM+ patients with patients with diabetes only (CA-DM+)[23] and two studies included CA+DM-, CA-DM+ and patients without both diseases (CA-DM-) for comparison[26,27]. Two studies, based on the same data, only included CA+DM+, and did not include a comparison group[19,20]. Of the 10 included studies, 8 focused on HRQoL, self-perceived health status, functioning or symptoms, while 2 studies assessed the impact of cancer and its treatment on diabetes self-management. Most studies used a validated questionnaire. The Short Form (SF)-36 was used most frequently to assess HRQoL or self-perceived health status[21,22,25], other studies used the Health Utility Index Mark 3 (HUI3)[26], the EuroQoL Group's EQ-5D[23], the Audit of Diabetes Dependent Quality of Life (ADDQoL)[23], the European Organization for Research and Treatment of Cancer core Quality of Life Questionnaire (EORTC QLQ-C30)[27], or the University of California, Los Angeles, Prostate Cancer Index (UCLA-PCI)[22,24,25]. The EORTC QLQ-Chemotherapy-Induced Peripheral Neuropathy (CIPN)-20 was used to assess neuropathic symptoms[28]. Eight out of 10 studies conducted multivariate analyses and mainly adjusted for socio-demographic[19,21,22,24-28] and cancer-related covariates[19,21,22,25,27,28], while diabetes-related covariates[19] and lifestyle factors[24,26-28] were less often adjusted for.

Study quality

The 10 included studies scored a mean quality score of 10 out of 14, and scores ranged between 7 and 13. Four studies (40%) were classified as being of high quality and 6 (60%) of adequate quality according to our quality criteria. No studies were considered of low quality. The criteria that were least often met are (#4) the inclusion of a (healthy) normative sample for comparison, (#7) a description of at least two clinical variables regarding diabetes diagnosis, and (#10) information is given regarding differences in demographic and/or clinical characteristics of respondents versus non-respondents (all met by 3 studies) (Table 1).

HRQoL, functioning and symptoms

All included studies reported worse PROs among CA+DM+ compared to CA+DM-, CA-DM+ or CA-DM- on at least 1 studied item or subscale, except for 1 longitudinal study[25]. Nine out of the 10 included studies assessed more than 1 PRO, while 1 study only included a general measure of HRQoL[26].

General HRQoL

A large cross-sectional study conducted in Canada reported lowest average HRQoL scores for CA+DM+ (n=940) followed by CA+DM- (n=1,692), CA-DM+ (n=4,394) and CA-DM- (n=107,295) patients with average HUI3 scores ranging between 0.67 and 0.89 (i.e. where -0.36=worst possible health, 0=death, and 1=perfect health)[26]. The HUI3 indirectly measures HRQoL using 8 attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain) and a mean difference of 0.03 was considered as clinically

important. Multivariable regression analyses showed similar results with a lower HRQoL for CA+DM+, CA+DM- and CA-DM+ patients as compared to CA-DM- patients with beta's of -0.10, -0.04 and -0.04, respectively, which was regarded clinically relevant[26]. Similarly, lower general health was reported in a cross-sectional study among 65 prostate cancer patients with versus 525 without diabetes with average SF36 scores of 51.9 versus 62.5, which remained significant in multivariable analyses (beta=-0.13)[22]. A longitudinal study among prostate cancer patients did observe differences between CA+DM+ and CA+DM- in general health at baseline, but after adjustments for age, marital status, educational level, income, employment status, baseline HRQoL, cancer stage, primary treatment, baseline PSA and baseline Gleason score this difference did not remain significant[25]. Other studies did not report a worse general health among those with both cancer and diabetes[23,27].

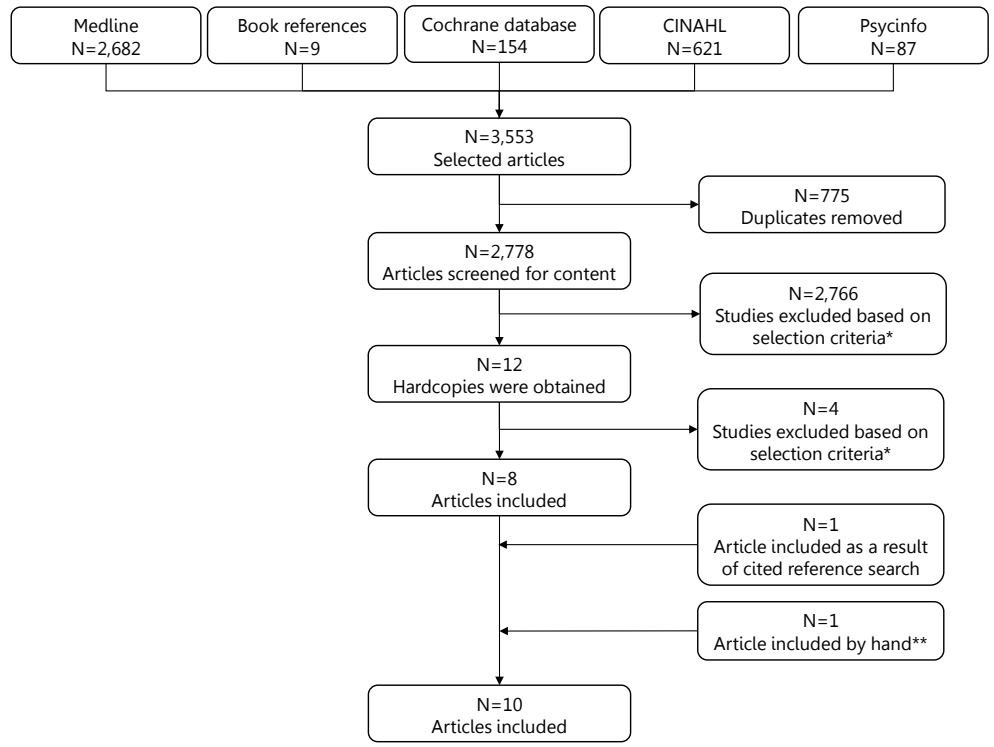

Figure 1 Flow chart of the selection process of the systematic literature search
*Selection criteria include: the study (1) includes patients with both cancer and diabetes, (2) PRO is primary or secondary outcome measure of the study, (3) is published in a peer-reviewed journal, and (4) is published in English
**Article of our own research group was accepted for publication on the 13th of January 2015 and published online on 3 February 2015

Table 2 Overview of the included studies

Study	Country	Design	Study sample		Instrument	Results	Quality score
Health-Related Quality of Life/self-perceived health/functioning							
Bowker et al. (2006)	Canada	Cross-sectional	113,587 patients with or without cancer (any type)	CA+DM+: 207 CA+DM-: 1,692 CA-DM+: 4,394 CA-DM-: 107,295	HUI3	HUI3 score: CA+DM+ vs CA-DM-: b= -0.10 (95%CI:-0.13 - -0.09), P-value<0.0001 CA-DM+ vs CA-DM-: b= -0.04 (95%CI:-0.05 - -0.04), P-value<0.0001 CA+DM- vs CA-DM-: b= -0.04 (95%CI:-0.05 - -0.03), P-value<0.0001	10
Hershey et al. (2012a)	USA	Cross-sectional	661 patients with cancer (any type)	CA+DM+: 76 CA+DM-: 585	SF36	Physical functioning: CA+DM- vs CA+DM+: b=12 (95%CI:7 - 18), P-value<0.0001	9
Latini et al. (2006)	USA	Longitudinal	1,248 prostate cancer patients	CA+DM+: 117 CA+DM-: 1,131	UCLA-PCI	Urinary function at follow-up: CA+DM+ vs CA+DM-: 72 ± 24 vs 77 ± 22, P-value=0.01	10
Mols et al. (2008)	The Netherlands	Cross-sectional	590 prostate cancer patients	CA+DM+: 65 CA+DM-: 525	SF36 UCLA-EPCI	General health: CA+DM+ vs CA+DM-: b=-0.13, P-value <0.01 Vitality: CA+DM+ vs CA+DM-: b=-0.12, P-value <0.01	13
Onitilo et al. (2013)	Australia	Cross-sectional	3,466 diabetes patients either with or without a history of breast or prostate cancer	Breast cancer: CA+DM+: 77 CA-DM+: 1,470 Prostate cancer: CA+DM+: 81 CA-DM+: 1,838	EQ-5D ADDQoL	In men with prostate cancer only: Problems with mobility: CA+DM+ vs CA-DM+: 51% vs 29%, P-value<0.001 Problems in usual activities: CA+DM+ vs CA-DM+: 35% vs 25%, P-value=0.035	11
Thong et al. (2011)	USA	Longitudinal	1,811 prostate cancer patients	CA+ and incident DM: 215 CA+ and prevalent DM: 239 CA+DM-: 1,357	SF36 Individual items on BF and SF	At baseline those with prevalent diabetes report significant lower HRQoL, but after adjustments in longitudinal analyses no differences in HRQoL between CA+DM+ and CA+DM- were observed.	10
Vissers et al. (2014)	The Netherlands	Cross-sectional	2,761 patients with or without colorectal cancer and/or diabetes	CA+DM+: 328 CA+DM-: 1,731 CA-DM+: 78 CA-DM-: 624	EORTC-QLQ-C30	Physical functioning CA+DM+ vs CA+DM-: beta=-3.8, P-value<0.01 Male sexual problems CA+DM+ vs CA+DM-: beta=9.4, P-value<0.01	12
Vissers et al. (2015)	The Netherlands	Cross-sectional	1,193 colorectal cancer patients	CA+DM+: 218 CA+DM-: 975	EORTC-QLQ-CIPN20	Neuropathic symptoms - Tingling fingers or hands CA+DM+ vs CA+DM-: OR=1.40 (95%CI:1.00-1.94) Tingling toes or feet CA+DM+ vs CA+DM-: OR=1.47 (95%CI:1.04-2.07) Numbness in toes or feet CA+DM+ vs CA+DM-: OR=1.83 (95%CI:1.28-2.62) Erection problems - males; CA+DM+ vs CA+DM-: OR=1.83 (95%CI:1.11-3.03)	11

Table 2 continues on next page

Continuation of Table 2

Study	Country	Design	Study sample	Instrument	Results	Quality score
Diabetes self-management						
Hershey et al. (2012b)	USA	Longitudinal	43 patients with a solid tumor and type I or II DM	SIC, Modified intrusiveness of illness inventory, SCI-R	Lower diabetes self-management after 8 weeks on chemotherapy as compared to baseline: 45.86 ± 2.65 vs. 50.84 ± 2.47 Higher symptom burden after 8 weeks on chemotherapy as compared to baseline: 32.57 ± 4.49 vs. 25.43 ± 3.81 Overall impact on diabetes self-management was moderate (16.47 ± 8.43, highest impact on: exercise (4.35 ± 2.36), blood sugar monitoring (3.73 ± 2.38) and ability to eat and drink (3.56 ± 2.31) Positive correlation between impact of cancer on diabetes self-management and symptom burden at 8 weeks (r=0.46, p=0.004)	7
Hershey et al. (2014)	USA	Longitudinal	43 patients with a solid tumor and type I or II DM	SIC, DCI, CIDS, OE, HADS, SCI-R	Living arrangements, years with DM, total number of medications, baseline DM self-management, DM self-efficacy and baseline and 8-week symptom severity were significant predictors of diabetes self-management.	7

ADDQoL=Audit of Diabetes Dependent Quality of Life, CIDS=Confidence In Diabetes Self-care, DCI=Diabetes Complication Index, EORTC QLQ-C30=European Organization for Research and Treatment of Cancer core Quality of Life Questionnaire, EPIC=Expanded Prostate Cancer Index Composite, EQ-5D=EuroQol Group's EQ-5D, FLIC=Functional Living Index Cancer, HADS=Hospital Anxiety and Depression Scale, HUI3=Health Utility Index Mark 3, OE=outcome expectancies, SCI-R=Self-Care Inventory Revised, SIC=Symptoms of Illness Checklist, SF-36=Short Form 36, UCLA-PCI=University of California, Los Angeles, Prostate Cancer Index

Physical functioning or mobility

Five studies included a measure of physical functioning or mobility. In a study with 76 CA+DM+ and 585 CA+DM, CA+DM+ scored on average 12 points lower on the physical functioning subscale of the SF-36 as compared to CA+DM-[21], as this difference was larger than 0.5 times the standard deviation it can be considered to be clinically relevant[29]. Similarly, a cross-sectional study found more problems with mobility and usual activities among men with prostate CA+DM+ as compared to CA-DM+, but this difference was not found among women with breast cancer[23]. Colorectal CA+DM+ reported a worse physical functioning as compared to CA+DM- (beta=-3.8)[27]. Two studies did not report lower physical functioning among CA+DM+[22,25], however, one study did report lower vitality among prostate CA+DM+ as compared to CA+DM- (beta=-0.12), which was considered a clinically relevant difference[22].

Sexual functioning

Sexual functioning was assessed in one study among colorectal CA+DM+[27] and in two studies with prostate CA+DM+[24,25]. Colorectal CA+DM+ reported more male sexual problems compared to colorectal CA+DM- (beta=9.4) in a cross-sectional study from the Netherlands[27]. Among prostate cancer patients, two longitudinal studies did not observe a significant association between comorbid diabetes and sexual functioning[24,25].

Urinary and bowel functioning

Three studies among prostate cancer CA+DM+ and CA+DM- patients also focused on prostate cancer specific symptoms, including urinary functioning and/or bowel functioning[22,24,25]. One study reported lower urinary function during follow-up among prostate CA+DM+ as compared to CA+DM- (mean score 72±24 vs 77±22)[24], but the other studies did not report differences in urinary or bowel functioning[22,25].

Neuropathic symptoms

A cross-sectional study by our research group among 218 colorectal CA+DM+ and an age- and sex-matched sample of 975 CA+DM- patients assessed differences in neuropathic symptoms[28]. CA+DM+ patients reported more neuropathic symptoms regardless of cancer treatment as compared with CA+DM- patients regarding tingling fingers or hands (OR=1.40; 95%CI:1.00-1.94), tingling toes or feet (OR=1.47 95%CI:1.04-2.07), numbness in toes or feet (OR=1.83; 95%CI:1.28-2.62) and erection problems among men (OR=1.83; 95%CI:1.11-3.03). However, the majority of reported symptoms were of mild severity.

Mental Health

CA+DM+ patients did not report worse mental health or emotional functioning compared to CA+DM- or CA-DM+ in 3 cross-sectional[21,22,27] and one longitudinal study[25]. One study included a measure of problems with anxiety, but no significant differences were found between prostate or breast CA+DM+ as compared to CA-DM+ patients in unadjusted analyses[23].

Diabetes self-management
Two studies, using the same longitudinal data, addressed problems with diabetes self-management among 43 patients with a solid tumor and type 1 or 2 diabetes[19,20]. One study showed that patients reported higher scores on symptom burden and lower scores on diabetes self-management after 8 weeks on chemotherapy as compared to baseline (mean 32.57±4.49 vs 25.43±3.81 and 45.86±2.65 vs 50.84±2.47, respectively)[20]. In addition, a moderate impact of cancer on diabetes self-management was observed, which mainly affected the ability to exercise, blood sugar monitoring, and ability to eat and drink. Moreover, in qualitative assessments many individuals indicated that they prioritized cancer care instead of diabetes care[20]. The other study mainly focused on predictors of diabetes self-management[19]. This study showed that living arrangements, years with DM, the total number of medications, baseline DM self-management, DM self-efficacy and baseline and 8-week symptom severity were significant predictors of diabetes self-management, while diabetes complications, cancer type, stage and treatment, outcome expectancies, and anxiety and depression were not[19].

Discussion

The majority of the included studies in this systematic review (i.e. 8 out of 10 studies) addressed HRQoL, self-perceived health, functioning or symptoms, and two studies, based on the same data, assessed diabetes self-management. In all included studies, CA+DM+ patients reported worse outcomes, but in 1 longitudinal study among prostate cancer patients, differences disappeared after adjustments[25]. CA+DM+ patients mainly scored lower on general HRQoL[22,26], physical functioning[21,23,27] and sexual functioning[27]. In addition, prostate CA+DM+ patients reported lower urinary functioning[24] and lower vitality[22], while colorectal CA+DM+ versus CA+DM- patients reported more neuropathic symptoms in a cross-sectional study[28]. Finally, among diabetes patients that also had concurrent cancer, symptom severity increased and diabetes self-management, mainly exercise, blood sugar monitoring, and the ability to eat and drink, was impaired after 8 weeks on chemotherapy[20].

Similar to the results found in our systematic review, literature shows that comorbidity has a significant impact on HRQoL. Several other studies that were not included in this review but included diabetes as one of the studied comorbid conditions showed that cancer patients with comorbidity reported lower HRQoL or functioning[30-33]. A few of those studies reported the impact of diabetes separately and found a poorer general health[30], lower physical functioning[30,33], more symptoms of nausea[31] and more erections problems among CA+DM+ men[32]. In line with these results, the number of comorbidities, including cancer, among patients with diabetes has also been shown to result in poorer HRQoL[34]. These studies were excluded from the present review as CA+DM+ patients were not the main sample, and as a result the number of included patients with both diseases was often low.

Although the included studies were of adequate to high quality, they differed substantially in design, population, and methodology. Different instruments were used to measure HRQoL which hampers comparison of the results. Moreover, different cancer types were studied and sample sizes in subgroups were generally low, particularly for CA+DM+ patients. The majority of studies included CA+DM+ and CA+DM- patients, although some studies additionally included a normative sample or CA-DM+ patients for comparison. As a result, information regarding diabetes characteristics was scarce with only 3 out of 10 studies including clinical data regarding diabetes. However, it is important to take the duration and severity of diabetes into account as this may influence the outcomes. Only 4 prospective studies were included, of which 2 were based on the same data, and these studies were conducted mainly among prostate cancer patients.

Despite the heterogeneity in patient samples and PROs studied, this systematic review also has several strengths. It is the first to summarize the literature on PROs among CA+DM+ patients. In addition, a broad search strategy was used and thereby a complete overview of the previous literature is presented. Finally, the quality of all included studies was assessed by two independent investigators with a 14-item checklist.

Directions for future research
Although previous studies suggest that having both cancer and diabetes results in worse outcomes, the evidence is scarce and many relevant topics have not been studied yet. This systematic review shows that the majority of studies focused on general HRQoL and physical function, however, only little attention has been paid to mental health. Mental health was assessed in 5 of the 10 included studies but did not appear to be deteriorated in CA+DM+ patients as compared with CA+DM- and CA-DM+ patients. However, this might be a result of the used instrument, as all studies used a subscale of a HRQoL instrument, which might not be sensitive to more specific symptoms of anxiety or depression. Depression is a common problem in both cancer and diabetes patients. Previous research shows that depression is highly prevalent, in about a third of all cancer as well as diabetes patients and is associated with worse prognostic outcomes[35-38]. Therefore, it is possible that CA+DM+ patients might encounter more mental health issues, which were not picked up in the limited studies in this review. Thus, future studies should focus on mental health issues, including depression among CA+DM+ patients.

Previous studies show that among both cancer and diabetes patients BMI, physical activity, and smoking are significant predictors of HRQoL[39-43]. However, only 4 of the studies included in this review adjusted for lifestyle factors of which 3 only included BMI[24,27,28] and 1 study additionally adjusted for physical activity and smoking[26]. These studies showed that CA+DM+ patients have a higher BMI[24,26-28] and are less physically active[26] at baseline than those without diabetes. Although, these studies did observe lower HRQoL among CA+DM+ versus CA+DM- patients independent of the adjustment for lifestyle factors, more research is needed. It is important to assess whether the poorer lifestyle, rather than clinical factors, of CA+DM+ patients is responsible for the lower

HRQoL in this group. Moreover, future research should focus on the effect of changes in lifestyle factors and their impact on HRQoL; with that knowledge interventions can be developed to improve HRQoL on the long term.

Elderly often live with several chronic illnesses such as cancer and diabetes, which poses a burden on patients. Due to the improved survival, self-management of these chronic diseases is becoming more important. This review included two studies on diabetes self-management which showed that cancer patients performed fewer diabetes self-management behaviors, such as monitoring of the blood glucose levels and exercising, after 8 weeks on chemotherapy[20]. Moreover, qualitative research showed that diabetes patients who develop cancer prioritize their cancer care over their diabetes care[20]. Among diabetes patients, self-management is widely studied and a previous literature review and meta-analysis shows that self-management interventions can improve blood glucose levels, increase knowledge and self-efficacy, and eventually might reduce costs of healthcare utilization[44]. It is important that both patients as well as specialists recognize the importance of self-management of multiple chronic illnesses. It is important that patients are able to utilize their resources and feel that they are in control of life and solve problems when necessary. Therefore, we believe that empowerment of patients and improving self-management behavior are important topics to address in future studies among patients with multiple chronic diseases.

Conclusion

In conclusion, this systematic review indicates that having both cancer and diabetes results in worse PROs. However, a relatively low number of studies was included and no definitive conclusions can be drawn because of the heterogeneity of the included studies. The included studies were of reasonable quality but a main issue was that clinical information regarding diabetes was missing. More prospective studies with sufficient sample sizes are needed to establish these findings. As this research area is largely neglected and the majority of studies focused on HRQoL and physical function, future research should focus on other PROs that are highly prevalent among both cancer and diabetes patients such as mental health, including depression. In addition, as the occurrence of multiple chronic diseases poses important constraints on a person's life and their health care, topics such as self-care and patient empowerment should receive more attention in future research.

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2

2

Appendix A Search strategy for all databases which were searched on August 28, 2013 and updated on January 27, 2015

MEDLINE (Ovid and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations)

1. exp *Diabetes Mellitus/
2. diabet$.ti.
3. 1 or 2
4. exp *Neoplasms/
5. (cancer$ or neoplasm$ or oncolog$).ti.
6. 4 or 5
7. 3 and 6
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.ab.
12. drug therapy.fs.
13. randomly.ab.
14. trial.ab.
15. groups.ab.
16. or/8-15
17. (animals not (humans and animals)).sh.
18. 16 not 17
19. 7 and 18
20. exp Epidemiologic Studies/
21. cohort$.tw.
22. (case$ and control$).tw.
23. (case$ and series).tw.
24. case reports.pt.
25. (case$ adj2 report$).tw.
26. (case$ adj2 stud$).tw.
27. Cross-Sectional.tw.
28. prevalen$.tw.
29. retrospective.tw.
30. or/20-29
31. (animals not (humans and animals)).sh.
32. 30 not 31
33. 7 and 32
34. 19 or 33
35. limit 34 to english language

The Cochrane Library

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees
#2 diabet*:ti
#3 #1 or #2
#4 MeSH descriptor: [Neoplasms] explode all trees
#5 (cancer* or neoplasm* or oncolog*):ti
#6 #4 or #5
#7 #3 and #6

CINAHL (EBSCOhost)

S1 (MM "Diabetes Mellitus+")
S2 TI diabet*
S3 S1 OR S2
S4 (MM "Neoplasms+")
S5 TI (cancer* or neoplasm* or oncolog*)
S6 S4 OR S5
S7 S3 AND S6

PsycINFO (Ovid)

1. diabetes mellitus/
2. diabet$.ti.
3. 1 or 2
4. exp neoplasms/
5. (cancer$ or neoplasm$ or oncolog$).ti.
6. 4 or 5
7. 3 and 6

CHAPTER 3

THE IMPACT OF COMORBIDITY ON HEALTH-RELATED QUALITY OF LIFE AMONG CANCER SURVIVORS: ANALYSES OF DATA FROM THE PROFILES REGISTRY

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Journal of Cancer Survivorship, 2013; 7(4):602-613

Abstract

Purpose
The aim of this study was to assess the difference in explained variance of Health-Related Quality of Life (HRQoL) between comorbidity, sociodemographic characteristics and cancer characteristics. This association was assessed among thyroid cancer, colorectal cancer, and (non-)Hodgkin's lymphoma patients.

Methods
Data from three large population-based surveys on survivors of thyroid cancer, colorectal cancer, and (non-)Hodgkin's lymphoma were used. Cancer-specific HRQoL was assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) of which physical function, emotional function, fatigue, and pain were included in the analyses. Comorbidity was assessed using the Self-reported Comorbidity Questionnaire. The association between comorbidity and HRQoL was assessed with multivariate linear regression models. Semi-partial R^2 was reported to assess the amount of variance in HRQoL explained by comorbidity in comparison with sociodemographic and cancer characteristics.

Results
In total, 3,792 cancer survivors were included in this analysis. The variance in HRQoL subscales explained by comorbidity was higher compared with sociodemographic and cancer characteristics for physical function (11-17 vs. 2-4 and 1-2 %, respectively) and emotional function (7-17 vs. 1-3 and 1-3 %, respectively), regardless of cancer type. In addition, comorbidity explained 7-20 and 11-13 % of the variance in pain and fatigue, respectively, compared to 0-4 % for both sociodemographic and cancer characteristics. Osteoarthritis and back pain were strongly associated with physical function and pain, while depression was strongly associated with emotional function. Depression and back pain were strongly associated with fatigue.

Conclusions
This study showed that comorbidity explained more variance in physical and emotional function, pain, and fatigue in comparison with sociodemographic and cancer characteristics in cancer survivors, regardless of cancer type. Our findings emphasize the importance of adjusting for the presence of comorbid diseases when assessing HRQoL in cancer survivors.

Introduction

Comorbidity is a complex issue in cancer research. Worldwide, there is a trend of aging of the population[1]. At the same time the number of cancer survivors is rapidly increasing due to earlier diagnosis and more effective treatments[2]. Together, these two trends increase the number of patients who survive cancer and have coexisting disease(s), comorbidity. In the Netherlands, around 60% of elderly cancer patients aged 65 years or older suffer from at least one other serious condition with the highest prevalence being previous cancer, heart disease, hypertension, chronic obstructive pulmonary disease (COPD), and diabetes mellitus[3].

Recently, in cancer research, more attention is being paid to health-related quality of life (HRQoL) of cancer survivors[4], where previously the focus was more on objective outcome measures such as treatment effects and mortality. Comorbid diseases generally affect patients' HRQoL negatively, with somatic comorbid conditions affecting mainly physical HRQoL and psychiatric disorders affecting mainly psychosocial aspects of HRQoL[5,6]. A study among head and neck cancer patients showed that having two or more comorbid conditions was strongly associated with decreased HRQoL subscales[7,8]. Another previous study among 158 prostate cancer survivors showed that the Charlson combined comorbidity index impacted on global health and physical function domains of HRQoL[9]. Furthermore, severe comorbidity among lung cancer patients resulted in poorer HRQoL compared to lung cancer patients with no severe comorbidity[10]. Our previous research showed that comorbidity is a strong independent predictor of HRQoL in colon and rectal cancer survivors[11,12]. Furthermore, disease characteristics were less important in predicting HRQoL in cancer survivors, compared with social and demographic characteristics[13,14]. Previous studies mainly focused on head and neck cancer, lung cancer and prostate cancer patients and all studies found an association between comorbidity and a lower HRQoL. This implies that comorbidity might impact on HRQoL generalizable to a wider range of cancer types.

Furthermore, not much attention has been paid to the relative impact of comorbidity on HRQoL. Most studies do not investigate the variance in HRQoL explained by comorbidity, while this effect size can address the relative importance of comorbidity in comparison with sociodemographic characteristics and cancer characteristics. One study conducted among inpatients showed that comorbidity explained 20-60 % of the total variance of the model predicting HRQoL subscales[15]. One previous study among breast cancer patients found that comorbidities explained most variance on nearly all subscales of HRQoL in comparison with demographics and clinical variables[16] Furthermore, comorbidity was found to be an independent prognostic indicator among cancer survivors[3]. While the number of comorbidities increases with age[17], the elderly are often less aggressively treated compared to younger cancer patients[3]. Therefore, we will also conduct a subanalysis among elderly cancer survivors.

The aim of this study was to assess the difference in explained variance of HRQoL between comorbidity, sociodemographic characteristics and cancer characteristics. This association was assessed among thyroid cancer, colorectal cancer, and (non-)Hodgkin's lymphoma patients. We hypothesized that (1) comorbidity explains a similar or higher amount of variance in HRQoL measures compared with sociodemographic and cancer characteristics, (2) comorbidity has an impact on HRQoL regardless of cancer type and (3) there is a higher prevalence of comorbidity and a higher impact of comorbidity on HRQoL among the elderly cancer patients. The results of this study could highlight the importance of including and correcting for a measure of comorbidity in studies addressing HRQoL among cancer survivors.

Methods

Subjects

For this study, data from three large population-based surveys on survivors of thyroid cancer, colorectal cancer, and non-Hodgkin's and Hodgkin's lymphoma conducted between 2008 and 2010 were used. The aim of these surveys was to assess late treatment effects, physical, and mental HRQoL along with other patient-reported outcomes among cancer survivors. Data from these studies will become available online for noncommercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration from our patient-reported outcomes registry, PROFILES (www.profilesregistry.nl)[18].

The Eindhoven Cancer Registry (ECR), maintained by the Comprehensive Cancer Center South, records data on all newly diagnosed cancer patients in the southern region of The Netherlands covering an area with 2.3 million inhabitants and ten hospitals[19]. All thyroid cancer patients diagnosed between 1990 and 2008, all colorectal cancer patients diagnosed between 2000 and 2009, and all lymphoma patients diagnosed between 1999 and 2008 were eligible for participation in the surveys. All cancer patients were surveyed at least 6 months after their cancer diagnosis, in order to ensure that cancer treatment was completed at the time of the survey, and at most 10 years (colorectal cancer and (non-)Hodgkin's lymphoma) to 20 years (thyroid cancer) after cancer diagnosis. Detailed flow charts of the patient samplings have been reported elsewhere[20-22]. Patients who died prior to the study start were identified through the Central Bureau of Genealogy, which collects information on all deceased Dutch citizens via the civil municipal registries and hospital records. After excluding the deceased patients, the treating physicians verified the status of each eligible patient before the patient was approached for study participation (e.g., patients with serious cognitive impairment or who were in transition to terminal care were excluded). All eligible patients received an invitation letter with a login account and password to complete the survey online. If patients did not have access to internet or preferred to take the survey on paper, they could return a postcard, and they received the paper questionnaire within 1 week. After 2 months, reminders were sent to patients who did not respond to the survey. More detailed information on the method of data collection is described elsewhere[18]. After completion of the data collection, data from each patient were linked to their clinical characteristics registered in the ECR. All surveys were approved by a medical ethics committee.

Clinical and sociodemographic characteristics

Information on clinical characteristics was available from the ECR, where date of cancer diagnosis, primary treatment, and cancer stage are routinely collected from medical records by trained registrars. Since the ECR only collects data on the primary tumor and treatment, it cannot be ascertained that patients were disease-free at the time of the survey. Sociodemographic characteristics, including age, gender, and educational level, were assessed in the questionnaire. In this study, education level was categorized as high (pre-university education, high vocational training or university) compared with medium or low.

Health-Related Quality of Life

All cancer survivors completed the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) (version 3.0) to assess cancer-specific quality of life. The QLQ-C30 is a 30-item self-report questionnaire which covers five function scales, a measure of global health or quality of life, and nine scales on symptoms and side effects[23]. Since the EORTC QLQ-C30 does not include an overall score of all scales, and in order to prevent multiple testing and avoid an associated type 1 error, the four most important or distinctive scales were selected. Physical function was included; this scale is hypothesized to be most distinctive for the somatic health of different subgroups of cancer survivors[11,21]. Furthermore, the emotional function scale was included to investigate the impact of comorbidity on mental health as well. Finally, the symptoms pain and fatigue were included since these symptoms are highly prevalent among different groups of cancer survivors[24-26]. All items were scored on a scale from 1 (not at all) to 4 (very much) and then linearly transformed to a 1 to 100 scale; a higher score on function domains represents better function and quality of life, while a higher score on symptom scales represents more symptoms[27].

Comorbidity

Comorbidity was assessed using a modified version of the Self-Administered Comorbidity Questionnaire[15]. The questionnaire addressed the prevalence, hindrance in daily activity, and treatment of 14 comorbidities including heart disease, stroke, high blood pressure, COPD/asthma, diabetes, stomach disease, kidney disease, liver disease, anemia, depression, thyroid disease, osteoarthritis, back pain, and rheumatoid arthritis. Since measuring hindrance in daily activities could be intertwined with measures of HRQoL, this could pose a confounding effect in our planned analyses. Therefore, we only addressed the number of prevalent comorbidities, and not treatment, and hindrance in daily activities, resulting in a score ranging between 0 and 14.

In addition, the effect of individual comorbidities on HRQoL was studied among the two largest cancer patient samples including colorectal cancer and non-Hodgkin's lymphoma patients. Among thyroid cancer and Hodgkin's lymphoma patients, the prevalence of specific comorbidities was not high enough, with 10 out of 14 and 14 out of 14 comorbidities being prevalent in less than 50 patients, respectively. Stroke, stomach, kidney, and liver diseases were prevalent in less than 5 % of the colorectal cancer and non-Hodgkin's lymphoma patients and were therefore excluded from further analysis as well.

Statistical analyses

Differences in baseline characteristics of the study population were analyzed using analysis of variance or chi-square, where appropriate. Unadjusted associations between the number of prevalent comorbidities (0, 1 or ≥2) and HRQoL subscales were studied and presented graphically.

Multivariate linear regression models were constructed to assess the variance in HRQoL subscales explained by the number of comorbidities, which was entered as a continuous variable into the model. Explained variance was reported as the semi-partial correlation coefficient in percentages in order to assess the unique contribution of each independent variable. The semi-partial correlation coefficients (R^2) of age, gender, and education were summed and further referred to as sociodemographic characteristics. Similarly, the coefficients of years after cancer diagnosis, primary cancer treatment, and, where appropriate, cancer stage, are further referred to as cancer characteristics. Thereafter, all comorbidities, with an arbitrarily chosen prevalence of 5% or higher, were included separately into the model to study the effect of each individual comorbid disease on HRQoL domains. Since anemia (3-8 %) has previously been reported as being an important long-term effect of cancer treatment in non-Hodgkin's and Hodgkin's lymphoma patients, this disease was included in further analyses[28].

A subanalysis among the elderly aged 70 years or older was conducted to investigate whether the association between comorbidity and HRQoL domains was different from the total study population by using a comparable method as for the main analyses. We defined elderly oncology patients as those ≥70 years old, according to the European Society for Medical Oncology[29]. Hodgkin's patients were excluded from this analysis since only 13 Hodgkin's patients were 70 years or older. Due to the large number of statistical tests conducted in this study and to avoid type 1 errors, all differences with a P-value <0.01 were indicated as statistically significant. All statistical analyses were performed using SAS statistics (version 9.2 for Windows, SAS institute Inc., Cary, NC).

Results

Characteristics of the study population

Seventy-one percent of the 5,317 invited cancer survivors returned a completed questionnaire; 892 invited patients actively refused or did not complete the survey for other reasons; and the address of 633 patients could not be verified (Figure 1). Response rates were 54, 73, and 67% among thyroid cancer, colorectal cancer, and (non-)Hodgkin's lymphoma patients, respectively. Respondents were on average 2 years younger and 6% more often male and surveyed closer to their cancer diagnosis compared with non-respondents. In addition, respondents were 4% more often treated with surgery and 6% more often treated with chemotherapy or surgery and radiotherapy. Detailed information of the study populations is described elsewhere[20,21,30]. In total, 3,792 patients were included in the present study (Table 1). Hodgkin's lymphoma patients were the youngest and most highly educated compared to the other cancer patients included.

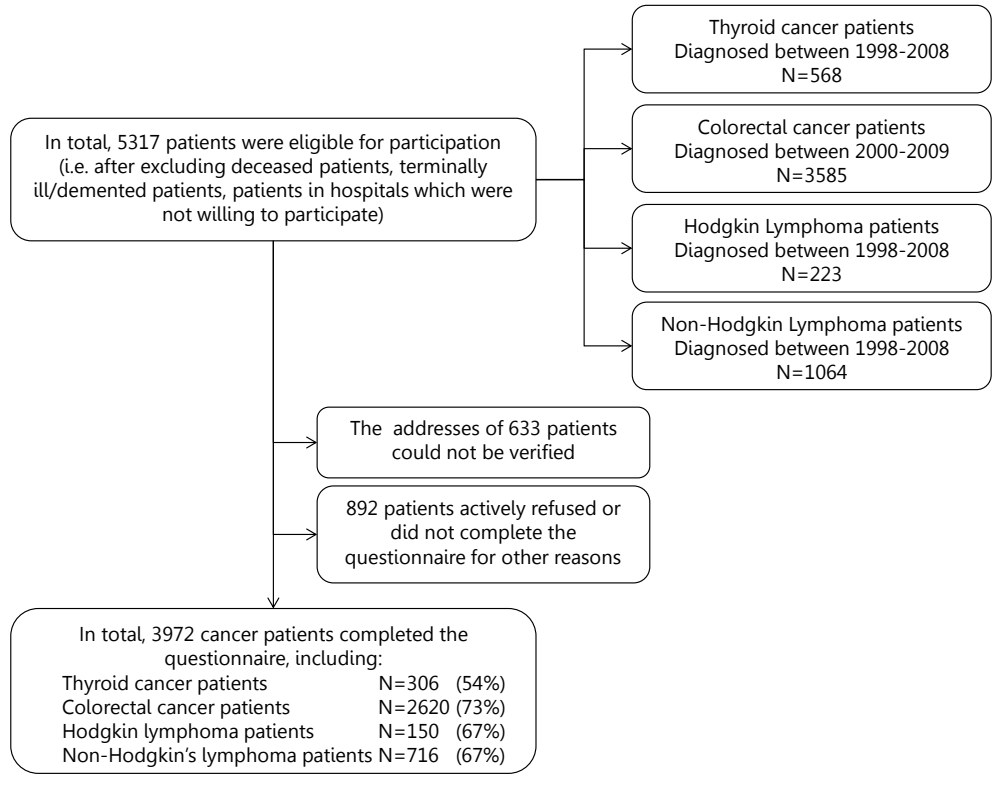

Figure 1 Flowchart of the study process

Table 1 Characteristics of the study population in means ± standard deviation or n(%)

	Thyroid cancer (n=306)	Colorectal cancer (n=2620)	Hodgkin's lymphoma (n=150)	Non-hodgkin's lymphoma (n=716)	P-Value
Sociodemographic characteristics					
Age	56±15	69±10	47±15	64±12	<0.0001
Gender					
Male	76 (25)	1446 (55)	81 (54)	439 (61)	<0.0001
Female	230 (75)	1174 (45)	69 (46)	277 (39)	
Educational level					
Medium or low	225 (74)	2083 (80)	101 (68)	532 (77)	<0.0001
High	80 (26)	508 (20)	48 (32)	163 (23)	
Cancer characteristics					
Years after diagnosis	10±5	5±3	5±3	5±3	<0.0001
Tumor stage					
1	172 (58)	778 (30)	NA	100 (33)	<0.0001[1]
2	59 (20)	945 (37)	NA	77 (25)	
3	48 (16)	723 (28)	NA	54 (18)	
4	20 (7)	114 (4)	NA	76 (25)	
Treatment					
Surgery and iodine ablation	212 (70)				<0.0001
Surgery only	83 (27)	1256 (48)		11 (2)	
Surgery and radiotherapy	9 (3)	588 (23)		6 (1)	
Surgery and chemotherapy		545 (21)		9 (11)	
Surgery, radio- and chemotherapy		203 (8)		10 (11)	
Chemotherapy only		14 (1)	55 (37)	303 (44)	
Radiotherapy only		2 (0)	4 (3)	62 (9)	
Watchful waiting			1 (1)	187 (27)	
Radio- and chemotherapy			90 (60)	85 (12)	
Stemcell transplantation				1 (0)	
Stemcell transplantation and chemotherapy				22 (3)	
HRQoL (QLQ-C30)					
Physical functioning	83±20	80±21	87±16	80±20	0.0002
Emotional functioning	84±20	86±19	83±23	84±21	0.04
Pain[2]	17±25	16±24	13±22	16±25	0.27
Fatigue[2]	28±25	22±24	28±27	28±25	<0.0001

[1]Excluding Hodgkin's lymphoma patients
[2]Pain and fatigue are scored in opposite direction with higher scores indicating more symptoms
NA = Not applicable

Thyroid cancer patients were surveyed furthest from their diagnosis (10±5 years) compared with other cancer patients included (5±3 years). Primary cancer treatment and cancer stage differed significantly between the four different cancer types. Hodgkin's lymphoma patients scored highest on physical function compared to the other cancer patients. Emotional function was highest, while fatigue symptoms were lowest among colorectal cancer survivors.

Comorbidity

Colorectal and thyroid cancer patients suffered from most comorbid diseases with 46 and 44% suffering from two or more comorbid conditions, respectively (Table 2). Heart disease was most prevalent among colorectal cancer and non-Hodgkin's lymphoma patients with an approximate prevalence of 20%. High blood pressure (35%) and diabetes (15%) were most prevalent among colorectal cancer survivors. Anemia was highest among non-Hodgkin's lymphoma patients (8%), while thyroid disease was most prevalent among thyroid cancer patients (30%) and Hodgkin's lymphoma patients (12%).

Table 2 Frequencies (n(%)) of the self-reported number and type of comorbidity among the study population

	Thyroid cancer (n=306)	Colorectal cancer (n=2620)	Hodgkin's lymphoma (n=150)	Non-Hodgkin's lymphoma (n=716)	P-Value
Number of comorbidities (n(%))					
None	75 (25)	613 (25)	64 (46)	189 (29)	<0.0001
1	92 (31)	708 (29)	43 (31)	205 (31)	
≥2	133 (44)	1126 (46)	32 (23)	266 (40)	
Types of comorbid diseases (n(%))					
Heart disease	33 (11)	462 (19)	13 (9)	130 (20)	0.0002
Stroke	4 (1)	66 (3)	2 (1)	13 (2)	0.33
Hypertension	79 (26)	862 (35)	15 (11)	141 (21)	<0.0001
Asthma/COPD	30 (10)	266 (11)	17 (12)	75 (11)	0.89
Diabetes	22 (7)	356 (15)	6 (4)	49 (7)	<0.0001
Stomach disease	5 (2)	41 (2)	1 (1)	13 (2)	0.78
Kidney disease	8 (3)	100 (4)	1 (1)	13 (2)	0.01
Liver disease	1 (0)	78 (3)	1 (1)	6 (1)	0.0002
Anemia	13 (4)	117 (5)	4 (3)	55 (8)	0.001
Thyroid disease	89 (30)	117 (5)	16 (12)	31 (5)	<0.0001
Depression	21 (7)	170 (7)	14 (10)	52 (8)	0.49
Osteoarthritis	76 (25)	635 (26)	21 (15)	264 (25)	0.04
Back pain	98 (33)	664 (27)	23 (17)	160 (24)	0.002
Rheumatoid arthritis	26 (9)	164 (7)	4 (3)	46 (7)	0.16

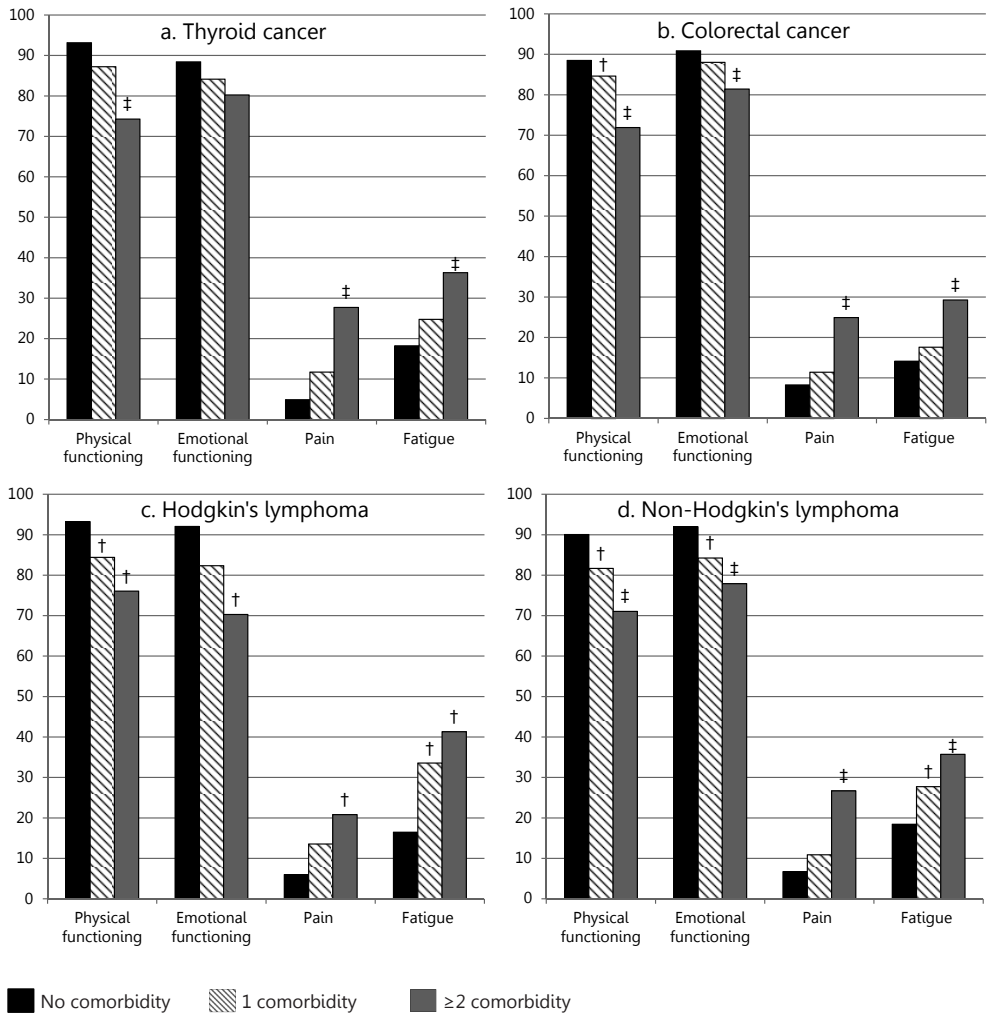

Figure 2a-d Means of four domains of the QLQ-C30 questionnaire according to the number of comorbidities among thyroid- (a), colorectal cancer (b), Hodgkin's lymphoma (c) Hodgkin's lymphoma (d.) Non-Hodgkin's lymphoma

†Significantly different from participants with no comorbidity (P-value<0.01)

‡Significantly different from participants with no comorbidity and those with one comorbidity (P-value<0.01)

Pain and fatigue are scored in opposite direction with higher scores indicating more symptoms

Number of comorbidities and HRQoL

Among all cancer survivors, except for thyroid cancer patients, having one and/or two or more comorbidities was significantly associated with lower physical and emotional function and higher levels of pain and fatigue (Figure 2a-d). Among thyroid cancer patients, no significant difference in emotional function between no, one, or two or more comorbidities was observed. Similarly, physical function was lower, while levels of pain and fatigue were higher among thyroid cancer patients having one and/or two comorbidities compared with those who had no comorbidity. Multivariate linear regression models showed that the number of comorbidities was strongly related to the studied subscales of the QLQ-C30, with a P-value <0.01 among all cancer survivors. All standardized betas were in the expected direction with more comorbidities resulting in lower physical and emotional function (standardized betas; −0.3 to −0.5). Similarly, having more comorbidities was associated with higher levels of pain and fatigue, with all standardized betas ranging between 0.3 and 0.5.

These models also showed that the variance explained by the number of comorbidities was higher compared with sociodemographic and cancer characteristics for all cancer survivors (Figure 3a-d). The number of comorbidities explained 11-17% of the variance in physical function compared with 2-4 and 1-2% for sociodemographic and cancer characteristics, respectively. A 7-17% of the variance in emotional function was explained by the number of comorbidities compared with 1-3% for both sociodemographic and cancer characteristics. Finally, the number of comorbidities explained 7-20 and 11-13% of the variance in pain and fatigue, respectively, compared with 0-4% for both sociodemographic and cancer characteristics. When including the overlap between the studied predictors of HRQoL as well, the total explained variance (R^2) of the models ranged between 9 and 27% (Figure 3a-d).

Individual comorbidities and HRQoL

Including the selected comorbidities separately in the model resulted in higher proportions of explained variance (2-11%) for all studied subscales compared to including the number of comorbidities (Table 3 and Figure 3). Variance in physical function was explained most by heart disease and back pain with 2-4% among colorectal and non-Hodgkin's lymphoma patients (Table 3). Depression explained most variance in emotional function with 12 and 8% among colorectal and non-Hodgkin's lymphoma patients, respectively. Variance in pain was explained most by back pain with around 7%, and variance in fatigue was mainly explained by depression and back pain with 2-3%. Again, all significant standardized betas were in the expected direction ranging between −0.1 and −0.2 for physical function, between −0.1 and −0.4 for emotional function, between 0.1 and 0.3 for pain, and between 0.1 and 0.2 for fatigue. The total explained variance (R^2) in HRQoL ranged between 20 and 30% across the different models.

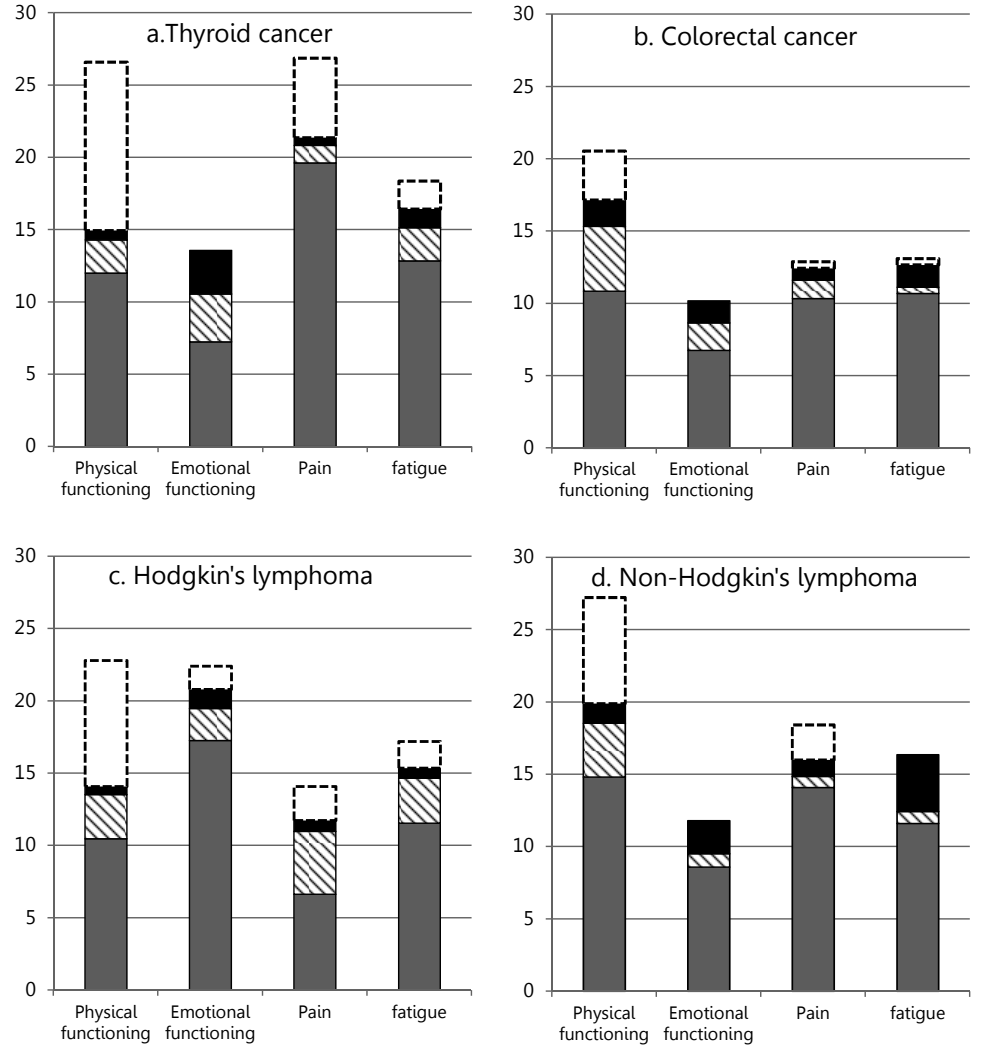

Figure 3a-d Variance (semi-partial R^2(%)) explained by sociodemographic- (age, gender and educational level), cancer characteristics (primary treatment, stage, and years after diagnosis), and the number of comorbidities among thyroid- (a), colorectal cancer (b), Hodgkin's lymphoma (c) Hodgkin's lymphoma (d.) Non-Hodgkin's lymphoma

Elderly

Comorbidity among thyroid cancer, colorectal cancer, and non-Hodgkin's lymphoma patients was significantly higher among the elderly. Fifty-two percent of those aged ≥70 years suffered from two or more comorbid conditions compared with 38% of survivors younger than 70 years old. Compared to patients aged <70 years old, the prevalence of heart disease (28 vs 11%), stroke (4 vs 1%), hypertension (38 vs 27%), diabetes (16 vs 10%), anemia (7 vs 4%), and osteoarthritis (31 vs 21%) was significantly (P-value<0.01) higher among elderly aged ≥70 years. Thyroid disease and depression were less prevalent among the elderly aged ≥70-years compared to the younger patients with 5 vs 8% and 6 vs 8%, respectively. When studying the association between the number of comorbidities and HRQoL outcomes in multivariate regression models, similar results as for the total study population were found for elderly colorectal cancer patients (Figure 4b). Among elderly thyroid cancer patients, the number of comorbidity explains more of the variance in emotional function, pain, and fatigue compared to the total sample (Figure 4a). Among elderly non-Hodgkin's patients, the number of comorbidities explained less while cancer characteristics explained more variance in all studied subscales compared with the total population (Figure 4c). When including the overlap between the studied predictors of HRQoL, the total explained variance (R^2) of the models ranged between 9 and 46%.

Table 3 Variance (R^2(%)) in health related quality of life measures explained by most frequent comorbidities, age and cancer characteristics. Thyroid and Hodgkin's lymphoma patients were not included due to the low prevalence (N<50) of most comorbidities

	Colorectal cancer				Non-Hodgkin's lymphoma			
	PF	EF	PA	FA	PF	EF	PA	FA
Heart disease	1.9 ‡	0.7 ‡	0.4 †	1.9 ‡	3.6 ‡	1.3 †	0.3	1.8 †
Hypertension	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Asthma/COPD	1.8 ‡	0.3 †	0.5 †	1.2 ‡	0.1	0.1	0.0	0.3
Diabetes	0.4 †	0.0	0.0	0.1	0.8 †	0.0	0.2	0.1
Anemia	1.1 ‡	0.0	0.7 ‡	0.7 ‡	0.2	0.0	0.2	0.1
Thyroid disease	0.1	0.2	0.2	0.0	0.0	0.1	0.1	0.0
Depression	1.0 ‡	12.0 ‡	0.6 ‡	3.2 ‡	1.2 †	7.9 ‡	0.9 †	2.6 ‡
Osteoarthritis	0.4 †	0.0	1.6 ‡	0.2	1.6 †	0.2	3.3 ‡	0.7
Back pain	1.6 ‡	1.2 ‡	6.5 ‡	2.0 ‡	2.5 ‡	3.8 ‡	7.2 ‡	2.9 ‡
Rheumatoid Arthritis	0.2	0.2 †	0.9 ‡	0.1	1.6 †	0.3	2.4 ‡	2.0 †
Sociodemographic characteristics[1]	4.5 ‡	1.0 ‡	0.8 †	0.4 †	3.3 †	0.6	0.5	0.5
Cancer characteristics[2]	2.0 ‡	1.6 †	0.9 †	1.6 †	1.4	2.7	0.9	4.2 †
Total R^2	23.6	20.7	21.3	17.3	29.8	20.1	26.2	20.5
Adjusted R^2	22.9	20.0	20.6	16.6	27.1	17.1	23.4	17.4

†P-value <0.01, ‡P-value <0.0001
PF: physical function, EF: emotional function, PA: pain, FA: fatigue
[1]Sociodemographic characteristics include age, gender and educational level, variable is regarded as statistically significant if at least 1 of the cancer characteristics has a P-value<0.01 (†) or P-value<0.0001 (‡)
[2]Cancer characteristics include time since cancer diagnosis, primary treatment and stage where applicable, variable is regarded as statistically significant if at least 1 of the cancer characteristics has a P-value<0.01 (†) or P-value<0.0001 (‡)

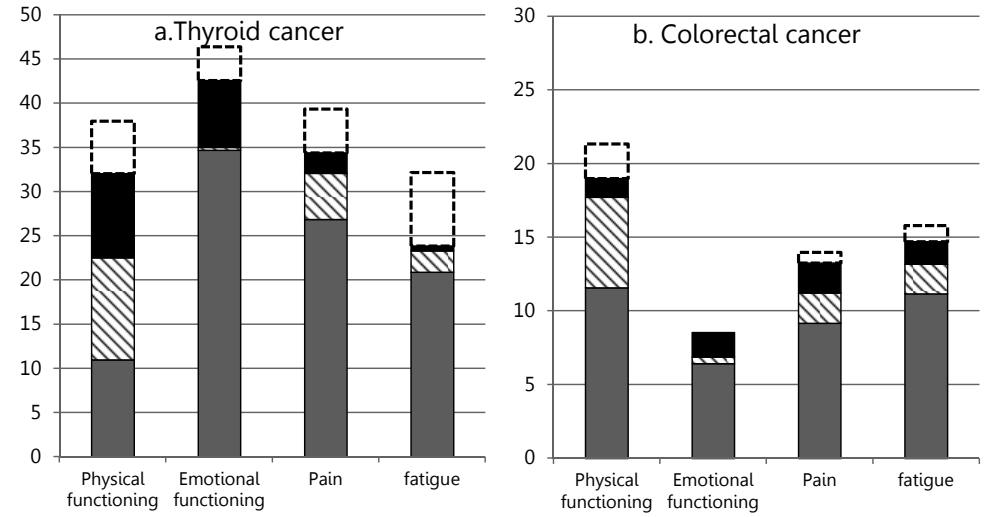

Figure 4a-c Variance (semi-partial R^2(%)) explained by sociodemographic- (age, gender and educational level), cancer characteristics (primary treatment, stage, and years after diagnosis), and the number of comorbidities among elderly (≥70 years) thyroid- (a), colorectal cancer (b), and non-Hodgkin's lymphoma patients (c) Non-Hodgkin's lymphoma

Discussion

In this study, we showed that in comparison with sociodemographic and cancer characteristics, comorbidity explained more variance in physical function, emotional function, pain, and fatigue. This was found regardless of cancer type. Similar patterns were seen for thyroid cancer, colorectal cancer, and (non-)Hodgkin's lymphoma patients. Among the elderly (≥70 years) thyroid cancer patients, comorbidity seemed to become more important, while in elderly (≥70 years) non-Hodgkin's lymphoma patients, cancer characteristics seemed to have greater impact on HRQoL compared to the results for the total population. As hypothesized, the prevalence of comorbidity was higher among the elderly, but did not have a higher impact compared to sociodemographic and cancer characteristics among all cancer survivors.

The total explained variance found in the models predicting physical function, emotional function, pain, and fatigue ranged between 9 and 27%. This amount of explained variance is comparable to that of a previous study conducted among hospitalized patients who reported a total explained variance of 25, 19, and 20% for physical functioning, bodily pain, and vitality, respectively[15]. Comorbidity explained about 7-19% of the variance in HRQoL in our study. A previous study among breast cancer patients found that comorbidity explained less variance ranging between 0 and 10%, which might be the result of this different study population[16]. In general, the total explained variance in our study is still somewhat low, with a maximum of 27% of the variance explained. Other factors, which we did not take into account, could have contributed to the unexplained variance. Previous studies showed that personality traits such as neuroticism and coping strategies are also associated with HRQoL[31] and might have played a role. Another possible predictor is social support[32,33], which might contribute to the studied association. In addition, symptoms of pain and fatigue are found to be associated with physical function[16] and omitting these symptoms could account for the low amount of explained variance in physical function that we found.

Among thyroid cancer patients, comorbidity seemed to increase in importance among the elderly compared with the total thyroid cancer sample. This might be a result of the increased prevalence of heart disease, high blood pressure, diabetes, and rheumatoid arthritis among the elderly. Similar results were found in a study among breast cancer patients, in which the impact of cancer and its treatment attenuated over time, while multimorbidity had greater impact on functional decline[34]. However, the prevalence of comorbidity was also higher among elderly colorectal cancer and non-Hodgkin's lymphoma patients where this higher importance of comorbidity was not observed. Among non-Hodgkin's lymphoma patients, the opposite was found, with comorbidity explaining less of the variance in HRQoL among the elderly compared to the total sample. Instead, cancer characteristics were more important among the elderly non-Hodgkin's lymphoma patients. This difference between the young and elderly non-Hodgkin's lymphoma patients could not be explained by differences in cancer stage,

primary treatment, and time since diagnosis or type of non-Hodgkin's lymphoma (indolent or aggressive). Non-Hodgkin's lymphoma patients often receive intensive medical treatment which can interfere with HRQoL long after their treatment[35,36]. But why elderly experience lower HRQoL as a result of cancer characteristics is unclear. Future studies should further assess the complex association between comorbidity and HRQoL among elderly cancer survivors.

This study contributes to the paucity of knowledge on the association between comorbidity and HRQoL in cancer survivors. It showed that comorbidity explained more of the variance in HRQoL compared with sociodemographic and cancer characteristics. Therefore, these results can contribute to further research addressing the challenging issue of the effect of comorbidity on HRQoL in cancer patients. In addition, clinicians should become more aware of the impact of comorbidity on HRQoL and provide necessary psychological support to assist self-management of comorbid diseases.

The self-reported nature of our comorbidity assessment could be advantageous, since self-report shows high agreement with physician diagnoses[37], while comorbidity in administrative data is often underreported[38]. In addition, this is a large population-based study with a high response rate which enabled the identification of the comorbidities that were strongly associated with separate HRQoL subscales.

The inclusion of long-term survivors could have resulted in survivorship bias. This might especially be an issue among colorectal cancer and non-Hodgkin's lymphoma patients, since these patients have generally a worse prognosis compared to the other cancer types. As such, the possible inclusion of a healthier sample could have underestimated the prevalence of comorbidity. Furthermore, patients who are unable to complete questionnaires, due to severe illness or cognitive impairments, were excluded, while these patients are more likely to have a high burden of comorbidities as well. This could have resulted in an underestimation of the found association. In addition, our inclusion of the cancer types in this analysis is somewhat arbitrary, which was based on the availability of QLQ-C30 scores for comparison. However, we expect similar results in different cancer types as our results are in line with other studies focusing on other cancers. Furthermore, the cross-sectional study design makes the direction of the association between comorbidity and HRQoL debatable. We cannot ascertain whether the self-reported comorbid conditions were present before the cancer diagnosis or developed thereafter. In addition, it is questionable whether the comorbidities measured in this study are independent predictors of HRQoL, since comorbid conditions can interact with treatments or could be caused by cancer treatment and synergistically lower HRQoL[39]. For example, anemia is common in cancer patients, and the risk of anemia increases when patients receive chemotherapy for a longer time[28], while thyroid disease is common among thyroid cancer patients and among Hodgkin's lymphoma survivors treated with external radiotherapy[40]. Furthermore, the prevalence of thyroid disease might have been overestimated among thyroid cancer patients as these patients might have reported

having thyroid disease as a result of their cancer diagnosis. However, sensitivity analyses among thyroid cancer patients excluding thyroid disease as a comorbidity revealed similar findings (data not shown). In addition, some comorbid conditions might increase the risk of complications from cancer therapy, with, for example, diabetes increasing the risk of neuropathy in patients treated with paclitaxel[41], and hypertension and obesity increasing the risk of heart failure in patients treated with trastuzumab[42,43]. Furthermore, lifestyle factors, such as eating patterns and physical activity, were out of the scope of this study but could have influenced the association between comorbidity and HRQoL. Therefore, future research should address the complex association between comorbidity and lifestyle factors and its association with HRQoL.

In conclusion, this study showed that comorbidity explains more variance in physical and emotional function, and pain and fatigue compared with sociodemographic and cancer characteristics in cancer survivors, regardless of cancer type. These results emphasize the importance of adjusting for the presence of comorbid diseases when assessing HRQoL in cancer survivors. Future research should focus on the prevention and treatment of comorbidity to improve HRQoL in cancer patients.

3

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CHAPTER 4

THE INDIVIDUAL AND COMBINED EFFECT OF COLORECTAL CANCER AND DIABETES ON HEALTH-RELATED QUALITY OF LIFE AND SEXUAL FUNCTIONING: RESULTS FROM THE PROFILES REGISTRY

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Abstract

Purpose
This study examined the individual and combined effect of having colorectal cancer (CRC) and diabetes mellitus (DM) on Health-Related Quality of Life (HRQoL) and sexual functioning.

Methods
Data from questionnaires collected in 2010 among CRC patients and a sample of the general Dutch population were used. All persons older than 60 years were included in this study. DM prevalence among the CRC sample as well as the sample of the general population was self-reported. HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire version 3.0 (QLQ-C30), and sexual functioning was assessed with four scales from the EORTC-QLQ-CR38.

Results
In total 624 persons without CRC and DM, 78 persons with DM only, 1,731 with CRC only, and 328 with both CRC and DM were included. Having both CRC and DM did not result in lower HRQoL and sexual functioning than the sum of the individual effects of both diseases. CRC, irrespective of having DM, was associated with lower scores on most EORTC-QLQ-C30 subscales, except global health, pain, and appetite loss. CRC was also independently associated with more erection problems among males. DM, irrespective of having CRC, was associated with lower physical functioning and more symptoms of dyspnea.

Conclusions
Having both CRC and DM did not result in lower HRQoL and sexual functioning than the sum of the individual effects of both diseases. As CRC was found to be consistently associated with lower functioning and more symptoms, CRC and its treatment seem to contribute stronger to lower HRQoL and sexual functioning compared with DM.

Introduction

Due to aging of the population, the number of elderly suffering from multiple chronic diseases is increasing[1]. Both cancer and diabetes belong to the four main types of chronic diseases, which are among the leading causes of deaths world-wide with 7.6 million and 1.3 million deaths in 2008, respectively[2]. Colorectal cancer (CRC) is one of the most common cancers with over one million new cases worldwide each year[3]. As CRC and diabetes have several overlapping risk factors, including obesity, sedentary lifestyle, and Western diet[4,5], they often co-occur. As a result, diabetes is one of the most prevalent chronic diseases among CRC patients with a prevalence of 14%[6].

Previous studies showed a higher mortality among CRC patients with diabetes compared to those without and suggested that diabetes increases the risk of complications and recurrence among CRC patients[7,8]. Despite the recognition of the link between CRC and diabetes on prognostic outcomes in current literature, little is known on patient reported outcomes such as Health-Related Quality of Life (HRQoL) and sexual functioning for CRC patients with comorbid diabetes.

Previous studies among patients with only CRC report lower role, cognitive, and social functioning; more symptoms of dyspnea, constipation, and diarrhea; and more financial difficulties compared to a normative sample even 10 years after CRC diagnosis[9]. Moreover, CRC patients report lower sexual functioning compared to the general population[10,11], possibly as a result of surgery[12]. Similarly, patients with only diabetes report lower HRQoL compared to the general population[13]. Furthermore, a link between diabetes and sexual dysfunction is widely recognized, with most research focusing on the high prevalence (up to 75%) of erectile problems among men[14].

Although both CRC and diabetes individually affect HRQoL and sexual functioning, it remains unclear to what extent CRC and diabetes have independent negative effects on HRQoL and sexual functioning. Only five previously conducted studies investigated the combined effect of cancer and diabetes on HRQoL[15-19]. Of these studies, three were among prostate cancer patients[16-18] and found a small negative effect of diabetes on general health and vitality[17,18], and urinary function[16]. Two studies included patients with different cancer types[15,19] and showed significantly lower HRQoL[15] among persons with cancer and diabetes compared to persons without both diseases or with only cancer or diabetes. Furthermore, cancer patients with diabetes scored lower on physical functioning compared with cancer patients without diabetes[19]. No previous studies focused on sexual functioning among patients with both cancer and diabetes.

With the increasing number of cancer patients also suffering from diabetes and only a few studies on patient reported outcomes among individuals with both diseases, this study aims to assess the individual and combined effects of having CRC and diabetes on HRQoL and sexual functioning. As both CRC and diabetes independently affect HRQoL and sexual functioning and having diabetes results in more complications and cancer

recurrence among CRC patients[7,8] we hypothesize that the combined effect of CRC and diabetes results in an even worse HRQoL and sexual functioning than the sum of the individual effects of CRC and diabetes. If the co-occurrence of CRC and diabetes results in a greater negative effect on HRQoL and sexual functioning, future interventions should aim at this patient group to address symptoms and functional problems most efficiently.

Methods

Study population

Data from a large population-based survey conducted in 2010 among CRC patients with Diabetes Mellitus (CRC+DM+) or without DM (CRC+DM−) diagnosed between 2000 and 2009, were used. Details of the data collection are described elsewhere[20]. Data were collected within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) registry[21]. PROFILES registry includes a large web-based component and is linked to clinical data from the Eindhoven Cancer Registry (ECR). The ECR is part of the Comprehensive Cancer Centre South (CCCS) and records all newly diagnosed cancer patients in the southern region of the Netherlands, covering an area with 2.3 million inhabitants and 10 hospitals[22]. Clinical characteristics including primary cancer treatment, stage, and time since diagnosis were retrieved from the ECR. Data from the PROFILES registry will be available for noncommercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl)[21].

To compare the data on CRC patients with persons without CRC and DM (CRC−DM−) or with only DM (CRC−DM+), a subsample of the general Dutch population was used. Those who reported having cancer were excluded from the analysis. Data collection for this sample of the general population was conducted by CentERdata (www.centerdata.nl) in 2010. CentERdata uses the CentERpanel for data collection which is an online household panel and includes over 2,000 households which are representative of the Dutch-speaking population in The Netherlands. The method of data collection has been described elsewhere[23].

As the sample of the general population was significantly younger than the CRC patients (54±5 vs 70±10), only participants aged ≥60 years from the general population and CRC samples were included. Persons with DM were identified from responses to the Self-Administered Comorbidity Questionnaire (SCQ)[24]. Persons were asked whether they had DM in the previous year or currently, and no data were available regarding DM type and duration or timing of DM, i.e., either before or after CRC diagnosis. Besides DM, the SCQ also assesses the prevalence of 13 other comorbid conditions. For this analysis, additional comorbidity was categorized as none, one prevalent, or ≥2 prevalent comorbidities, excluding DM. Data on demographic characteristics including age, gender, and education were also collected. Body mass index (BMI) was available for CRC patients only.

Health-related quality of life

HRQoL was assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire version 3.0 (QLQ-C30)[25]. This self-report instrument has 30 items from which scores on global health status, five functional scales, three symptom scales, and six single items on symptoms and financial impact are derived. All items were scored on a scale from 1 (not at all) to 4 (very much), except for the global health items which were scored from 1 (very poor) to 7 (excellent). Scores were linearly transformed to a 1-100 scale. Higher scores on functioning and global health domains represent better functioning and HRQoL, while a higher score on symptom scales represents more symptoms.

Sexual functioning

Seven items on sexual functioning derived from the EORTC Quality of Life Group Item Bank[23,26] were used. Items on sexual activity and interest and one item on sexual enjoyment were included. Furthermore, women were asked about sexual problems, including lubrication problems and pain during sexual intercourse. For men, assessed sexual problems included problems with getting or maintaining an erection and ejaculation problems. All scales were linearly transformed to a 1-100 scale with a higher score on sexual functioning and enjoyment representing better sexual functioning and a higher score on male and female sexual problems indicating more complaints. No score on male sexual problems could be calculated for the sample from the general population as data on ejaculation problems were not collected among this sample. Therefore, the individual items on male sexual problems, including erection and ejaculation problems, were addressed separately. The presence of erection or ejaculation problems was dichotomized (yes/no). Having problems was defined by response categories "quite a bit" or "very much," while having no problems was defined as "not at all" and "a little," as previously done[10].

Statistical analysis

Differences in baseline characteristics between CRC−DM−, CRC−DM+, CRC+DM−, and CRC+DM+ persons were analyzed by means of analysis of variance (ANOVA), chi-square tests, and independent T-tests, where appropriate. Clinically relevant differences were assessed with the evidence-based guidelines for the interpretation of mean differences in EORTC-QLQ-C30 subscales[27]. The clinically relevant differences are defined as small (3-19 points), medium (7-29 points), and large (14-29 points), depending on the studied subscale[27]. For sexuality items, Norman's threshold of half a standard deviation was regarded as a relevant change[28].

Multivariable linear regression models with HRQoL subscales as dependent variables and CRC and DM as independent variables were constructed. To assess whether the combined effects of having CRC and DM on HRQoL and sexual functioning go beyond the sum of their separate effects, we tested for biological interaction. Biological interaction is studied as deviation from additivity[29,30]. We used linear regression models to test for

biological interaction, where the regression coefficient of the interaction term estimates the effect as deviation from additivity. To test for a biological interaction effect of both diseases, besides a separate dichotomous variable for CRC and DM, an interaction term (CRC×DM) was included in the regression model (model 1)[30]. To study which disease has a greater negative effect on HRQoL and/or sexual functioning, the individual effects of CRC and DM were studied in similar multivariable regression models without the inclusion of the interaction terms (model 2). Similarly, the main effect of DM on HRQoL and sexual functioning was assessed in CRC patients only (model 3). All multivariable linear regression models were adjusted for gender, age, education, and number of comorbid conditions excluding DM. Model 3 additionally adjusted for BMI, cancer stage, primary cancer treatment, and time since cancer diagnosis. The models with sexual functioning scales as dependent variables were stratified for gender, and only persons with a partner were included. For all multivariable linear regression models, unstandardized betas were reported. We used multivariable logistic regression models to study the individual effects of CRC and DM on erection problems and the effect of DM on ejaculation problems among CRC patients only. Odds ratios (ORs) and 99% confidence intervals (CIs) were reported. We did not test for a biological interaction effect on erection and ejaculation problems, as logistic models test interaction as deviation from multiplicativity and not additivity[29]. Due to the high number of statistical tests conducted, a P-value of <0.01 was regarded as statistically significant. All statistical analyses were performed using SAS statistics (version 9.2 for Windows, SAS Institute, Inc., Cary, NC).

Results

Characteristics of the study population

In total, 944 of the 2,619 persons from the general population sample and 3,030 of the 3,585 persons with CRC were aged ≥60 years. Of these, 819 (87%) persons from the general population and 2,215 (73%) CRC patients returned a complete questionnaire. We excluded those who did not report whether they had DM (n=157) and those from the general population sample who reported having been diagnosed with cancer (n=116). The final analysis included 624 CRC−DM−, 78 CRC −DM+, 1,731 CRC+DM−, and 328 CRC+DM+ persons. Among the CRC patients aged >60 years, respondents differed from the nonrespondents and those with unverified addresses with regard to gender (55% of males vs 46 and 48%, respectively), mean age (72 vs 75 and 74 years, respectively), and cancer treatment (51% treated with surgery only vs 61 and 62%, respectively). Among the sample of the general population, no differences were observed between respondents and nonrespondents aged ≥60 years (results not shown).

A difference in gender was found with 68% of males among CRC−DM+ and 63% among CRC+DM+ patients as compared to 57% of males among CRC−DM− and 54% among CRC+DM− patients, P-value=0.003 (Table 1). CRC+ DM+ persons were oldest (73±6), followed by CRC+DM−(72±7), CRC−DM+(69±7), and CRC−DM−(68±7), P-value <0.0001. CRC−DM− and CRC−DM+ persons were highly educated compared with CRC+DM− and

Table 1 Patient- and cancer characteristics of the study population

	General population sample		Colorectal cancer sample		
	CRC−DM−	CRC−DM+	CRC+ DM−	CRC+DM+	P-value[a]
	n=624	n=78	n=1,731	n=328	
Patient characteristics					
Gender (n(%))					
Male	347 (57)	53 (68)	937 (54)	207 (63)	0.003
Female	260 (43)	25 (32)	794 (46)	121 (37)	
Age (mean ± SD)	68±7	69±7	72±7	73±6	<0.0001
Education (n(%))[b]					
Low	38 (6)	5 (6)	348 (20)	94 (29)	<0.0001
Medium	355 (57)	46 (59)	1,039 (61)	184 (57)	
High	229 (37)	27 (35)	327 (19)	47 (14)	
Number of comorbidities (n(%))					
0	179 (29)	12 (15)	462 (27)	42 (13)	<0.0001
1	209 (33)	25 (32)	550 (32)	93 (28)	
≥2	236 (38)	41 (53)	719 (42)	193 (59)	
Partner (n(%))					
No	136 (22)	18 (23)	399 (23)	97 (30)	0.04
Yes	488 (78)	60 (77)	1,317 (77)	228 (70)	
BMI (mean ± SD)			26±4	29±4	<0.0001
Cancer characteristics					
Stage (n(%))					
1			517 (31)	100 (31)	0.83
2			640 (38)	128 (40)	
3			466 (28)	81 (25)	
4			66 (4)	12 (4)	
Time since diagnosis (mean ± SD)			5±3	5±3	0.52
Treatment (n(%))					
Surgery only			859 (50)	179 (55)	0.42
Surgery & radiotherapy			387 (22)	62 (19)	
Surgery & chemotherapy			351 (20)	64 (20)	
Surgery, radiotherapy & chemotherapy			116 (7)	19 (6)	
Chemotherapy only			10 (1)	2 (1)	
Radiotherapy only			1 (0)	1 (0)	

[a]Differences in patient characteristics between CRC−DM−, CRC−DM+, CRC+DM−and CRC+DM+ were tested with ANOVA for continuous outcomes and Chi-square tests for categorical outcomes. Differences in cancer characteristics between CRC+DM− and CRC+DM+ were tested with independent T-tests for continuous outcomes and Chi-square tests for categorical outcomes

[b]Education levels included low = no/primary school; medium = lower general secondary education/vocational training; or high =pre-university education/high vocational training/university.

CRC+DM+ persons (P-value <0.0001). CRC−DM+ and CRC+DM+ persons had the most prevalent comorbidities with 53 and 59% having ≥2 comorbid diseases, respectively. CRC+DM+ persons had a higher BMI but did not differ in cancer characteristics compared with CRC+DM− persons.

Differences in HRQoL and sexual functioning

Unadjusted means showed that CRC+DM+ reported lowest scores on global health (73±21) followed by CRC−DM+ (76 ±14), CRC+DM− (78±19), and CRC−DM− (79±15), P-value <0.0001 (Table 2). Physical functioning and cognitive functioning were highest among CRC−DM− persons and were lower among CRC−DM+, CRC+DM−, and CRC+ DM+ persons. A similar pattern was found for fatigue, nausea/vomiting, dyspnea, diarrhea, and financial problems with the least problems among CRC−DM− persons and increasing symptom scores among CRC−DM+, CRC+DM−, and CRC+DM+ persons, respectively. In general, the observed differences were of small or medium clinical relevance[27].

Table 2 Unadjusted means (± standard deviation) of HRQoL subscales among CRC−DM−, CRC−DM+, CRC+DM− and CRC+DM+ persons

	General population sample		Colorectal cancer Sample		
	CRC−DM−	CRC−DM+	CRC+DM−	CRC+DM+	P-value
	n=624	n=78	n=1,731	n=328	
Health-Related Quality of Life					
Global health	79±15	76±14	78±19	73±21[a]	<0.0001
Physical functioning	87±16	84±17	80±20[a]	72±23[b]	<0.0001
Emotional functioning	90±15	91±15	87±18	85±20	<0.0001
Role functioning	87±21	89±17	81±27[a]	77±29[a]	<0.0001
Cognitive functioning	91±15	91±14	86±19[a]	83±22[a]	<0.0001
Social functioning	94±15	94±13	87±22[a]	87±23[a]	<0.0001
Pain	18±23	13±18	16±24	18±26	0.16
Fatigue	16±19	19±19	20±23	26±25[a]	<0.0001
Nausea/vomiting	2±8	3±8	3±11	5±12[a]	0.0003
Dyspnea	9±19	10±18	15±25[a]	22±30[b]	<0.0001
Insomnia	15±24	10±17[a]	21±29[a]	20±28[a]	<0.0001
Appetite loss	2±11	7±17[a]	6±17	7±18[a]	<0.0001
Constipation	5±14	3±10	9±20	9±20	<0.0001
Diarrhea	3±12	6±18[a]	10±22[a]	12±21[b]	<0.0001
Financial problems	3±11	3±9	5±16	7±16[a]	<0.0001

CRC−DM− persons without colorectal cancer and diabetes, CRC−DM+ persons with only diabetes, CRC+DM− persons with only colorectal cancer, CRC+DM+ persons with colorectal cancer and diabetes
[a]Small and [b]medium clinical relevant difference compared to CRC-DM- persons according to Cocks et al.[27]

Figure 1 Unadjusted means of sexual functioning scales among CRC−DM−, CRC−DM+, CRC+DM− and CRC+DM+ patients with a partner stratified for men (a) and women (b)
CRC−DM− persons without colorectal cancer and diabetes, CRC−DM+ persons with only diabetes, CRC+DM− persons with only colorectal cancer, CRC+DM+ persons with colorectal cancer and diabetes
[a]Clinical relevant difference compared to CRC−DM−persons according to Norman et al.[28]
[b]The scale on male sexual problems could not be calculated among the sample of the general population (CRC−DM− and CRC−DM+) because only erectile problems and not ejaculation problems were assessed.
[c]Female sexual problems were not included as they were not assessed among the sample of the general population (CRC−DM− and CRC−DM+) and only 17 CRC+DM+ women responded to these questions

Sexual functioning was highest among CRC−DM− and lower among CRC−DM+, CRC+DM−, and CRC+DM+ in both men and women (both P-values of <0.0001) (Figure 1a, b). Sexual enjoyment among men was lowest among CRC+DM− (Figure 1a). Among women, sexual enjoyment was lowest among CRC patients either with or without DM (Figure 1b). CRC+DM+ men reported more male sexual problems compared with CRC+DM− men, 55±38 versus 45±37, respectively (P-value=0.006). As the number of CRC−DM− women with a partner who responded to the questions on sexual functioning (n=10), sexual enjoyment (n=5), and female sexual problems (n=1) was low, no multivariable analyses were conducted regarding sexual functioning among women.

Individual and combined effects of CRC and DM on HRQoL and sexual functioning

No biological interaction effect of CRC and DM on any of the HRQoL and sexual functioning scales was found in the linear regression models (Table 3, model 1). Since the interaction terms were not significant, they were excluded in the models estimating the main effects of CRC and DM (Table 3, model 2). CRC, irrespective of having DM, was associated with lower functioning and worse symptom scores on most EORTC-QLQ-C30 subscales, except global health, pain, and appetite loss. Furthermore, CRC was independently associated with lower sexual functioning among men. DM, irrespective of having CRC, was associated with lower physical functioning and more symptoms of dyspnea. Finally, when including only CRC patients (Table 3, model 3), CRC+DM+ persons reported lower physical functioning and more male sexual problems than CRC+DM− persons.

Male sexual problems, including erection and ejaculation problems, were studied separately in more detail. Erection problems were reported among 15% of CRC−DM−, 27% of CRC−DM+, 48% of CRC+DM−, and 59% of CRC+ DM+ men (P-value <0.0001). Adjusted multivariable logistic regression models showed that CRC, irrespective of having DM, resulted in more erection problems (OR=4.3; 95%CI:2.6-7.3) while having DM, irrespective of having cancer, did not result in more erection problems (OR=1.5; 95%CI:0.9- 2.4). Data on ejaculation problems were collected only among men with CRC. No difference in ejaculation problems was found between CRC+DM−and CRC+DM+ men (39 and 48%, respectively, P-value=0.04). Again, after adjustments, no main effect of DM on ejaculation problems among CRC males was found (OR=1.6; 95%CI:0.9-2.7).

Table 3 Adjusted multivariable linear regression models to assess differences in HRQoL and sexual functioning among patients with or without CRC and/or DM. Unstandardized regression coefficients are shown in the table

Dependent variables	Analysis with total sample									Analysis with CRC sample only	
	Model 1[a]					Model 2[a]				Model 3[b]	
	DM		CRC		CRC*DM	DM		CRC		DM	
HRQoL											
Global health	-0.7		0.2		-1.6	-2.0		-0.0		-2.6	
Physical functioning	-1.3		-3.8	**	-3.9	-4.3	**	-4.2	**	-3.8	*
Emotional functioning	2.1		-2.6	*	-2.9	-0.3		-3.0	*	-1.7	
Role functioning	4.6		-4.1	*	-5.4	0.4		-4.7	**	-0.8	
Cognitive functioning	1.2		-3.3	*	-2.8	-1.0		-3.7	**	-1.7	
Social functioning	1.5		-5.9	**	-0.5	1.1		-6.0	**	1.0	
Pain	-7.3	*	-2.7		6.5	-2.1		-1.9		-0.8	
Fatigue	1.3		2.9	*	1.7	2.7		3.1	*	3.5	
Nausea/vomiting	0.9		1.3		-0.1	0.8		1.3	*	1.2	
Dyspnea	-0.9		3.2	*	5.4	3.4	*	3.9	*	3.1	
Insomnia	-6.1		4.9	*	3.1	-3.6		5.3	**	-2.5	
Appetite loss	3.8		2.1	*	-3.1	1.4		1.8		2.3	
Constipation	-2.6		3.2	*	2.2	-0.9		3.5	**	0.4	
Diarrhea	2.6		7.2	**	-1.9	1.1		7.0	**	1.0	
Financial problems	-0.6		2.2	*	1.4	0.5		2.4	*	0.6	
Sexual functioning among men[c]											
Sexual functioning	-1.4		-8.0	**	1.0	-0.7		-7.9	**	-0.8	
Sexual enjoyment	-0.7		-3.9		6.4	3.6		-3.0		5.6	
Male sexual problems	NA		NA		NA	NA		NA		9.4	*

CRC−DM− persons without colorectal cancer and diabetes, CRC−DM+ persons with only diabetes, CRC+DM− persons with only colorectal cancer, CRC+DM+ persons with colorectal cancer and diabetes, NA not applicable [the male sexual problems scale could not be calculated among the sample of the general population (CRC−DM−and CRC−DM+) because only erectile problems and not ejaculation problems were assessed]

*P-value <0.01,

**P-value <0.0001

[a]Adjusted for sex, age, education and comorbidity

[b]Adjusted for sex, age, education, comorbidity, BMI, cancer stage, time since cancer diagnosis and primary cancer treatment

[c]Analyses on sexual functioning scales are only conducted among men with a partner, all models on sexual functioning are adjusted for age, education and comorbidity and model 3 is additionally adjusted for BMI, cancer stage, time since cancer diagnosis and primary cancer treatment

Discussion

This cross-sectional study showed that CRC, irrespective of having DM, is significantly associated with poorer functioning and more symptoms, except for global health, pain, and appetite loss. Moreover, CRC is independently associated with lower sexual functioning and more erection problems among males. Having DM, irrespective of having CRC, is associated with lower physical functioning and more symptoms of dyspnea, but not with sexual functioning. Importantly, having both CRC and DM did not result in more negative outcomes than the sum of their individual effects.

From this study, we can conclude that CRC and its treatment seem to contribute stronger to a lower HRQoL compared to DM. CRC was found to be consistently associated with lower functioning and more symptoms. This is in line with the previous literature, reporting better HRQoL for patients with DM compared with patients with other chronic conditions like cardiac problems, arthritis, and lung problems[13]. It is possible that patients perceive cancer as a more life-threatening disease than DM, which might explain the stronger association of cancer with HRQoL. Indeed, it was found that the diagnosis of type 2 DM itself does not have a negative impact on perceived health status[31].

An important finding of this study is the impact of CRC on sexual problems, especially among men. CRC was independently associated with a 4.3 times higher likelihood to report erection problems, irrespective of DM status. A previous study among another CRC cohort reported more male sexual problems among rectal cancer patients, compared with colon cancer patients[10]. While these differences were also apparent in our study, we could not test the effect of tumor type on sexual functioning in multivariable analyses. This was due to the low number of colon cancer patients (n=79) and rectal cancer patients (n=49) with DM who filled out the questions on sexual functioning. However, when adjusting for cancer type, i.e., rectal or colon cancer, in our analyses, results were similar as presented here (results not shown).

It is known that a high BMI is associated with a higher risk of developing DM and impaired HRQoL[32]. This could have influenced some of our results as BMI was not included in all statistical models since BMI was not available for the sample of the general population. BMI significantly contributed to worse physical functioning, more fatigue, more dyspnea, less appetite loss, fewer problems with constipation, and better emotional functioning, when included as a covariate in the model among persons with CRC. The effect of BMI and other lifestyle factors on HRQoL of cancer patients with DM will be studied in more detail in future longitudinal analyses of this study cohort.

This study has several limitations. First, this was a secondary analysis of previously collected data which resulted in the inclusion of an unbalanced number of persons per studied group. As a result, sexual problems could not be assessed in stratified analysis

for rectal and colon cancer patients. Furthermore, after including only persons aged ≥60 years, baseline characteristics still differed across groups. While we addressed this issue by including a range of relevant variables for adjustment in the multivariable regression models, this might not be sufficient, resulting in possible residual confounding. Moreover, the self-reported measure of DM did not discriminate between types 1 and 2 DM. Furthermore, no information on the time of DM diagnosis, either before or after cancer diagnosis was available. People who already live longer with DM might have reached a better metabolic control of their blood sugar levels, and this could have resulted in an underestimation of the main effect of DM. Also, we had no detailed clinical information on duration of DM, blood glucose levels, and DM treatment and complications. It has previously been shown that DM complications are strongly associated with HRQoL[13,33] and thus, it is possible that this has influenced our results. In addition, as we included cancer patients 1 to 10 years after their cancer diagnosis, our patient selection might be influenced by a survivorship bias, and therefore, these results might not be generalizable to all colorectal cancer patients. Finally, we cannot prove causality due to the cross-sectional study design.

In conclusion, having both CRC and DM did not result in a worse HRQoL and sexual functioning than the sum of the individual effects of CRC and DM. As CRC was found to be consistently associated with lower functioning and more symptoms, CRC and its treatment seem to contribute stronger to a lower HRQoL and sexual functioning compared with DM. However, as DM was also independently associated with some of the studied subscales, the clinical management of comorbid diseases among cancer patients remains an important aspect of clinical care. This study provides an insight to the effect of both cancer and DM on long-term problems with HRQoL and sexual functioning. These patient reported outcomes are becoming more important; however, more research is needed to prove their relevance in treatment evaluation.

4

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4

CHAPTER 5

THE IMPACT OF DIABETES ON NEUROPATHIC SYMPTOMS AND RECEIPT OF CHEMOTHERAPY AMONG COLORECTAL CANCER PATIENTS: RESULTS FROM THE PROFILES REGISTRY

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Abstract

Purpose
This study assessed differences in neuropathic symptoms between colorectal cancer (CRC) patients with and without diabetes. Moreover, we aimed to explore whether neuropathic symptoms could be explained by the receipt of chemotherapy as it was previously shown that cancer patients with diabetes less often receive chemotherapy.

Methods
Data from a cross-sectional study among CRC patients (2-11 years after diagnosis) was used. Data were collected by the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry which is linked to clinical data from the population-based Eindhoven Cancer Registry. Diabetes status was self-reported and neuropathic symptoms were measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20).

Results
Two hundred eighteen CRC patients with diabetes were matched on age and sex to 975 CRC patients without diabetes. After adjustments for cancer treatment including chemotherapy and other covariates, logistic regression models showed that CRC patients with diabetes experienced more mild to severe neuropathic symptoms, including tingling fingers or hands (odds ratio (OR)=1.40; 95% confidence interval (CI):1.00-1.94), tingling toes or feet (OR=1.47; 95%CI:1.04-2.07), numbness in toes or feet (OR=1.83; 95%CI:1.28-2.62) and erection problems among men (OR=1.83; 95%CI:1.11-3.03) as compared to CRC patients without diabetes. No differences in cancer treatment were found between CRC patients with and without diabetes.

Conclusion
CRC patients with diabetes experienced more neuropathic symptoms, regardless of cancer treatment, suggesting that diabetes itself rather than treatment with chemotherapy results in more neuropathic symptoms among cancer patients with diabetes compared to those without.

Introduction

Due to the aging of the population, the number of elderly suffering from multiple chronic diseases is increasing[1]. A recent review shows that at least half of the elderly aged 60 years or older are living with two or more chronic diseases[2]. Both cancer and diabetes belong to the four most common chronic diseases, which are among the leading causes of death worldwide with 7.6 million and 1.3 million deaths in 2008, respectively[3]. Colorectal cancer (CRC) is one of the most common cancers with over one million new cases worldwide each year[4]. CRC and diabetes often co-occur, mostly as a result of overlapping risk factors, including obesity, a sedentary lifestyle, and a western diet[5,6]. As a result, diabetes is prevalent among 14% of CRC patients[7], compared to 8% in the general Dutch population[8]. CRC patients with diabetes have about a 30% higher mortality risk compared to CRC patients without diabetes[9,10]. Having diabetes seems to increase the risk of complications and cancer recurrence among CRC patients[10]. Moreover, cancer patients with diabetes are less aggressively treated for their cancer[9,11] are more often hospitalized and are more likely to suffer from chemotherapy-related toxicity[11].

Among cancer patients, neuropathic symptoms are often induced by chemotherapeutic agents including taxanes and platinum agents, such as oxaliplatin[12]. The incidence of chemotherapy-induced peripheral neuropathy is strongly dependent on the type of agent, duration of administration and dosage used[12]. Neuropathic symptoms can be reversed, but a significant number of patients continue experiencing neuropathic symptoms many years after treatment is completed[13-16]. A previous study showed that around 10% of CRC patients (2-11 years after diagnosis) still reported mainly sensory symptoms, with a higher prevalence among those who were treated with oxaliplatin[16]. Similarly, neuropathy is one of the most common complications of diabetes, with a prevalence around 30%[17-19]. Neuropathy is a result of cellular damage caused by oxidative stress and inflammation as a consequence of hyperglycemia and dyslipidaemia in diabetes[20]. The most common presentation is distal symmetrical polyneuropathy characterized by numbness, tingling, pain or weakness mainly occurring in the feet[20]. Diabetes patients with neuropathy report a lower quality of life[21], have an increased risk of falling[21], and have a higher risk of ulcerations which in turn may lead to amputation of the lower extremities[22,23].

Despite the high prevalence of neuropathy among cancer and diabetes patients, little is known about neuropathic symptoms among patients with both cancer and diabetes. Therefore, the aim of this study was to assess neuropathic symptoms among CRC patients with and without diabetes. As it was previously shown that cancer patients with diabetes less often receive adjuvant chemotherapy[9], we evaluated potential differences in treatment between cancer patients with and without diabetes. It is expected that oncologists are more reluctant to treat diabetes patients, who already have an elevated risk of developing neuropathy, with chemotherapies that may induce neuropathy. We therefore hypothesize that CRC patients with diabetes are less often treated with chemotherapy including oxaliplatin. Subsequently, the expected selective treatment

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of diabetes patients with chemotherapy may result in less or perhaps similar levels of neuropathic symptoms as compared with CRC patients without diabetes.

Materials and methods

Study population

Data from the second wave of a longitudinal population-based survey among CRC patients was used. The survey started in 2010 and the second data wave was conducted in 2011 and included a self-reported measure on neuropathic symptoms. Data was collected within the framework of the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry[24]. The PROFILES registry is linked directly to clinical data from the Eindhoven Cancer Registry (ECR) which records all newly diagnosed cancer patients in the south of the Netherlands covering an area with 2.3 million inhabitants and 10 hospitals[25].

Data collection

All CRC patients diagnosed between January 2000 and June 2009 were sampled from the ECR and invited for the survey in 2011 (i.e., all patients were surveyed 2-11 years after cancer diagnosis). Patients who died prior to the study start, patients with serious cognitive impairment or those who were in transition to terminal care were excluded. All eligible patients received an invitation letter from their (ex-)attending specialist with login codes to the online survey and a postcard to request a paper version whichever they preferred. Only those who responded in the first wave in 2010 were invited for the second wave and reminders were sent after 2 months. Data from the PROFILES registry is available for non-commercial scientific research and subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl)[24]. More details of the data collection are described elsewhere[26].

Socio-demographic and clinical characteristics

Age and sex along with other clinical characteristics including primary cancer treatment, stage, and time since diagnosis were retrieved from the ECR. Additional data on marital status, educational level, and height and weight (used to calculate body mass index (BMI)) were addressed in the survey. Having diabetes was self-reported and measured with the Self-administered Comorbidity Questionnaire (SCQ)[27]. All patients reported whether they had diabetes at the time of questionnaire completion in 2011 or in the past 12 months. In addition, the year of diabetes diagnosis was self-reported in the survey. Similarly, comorbidities other than diabetes were assessed with the SCQ[27].

Peripheral neuropathy

Peripheral neuropathy was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20)[28] which consists of 20 items scored on a four point Likert scale ranging from (1) "Not at all" to (4) "Very much." As diabetes is also associated

with an increased risk of peripheral neuropathy it is difficult to disentangle chemotherapy induced neuropathy from diabetes related neuropathy. Therefore, throughout this paper we will use the general term "peripheral neuropathy."

Differences in treatment between colorectal cancer patients with and without diabetes

Previous studies show that colon cancer patients with diabetes were more often operated and had a lower hazard (albeit not statistically significant) of receiving chemotherapy than those without diabetes[9]. Therefore we assessed differences in treatment between CRC patients with and without diabetes among an age- and sex- matched survey sample, as well as among the unmatched original sample from the ECR. We also investigated this latter sample from the ECR to assess whether our survey sample was biased as a result of survivorship, i.e., that only the healthiest patients responded to our questionnaire. Therefore, we selected all patients diagnosed between January 2000 and June 2009 who were alive prior to the study start of the survey at the 1st of November 2010. As the ECR collects data on comorbidity at cancer diagnosis from the medical records since 1993, diabetes status of the unmatched original sample with CRC patients was retrieved from the ECR.

Statistical analyses

To account for large differences in age distribution, patients with diabetes from the survey sample were matched on age group and sex to those without diabetes. For patients with (n=218) and without (n=1307) diabetes, six strata were formed using age (i.e. <60, 60-70, or ≥70 years old) and sex (male and female). Within each stratum, a maximum number of persons from the patients without diabetes were randomly matched based on the strata frequency distribution of the patients with diabetes. Differences in sociodemographic and clinical characteristics were assessed with independent sample T-tests and chi-square tests where appropriate. Differences in neuropathic symptoms between CRC patients with and without diabetes were assessed per individual item of the EORTC QLQ-CIPN20. The burden of neuropathic symptoms was dichotomized into two categories: mild to severe symptom burden (response categories "a little," "quite a bit," and "very much") and no symptom burden (response category "not at all"). Differences in the burden of neuropathic symptoms between CRC patients with and without diabetes were assessed with univariate chi-square tests and with multivariable logistic regression models adjusted for BMI, educational level, the number of comorbid conditions (excluding diabetes) and cancer treatment (including a dichotomous variable for surgery, radiotherapy and chemotherapy).

Differences in primary cancer treatment were assessed among the matched survey sample and the unmatched original sample from the ECR with independent T-tests and chi-square tests where appropriate. For both groups, differences in the receipt of chemotherapy and/or radiotherapy between CRC patients with and without diabetes were assessed with multivariable logistic regression models adjusted for sex, age at

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cancer diagnosis, and stage. A P-value<0.05 was regarded as statistically significant and all analyses were conducted using SAS statistics (version 9.3, SAS Institute Inc., Cary, NC).

Results

Study population

Of the 1981 CRC patients who were eligible for participation in 2011, 1643 (83%) responded and filled out the questionnaire. Of the 1643 respondents, 118 (7%) did not fill out whether they had diabetes or not and were excluded. Two hundred eighteen (13%) patients reported having diabetes and were matched on age and sex to 975 patients without diabetes. CRC patients with diabetes (CRC+DM+) were lower educated (21 vs 14% with a low education, P-value=0.03), had a higher BMI (38 vs 15% with a BMI ≥30 kg/m2, P-value<0.0001), and reported more comorbid conditions (47 vs 37% with ≥2 comorbid conditions, P-value=0.0005) as compared with CRC patients without diabetes (CRC+DM-) (Table 1). No differences were found between CRC+DM- and CRC+DM+ patients regarding marital status, cancer stage at diagnosis, cancer type, and initial treatment. In addition, no differences were found regarding time since diagnosis, both patients with and without diabetes were surveyed on average 6 years (SD=2.8 years) after diagnosis. One hundred eighty-three (84%) CRC+DM+ patients reported their diabetes diagnosis date and were diagnosed on average 9.5±9.6 years prior to the study start (Table 1).

Differences in the burden of neuropathic symptoms between CRC patients with and without diabetes

Up to 39% of CRC+DM+ patients reported having mild to severe neuropathic symptoms (Table 2). In addition CRC+DM+ patients more often reported mild to severe neuropathic symptoms, regarding tingling fingers or hands (34 vs 25%, P-value=0.008), tingling toes or feet (31 vs 22%, P-value=0.0004), numbness in toes or feet (29 vs 18%, P-value=0.0002), aching or burning pain in toes or feet (20 vs 14%, P-value=0.02), and more trouble standing or walking (23 vs 15%, P-value=0.005) as compared with CRC+DM- patients. Moreover men from the CRC+DM+ group reported more problems with getting or maintaining an erection (84 vs 74%, P-value=0.01). After adjustments for BMI, the number of comorbid conditions, educational level and cancer treatment (including surgery, radiotherapy and chemotherapy) in multivariable logistic regression models, patients with DM were more likely to report mild to severe symptoms including tingling fingers or hands (odds ratio (OR)=1.40; 95% confidence interval (CI):1.00-1.94, P-value=0.05), tingling toes or feet (OR=1.47; 95%CI:1.04-2.07, P-value=0.03), numbness in toes or feet (OR=1.83; 95%CI:1.28-2.62, P-value=0.001) and erection problems among men (OR=1.83; 95%CI:1.11-3.03, P-value=0.02).

Table 1 Sociodemographic and clinical characteristics of the study population

	CRC+DM+ n=218	CRC+DM- n=975	P-value
Patient characteristics			
Sex (n(%))			
Male	146 (67)	653 (67)	1
Female	72 (33)	322 (33)	
Age (mean ± SD)	71.3±8.1	70.8±8.6	0.37
Education (n(%))[a]			
Low	45 (21)	138 (14)	0.03
Medium	128 (59)	580 (60)	
High	44 (20)	248 (26)	
Marital status			
Married/with partner	160 (74)	781 (81)	0.07
Divorced/Single	18 (8)	76 (8)	
Widowed	37 (17)	112 (12)	
BMI (n(%))			
< 25 kg/m^2	41 (19)	346 (36)	<0.0001
25 - 30 kg/m^2	93 (43)	482 (50)	
≥ 30 kg/m^2	83 (38)	143 (15)	
Comorbid conditions (n(%))			
0	35 (16)	277 (28)	0.0005
1	80 (37)	335 (34)	
≥2	103 (47)	363 (37)	
Diabetes duration at study start (mean number of years ± SD)	9.5±9.6		
Diabetes duration at study start (n(%))			
< 5 years	69 (32)		
5-10 years	52 (24)		
≥ 10 years	62 (28)		
Missing	35 (16)		
Cancer characteristics			
Age at cancer diagnosis (mean ± SD)	65.5±8.2	64.9±8.9	0.34
TNM stage (n(%))			
I	66 (30)	297 (30)	0.49
II	84 (39)	347 (36)	
III	61 (28)	272 (28)	
IV	5 (2)	33 (3)	
Unknown	2 (1)	26 (3)	
Cancer type (n(%))			
Colon cancer	129 (59)	587 (60)	0.78
Rectal cancer	89 (41)	388 (40)	
Primary treatment (n(%))			
Surgery only	107 (49)	468 (48)	0.61
Surgery and radiotherapy	43 (20)	231 (24)	
Surgery and chemotherapy	50 (23)	192 (20)	
Surgery, radio- and chemotherapy	17 (8)	80 (8)	
Chemotherapy only	1 (0)	2 (0)	
Oxaliplatin (n(%))[b]	21 (26)	75 (20)	0.19
Time since diagnosis (mean ± SD)	5.9±2.7	6±2.8	0.75

[a]Education levels included low=no/primary school; medium=lower general secondary education/vocational training; or high=pre-university education/high vocational training/university.
[b]Only patients diagnosed after 2008 were included, as oxaliplatin was completely registered from 2008 onwards

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As most differences between CRC+DM- and CRC+DM+ patients were found on the sensory items of the EORTC QLQ-CIPN20 (Table 2), we additionally assessed the burden of the sensory symptoms according to the original response categories (Figure 1). This revealed that ≤3 % of both CRC+DM- and CRC+DM+ patients reported being "very much" affected on any of the sensory items presented in Figure 1. The response category "a little" was chosen more often (i.e. ranged between 2 and 4% for trouble distinguishing temperature of hot and cold water to up to 27 and 33% for trouble hearing for CRC+DM- and CRC+DM+ patients, respectively).

Treatment differences between CRC+DM- and CRC+DM+

Among the matched survey sample, no difference was found in primary cancer treatment between CRC+DM- and CRC+DM+ patients (Table 1). Similarly in multivariable logistic regression models excluding stage I CRC patients and adjusted for sex, age at cancer diagnosis and cancer stage, no association was found between diabetes and the receipt of chemotherapy (OR=1.27; 95%CI:0.79-2.04, P-value=0.33), radiotherapy (OR=0.88; 95%CI:0.59-1.34, P-value=0.56), nor for the receipt of oxaliplatin (OR=1.58; 95%CI:0.73-3.39, P-value=0.25). Differences in treatment were also addressed in the original, unmatched sample from the ECR (Table 3). A total of 5733 CRC patients were included, of whom 613 (11%) had diabetes, 4642 (81%) did not have diabetes, and of 478 (8%) patients the diabetes status was unknown at cancer diagnosis. CRC+DM+ patients were more often treated with surgery only (61 vs 54%, P-value=0.008), and less often treated with oxaliplatin (16 vs 22%, P-value=0.03, Table 3) as compared to CRC+DM- patients. However, multivariable regression models excluding stage I CRC patients and adjusted for sex, age at cancer diagnosis and cancer stage did not show an association between diabetes and the receipt of chemotherapy (OR =1.08; 95%CI:0.81-1.44, P-value=0.59), radiotherapy (OR=0.79; 95%CI:0.61-1.03, P-value=0.09), nor oxaliplatin (OR=0.78; 95%CI:0.47-1.30, P-value=0.34), implying that observed differences were associated with confounding variables.

Table 2 Differences in neuropathic symptoms between colorectal cancer patients with and without diabetes

	CRC+DM+ n=218	CRC+DM- n=975	P-value
	Mild to severe symptom burden[a]	Mild to severe symptom burden[a]	
Sensory symptoms and problems (n(%))			
1. Tingling fingers or hands?	74 (34)	243 (25)	0.008[#]
2. Tingling toes or feet?	68 (31)	210 (22)	0.004[#]
3. Numbness in fingers or hands?	48 (22)	164 (17)	0.09
4. Numbness in toes or feet?	63 (29)	173 (18)	0.0002[#]
5. Aching or burning pain in fingers or hands?	30 (14)	100 (10)	0.15
6. Aching or burning pain in toes or feet?	44 (20)	133 (14)	0.02
9. Trouble standing or walking?	49 (23)	143 (15)	0.005
10. Trouble distinguishing temperature of hot and cold water?	12 (6)	34 (4)	0.17
18. Trouble hearing?	97 (45)	379 (39)	0.16
Motor scale (n(%))			
7. Cramps in hands?	48 (22)	204 (21)	0.73
8. Cramps in feet?	65 (31)	254 (27)	0.25
11. Trouble holding a pen which made writing difficult?	28 (13)	105 (11)	0.4
12. Trouble handling small objects (e.g. buttoning a blouse)?	61 (28)	249 (26)	0.51
13. Trouble opening jar/bottle due to loss of strength in hands?	65 (30)	270 (28)	0.56
14. Trouble walking because your feet come down to hard?	25 (12)	75 (8)	0.08
15. Trouble walking stairs or standing up from a chair due to weakness in legs?	69 (32)	246 (26)	0.06
19. Only for those driving cars: Trouble driving due to use of pedals?	13 (8)	50 (6)	0.48
Autonomic scale (n(%))			
16. Dizziness after standing up?	51 (24)	211 (22)	0.63
17. Blurry vision?	48 (22)	188 (20)	0.37
20. Only for males: Trouble getting or maintaining an erection?	118 (84)	463 (74)	0.01[#]

[a]Mild to severe symptom burden reflect the response categories: 'a little', 'quite a bit' and 'very much'
[#]Remains statistically significant (P<0.05) in a multivariable logistic regression model adjusted for BMI, the number of comorbid conditions, educational level and cancer treatment (including dichotomous variables for surgery, radiotherapy and chemotherapy)

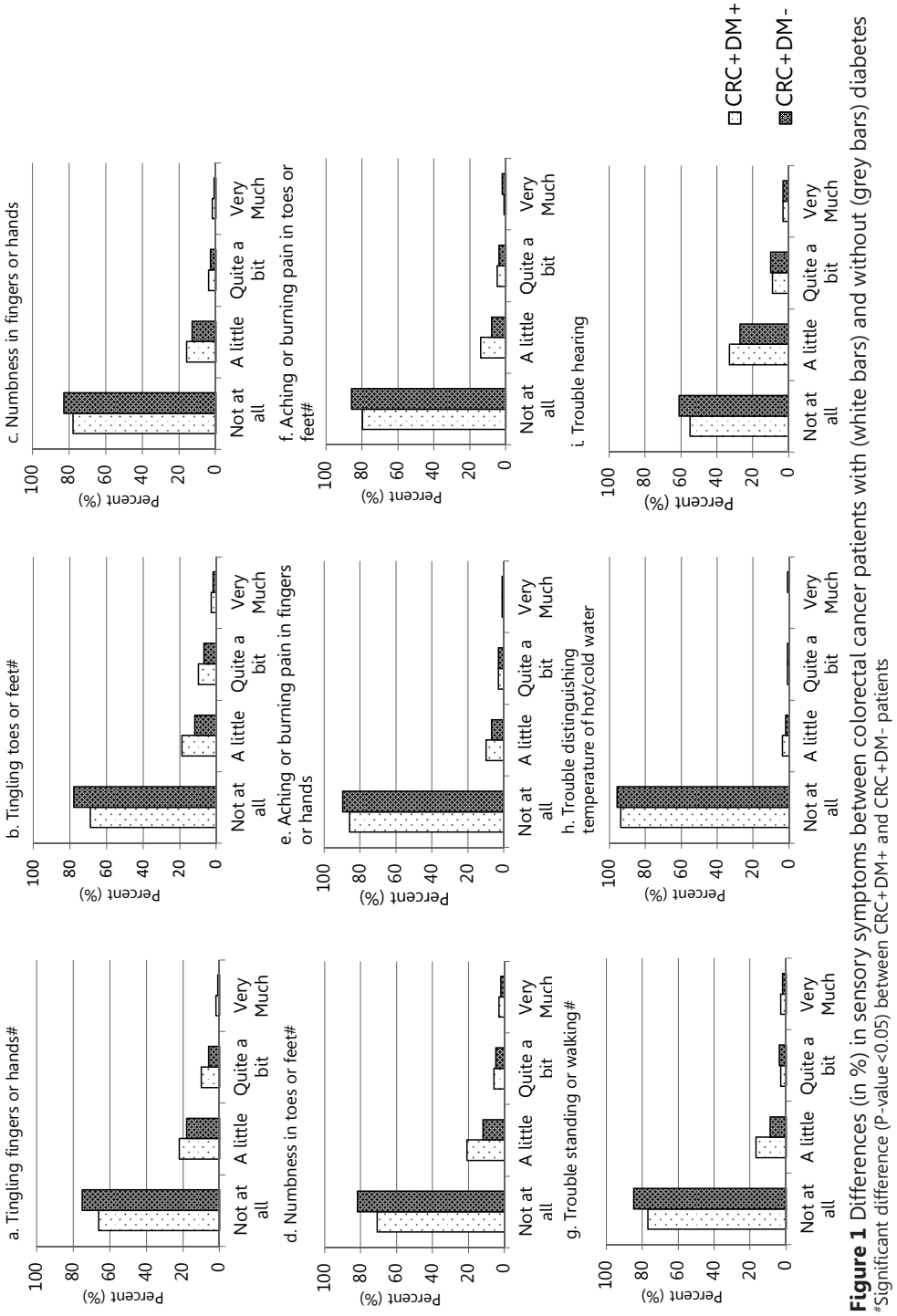

Figure 1 Differences (in %) in sensory symptoms between colorectal cancer patients with (white bars) and without (grey bars) diabetes
#Significant difference (P-value <0.05) between CRC+DM+ and CRC+DM- patients

Table 3 Differences in patient and clinical characteristics among CRC patients with and without diabetes from the unmatched, original selection drawn from the ECR

	CRC+DM+ (ECR) N=613	CRC+DM- (ECR) N=4642	P-value
Sex (N(%))			
Male	316 (52)	2443 (53)	0.62
Female	297 (48)	2199 (47)	
Age at cancer diagnosis (mean±SD)	69.6±8.6	65.3±11.0	<0.0001
Stage (N(%))			
I	165 (27)	1363 (29)	0.11
II	265 (43)	1805 (39)	
III	145 (24)	1186 (26)	
IV	13 (2)	142 (3)	
Unknown	25 (4)	146 (3)	
Treatment (N(%))			
Su only	372 (61)	2492 (54)	0.008
Su + RT	103 (17)	944 (20)	
Su + CT	100 (16)	824 (18)	
Su + RT + CT	32 (5)	351 (8)	
Other	6 (1)	31 (1)	
Oxaliplatin (N(%))[a]			
No	176 (84)	918 (78)	0.03
Yes	33 (16)	263 (22)	

[a]Only patients diagnosed after 2008 were included, as oxaliplatin was completely registered from 2008 onwards

Discussion

This study shows that CRC patients with diabetes reported a higher frequency of neuropathic symptoms compared to age- and sex-matched CRC patients without diabetes. Differences in neuropathic symptoms appeared not to be related to differences in receipt of chemotherapy. CRC patients with diabetes reported more symptoms of tingling fingers or hands, tingling and numbness of toes or feet, and erection problems among men. This study also showed that the majority of the reported symptoms were of mild severity. Although we hypothesized that clinicians might be reluctant with the treatment of chemotherapy among those with diabetes, we did not observe differences in cancer treatment between cancer patients with and without diabetes.

Using data pooled from three randomized controlled trials, a study of 1585 CRC patients, of whom 135 had diabetes, assessed whether the presence of diabetes influenced the incidence, severity and course of neuropathy with oxaliplatin therapy[29]. That study did not observe an influence of diabetes on the development of neuropathy in CRC patients receiving oxaliplatin therapy; however, neuropathy was assessed before and during

treatment, while long-term effects were not addressed[29]. In contrast, most previous studies did not assess the impact of diabetes on neuropathic symptoms among cancer patients as primary objective but mainly adjusted for diabetes in multivariable analyses. For example, one study assessed the association between neuropathy and breast cancer recurrence in a clinical trial among 4544 breast cancer patients, showing that hyperglycemia was associated with a higher likelihood of peripheral neuropathy (OR=1.42; 95%CI:1.13-1.78)[30]. In contrast, other studies that included diabetes as a predictor for the development of neuropathic symptoms did not find an association[31-33]. A study among 169 resected CRC patients, including 29 CRC patients with diabetes, showed no association between having diabetes and the presence of neuropathic symptoms in unadjusted analyses[33]. Moreover, a study among 340 multiple myeloma patients receiving bortezomib, of which 39 patients also had diabetes, again showed that diabetes was not a predictor for the development of peripheral neuropathy[32]. Moreover, a study among 45 patients with different cancer types up to 6 years after the receipt of cisplatin or oxaliplatin did not identify diabetes as a determinant for persistent neuropathy[31]. Another, relatively small study (n=62), showed that colon cancer patients with diabetes (n=15) did not have a higher prevalence of peripheral neuropathy (unadjusted OR=2.8, P-value=0.10) but they did develop neuropathy at a lower dose of oxaliplatin treatment (338 vs 610 mg/m^3) as compared with colon cancer patients without diabetes[34]. However, comparison of our results with the results from these previous studies is difficult as the earlier studies assessed the effect of diabetes on neuropathy mainly as a covariate rather than as a primary study objective. As the prevalence of diabetes in these studies was often low, most were underpowered to detect a true diabetes effect. Moreover, previous studies evaluated different therapeutic agents, and the study populations of these previous studies are very heterogeneous. Furthermore, most studies used clinical diagnoses to grade the severity of neuropathic symptoms[32-34] and therefore mainly focused on more severe (e.g. ≥grade 2 from the Common Terminology Criteria for Adverse Events (CTAE)) neuropathic symptoms. As most symptoms are subjective in nature, we believe that it is important to not only neurologically test neuropathy symptoms but also assess self-reported neuropathy. Importantly, we observed a high prevalence of symptoms, but apparently with a somewhat lower intensity. Using clinical diagnosis and cutoff values to define neuropathy as was done in previous studies might underestimate less severe, but highly prevalent symptoms. There should be more awareness for the less severe symptoms as patients who report multiple symptoms with a low severity can experience a significant impact on their daily life.

We observed a higher burden of neuropathic symptoms among CRC patients with diabetes as compared to those without diabetes, regardless of cancer treatment (including chemotherapy). This suggests that diabetes itself and not the treatment with chemotherapy might be responsible for the found effects. It could be that diabetes severity and duration might have influenced our results. In this study, 106 (58%) of the 183 CRC+DM+ patients who reported the date of their diabetes diagnosis were diagnosed with diabetes prior to their cancer diagnosis (mean 8.9±9.5 years prior to

cancer diagnosis), indicating that these patients already might have had significant neuropathic symptoms at CRC diagnosis. If the diabetes itself and not the treatment with chemotherapy results in more neuropathic symptoms among cancer patients with diabetes, clinicians do not need to be reluctant with the treatment with chemotherapy among cancer patients with diabetes. However, more longitudinal studies addressing neuropathic symptoms at cancer diagnosis (i.e. before the start on chemotherapy) should be conducted to confirm our results.

No differences in cancer treatment were observed between CRC patients with and without diabetes. In contrast, a previous analysis by our group showed that cancer patients with diabetes were less likely to receive adjuvant chemotherapy, albeit this did not reach statistical significance[9]. A more recent, longitudinal analyses in our region revealed that differences in treatment between CRC patients with and without diabetes decreased over time[35]. Multivariable regression models showed only a difference among stage III colon cancer patients with those with diabetes being less likely to be treated with chemotherapy compared to those without diabetes (OR=0.7; 95%CI:0.5-0.9)[35]. As we included stage II, III and IV colon as well as rectal cancer patients in our current evaluation and numbers were too low to further stratify, this might explain why we did not observe differences in cancer treatments.

This study contributes to the limited data available regarding neuropathic symptoms among cancer patients with and without diabetes. Strengths of this study include its self-reported measure of neuropathic symptoms, which might be more sensitive to mild symptoms, the large population-based sample, and the high response rate. However, this study has several limitations; first, diabetes prevalence was self-reported at time of the questionnaire. As a result, some patients may have had unrecognized type 2 diabetes and no distinction could be made between type 1 and type 2 diabetes; we did not have information regarding blood glucose levels, and other complications. In addition, information regarding the burden of neuropathic symptoms prior to cancer treatment was not available. Furthermore, we do not have any detailed information regarding the chemotherapeutic agents used, except for oxaliplatin which was only available for a subset of our sample as it was registered by the ECR from 2008 onwards. However, it has previously been shown that severity of neuropathic symptoms depends on type of chemotherapeutic agent, dose and the number of cycles administered[12]. As the occurrence of neuropathic symptoms often result in a decrease of the chemotherapy dosage, it is possible that those with acute neuropathic symptoms did not develop chronic neuropathic symptoms later on due to dose adjustments. Future research should study the impact of diabetes on peripheral neuropathy among cancer patients prospectively and assess neuropathic symptoms according to the type and dosage of different treatments used.

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In conclusion, this study shows that CRC patients with diabetes more frequently report a mild to severe neuropathic symptom burden compared to CRC patients without diabetes, mainly regarding tingling fingers or hands, tingling and numbness of toes or feet and erection problems among men. The higher neuropathic symptom burden appeared not to be associated with differences in chemotherapy treatment, suggesting that diabetes itself rather than chemotherapy results in more symptoms among cancer patients with diabetes compared to those without.

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CHAPTER 6

PROSPECTIVELY MEASURED LIFESTYLE FACTORS AND BMI EXPLAIN DIFFERENCES IN HEALTH-RELATED QUALITY OF LIFE BETWEEN COLORECTAL CANCER PATIENTS WITH AND WITHOUT COMORBID DIABETES

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Submitted

Abstract

Purpose
To assess the longitudinal association between lifestyle factors, BMI and Health-Related Quality of Life (HRQoL) among colorectal cancer patients with (CRCDM+) and without diabetes (CRCDM-).

Methods
Data from a longitudinal study among CRC patients diagnosed between 2000 and 2009 were used. Clinical characteristics were retrieved from the Netherlands Cancer Registry and questionnaires were sent in 2010, 2011 and 2012 using the Patient Reported Outcomes Following Initial Treatment and Long term Evaluation of Survivorship (PROFILES) registry. Lifestyle (including moderate-to-vigorous physical activity (MVPA), smoking and alcohol use), Body Mass Index (BMI), diabetes status and HRQoL were assessed in the questionnaire.

Results
1,739 (49%) patients responded to ≥2 questionnaires, of whom 126 CRCDM+ and 789 CRCDM- patients were included. CRCDM+ patients had a higher BMI (26.4±3.7 vs. 29.1±4.2 kg/m^2), whereas the number of alcohol users was lower (50 vs 70%, p-value<0.0001) among CRCDM+ as compared to CRCDM- patients. Analyses adjusted for sociodemographic and cancer characteristics showed that CRCDM+ patients reported statistically significantly lower physical function (beta=-5.76; SE=1.67), global QoL (beta=-4.31; SE=1.48) and more symptoms of fatigue (beta=5.38; SE=1.95) than CRCDM- patients. However, these effects disappeared after adjustments for lifestyle factors and BMI which were all significant predictors of HRQoL. Additional adjustment for comorbidity further attenuated the main effect of DM on HRQoL.

Conclusions
Diabetes was not independently associated with HRQoL but deteriorated HRQoL among CRCDM+ patients seem to be explained by an unhealthier lifestyle and other comorbid conditions. Moreover, residual confounding cannot be ruled out.

Introduction

Nowadays, the number of patients with several chronic diseases or comorbidity is increasing due to the increased life expectancy and aging of the population[1]. Both cancer and diabetes are common chronic diseases and were among the leading causes of death worldwide in 2008, with 7.6 and 1.3 million deaths due to cancer and diabetes, respectively[2]. Among cancer patients, diabetes is one of the most frequently observed comorbidities with a prevalence of 14% among colorectal cancer (CRC) patients[3]. Previous literature shows that patients with diabetes have an increased risk to develop CRC[4], and that patients with both CRC and diabetes have about a 30% higher mortality risk[5]. Beside these poorer prognostic outcomes, studies also indicate that patients with both cancer and diabetes have a poorer Health-related Quality of Life (HRQoL)[6-10].

Previous studies mainly reported a lower general HRQoL[6,9], physical function or mobility[7,10] and vitality[9] among cancer patients with diabetes, compared to cancer patients without diabetes. However, the majority of these studies focused on prostate cancer patients[8,9,11,12] and had a cross-sectional study design[6,7,9-11]. More importantly, only 3 studies adjusted their analyses for lifestyle factors[6,8,10], of which 2 only included Body Mass Index (BMI) and no other lifestyle factors such as physical activity, smoking or alcohol use[8,10].

Lifestyle factors have been shown to be important predictors of HRQoL among both CRC and diabetes patients. Several studies show that an increasing number of healthy lifestyle factors is associated with better HRQoL scores among CRC patients[13-15] as well as among diabetes patients[16]. Regarding the independent effect of lifestyle factors two longitudinal studies among CRC patients showed that physically active (i.e. at least 150 min/week) patients reported a higher general HRQoL as compared to patients who were insufficiently active or inactive[17,18]. Another cross-sectional study from the UK reported that CRC patients who are physically active, and have a moderate alcohol intake reported better functioning and lower levels of fatigue compared to those who did not consume alcohol[13]. No significant association between smoking and HRQoL was found[13]. In contrast, analyses of the Women's Health Study showed that persistent smoking among women with breast, colorectal and endometrial cancer were more likely to report poor physical function, poor mental health, and lower role emotional function as compared to non-smoking patients[19]. Among diabetes patients, similar associations between lifestyle and HRQoL were found. Two cross-sectional studies showed that physical activity was positively associated, whereas BMI was negatively associated with both physical and mental health[20,21]. Smoking was less often studied, but a large study (n=16,428) from the US showed that patients who were not smoking were less likely to report a poor or fair health (OR=0.71; 95%CI: 0.56-0.89)[16].

As CRC patients with diabetes (CRCDM+) are expected to have a poorer lifestyle than CRC patients without diabetes (CRCDM-), these poorer lifestyle behaviors might explain the poorer HRQoL found among CRCDM+ versus CRCDM- patients[6-10]. Moreover, prospective

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studies on differences in HRQoL between CRCDM+ and CRCDM- patients are missing. Therefore, this study aims to assess differences between CRCDM+ and CRCDM- patients in (1) lifestyle, (2) HRQoL measured prospectively and (3) to assess whether lifestyle factors explain the differences in HRQoL between CRCDM+ and CRCDM- patients. As the main focus of this study was to assess the effect of individual lifestyle factors on HRQoL longitudinally, we confined the analyses to the independent lifestyle effects and did not include a composite lifestyle score. We hypothesize that CRCDM+ patients have a poorer lifestyle and lower HRQoL as compared to CRCDM- patients.

Methods

Setting and study population

Data from a large population-based study among CRC patients were used. All CRC patients diagnosed between January 2000 and June 2009 were sampled from the southern area of the Netherlands Cancer Registry (NCR). The NCR contains clinical data on all newly diagnosed cancer patients in the Netherlands. The southern area comprises 2.4 million inhabitants, 10 hospitals and 2 radiotherapy institutes. After the initial patient selection, the Patient Reported Outcomes Following Initial Treatment and Long term Evaluation of Survivorship (PROFILES) registry was used for the longitudinal patient reported data collection[22]. Patients with cognitive impairments, unverifiable addresses and patients who died prior to the study start were excluded from the initial selection. The remaining CRC patients were invited to participate in 2010 (T1), 2011 (T2) and 2012 (T3). Ethical approval for the study was obtained from a local certified Medical Ethics Committee of the Maxima Medical Centre Veldhoven. A complete overview of the selection process can be found elsewhere[17]. The primary objective of this longitudinal study was to identify the HRQoL and health-care use of long-term CRC survivors, and relate the outcomes to patient and cancer characteristics. For this secondary analysis we only included CRC patients who were less than 5 years after cancer diagnosis when they completed their first questionnaire. This cut-off was chosen as previous research shows that patients change their lifestyle shortly after cancer diagnosis[23] Thus we expect to see most changes in lifestyle as well as in HRQoL within 5 years after diagnosis. Moreover, CRC patients with unknown diabetes status (n=5) or those who developed diabetes after completion of the first questionnaire (n=16) were excluded from this analyses. Data from this longitudinal study are (partly) available online for noncommercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration from PROFILES (www.profilesregistry.nl).

Data collection

CRC patients were invited for participation via the PROFILES registry and a letter from their (ex-) attending specialist to inform them of the study. The letter included a secured link with login and password to the online questionnaire, or patients could request a paper version of the questionnaire via a reply card, whichever they preferred. After two

months, a reminder with a paper questionnaire was sent. Patients were reassured that nonparticipation had no consequences for their follow-up care or treatment.

Diabetes status, sociodemographic and clinical characteristics

Diabetes status was self-reported using the Self-administered Comorbidity Questionnaire[24]. Patients filled out whether they had diabetes in the past year or currently. Patients who reported having diabetes at the first questionnaire were classified as having diabetes. No distinction was made between type 1 and 2 diabetes. Month and year of diabetes diagnosis were reported only at T2. Similarly the SCQ was used to assess comorbidities other than diabetes, including heart disease, high blood pressure, stroke, lung disease, anemia, kidney disease, stomach disease, liver disease, thyroid disease, depression, arthrosis, rheumatoid arthritis, and back pain. Age, gender and clinical information including cancer diagnosis date, primary cancer treatment and cancer stage were derived from the NCR. Moreover, patients reported their educational level which was categorized as low (no/primary school), medium (lower general secondary education/ vocational training) or high (pre-university education/high vocational training/university) educational level.

Lifestyle measures

Lifestyle measures were self-reported in the questionnaires and include smoking, alcohol use, height and weight and physical activity. Both smoking and alcohol were assessed as (1) never, (2) former and (3) current use. Number of cigarettes smoked per day and glasses of alcohol drunk per week were also reported. However, as the number of smokers and current alcohol users among CRCDM+ patients was low (i.e. n=13 and n=70 of the 126 included CRCDM+ patients, respectively), no measure of moderate and heavy drinking or smoking was included. Self-reported body height and weight were used to calculate BMI. Physical activity was measured using questions derived from the validated European Prospective Investigation into Cancer (EPIC) physical activity questionnaire[25]. Patients filled out how much time they spent on walking, cycling, gardening, household activities and sports, six different sport types could be specified, during winter and summer. The mean scores for all activities during winter and summer were averaged. To assess the intensity, metabolic equivalent intensity (MET) scores based on previous classifications were assigned to each activity[26,27]. Hours per week spent on moderate to vigorous physical activity (MVPA) were calculated by summing all activities with a MET-score ≥3, and include walking (MET=3.5), cycling (MET=4), gardening (MET=5) and various sports with a MET-score ≥3. Household activities (MET=3.5) were not considered as MVPA in accordance with previous research[28]. To correct for outliers, all activity scores greater than the 95th percentile were replaced by the 95th percentile.

Health-Related Quality of Life

The validated European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire (EORTC-QLQ)-C30 was used to assess HRQoL[29,30]. As previous research shows that cancer patients with diabetes mainly score lower on physical function[7,10,11],

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general HRQoL[6,9] and vitality[9] as compared to those without diabetes, and to prevent type 1 errors as a result of multiple testing, only the global QoL, physical function, and fatigue scales were included in these analyses. All items were answered on a 4-point Likert scale ranging from 'not at all' to 'very much', while the questions regarding global QoL were scored on a 7-point scale. Item scores were linearly transformed to a 1 to 100 scale. Higher scores on global QoL and physical function represent better functioning, while a higher score on fatigue symptoms correspond to more fatigue.

Statistical analyses

Differences in characteristics between respondents and non-respondents at T1, between patients who completed 1 versus those who completed ≥2 questionnaires, and CRCDM+ and CRCDM- patients of the final study sample were analyzed. Continuous variables were checked for normality. If variables were normally distributed the independent samples t-tests was used. Otherwise the non-parametric Wilcoxon-Mann-Whitney test was used to assess differences between the groups. The Chi-square test was used for categorical variables.

First, differences in BMI and MVPA between CRCDM+ and CRCDM- patients at each time point were assessed with independent samples t-tests. Smoking and alcohol status over time was recoded into 1 categorical variable with 4 categories: persistent smokers/alcohol users, persistent former smokers/alcohol users, persistent non-smokers/alcohol users and patients with fluctuating smoking/alcohol status. Patients were assigned to the persistent categories when they reported the same category on all questionnaires, otherwise they were included in the fluctuating status category. Differences in smoking and alcohol category between CRCDM+ and CRCDM- patients were assessed with Chi-square tests.

In order to gain insight into the differences in HRQoL between CRCDM+ and CRCDM- patients with different lifestyle behaviors, we reported unadjusted means of physical function, global QoL and fatigue stratified by diabetes status for each lifestyle factor measured at T1. To adjust for the dependence of observations within subjects, generalized linear mixed models, using an unstructured covariance structure were constructed. First differences in lifestyle factors between CRCDM+ and CRCDM- patients over time were assessed in a model that included the main effects of DM, time and the interaction between DM and time. When the interaction term was significant the results for CRCDM+ and CRCDM- patients were stratified, otherwise the interaction term was removed from the model in order to interpret the main effects of DM and time. Second, similar general linear mixed models were used to assess the main effects of DM and time on global QoL, physical function and fatigue. Both models that addressed differences in lifestyle and HRQoL were adjusted for sociodemographic (age, sex, educational level) and clinical characteristics (time since cancer diagnosis, cancer stage and treatment). Finally, the models predicting HRQoL were additionally adjusted for lifestyle factors to assess whether differences in HRQoL between CRCDM+ and CRCDM- could be explained by lifestyle. To examine the independent between and within-subject effects of BMI and MVPA on HRQoL, 2 terms were included in the model; a between term, represented by a person's average BMI or MVPA over the two or three time points, as well as a within term, represented by the difference between a person's BMI or MVPA at one time point and that persons average BMI or MVPA over the two or three time points. The categorical variables (i.e. persistent and fluctuating use) for both smoking and alcohol use were included in the generalized linear mixed models. The continuous variables (i.e. age and time since cancer diagnosis) were grand-mean centered in order to correctly interpret all model parameters. Moreover, as we expect that cancer patients with diabetes have more comorbid conditions other than diabetes and as comorbidity has previously been shown to impact on HRQoL among cancer patients[31], we conducted a sensitivity analyses to see whether comorbidity other than diabetes explain the differences in HRQoL (i.e. beyond lifestyle factors) between CRCDM+ and CRCDM- patients. As information on the duration of diabetes at the study start was available for a subsample, we also assessed whether there were differences between CRCDM+ with a diabetes duration <6.5 years and ≥6.5 years versus CRCDM- patients in a sub-analysis. This cut-off was based on the median diabetes duration. A p-value <0.05 was regarded as statistically significant and all analyses were conducted using SAS statistics version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Patient selection process

Of the 3,585 eligible CRC patients, 2,625 (73%) responded to the first questionnaire and 1,739 (49%) responded to ≥2 questionnaires. After excluding patients who were ≥5 years after cancer diagnosis, patients with an unknown diabetes status (n=5, 1%) and those who developed diabetes during the study period (n=16, 2%), 126 CRCDM+ and 789 CRCDM- patients were included (Figure 1). Full details of the studies selection process can be found online at http://www.profilesregistry.nl/dataarchive/study_units/view/22 under 'Data & Documentation'. More details of the study process, the comparison of responders with non-responders and the comparison of those who completed 1 versus ≥2 questionnaires are reported elsewhere[17]. In general, respondents at T1 were significantly younger, more often male, and more often diagnosed with stage I disease than non-respondents. CRC patients who completed ≥2 versus only 1 questionnaire were younger (68.4±9.4 vs. 71.3±9.4 years), less often female (43 vs. 49%), and less often diagnosed with stage IV disease (3 vs. 7%). Moreover, CRC patients who completed ≥2 versus 1 questionnaire were more likely to consume alcohol (73 vs. 61%), were more physically active (12±9 vs. 9±9 hours/week spent on MVPA), and reported a higher global QoL (79±18 vs. 73±21), higher physical function (82±19 vs. 75±23) and lower fatigue levels (20±22 vs. 26±26).

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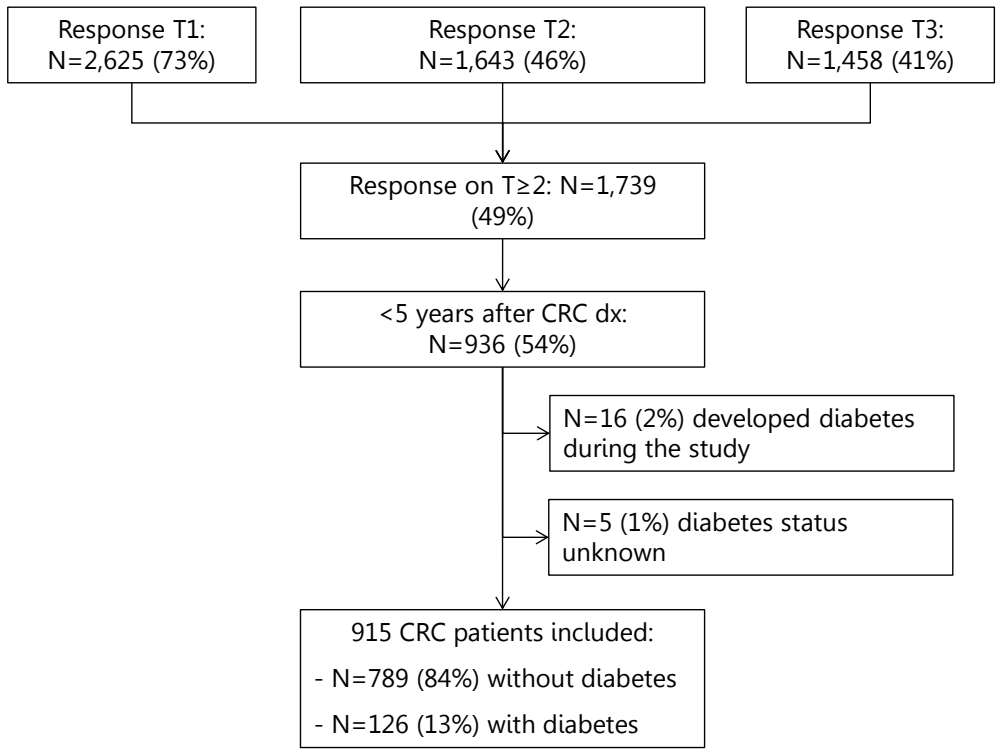

Figure 1 Flowchart of the study process

Differences in characteristics and lifestyle factors over time between CRCDM+ and CRCDM-

CRCDM+ patients were lower educated (24 versus 14% with a low education) and had more comorbid conditions other than diabetes (50% versus 35% with ≥2 comorbid conditions other than diabetes, Table 1). Diabetes duration was available for 95 (75%) CRCDM+ patients and CRCDM+ patients were diagnosed with diabetes on average 8.3±7.2 years prior to the study start. No differences between CRCDM+ and CRCDM- patients were found on sex, age, cancer stage, time since cancer diagnosis and cancer treatment.

CRCDM+ patients had a significantly higher BMI at T1 (29.1±4.2 vs. 26.4±3.7 kg/m^2), T2 (28.6±4.3 vs. 26.5±4.4 kg/m^2) and T3 (29.1±4.1 vs. 26.4±3.9 kg/m^2, all P-values<0.0001, Figure 2a). In adjusted generalized linear mixed models, no interaction of DM*time was found, indicating that BMI did not differ between both groups over time. After removing the interaction term, a main effect for diabetes (Beta=2.44; SE=0.35, p-value<0.0001) but not for time (p-value=0.06) on BMI was observed. No difference between CRCDM+ and CRCDM- in MVPA at T1 (p-value=0.07), T2 (p-value=0.27) or T3 (p-value=0.59) was observed (Figure 2b). Again, no interaction between DM and time was observed,

indicating that MVPA did not differ between both groups over time. No main effect of DM was observed while MVPA did significantly change over time (p-value=0.01). Although, there were slightly more CRCDM+ patients who persistently reported to be ex-smokers (63 vs 53%), no overall difference in smoking status between CRCDM+ and CRCDM- was observed (p-value=0.09). However, among CRCDM+ there were fewer patients who persistently reported to use alcohol (50 vs. 70%, p-value<0.0001). Both smoking and alcohol status were quite stable over time with 8% (n=77) and 13% (n=126) reporting fluctuating smoking and alcohol status during the study period, respectively.

Table 1 Sociodemographic and clinical characteristics (T1) of the study population

n(%) or mean ± SD	CRCDM+ n=126	CRCDM- n=789	P-value
Male	80 (63)	453 (57)	0.2
Age (years)	70±8	68±10	0.06[b]
Educational level[a]			
Low	30 (24)	113 (14)	0.02
Medium	73 (58)	488 (62)	
High	23 (18)	184 (23)	
Comorbidity other than diabetes			
0	20 (16)	241 (32)	0.0006
1	42 (34)	251 (33)	
≥2	61 (50)	263 (35)	
Cancer stage			
I	38 (30)	218 (28)	0.40
II	41 (33)	264 (33)	
III	41 (33)	236 (30)	
IV	5 (4)	38 (5)	
Unknown	1 (1)	33 (4)	
Time since diagnosis (years)	3±1	3±1	0.16[b]
Surgery	124 (98)	785 (99)	N/A
Chemotherapy	46 (37)	258 (33)	0.40
Radiotherapy	36 (29)	262 (33)	0.3
Diabetes duration (years)	8.3±7.2		
Diabetes duration – categorical			
<6.5 years	47 (37)		
≥6.5 years	48 (38)		
Unknown	31 (24)		

[a]Education levels included the following categories: low=no/primary school; medium=lower general secondary education/vocational training; or high=pre-university education/high vocational training/university
[b]Statistical difference tested with the non-parametric Wilcoxon-Mann-Whitney test
N/A: No valid p-value could be obtained as the number of patients who did not receive surgery was too low (i.e. 2 CRCDM+ and 4 CRCDM- patients) to conduct a valid Chi-square test

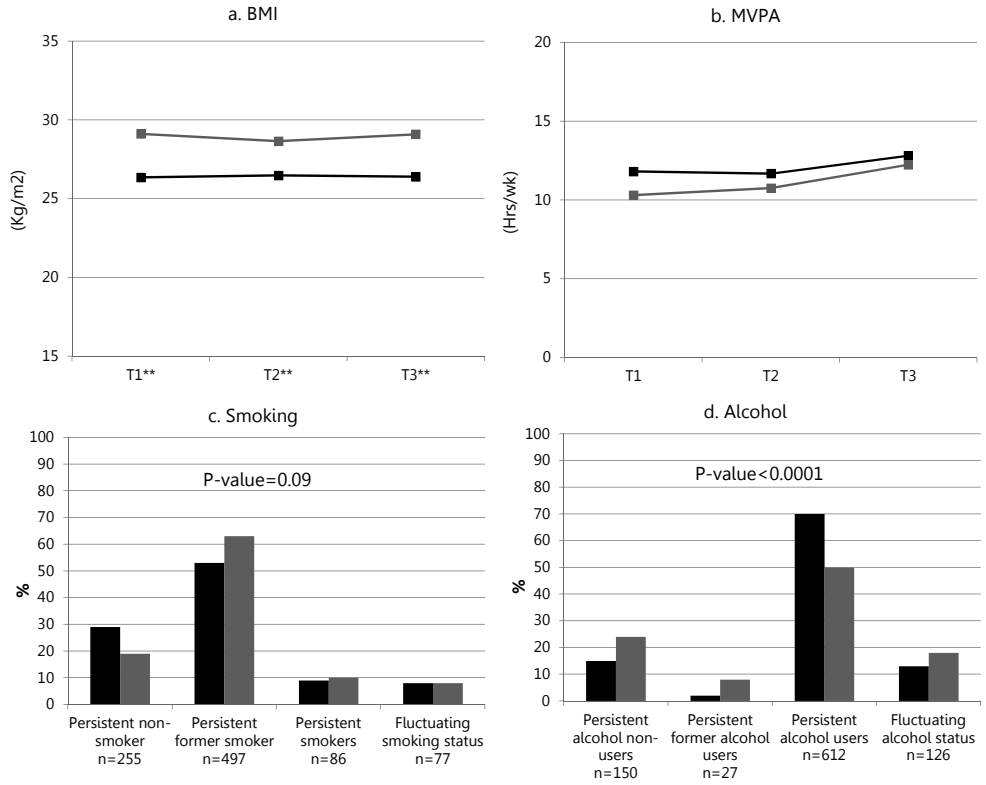

Figure 2 Differences in BMI (a.), MVPA (b.), smoking (c.) and alcohol (d.) use between CRCDM- (■) and CRCDM+(■)
**Significant difference between CRCDM+ and CRCDM- using independent samples T-test with P-value<0.0001
BMI=Body Mass Index, MVPA=Moderate-to-vigorous physical activity

Differences in HRQoL and the impact of lifestyle on HRQoL among CRCDM+ and CRCDM- patients

Physical function was lowest among CRCDM+ patients with BMI ≥30 kg/m^2 (mean at T1: 68±23) and highest among CRC patients with BMI between 25-30 kg/m^2 (at T1: both CRCDM- and CRCDM+: 84 ±18, Figure 3). CRCDM- patients with ≥14 hours/week MVPA reported highest physical function (at T1: 89±14), whereas inactive CRC patients report the lowest physical function (at T1, CRCDM-: 59±24 and CRCDM+ patients: 58±26). CRCDM- and CRCDM+ patients who never smoked reported highest physical function (at T1 84±16 and 76±19, respectively), while smokers reported lowest physical function with 78±19 and 62±32, respectively. Alcohol users reported higher physical function as compared to former or never users. For global QoL and fatigue similar patterns were observed. In general, smokers, obese patients (BMI≥30kg/m^2) and inactive patients reported lowest QoL and most fatigue, while alcohol drinkers reported highest global QoL and lowest fatigue (data not shown).

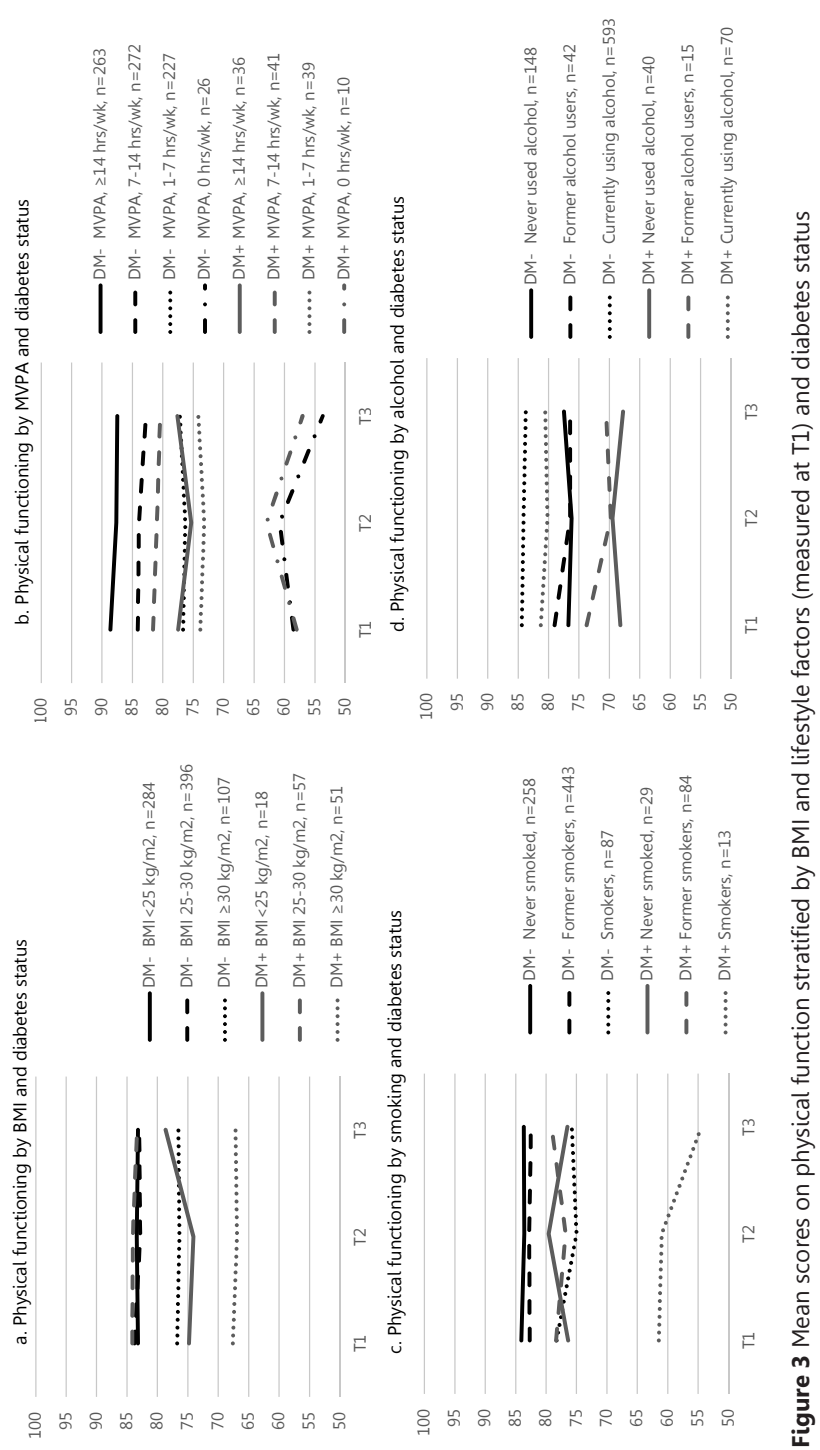

Figure 3 Mean scores on physical function stratified by BMI and lifestyle factors (measured at T1) and diabetes status

In adjusted generalized linear mixed models, no interaction effect between DM and time was found on any of the HRQoL scales, meaning that HRQoL did not differ between CRCDM+ and CRCDM- patients over time. After removing the interaction term, CRCDM+ patients reported significantly lower physical function (beta=-5.76; SE=1.67), global QoL (beta=-4.31; SE=1.48), and more fatigue (beta=5.38; SE=1.95) than CRCDM- patients. However, after additional adjustments for BMI, MVPA, smoking and alcohol use the main effect of diabetes disappeared for all three subscales (Table 2, model 2). With each point increase in BMI, physical function decreased (beta=-0.71; SE 0.15), and symptoms of fatigue increased (beta=0.47; SE=0.18). No within-subject effect of BMI was found, i.e. individual changes in BMI during the study period were not associated with changes in HRQoL. With each hour increase in MVPA per week, physical function (beta=0.64; SE=0.07), and global QoL increased (beta=0.35; SE=0.07) whereas symptoms of fatigue decreased (beta=-0.50; SE=0.09). A within-subject effect was found for both physical function and fatigue indicating that when a person increased their MVPA with 1 hour per week above their average MVPA during the study period, their physical function increased with 0.09 points (SE=0.04) and their fatigue score decreased with 0.15 (SE=0.06). Persistent smoking as compared to never smoking was associated with lower physical function and global QoL and more fatigue. In contrast, persistent drinking during the study period was associated with higher physical function and global QoL and less fatigue.

After additionally adjusting the full model 2 for comorbidity (i.e. 1 or ≥2 versus 0 comorbidity), the main effect of diabetes was attenuated even further for physical function (beta DM+ vs DM-=-0.85, SE=1.56), global quality of life (beta DM+ vs DM-=-1.43, SE=1.48) and fatigue (beta DM+ vs DM-=1.11, SE=0.56). All lifestyle factors remained independently associated with HRQoL and estimates were similar to those presented in model 2, Table 2.

We also included diabetes duration and used a categorical variable including CRCDM-, CRCDM+ with <6.5 years diabetes duration, CRCDM+ with ≥6.5 years diabetes duration and CRCDM+ with unknown diabetes duration in the model. We found that in model 1 CRCDM+ with short diabetes duration (i.e. <6.5 years) was associated with worse global QoL (beta=-5.02, SE=2.32) while longer term diabetes duration (i.e. ≥6.5 years) was associated with lower physical function (beta=-6.56, SE=2.56, data not shown). After adjustment for both lifestyle factors and comorbidity, these effects attenuated to non-significance.

Table 2 The results of generalized linear mixed models to assess the effect of diabetes and lifestyle factors on physical function, global quality of life and fatigue

	Physical function		Global quality of life		Fatigue	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	beta (se)	beta (se)	beta (se)	beta (se)	beta (se)	beta (se)
DM+ vs. DM-	-5.76 (1.67)*	-2.12 (1.61)	-4.31 (1.48)*	-2.66 (1.53)	5.38 (1.95)*	2.26 (1.95)
Time						
T2 vs. T1	-0.95 (0.71)	-0.69 (0.70)	-2.67 (0.75)*	-2.12 (0.75)*	1.53 (0.92)	1.20 (0.92)
T3 vs. T1	-2.29 (1.25)	-1.82 (1.19)	-2.51 (1.21)*	-2.60 (1.21)*	2.30 (1.55)	1.67 (1.52)
BMI (kg/m^2)						
Between[a]		-0.71 (0.15)**		-0.24 (0.14)		0.47 (0.18)*
Within[b]		0.06 (0.12)		-0.03 (0.15)		0.22 (0.17)
MVPA (hrs/wk)						
Between[a]		0.64 (0.07)**		0.35 (0.07)**		-0.50 (0.09)**
Within[b]		0.09 (0.04)*		0.05 (0.05)		-0.15 (0.06)*
Smoking						
Persistent former vs. never		-3.98 (1.34)*		-2.88 (1.27)*		2.66 (1.63)
Persistent current vs. never		-10.24 (2.06)**		-5.52 (1.95)*		8.21 (2.50)*
Fluctuating vs. persistent never		-5.55 (2.16)*		-3.01 (2.06)		4.61 (2.63)
Alcohol						
Persistent former vs. never		-4.27 (3.59)		-0.98 (3.40)		0.20 (4.36)
Persistent current vs. never		5.97 (1.68)*		3.98 (1.60)*		-7.01 (2.06)*
Fluctuating vs. persistent never		3.72 (2.05)		0.74 (1.95)		-3.10 (2.49)

BMI=Body Mass Index, MVPA=Moderate-to-vigorous physical activity
Model 1: Model to assess main effects of diabetes and time on HRQoL adjusted for age, sex, time since cancer diagnosis, cancer stage (stage I, II, III versus stage IV), cancer treatment (radiotherapy: yes/no and chemotherapy: yes/no) and educational level (Medium and high versus low educational level)
Model 2: Model 1 with additional adjustments for lifestyle factors
*P-value<0.05
**P-value<0.0001
[a]Between-subjects effects represented by the persons average over all time points
[b]Within-subjects effects represented by the difference between the average at one time point and the persons average over all time points

Discussion

This study shows that CRCDM+ and CRCDM- differed regarding lifestyle behaviors; CRCDM+ had a higher BMI, and were less likely to consume alcohol. No differences in MVPA and smoking status between CRCDM+ and CRCDM- patients were observed. In addition, prospectively measured physical function and global QoL were lower, while fatigue was higher among CRCDM+ patients as compared to CRCDM- patients. However, these differences in HRQoL outcomes disappeared after adjusting for lifestyle factors; BMI, MVPA, smoking and alcohol were all significant predictors of HRQoL. Further adjustment for comorbidity further attenuated the main effect of diabetes. This suggests that diabetes is not independently associated with HRQoL but that the found lower HRQoL scores among CRCDM+ patients seems to be explained by an unhealthier lifestyle and other comorbid conditions.

A few studies assessed HRQoL among cancer patients with and without diabetes and adjusted for lifestyle factors; 2 studies adjusted for BMI only[8,10] and 1 study adjusted for BMI, physical activity and smoking[6]. In line with our results, all 3 studies reported higher BMI among cancer patients with versus without DM. Moreover, a large Canadian cross-sectional study (n=113,587) also reported lower physical activity (14 vs. 20% being active), and no clear differences in the frequency of smoking (18 vs. 16%) between both groups[6]. In contrast to our results, after adjustment for BMI (and smoking), all 3 studies reported a lower HRQoL among cancer patients with versus without diabetes[6,8,10]. The large Canadian cross-sectional study found a lower Health Utility Index-3 score among cancer patients versus without DM with beta=-0.04 (95%CI:-0.05;-0.03)[6]. A longitudinal study among prostate cancer patients (n=1,248) reported a lower urinary function among prostate cancer patients with versus without diabetes, while no differences were found on other urinary and sexual function subscales[8]. In our previous cross-sectional study, we observed a lower physical function (beta=-3.8) and more male sexual problems (beta=9.4) among CRCDM+ versus CRCDM- patients[10]. The different cancer types studied, and the different measurements used in previous studies hamper comparison of the results. This study shows that besides BMI and smoking, MVPA and alcohol use were also independently associated with HRQoL and should be taken into account when comparing HRQoL between cancer patients with and without diabetes. Only adjusting for BMI might not be sufficient. Alcohol consumption was associated with better HRQoL which is in line with previous research[13]. We assume that the alcohol users in our study consumed moderate amounts which may be associated with fewer comorbid conditions such as cardiovascular disease. Vice versa patients with severe chronic disease might consume less alcohol. The results of the present study emphasize that health professionals still need to encourage and support cancer patients in improving their lifestyle behaviours. Besides, providing adequate information on behaviour change, health professionals also have to consider attitudes and motivations[32].

In this study no information on clinical data regarding diabetes diagnosis was available. However, we did have information regarding self-reported diabetes duration for 75% of the CRCDM+ patients. One might expect that patients with a longer diabetes duration develop more complications which in turn lead to lower HRQoL. We showed that CRCDM+ with a diabetes duration <6.5 years had lower global QoL while CRCDM+ patients with a diabetes duration ≥6.5 years had a lower physical function as compared to CRCDM- patients. These differences were attenuated after adjustments for comorbidity and lifestyle, similar as in the main analyses. The absence of a consistent pattern might be due to the stratification which resulted in a low number of patients per group.

As cardiovascular diseases and kidney diseases are common among patients with diabetes[33] and comorbidity is significantly associated with HRQoL[31] we additionally adjusted model 2 for comorbidity in a sensitivity analysis. We initially did not adjust for comorbidity as adjustment for both lifestyle factors and comorbidity might lead to an overadjusted model. From literature we know that impaired glucose tolerance, insulin resistance, obesity, dyslipidemia, and hypertension co-occur more often than might expected by chance[34]. This group of risk factors is also known as the Metabolic syndrome[34]. Thus the metabolic syndrome might be part of the causal pathway for the development of diabetes. As we had no information on the date of diagnosis of the other comorbid conditions, we cannot ascertain whether these conditions developed after, and possibly as a result of, diabetes.

Obesity, physical inactivity, smoking and alcohol use are all risk factors for both CRC and diabetes[35]. Although these lifestyle factors might have influenced the development of both diabetes and cancer among patients in this study, our results show that changes in lifestyle habits can improve HRQoL after the diagnosis of both diseases: patients who increased their physical activity during the study period reported higher physical function and less symptoms of fatigue. Among cancer survivors, several lifestyle interventions focused on improving dietary habits, smoking cessation or increasing physical activity show promising results[23]. Moreover, in recent years interventions have also focused on increasing physical and emotional condition prior to cancer treatment[36]. These prehabilitation studies showed promising results regarding morbidity, mortality, length of hospital stay and HRQoL[36]. However, sustainable long-term effects of these lifestyle and prehabilitation interventions are rarely studied. Thus, future studies should focus on the development of prehabilitation and lifestyle interventions that are effective on the long-term.

This study has several limitations. First, no information regarding lifestyle and HRQoL prior to cancer diagnosis were available. As data were collected 1 to 5 years after cancer diagnosis, patients might have adopted their lifestyle directly after diagnosis and prior to the data collection which could have influenced our results. In addition, no information regarding diet was available. Moreover, lifestyle factors were self-reported and may have been influenced by recall bias and social desirability. Previous research shows high

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correlations between self-reported and objectively assessed BMI, however, elderly (>60 years) often overreport their height and as a result BMI is underreported[37]. In addition, the patients included in these analyses are likely to be healthier as those with poorer health are less likely to participate in the study and to complete the follow-up questionnaires. As a result, absolute scores on HRQoL should be interpreted cautiously. However we do not expect the found association to be different as patients who did not respond or completed the follow-up are likely to report both poorer lifestyle behaviors and poorer HRQoL. Moreover, no data regarding diabetes type (i.e. type 1 or type 2), severity and complications were available, although we did conduct a sub-analysis including diabetes duration and additionally adjusted for comorbidity. Finally, diabetes was self-reported which could have resulted in misclassification. Despite these limitations, this population-based study with relatively high response, is the first to prospectively address differences in HRQoL between CRCDM+ and CRCDM- patients and the impact of lifestyle.

In conclusion, this study showed that CRCDM+ patients reported lower prospectively measured HRQoL as compared to CRCDM- patients; however these differences disappeared after adjustments for lifestyle and other comorbidities. These results suggest that lifestyle factors and comorbidity might explain the difference in HRQoL between CRCM+ and CRCDM- patients, although residual confounding cannot be excluded. As BMI, MVPA, smoking and alcohol use were all associated with HRQoL, this study underlines the importance of improving lifestyle behaviors among CRC patients, either with or without diabetes.

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PART II

THE IMPACT OF CANCER AND DIABETES ON MORTALITY

CHAPTER 7

THE EFFECT OF LIFESTYLE CLUSTERS ON MORTALITY AMONG COLORECTAL CANCER PATIENTS WITH AND WITHOUT DIABETES: RESULTS FROM THE PROFILES REGISTRY

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Abstract

Objectives
This study assessed whether smoking, alcohol consumption, moderate-to-vigorous physical activity (MVPA) and body mass index (BMI), can explain the increased mortality rates among colorectal cancer patients with diabetes (CRC+DM+). We also examined the effect of lifestyle clusters to identify patients who need to be targeted for future intervention and prevention measures.

Methods
Data regarding diabetes and lifestyle were retrieved from two population-based studies conducted in 2009 and 2010 among CRC patients. Clinical data were retrieved from the Netherlands Cancer Registry, and overall mortality from the municipal personal records database (with follow-up till December 2014).

Results
3,423 CRC patients were included of whom 497 (15%) reported to have diabetes. Four lifestyle clusters were identified; a 'healthy', 'moderately healthy', 'overweight' and 'smoking' cluster. CRC+DM+ patients had a higher mortality (HR=1.29; 95%CI:1.04-1.62) than patients without diabetes (CRC+DM-). The independent effect of diabetes was attenuated after adjustments for individual lifestyle factors, although the HR remained elevated (HR=1.24; 95%CI:0.98-1.56). In a separate model that included the lifestyle clusters, diabetes remained associated with a statistically significant increased mortality (HR=1.29; 95%CI:1.02-1.61). Patients in the 'smoking' cluster (70% current smokers with a low BMI and low MVPA) had the most markedly increased mortality risk as compared to patients with a relatively healthy lifestyle (HR=3.66; 95%CI:2.49-5.38).

Conclusions
After adjustment for lifestyle clusters, diabetes remained independently associated with increased mortality among CRC patients, suggesting that the excess mortality among CRC+DM+ versus CRC+DM- patients cannot be fully explained by lifestyle factors.

Introduction

Colorectal cancer (CRC) and diabetes are increasingly co-occurring. Diabetes is prevalent among 14% of Dutch CRC patients[1]. The link between cancer and diabetes has been extensively studied and diabetes has been associated with a 30% increased CRC risk[2]. In a meta-analysis, CRC patients with diabetes (CRC+DM+) had a 32% higher overall mortality risk as compared to patients without diabetes (CRC+DM-)[3]. A more recent meta-analysis found a slightly lower effect (HR=1.17; 95%CI:1.09-1.25)[4]. The mechanisms explaining why having both CRC and diabetes is associated with higher mortality are still unclear. Although lifestyle factors may play a role, only 12 of the 21 studies included in the recent meta-analysis considered lifestyle factors[4]. Of these studies, only 3 reported a higher mortality among CRC+DM+ versus CRC+DM- patients[5-7]. Moreover, studies mainly adjusted for Body Mass Index (BMI) and/or smoking, often neglecting other potentially relevant lifestyle factors such as physical activity and alcohol consumption.

Lifestyle factors are important risk factors for both cancer and diabetes, and are independently associated with mortality. Among both CRC and diabetes patients, a U-shaped association with BMI was reported; being underweight or obese was associated with higher mortality while being normal or overweight was associated with lower mortality[8-10]. Moreover, meta-analyses reported that high versus low physical activity levels were associated with 41% and 42% lower overall mortality among both diabetes[11] and CRC[12] patients, respectively. Current or former smoking as compared with never smoking[13,14] and excessive alcohol consumption were associated with higher mortality while light to moderate alcohol consumption was associated with lower mortality in both cancer and diabetes patients[15,16].

Several studies that assessed the association between lifestyle factors and mortality included a sum score for lifestyle[17-19]. However, a sum score is a rather crude measure, while specific unhealthy lifestyle factors often co-occur. In a large Swiss study, smokers were less physically active and had higher alcohol consumption than former and non-smokers[20]. A German study identified five different health behavior clusters, and 75% of patients in the smoking cluster also reported inadequate physical activity and/or an unhealthy diet[21]. Identifying clusters of patients with a specific lifestyle pattern and poor outcomes might help to target patients who benefit most from future prevention and intervention measures.

To date, only a few studies that adjusted for lifestyle factors found an increased mortality risk for CRC+DM+ versus CRC+DM- patients. The aim of the current study is to assess whether lifestyle factors, including smoking, alcohol consumption, physical activity and BMI, explain the increased mortality rates among CRC+DM+ patients. Independent effects of lifestyle factors as well as effects of different lifestyle clusters will be identified and associated with mortality.

Material and methods

Study population

Data from two population-based CRC studies conducted in 2009 and 2010 in South Netherlands were used. Data collection was completed within the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry[22]. In short, PROFILES is an infrastructure for the collection of patient-reported outcomes and is linked directly to clinical data from the Netherlands Cancer Registry (NCR). The 2009 cohort includes a random selection of CRC patients aged ≤85 years and diagnosed in 1998-2007. The 2010 cohort includes all CRC patients diagnosed in 2000-2009[23]. Participants in 2009 were excluded from participation in 2010. All eligible patients were informed by a letter from their (ex-)attending specialist which explained that by completing the questionnaire they agreed with the linkage to their clinical data from the NCR. Reminders were sent within two months. Informed consent for all patients were obtained. Ethical approval for the study was obtained from a local certified Medical Ethics Committee of the Maxima Medical Centre Veldhoven.

Exposure assessment

We assessed current diabetes status with the Self-reported Comorbidity Questionnaire[24]. Lifestyle factors included self-reported smoking, alcohol use, BMI, and physical activity. Smoking and alcohol use were assessed in 3 categories (i.e. (1) never (2) former and (3) current use). BMI was calculated with self-reported height and weight. Physical activity was assessed with questions derived from the validated European Prospective Investigation into Cancer (EPIC) Physical Activity Questionnaire[25]. Patients reported the average time spent, during winter and summer, on walking, cycling, gardening, household activities, and sports. Hours per week spent on moderate-to-vigorous physical activity (MVPA) were derived from estimated metabolic equivalent intensity (MET) values assigned to each activity based on previously described classifications[26,27]. MPVA was calculated by summing all activities with a MET-score ≥3, and include walking (MET=3.5), cycling (MET=4), gardening (MET=5), and various sports with a MET-score ≥3. Household activities (MET=3.5) were not considered as MVPA[28]. Outliers on all activity scores, greater than the 95th percentile, were replaced by the 95th percentile. Patients with complete data on diabetes status and lifestyle factors were included in the analyses.

Outcome and follow-up

Overall mortality was obtained from the NCR linkage with the municipal personal records database. Follow-up time was measured from cancer diagnosis until death, loss to follow-up, or until the end of the study period at 31 December 2014, whichever occurred first. Patients with <1 year follow-up were excluded, as they might be in a palliative phase, and might therefore be less physically active and/or have lost weight prior to their death.

Covariates

Clinical data regarding cancer diagnosis were retrieved from the NCR and include date of cancer diagnosis, cancer stage, and primary cancer treatment. Sociodemographic data including age and sex were also retrieved from the NCR.

Statistical analyses

Differences in baseline characteristics and lifestyle factors between CRC+DM+ and CRC+DM- patients were assessed using independent samples T-Tests and Chi-Square tests, where appropriate. LatentGOLD 5.0[29] was used to determine different lifestyle clusters with latent class cluster models; smoking, alcohol consumption, MVPA, and BMI were used as cluster variables. Smoking and alcohol consumption were entered as nominal variables (1=never, 2=former and 3=current use). As both MVPA and BMI were not normally distributed, they were entered as ordinal variables using 9 (i.e. 0, >0-5, 5-9, 9-13, 13-17, 17-21, 21-25, 25-29 and ≥29 hours/week) and 8 (i.e. <20, 20-22.5, 22.5-25, 25-27.5, 27.5-30, 30-32.5, 32.5-35 and ≥35 kg/m^2) categories, respectively. The optimal number of clusters was based on the model with the lowest Bayesian information criterion (BIC) which indicates the best fit. Patients were assigned to the cluster for which the posterior probability was highest. The clusters were exported and their impact on mortality were further analyzed in SAS.

Cox regression models with time since cancer diagnosis as underlying time scale were used to assess differences in mortality between CRC+DM+ and CRC+DM- patients. Lifestyle factors were assessed 1-11 years after cancer diagnosis, which might induce survivorship bias, as patients with shorter time since cancer diagnosis might have a higher mortality risk as compared with those who already lived longer at the time of the questionnaire. To minimize survivorship bias, the model was left-truncated and the time of questionnaire completion was set as entry time. We assessed the impact of individual lifestyle factors (i.e. smoking, alcohol consumption, BMI, and MVPA) and the derived lifestyle clusters on the association between diabetes and mortality. A p-value <0.05 was regarded as statistically significant and all analyses were conducted using SAS statistics version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics

Respondents included 1,371 (75%) patients from the 2009 cohort and 2,625 (75%) patients from the 2010 cohort (Figure 1). Characteristics of the non-respondents are described elsewhere[23]. After excluding those with incomplete follow-up data, diabetes status or lifestyle factors, 3,423 CRC patients were included in the present study, of whom 15% (n=497) reported having diabetes. There were more male CRC+DM+ than CRC+DM-patients (61% versus 55%). Furthermore, CRC+DM+ patients were older at cancer diagnosis (67±8 versus 64±10 years) and lower educated (24% versus 10%) than CRC+DM- patients (Table 1). No differences were found in cancer stage, treatment or

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follow-up time. In total, 503 patients died; 97(20%) CRC+DM+ and 406(14%) CRC+DM- patients.

Lifestyle

There were fewer current (8% versus 12%) and more former (63% versus 55%) smokers among CRC+DM+ as compared with CRC+DM- patients. Moreover, CRC+DM+ patients were less likely to be current drinkers (57% versus 72%), were less physically active (MVPA: 9.3±8.5 versus 11.3±8.8 hours/week), and had a higher BMI (28.9±4.4 versus 26.4±4.1 kg/m^2) than CRC+DM- patients. Differences in BMI were mainly apparent in the obesity category, with 34% and 15% of CRC+DM+ and CRC+DM- patients, respectively, being obese.

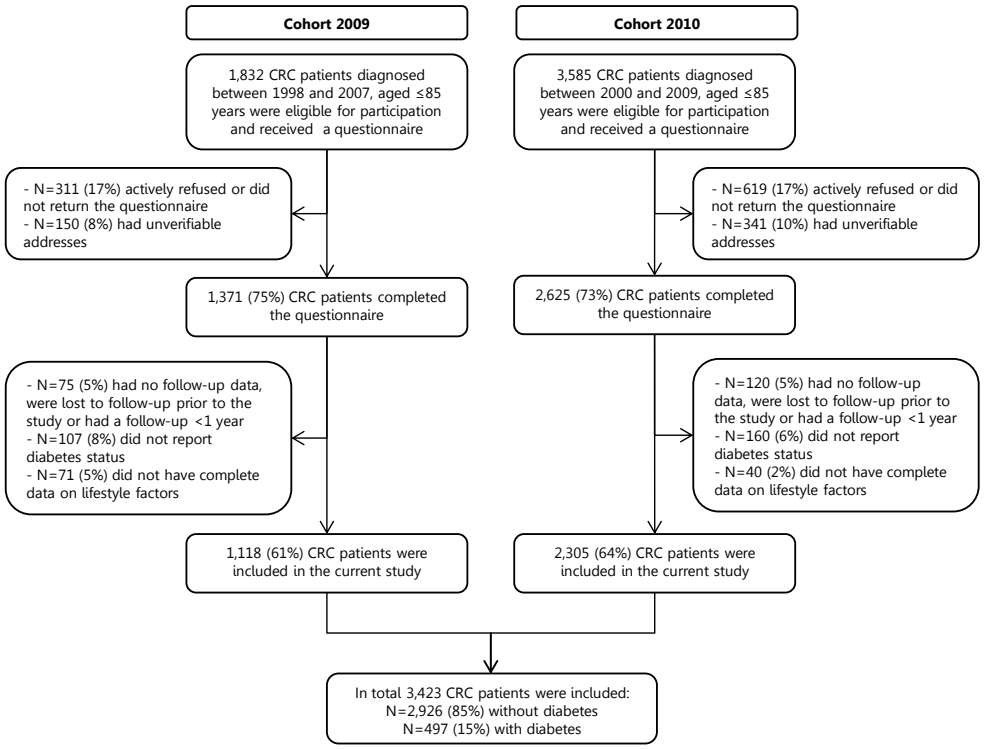

Figure 1 Flowchart of the study population

Table 1 Baseline characteristics of the study population

	CRC patients		
n(%) or mean±SD	With diabetes (n=497, 15%)	Without diabetes (n=2,926, 85%)	P-value
Sex - Male	303 (61)	1,595 (55)	0.007
Age at questionnaire	71.8±7.7	68.6±9.8	<0.0001
Age at cancer diagnosis	66.9±7.9	63.7±10.0	<0.0001
Education			
Low	117 (24)	547 (19)	0.02
Medium	269 (55)	1,755 (61)	
High	102 (21)	591 (20)	
Cancer stage			
I	150 (30)	867 (30)	0.21
II	203 (41)	1,080 (37)	
III	125 (25)	823 (28)	
IV	11 (2)	106 (4)	
Unknown	7 (1)	50 (2)	
Cancer treatment - Surgery	495 (100)	2,912 (100)	0.82
Cancer treatment - Chemotherapy	129 (26)	839 (29)	0.21
Cancer treatment - Radiotherapy	128 (26)	851 (29)	0.13
Follow-up			
Time between questionnaire and cancer dx	4.9±2.7	4.8±2.8	0.63
Time between cancer dx and end follow-up	8.9±2.9	9.0±2.9	0.62
Time between questionnaire and end follow-up	4.0±1.2	4.2±1.1	0.01
Status at the end of follow-up			
Alive	400 (80)	2,520 (86)	0.001
Dead	97 (20)	406 (14)	
Lifestyle			
Smoking			
Never	144 (29)	960 (33)	0.006
Former	311 (63)	1,620 (55)	
Current	42 (8)	346 (12)	
Alcohol			
Never	165 (33)	621 (21)	<0.0001
Former	51 (10)	184 (6)	
Current	281 (57)	2,121 (72)	
MVPA (hours/week)	9.3±8.5	11.3±8.8	<0.0001
BMI (kg/m^2)	28.9±4.4	26.4±4.1	<0.0001
BMI			
<20 kg/m^2	3 (1)	85 (3)	<0.0001
20-25 kg/m^2	80 (16)	1,016 (35)	
25-30 kg/m^2	244 (49)	1,399 (48)	
≥30 kg/m^2	170 (34)	426 (15)	

BMI=Body Mass Index, MVPA=Moderate-to-Vigorous Physical Activity

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Latent class analyses yielded 4 lifestyle clusters: 1. Healthy (n=905), 2. Moderately healthy (n=2,033), 3. Overweight (n=381), and 4. Smoking (n=104, Table 2). The healthy Cluster 1, was characterized by a low number of current smokers (3%), a majority of current alcohol consumers (67%), and highly physically active patients (MVPA 12.4±8.5 hours/week) with a normal BMI (25.7±3.2 kg/m^2). The moderately healthy Cluster 2 was similar to cluster 1 regarding MVPA (12.2±8.8 hours/week) and BMI (26.7±3.8 kg/m^2) but only included former (87%) and current smokers (13%). Overweight cluster 3, included mainly overweight/obese patients (BMI: 31.2±4.9 kg/m^2), who were less physically active (MVPA: 2.7±3.0 hours/week). Cluster 4 mainly included smokers (69%) with low physical activity (MVPA: 4.0±4.1 hours/week) and a low BMI (20.3±2.0 kg/m^2). 'Moderately healthy' patients within cluster 2 were younger (64.0±9.3 years) than healthy cluster 1 and overweight cluster 3 (both 67.5±9.9 years) and smoking cluster 4 (66.5±10.9 years, data not shown). No differences in cancer stage or treatment were found among the 4 lifestyle clusters. Diabetes prevalence was highest in overweight cluster 3 (n=109, 29%), and lowest in smoking cluster 4 (n=5, 5%).

Table 2 Lifestyle characteristics of the patients in different clusters constructed using latent class analysis

	Cluster 1 (HEALTHY) (n=905,26%)	Cluster 2 (MODERATELY HEALTHY) (n=2,033,59%)	Cluster 3 (OVERWEIGHT) (n=381,11%)	Cluster 4 (SMOKING) (n=104,3%)	P-value
Smoking					
Never	881 (97)	0 (0)	202 (53)	21 (20)	<0.0001
Former	0 (0)	1,775 (87)	145 (38)	11 (11)	
Current	24 (3)	252 (13)	34 (9)	72 (69)	
Alcohol					
Never	265 (29)	160 (8)	306 (80)	55 (53)	<0.0001
Former	36 (4)	157 (8)	27 (7)	15 (14)	
Current	604 (67)	1,716 (84)	48 (13)	34 (33)	
MVPA (hours/week)	12.4±8.5	12.2±8.8	2.7±3.0	4.0±4.1	<0.0001
BMI (kg/m^2)	25.7±3.2	26.7±3.8	31.2±4.9	20.3±2.0	<0.0001
BMI					
<20 kg/m^2	28 (1)	14 (2)	0 (0)	46 (44)	<0.0001
20-25 kg/m^2	639 (31)	382 (42)	17 (4)	58 (56)	
25-30 kg/m^2	1,041 (51)	444 (49)	158 (41)	0 (0)	
≥30 kg/m^2	325 (16)	65 (7)	206 (54)	0 (0)	

BMI=Body Mass Index, MVPA=Moderate-to-Vigorous Physical Activity

Association between diabetes, lifestyle factors and mortality

Unadjusted Cox regression analysis confirmed the higher mortality among CRC+DM+ versus CRC+DM- patients (HR=1.44; 95%CI:1.16-1.80) (Model 1, Table 3). This effect remained in model 3 which was adjusted for age, sex, cancer stage, and cancer treatment (HR=1.29; 95%CI:1.04-1.62). Additionally adjusting for individual lifestyle factors slightly attenuated the increased mortality risk to non-significance (Model 4, HR=1.24; 95%CI:0.98-1.56). In Model 4, former and current versus never smoking was associated with higher mortality (HR=1.36; 95%CI:1.09-1.71 and HR=2.13; 95%CI:1.58-2.86, respectively). Moreover, current versus never alcohol use, higher MVPA (hours/week), and a BMI between 25 and 30 kg/m^2 versus 20-25 kg/m^2 was associated with lower overall mortality with HR=0.71 (95%CI:0.57-0.88), HR=0.97 (95%CI:0.95-0.98) and HR=0.79 (95%CI:0.65-0.97), respectively. After adjustment for the lifestyle clusters (Model 5), diabetes remained statistically significantly associated with a higher mortality (HR=1.29; 95%CI:1.02-1.61).

Table 3 The impact of diabetes on overall mortality using left-truncated Cox regression analyses

Model		HR (95%CI)
Model 1: Crude		
	DM+ versus DM-	1.44 (1.16-1.80)*
Model 2: Age, sex adjusted		
	DM+ versus DM-	1.25 (1.00-1.56)*
Model 3: Fully adjusted[†]		
	DM+ versus DM-	1.29 (1.04-1.62)*
Model 4: Model 3[†] + adjusted for independent lifestyle factors		
	DM+ versus DM-	1.24 (0.98-1.56)
	Smoking: former vs never	1.36 (1.09-1.71)*
	Smoking: current vs never	2.13 (1.58-2.86)*
	Alcohol: former vs never	0.83 (0.58-1.17)
	Alcohol: current vs never	0.71 (0.57-0.88)*
	MVPA (hours/week):	0.97 (0.95-0.98)*
	BMI[‡]: Underweight vs healthy weight	1.29 (0.81-2.05)
	BMI[‡]: Overweight vs healthy weight	0.79 (0.65-0.97)*
	BMI[‡]: Obese vs healthy weight	0.92 (0.70-1.20)
Model 5: Model 3[†] + adjusted for lifestyle in clusters		
	DM+ versus DM-	1.29 (1.02-1.61)*
	Cluster 2 versus 1	1.21 (0.95-1.54)
	Cluster 3 versus 1	1.57 (1.15-2.14)*
	Cluster 4 versus 1	3.66 (2.49-5.38)*

BMI=Body Mass Index, MVPA=Moderate-to-Vigorous Physical Activity
[†]Adjusted for age at cancer diagnosis, sex, cancer treatment and stage
[‡]Underweight: BMI <20 kg/m^2, healthy weight: BMI 20-25 kg/m^2, overweight: BMI 25-30 kg/m^2, obese: BMI ≥30 kg/m^2

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Moreover, as compared with the healthy cluster 1, both clusters 3 (overweight) and 4 (smoking) were associated with increased mortality with HR=1.57 (95%CI:1.15-2.14) and HR=3.66 (95%CI:2.49-5.38), respectively. In secondary analyses, we excluded patients with stage IV disease, but results remained the same (data not shown).

Discussion

This study confirmed previous research and showed that CRC+DM+ patients had a higher mortality risk as compared with CRC+DM- patients. Moreover, we found that this association could not be fully explained by BMI, physical activity, smoking, and alcohol consumption, or by lifestyle clusters. Furthermore, we identified four lifestyle clusters and found a significant increased mortality for patients in the overweight (HR=1.57) and the smoking (HR=3.66) clusters versus patients in the healthy cluster.

CRC+DM+ patients had a 29% higher mortality risk as compared with CRC+DM- patients, which is slightly higher than the 17% higher risk found in a recent meta-analysis[4]. This excess mortality was attenuated after the adjustment for independent lifestyle factors (HR=1.24; 95%CI:0.98-1.56), but remained after the adjustment for lifestyle clusters (HR=1.29; 95%CI:1.02-1.61). Thus the excess mortality among CRC+DM+ patients is likely to be explained by factors other than lifestyle, such as socioeconomic status (SES). Cancer patients with low SES more often have comorbidities than those with a high SES[30], and CRC patients with a low SES may present with higher cancer stage at diagnosis[31]. However, we found no difference in cancer stage between CRC+DM+ and CRC+DM- patients. Second, our previous report shows that CRC+DM+ patients have more treatment-related toxicities[32]. This might have led to discontinuation of treatment or dose adjustments. Third, patients with both diseases might perform less diabetes self-management behaviors[33]. They might prioritize their cancer care over diabetes care which may lead to more diabetes-related complications. Finally, hyperinsulinemia or increased levels of insulin-like growth factors are known to have a direct effect on tumor cell proliferation and angiogenesis[34] which may lead to higher risk of cancer recurrence and mortality among CRC+DM+ versus CRC+DM- patients[35]. Although lifestyle factors did not explain the increased mortality among CRC+DM+ patients, this group did have a poorer lifestyle than CRC+DM- patients.

In this study, we observed a U-shaped association between BMI and mortality, a higher mortality among current and former smokers, and negative association between physical activity and mortality consistent with previous research[8-12,36]. Current alcohol use was associated with lower mortality. Further analyses (data not shown) showed that 90% of current drinkers consumed moderate amounts of alcohol (i.e. ≤14 glasses and ≤ 21 glasses per week for women and men, respectively). This is in line with previous literature, in which moderate alcohol consumption was associated with lower mortality among both CRC and diabetes patients[15,16].

After identifying four different lifestyle clusters, we found that CRC patients who smoke, have a low MPVA, and low BMI (cluster 4) and overweight/obese patients (cluster 3) have an increased mortality risk (HR=3.66; 95%CI:2.49-5.38 and HR=1.57; 95%CI:1.15-2.14, respectively), than those with a healthy lifestyle (cluster 1). As expected, diabetes prevalence was highest among the overweight cluster (29%). However, it is possible that the majority of patients in the overweight cluster has undiagnosed diabetes or pre-diabetes, which we cannot account for. This study stresses the importance of assessing risk profiles, as specific combinations of lifestyle factors resulted in more marked associations with mortality. Future research should explore whether interventions targeted at combined, rather than single lifestyle factors result in better outcomes among CRC patients.

This study has several limitations. We had no information about lifestyle before cancer diagnosis. Previous studies show that ≈50% of patients stop smoking after cancer diagnosis, change their dietary habits, and engage more in physical activity[37]. These changes could have influenced our findings. Moreover, the self-reported lifestyle measures might have been influenced by social desirable responses. Although previous studies show a high correlation between self-reported and measured height and weight, older individuals (i.e. >60 years) often underreport their height and weight resulting in differences of up to 1 kg/m^2 in BMI[38]. Similarly, self-reported physical activity is influenced by social desirability[39]. Therefore, absolute numbers regarding lifestyle factors should be interpreted cautiously. Furthermore, having diabetes was self-reported and information regarding the type of diabetes, blood glucose control or diabetes complications was lacking. Finally, no data regarding cause of death were available. Despite these limitations, this study had a high response rate and includes a large population-based sample.

In conclusion, CRC+DM+ patients had a 29% higher mortality risk as compared with CRC+DM- patients, which could not be fully explained by lifestyle differences. Moreover, as CRC+DM+ patients reported poorer lifestyle behaviors than CRC+DM- patients, these patients need to become aware of the importance of pursuing a healthy lifestyle. Also, this study shows that smokers often engage less in MVPA and have a low BMI. Therefore the effectiveness of interventions targeted at combined, rather than single lifestyle factors is worthy of further investigation.

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CHAPTER 8

THE ASSOCIATION BETWEEN GLUCOSE LOWERING DRUG USE AND MORTALITY AMONG BREAST CANCER PATIENTS WITH TYPE 2 DIABETES

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Abstract

Objective
This study assessed the association between glucose lowering drug (GLD) use, including metformin, sulphonylurea derivatives and insulin, after breast cancer diagnosis and breast cancer-specific and all-cause mortality.

Methods
1,763 breast cancer patients, diagnosed between 1998 and 2010, with type 2 diabetes were included. Cancer information was retrieved from English cancer registries, prescription data from the UK Clinical Practice Research Datalink and mortality data from the Office of National Statistics (up to January 2012). Time-varying Cox regression models were used to calculate HRs and 95% CIs for the association between GLD use and breast cancer-specific and all-cause mortality.

Results
In 1,057 patients with diabetes before breast cancer, there was some evidence that breast cancer-specific mortality decreased with each year of metformin use (adjusted HR=0.88; 95%CI:0.75-1.04), with a strong association seen with over 2 years of use (adjusted HR=0.47; 95%CI:0.26-0.82). Sulphonylurea derivative use for less than 2 years was associated with increased breast cancer-specific mortality (adjusted HR=1.70; 95%CI:1.18-2.46) but longer use was not (adjusted HR=0.94; 95%CI:0.54-1.66). In 706 patients who developed diabetes after breast cancer, similar patterns were seen for metformin but sulphonylurea derivative use was strongly associated with cancer-specific mortality (adjusted HR=3.64; 95%CI:2.16-6.16), with similar estimates for short and long-term users.

Conclusions
This study provides some support for an inverse association between, mainly long-term, metformin use and (breast cancer-specific) mortality. In addition, sulphonylurea derivative use was associated with increased breast cancer-specific mortality, but this should be interpreted cautiously, as it could reflect selective prescribing in advanced cancer patients.

Introduction

Diabetes occurs in around 16% of breast cancer patients[1,2] and is associated with a 40% increased breast cancer-specific[3] and a 50% increased all-cause mortality[4].Metformin is currently used as primary treatment for Type 2 diabetes. If metformin monotherapy does not control hyperglycaemia sufficiently, sulphonylurea derivatives (SUs) or insulin may be added or switched to. Recently, metformin, has received much attention for its potential anti-tumour effects. Several laboratory studies show that metformin use is associated with cell growth suppression in breast cancer cells, possibly mediated by activation of 5'-adenosine monophosphate-activated protein kinase (AMPK)[5,6]. Observational studies also show that metformin use is associated with a 20-30% lower breast cancer incidence[7-9].

Four studies have investigated the association between metformin use and breast cancer-specific mortality or recurrence in breast cancer patients but reported conflicting results[10-13]. A 53% decreased breast cancer-specific mortality was reported for metformin use versus non-use among human epidermal growth factor receptor 2 positive (HER2+) breast cancer patients[10] whereas the other studies did not find any association[11-13]. These studies had several limitations such as small sample size[10,12,13], no investigation of dose-response[10,12,13] and some were restricted to specific breast cancer subtypes (i.e. HER2+[10] or triple negative breast cancer[13]). Additionally, the study that reported a favorable effect for metformin might have been influenced by immortal time bias[14], as metformin users were classified as users from breast cancer diagnosis onwards, and not from the time of actual drug initiation[10]. Only one study used time dependent Cox regression analyses to avoid immortal time bias, but did not include lifestyle-related covariates[11]. Conflicting results were also reported among studies that investigated the effect of Glucose Lowering Drugs (GLDs) on all-cause mortality[15,16]. One study reported no effect of metformin use prior or in the 3 months after breast cancer diagnosis on overall mortality[16], while another study did report a lower overall mortality among metformin users as compared to breast cancer patients without diabetes[15]. However, as these studies did not report on breast cancer-specific deaths, associations in these studies could reflect non-cancer deaths[15,16]. Further research is needed to establish the effect of metformin and other GLDs on the prognosis of breast cancer patients with type 2 diabetes.

Therefore, prompted by the promising preclinical evidence, our primary objective was to determine whether breast cancer patients with type 2 diabetes using metformin had reduced breast cancer-specific mortality and all-cause mortality. A secondary objective was to investigate the effect of other GLDs on breast cancer-specific and all-cause mortality.

Methods

Data sources

This retrospective cohort study used linked data from the Clinical Practice Research Datalink (CPRD), the National Cancer Data Repository (NCDR) and the Office of National Statistics (ONS). The CPRD contains demographical information, clinical diagnoses and prescription data for approximately 7% of the UK population[17]. The NCDR contains data on all cancer diagnoses in the UK cancer registries including data on diagnosis date, site of primary cancer, stage, and treatment. Data regarding deaths were retrieved from the ONS registration which included breast cancer-specific (ICD codes C50.0 to C50.9) and all-cause mortality. The CPRD, NCDR and ONS death data were linked (using an algorithm based upon NHS number, gender, date of birth and postcode) for cancer patients in England. A multicenter research ethics committee gave ethical approval for all observational research using CPRD data.

Study design

A cohort of female breast cancer patients, diagnosed between 1998 and 2009, with type 2 diabetes was identified. Diabetes diagnosis was defined using previously validated clinical Read codes[18] or the first prescription of a GLD defined below, whichever occurred first. This study includes patients with diabetes prior to breast cancer (prevalent diabetes) as well as patients who developed diabetes after breast cancer diagnosis (incident diabetes). Patients with type 1 diabetes, which was defined as having a type 1 diabetes diagnosis code and a prescription of insulin prior to breast cancer diagnosis for prevalent diabetes patients and within 6 months after diabetes diagnosis for patients with incident diabetes, were excluded. Cancer patients with a previous cancer diagnosis were excluded, apart from in situ neoplasms and non-melanoma skin cancers. The index date was defined as the date of breast cancer diagnosis for patients with prevalent diabetes and the date of diabetes diagnosis for patients with incident diabetes. Patients were excluded if the index date occurred before they were registered at a CPRD practice, CPRD records at their general practice (GP) were of research quality or if the index date occurred after death or censoring. Patients who received hormone therapy for more than 8 weeks prior their breast cancer diagnosis, or with diagnosed polycystic ovary syndrome were excluded. Follow-up started 6 months after the index date to remove deaths that occurred within this period, as it is unlikely that GLD medication use after diagnosis could influence such deaths. In the analysis of incident diabetes patients, the time since breast cancer diagnosis remained the underlying time variable and Cox regression models were left-truncated with follow-up beginning 6 months after diabetes diagnosis. The patients were followed till death, the end of registration or last date of data collection of their GP or end of ONS follow-up (10th of January 2012), whichever occurred first.

Exposure to GLDs

Exposure to metformin, SUs, other GLDs and insulin was identified using chapter 6.1 of the British National Formulary[19]. Days of exposure was calculated by dividing the prescribed quantity by the number of prescribed tablets/units per day. If the quantity or units per day was missing (<1 and <20% respectively), the most frequent quantity and the average daily dose per product were used. For insulin the units per day were not reported, so the days of exposure was set to 60 days for each prescription. Cumulative days of exposure to all GLDs was calculated in 30-day intervals.

Covariates

Cancer stage and treatment (surgery, radiotherapy and chemotherapy) within the 6 months after breast cancer diagnosis were retrieved from the NCDR. Hormone treatment (including tamoxifen and aromatase inhibitor use) in the 6 months after breast cancer diagnosis was derived from GP prescription records. Smoking and Body Mass Index (BMI) closest to the index date were determined from the GP records; records more than 5 years prior to the index date were ignored. Comorbidities prior to the index date were identified using clinical Read codes which were previously validated with an adapted version of the Charlson comorbidity index[18]. The use of Hormone Replacement Therapy (HRT) and low-dose aspirin and statin prior to the index date were retrieved from the GP records. HbA1c measures in % according to the National Glycohemoglobin Standardization Program (NGSP) were retrieved for the year prior to breast cancer diagnosis for prevalent diabetes patients and between 6 months prior and 6 months after diabetes diagnosis for incident diabetes patients. The HbA1c measurement closest to the index date was used in the analyses.

Statistical analyses

The main analyses used time-dependent Cox regression models with time to breast cancer-specific deaths and all-cause mortality as the outcome, where metformin, SU, other GLDs and insulin use were modelled as time-varying covariates. A 6-month lag was used, which removes all GLD prescriptions in the 6 months prior to the end of study or death (i.e. as medication use in these months might reflect end-of-life treatment), as previously recommended[20]. Exposure to GLDs was modelled using time-varying ever/never terms (i.e. patients are classified as unexposed until 6 months after first drug prescription and as exposed afterwards). In addition, a linear trend was fitted to assess per year exposure to GLDs, and time-varying terms for year of exposure to GLDs, with time-varying ever/never terms were included in the model as recommended[21]. Moreover short- and long-term exposure was modelled using categories (<2 years of exposure and ≥2 years of exposure). Hazard ratios (HR) and 95% confidence intervals (95%CIs) were reported.

An unadjusted model was constructed and included the use of metformin, SU, other GLDs and insulin. The fully adjusted model included the following covariates which were available for the entire cohort: age at breast cancer diagnosis, calendar year of

breast cancer diagnosis, diabetes duration for prevalent diabetes patients, breast cancer treatment within 6 months (i.e. dichotomous covariates for surgery, chemotherapy, radiotherapy and hormone therapy), the use of HRT prior to breast cancer diagnosis and comorbidities prior to the study start (including stroke, chronic pulmonary disease, congestive heart disease, diabetes with complications, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease).

Several sensitivity analyses based on the fully adjusted time-varying ever/never analysis were conducted and include additional adjustments for BMI, smoking, stage and HbA_{1c} measures. A sensitivity analysis restricted to patients who had a follow-up >1 year in which the lag was increased to 1 year was performed. Among prevalent diabetes patients, a simplified Cox regression analyses was performed comparing GLD use to non-use in the 6 months after diagnosis, removing the need for time varying covariates. Moreover, among prevalent diabetes patients, a nested case-cohort analysis was performed. Cases who died of breast cancer were matched on age (5-year intervals) and year of cancer diagnosis (2-year intervals) to up to 10 controls within the cohort who lived at least as long after diagnosis as their matched case. The exposure period was defined as the period from breast cancer diagnosis till 6 months prior to death for cases and a period of identical duration from breast cancer diagnosis was defined for the matched controls. Metformin, SU, insulin and other GLD use was determined in the exposure period. Conditional logistic regression was used to calculate odds ratios (OR) and 95%CIs. All statistical analyses were performed using STATA 13 (College Station, TX).

Results

Study population

1,057 patients with prevalent diabetes at breast cancer diagnosis and 706 patients with incident diabetes were included (Figure 1). The mean age of prevalent diabetes patients was 70.6 (SD=11.3) years at breast cancer diagnosis and they were diagnosed with diabetes on average 6.6 (SD=6.0) years prior (Table 1). During follow-up, metformin was used by 65%, SUs by 50%, insulin by 21% and other GLDs by 21% of the prevalent diabetes patients. 189 (18%) prevalent diabetes patients used no GLDs, 332 (31%) used 1 GLD and 536 (51%) used a combination of ≥2 GLDs. The most frequently used combinations were metformin and SUs (n=205, 19%), metformin monotherapy (n=187, 18%), and metformin, SUs and other GLDs (n=105, 10%). Patients who did not use GLDs or who used SUs during follow-up were leaner than other groups e.g. 29 and 16% had a BMI <25 kg/m^2, respectively, compared with 11% among metformin and insulin users. Insulin users had more complications (25%) than other groups and had the highest HbA1c levels (mean=8.2, SD=1.8 %NGSP). Mean follow-up time from breast cancer diagnosis was 4.4 years (SD=2.9 years, maximum 13.8 years) and a total of 348 prevalent diabetes patients died (150 were breast cancer-specific deaths).

Incident diabetes patients were on average 64.4 (SD=11.4) years at breast cancer diagnosis and were diagnosed with diabetes on average 3.3 (SD=2.6) years after breast cancer diagnosis (Table 1). Metformin use was similar compared to prevalent diabetes patients (62% versus 65% using metformin during follow-up) but the use of SU, insulin and other GLDs was lower with 30, 5 and 10% versus 50, 21 and 21%, respectively. 224 (32%) incident diabetes patients used no GLDs, 278 (39%) used 1 GLD and 204 (29%) used a combination of ≥2 GLDs. The most frequently used combinations were metformin monotherapy (n=235, 33%), metformin and SUs (n=115, 16%), and metformin, SUs and other GLDs (n=37, 5%). Metformin and other GLD users had the highest BMIs with respectively, 47 and 50% being obese as compared to 37 and 29% for SU and insulin users. HbA1c levels were highest among insulin users with an average of 8.2 %NGSP. Mean follow-up from diabetes diagnosis was 3.9 years (SD=2.7 years, and maximum 13.0 years) and a total of 134 patients died (68 were breast cancer-specific deaths).

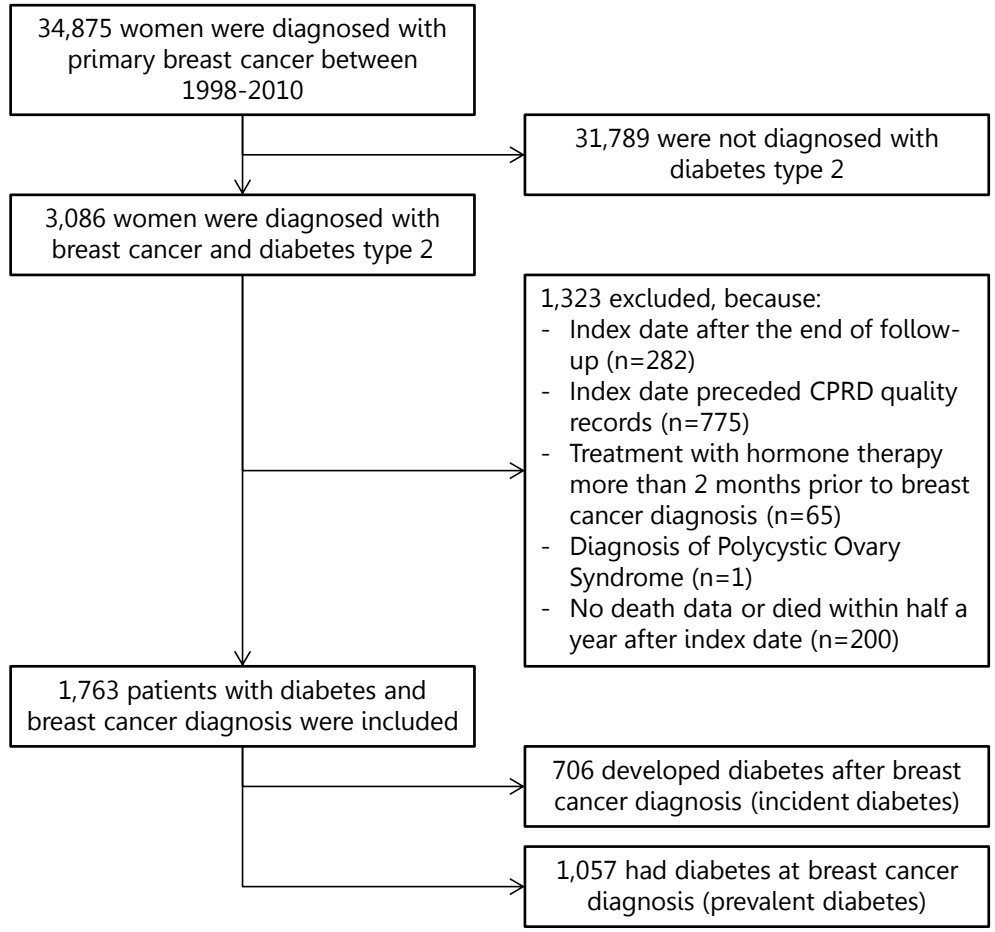

Figure 1 Patient selection

The association between GLD use and mortality

Breast cancer patients with prevalent diabetes

Breast cancer-specific mortality rates were lower in metformin users compared with non-users (HR=0.64; 95%CI:0.46-0.91), although this was attenuated after adjustment for potential confounders (adjusted HR=0.78; 95%CI:0.55-1.12) (Table 2). The majority of this attenuation could be explained by adjustment for age and year of breast cancer diagnosis (HR adjusted for age and year of diagnosis=0.79; 95%CI:0.55-1.12). Sensitivity analyses showed that adjustment for stage further attenuated the effect of metformin (HR=0.96; 95%CI:0.53-1.75) while increasing the lag to 1 year and the case-control analysis showed similar results (Table 4). The association was not observed per year of metformin use (unadjusted HR=0.88; 95%CI:0.75-1.04, adjusted HR=0.88; 95%CI:0.75-1.04) (Table 2). A more marked association with breast cancer-specific mortality was observed among individuals using metformin for ≥2 years (adjusted HR=0.47; 95%CI:0.26-0.82), rather than for shorter periods (adjusted HR=0.88; 95%CI:0.61-1.27). In sensitivity analyses the association between metformin use for ≥2 years was attenuated slightly after adjustment for BMI (HR=0.53; 95%CI:0.28-1.00), or after increasing the lag to 1 year (HR=0.54; 95%CI:0.30-1.00). Adjustment for stage at diagnosis (available for 39% of cases) further attenuated this association (HR=0.62; 95%CI:0.25-1.55) (data not shown).

Breast cancer-specific mortality was increased in SU users compared with non-users (HR=1.56; 95%CI:1.11-2.19), but attenuated after adjustments (HR=1.41; 95%CI:1.00-1.99). As before, the majority of this attenuation could be explained by adjustment for age and year of breast cancer diagnosis (HR adjusted for age and year of diagnosis=1.37; 95%CI:0.97-1.93). Sensitivity analysis showed that adjustments for BMI and smoking further attenuated the association; HR=1.36; 95%CI:0.94-1.99 and HR=1.27; 95%CI:0.86-1.89 respectively (data not shown). Additional adjustments for stage resulted in a slightly higher hazard ratio for SU use (HR=1.76; 95%CI:0.99-1.34), but the case-control analysis showed similar results (Table 4). No significant association was seen per year increase in SU use (unadjusted HR=0.96; 95%CI:0.81-1.14 and adjusted HR=0.96; 95%CI:0.81-1.15, Table 2). Further analysis revealed that SU use for <2 years was associated with an increase in breast cancer-specific mortality (HR=1.70; 95%CI:1.18-2.46) whereas longer use (≥2 years) was not (HR=0.94; 95%CI:0.54-1.66). A similar pattern was seen for insulin users, although based on smaller numbers. There was little evidence of an association between use of other GLDs and breast cancer-specific mortality.

Table 1 Descriptives of the study population including patients with prevalent diabetes at breast cancer diagnosis and incident diabetes after breast cancer diagnosis

	Prevalent diabetes (n=1,057)					
	Total	Metformin	SU	Insulin	Other GLDs	No GLD use
N(%)	1,057 (100)	688 (65)	528 (50)	220 (21)	220 (21)	189 (18)
Age at BC diagnosis (years)[a]	70.6 (11.3)	68.6 (11.0)	70.6 (11.2)	66.9 (10.6)	66.2 (10.5)	74.4 (11.1)
BMI (kg/m^2)						
< 25 kg/m^2	172 (16)	77 (11)	85 (16)	25 (11)	18 (8)	54 (29)
25 - 30 kg/m^2	325 (31)	219 (32)	175 (33)	66 (30)	63 (29)	52 (28)
≥30 kg/m^2	456 (43)	338 (49)	216 (41)	111 (50)	124 (56)	62 (33)
Missing	104 (10)	54 (8)	52 (10)	18 (8)	15 (7)	21 (11)
Smoking status						
Never	570 (54)	373 (54)	289 (55)	119 (54)	118 (54)	103 (55)
Ever	368 (35)	247 (36)	169 (32)	78 (35)	79 (36)	66 (35)
Missing	119 (11)	68 (10)	70 (13)	23 (10)	23 (10)	20 (11)
Comorbidities						
Diabetes with complications	131 (12)	82(12)	63 (12)	56 (25)	28 (13)	13 (7)
Stroke	109 (10)	61 (9)	58 (11)	25 (11)	20 (9)	21 (11)
Chronic pulmonary disease	209 (20)	138 (20)	102 (19)	36 (16)	52 (24)	37 (20)
Heart disease	163 (15)	82 (12)	75 (14)	41 (19)	23 (10)	33 (17)
Time between diabetes and breast cancer diagnosis (years)[a]	6.6 (6.0)	6.4 (5.4)	6.9 (5.8)	10.0 (6.9)	6.7 (5.0)	5.1 (6.0)
Time between breast cancer and diabetes diagnosis (years)[a]	-	-	-	-	-	-
HbA1c (%NGSP)[a]	7.2 (1.4)	7.4 (1.4)	7.5 (1.5)	8.2 (1.8)	7.6 (1.4)	6.1 (0.7)
GLD use after BC diagnosis						
Metformin	688 (65)	688 (100)	397 (75)	157 (71)	193 (88)	-
Sulphonylurea derivatives	528 (50)	397 (58)	528 (100)	101 (46)	167 (76)	-
Insulin	220 (21)	157 (23)	101 (19)	220 (100)	60 (28)	-
Other GLDs	220 (21)	193 (28)	167 (32)	60 (27)	220 (100)	-
No GLDs	189 (18)	-	-	-	-	189 (100)
Cancer stage						
I	167 (16)	109 (16)	81 (15)	41 (19)	40 (18)	32 (17)
II	186 (18)	131 (19)	100 (19)	42 (19)	44 (20)	27 (14)
III	43 (4)	26 (4)	22 (4)	8 (4)	8 (4)	9 (5)
IV	14 (1)	6 (1)	4 (1)	2 (1)	1 (0)	5 (3)
Missing	647 (61)	416 (60)	321 (61)	127 (58)	127 (58)	116 (61)
Cancer treatment in 6 months after BC diagnosis						
Surgery	817 (77)	561 (82)	413 (78)	172 (78)	188 (85)	139 (74)
Chemotherapy	152 (14)	118 (17)	76 (14)	39 (18)	42 (19)	14 (7)
Radiotherapy	419 (40)	305 (44)	209 (40)	97 (44)	104 (47)	58 (31)
Hormone treatment	821 (78)	520 (76)	415 (79)	166 (75)	156 (71)	155 (82)
HRT before BC diagnosis	284 (27)	205 (30)	136 (26)	84 (38)	80 (36)	43 (23)

[a]Values reported are means and SD

Table 1 continues on next page

Continuation of table 1

		Incident diabetes (n=706)				
N(%)	Total	Metformin	SU	Insulin	Other GLDs	No GLD use
	706 (100)	437 (62)	210 (30)	35 (5)	74 (10)	224 (32)
Age at BC diagnosis (years)[a]	64.4 (11.4)	62.1 (10.7)	64.6 (10.8)	61.6 (11.4)	60.9 (8.8)	67.7 (11.4)
BMI (kg/m^2)						
< 25 kg/m^2	55 (8)	26 (6)	14 (7)	4 (11)	3 (4)	26 (12)
25 - 30 kg/m^2	164 (23)	84 (19)	41 (20)	8 (23)	14 (19)	67 (30)
≥30 kg/m^2	280 (40)	204 (47)	78 (37)	10 (29)	37 (50)	66 (29)
Missing	207 (30)	123 (28)	77 (37)	13 (37)	20 (27)	65 (29)
Smoking status						
Never	345 (49)	200 (46)	90 (43)	14 (40)	29 (39)	126 (56)
Ever	250 (35)	164 (38)	76 (36)	16 (46)	31 (42)	71 (32)
Missing	111 (16)	73 (17)	44 (21)	5 (14)	14 (19)	27 (12)
Comorbidities						
Diabetes with complications	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stroke	40 (6)	16 (4)	9 (4)	2 (6)	1 (1)	21 (9)
Chronic pulmonary disease	139 (20)	89 (20)	41 (20)	8 (23)	18 (24)	41 (18)
Heart disease	64 (9)	34 (8)	21 (10)	2 (6)	5 (7)	23 (10)
Time between diabetes and breast cancer diagnosis (years)[a]	-	-	-	-	-	-
Time between breast cancer and diabetes diagnosis (years)[a]	3.3 (2.6)	3.1 (2.5)	2.7 (2.4)	2.4 (2.1)	2.6 (1.9)	3.9 (2.9)
HbA1c (%NGSP)[a]	7.2 (1.4)	7.5 (1.6)	7.9 (1.7)	8.2 (2.3)	7.9 (1.7)	6.5 (4.9)
GLD use after BC diagnosis						
Metformin	437 (62)	437 (100)	172 (82)	28 (80)	72 (97)	-
Sulphonylurea derivatives	210 (30)	172 (39)	210 (100)	22 (63)	47 (64)	-
Insulin	35 (5)	28 (6)	22 (10)	35 (100)	13 (18)	-
Other GLDs	74 (10)	72 (16)	47 (22)	13 (37)	74 (100)	-
No GLDs	224 (32)	-	-	-	-	224 (100)
Cancer stage						
I	140 (20)	89 (20)	30 (14)	2 (6)	10 (14)	46 (21)
II	175 (25)	120 (27)	61 (29)	15 (43)	20 (27)	41 (18)
III	24 (3)	10 (2)	6 (3)	3 (9)	2 (3)	12 (5)
IV	9 (1)	4 (1)	6 (3)	0 (0)	0 (0)	2 (1)
Missing	358 (51)	214 (49)	107 (51)	15 (43)	42 (57)	123 (55)
Cancer treatment in 6 months after BC diagnosis						
Surgery	626 (89)	399 (91)	190 (90)	34 (97)	70 (95)	190 (85)
Chemotherapy	163 (23)	119 (27)	64 (30)	15 (43)	21 (28)	32 (14)
Radiotherapy	337 (48)	225 (51)	103 (49)	14 (40)	40 (54)	97 (43)
Hormone treatment	516 (73)	302 (69)	153 (73)	23 (67)	50 (68)	175 (78)
HRT before BC diagnosis	240 (34)	153 (35)	61 (29)	17 (49)	30 (41)	75 (33)

[a]Values reported are means and SD

Table 2 The association between GLD use and breast cancer-specific and all-cause mortality among breast cancer patients with prevalent diabetes.

	Nos. of BC /all deaths	Nos. of patients	Person years	Unadjusted analyses		Adjusted analyses			
				Ever versus never[a]	Per year of use[b]	Ever versus never[a,c]	Per year of use[b,c]	<2 years use versus none[c]	≥2 years use versus none[c]
				HR (95% CI)	HR (95% CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Breast cancer-specific mortality									
Metformin									
Yes	77	688	2,512	0.64 (0.46-0.91)*	0.88 (0.75-1.04)	0.78 (0.55-1.12)	0.88 (0.75-1.04)	0.88 (0.61-1.27)	0.47 (0.26-0.82)*
No	73	369	1,612						
SU									
Yes	78	528	1,839	1.56 (1.11-2.19)*	0.96 (0.81-1.14)	1.41 (1.00-1.99)	0.96 (0.81-1.15)	1.70 (1.18-2.46)*	0.94 (0.54-1.66)
No	72	529	2,286						
Insulin									
Yes	29	220	733	1.25 (0.82-1.89)	1.03 (0.84-1.26)	1.37 (0.87-2.14)	1.04 (0.85-1.28)	1.63 (0.99-2.68)	1.05 (0.51-2.18)
No	121	837	3,391						
Other GLDs									
Yes	25	220	705	1.00 (0.63-1.57)	0.96 (0.73-1.25)	1.12 (0.70-1.78)	0.92 (0.70-1.21)	1.26 (0.76-2.08)	1.10 (0.48-2.52)
No	125	837	3,419						
All-cause mortality									
Metformin									
Yes	174	688	2,512	0.62 (0.50-0.78)*	0.91 (0.82-1.01)	0.85 (0.67-1.07)	0.93 (0.84-1.03)	0.90 (0.70-1.16)	0.70 (0.49-0.99)*
No	174	369	1,612						
SU									
Yes	175	528	1,839	1.51 (1.21-1.89)*	0.92 (0.83-1.02)	1.26 (1.01-1.58)*	0.89 (0.79-0.99)*	1.49 (1.17-1.91)*	0.85 (0.59-1.22)
No	173	529	2,286						
Insulin									
Yes	65	220	733	1.20 (0.91-1.58)	0.92 (0.81-1.06)	1.35 (1.00-1.81)	0.95 (0.83-1.09)	1.57 (1.13-2.18)*	1.00 (0.60-1.65)
No	283	837	3,391						
Other GLDs									
Yes	47	220	705	0.77 (0.56-1.06)	0.94 (0.78-1.13)	0.95 (0.68-1.31)	0.91 (0.75-1.10)	1.00 (0.69-1.46)	0.93 (0.53-1.62)
No	301	837	3,419						

[a]Model includes ever versus never exposure to metformin, sulphonylurea derivatives (SU), insulin and other GLDs
[b]Model includes cumulative exposure to metformin, SU, insulin and other GLDs per year and is additionally adjusted for ever versus never exposure to metformin, SU, insulin and other GLDs
[c]Model is adjusted for age at BC diagnosis, diabetes duration (years) before BC, year of BC diagnosis, BC treatment (surgery, radiotherapy, chemotherapy and hormone therapy within 6 months after BC diagnosis), hormone replacement therapy prior to BC diagnosis (yes/no) and comorbidity (stroke, chronic pulmonary disease, congestive heart disease, diabetes with complications, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease) prior to BC diagnosis (yes/no)
*P-value<0.05

Breast cancer patients with incident diabetes

No association between breast cancer-specific mortality and metformin use was seen among breast cancer patients with incident diabetes (unadjusted HR=0.97; 95%CI:0.58-1.71, adjusted HR=0.99; 95%CI:0.58-1.71). However, cumulative exposure to metformin was associated with breast-cancer specific mortality (HR=0.73; 95%CI:0.56-0.95), and this effect remained after adjustments (HR=0.73; 95%CI:0.56-0.96). Although not significant, similar patterns to those with prevalent diabetes were observed for ≥2 years metformin use (Table 3).

Ever versus never use of SUs was associated with substantially higher breast cancer-specific mortality (unadjusted HR=3.41; 95%CI:2.07-5.64 and adjusted HR=3.15; 95%CI:1.87-5.30). Additional adjustment for stage and the use of a 1 year lag slightly attenuated the association but this effect remained significant (Table 4). No association between breast cancer-specific mortality and cumulative SU exposure per year was observed (adjusted HR=0.88; 95%CI:0.66-1.16) (Table 3). Both <2 years and ≥2 years SU use were associated with higher breast cancer-specific mortality (HR=3.51; 95%CI:2.04-6.06 and HR=3.51; 95%CI:1.31-9.36, respectively). The low number of incident diabetes patients using insulin or other GLDs hampered the calculation of reliable estimates of mortality risk. For both prevalent and incident diabetes patients, additional adjustments for statin and aspirin use prior to breast cancer diagnosis did not materially affect observed associations between GLD use and breast cancer-specific mortality (data not shown). Analysis of all-cause mortality, also shown in Table 2 and 3, displayed similar patterns to the breast cancer-specific analyses.

Table 3 The association between GLD use and breast cancer-specific and all-cause mortality among breast cancer patients with incident diabetes.

	Nos. of BC /all deaths	Nos. of patients	Person years	Unadjusted analyses		Adjusted analyses			
				Ever versus never[a]	Per year of use[b]	Ever versus never[a,c]	Per year of use[b,c]	<2 years use versus none[c]	≥2 years use versus none[c]
				HR (95% CI)	HR (95% CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Breast cancer-specific mortality									
Metformin									
Yes	40	437	1,363	0.97 (0.58-1.64)	0.73 (0.56-0.95)*	0.99 (0.58-1.71)	0.73 (0.56-0.96)*	1.17 (0.68-2.03)	0.47 (0.17-1.27)
No	28	269	1,063						
SU									
Yes	33	210	578	3.41 (2.07-5.64)*	0.85 (0.65-1.12)	3.15 (1.87-5.30)*	0.88 (0.66-1.16)	3.51 (2.04-6.06)*	3.51 (1.31-9.36)*
No	35	496	1,848						
Insulin									
Yes	3	35	88	0.98 (0.30-3.23)	0.60 (0.15-2.45)	0.93 (0.27-3.20)	0.62 (0.15-2.53)	1.15 (0.32-4.19)	-
No	65	671	2,338						
Other GLDs									
Yes	4	74	232	0.42 (0.14-1.23)	1.94 (1.01-3.70)*	0.40 (0.13-1.17)	1.52 (0.78-2.95)	0.35 (0.08-1.49)	0.61 (0.13-2.91)
No	64	632	2,194						
All-cause mortality									
Metformin									
Yes	69	437	1,363	0.70 (0.48-1.01)	1.03 (0.89-1.19)	0.79 (0.54-1.17)	1.04 (0.90-1.21)	0.81 (0.54-1.22)	0.66 (0.37-1.19)
No	65	269	1,063						
SU									
Yes	56	210	578	2.71 (1.88-3.92)*	1.01 (0.85-1.19)	2.50 (1.71-3.66)*	0.98 (0.83-1.16)	2.60 (1.73-3.91)*	2.15 (1.11-4.16)*
No	78	496	1,848						
Insulin									
Yes	7	35	88	1.33 (0.60-2.95)	0.61 (0.28-1.33)	1.41 (0.61-3.23)	0.66 (0.31-1.42)	1.69 (0.68-4.20)	0.68 (0.09-5.13)
No	127	671	2,338						
Other GLDs									
Yes	9	74	232	0.51 (0.25-1.07)	0.99 (0.61-1.59)	0.53 (0.25-1.11)	0.90 (0.56-1.44)	0.62 (0.27-1.42)	0.31 (0.07-1.39)
No	125	632	2,194						

[a]Model includes ever versus never exposure to metformin, sulphonylurea derivatives (SU), insulin and other GLDs

[b]Model includes cumulative exposure to metformin, SU, insulin and other GLDs per year and is additionally adjusted for ever versus never exposure to metformin, SU, insulin and other GLDs

[c]Model is additionally adjusted for age at BC diagnosis, year of BC diagnosis, BC treatment (surgery, radiotherapy, chemotherapy and hormone therapy within 6 months after BC diagnosis), hormone replacement therapy prior to BC diagnosis (yes/no) and comorbidity (stroke, chronic pulmonary disease, congestive heart disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease) prior to BC diagnosis (yes/no)

*P-value<0.05

Table 4 Sensitivity analyses assessing the association between GLD use and breast cancer-specific mortality among prevalent and incident diabetes patients

	Nos. of BC deaths	Nos. of patients	Metformin Ever versus never HR (95%CI)	SU Ever versus never HR (95%CI)	Insulin Ever versus never HR (95%CI)	Other GLDs Ever versus never HR (95%CI)
Prevalent diabetes patients (n=1,057)						
Main ever/never analysis (Table 2)[a,b]	150	1057	0.78 (0.55-1.12)	1.41 (1.00-1.99)	1.37 (0.87-2.14)	1.12 (0.70-1.78)
Analysis in patients with available stage[a,b]	57	410	0.90 (0.52-1.55)	1.38 (0.80-2.40)	1.01 (0.50-2.04)	1.25 (0.62-2.50)
Additionally adjusted for stage[a,b]	57	410	0.96 (0.53-1.75)	1.76 (0.99-3.14)	1.33 (0.61-2.90)	1.44 (0.69-2.97)
Used a lag of 1 year instead of 6 months[a,b]	132	987	0.76 (0.52-1.12)	1.23 (0.85-1.78)	1.70 (1.06-2.72)	1.38 (0.85-2.24)
Use of GLDs in 6 months after BC diagnosis (not time-varying)[a]	150	1057	0.75 (0.53-1.07)	1.28 (0.91-1.81)	1.07 (0.60-1.91)	1.40 (0.80-2.42)
Case control analysis[a,d]		1522	0.78 (0.53-1.15)	1.41 (0.98-2.04)	1.35 (0.81-2.25)	1.07 (0.63-1.81)
Incident diabetes patients (n=706)						
Main ever/never analysis (Table 3)[b,c]	68	706	0.99 (0.58-1.71)	3.15 (1.87-5.30)	0.93 (0.27-3.20)	0.40 (0.13-1.17)
Analysis in patients with available stage[b,c]	38	348	0.87 (0.41-1.83)	3.72 (1.84-7.51)	0.97 (0.13-7.41)	0.18 (0.02-1.37)
Additionally adjusted for stage[b,c]	38	348	0.93 (0.45-1.95)	2.80 (1.34-5.87)	0.56 (0.06-5.37)	0.18 (0.02-1.39)
Used a lag of 1 year instead of 6 months[b,c]	53	623	1.19 (0.65-2.20)	2.88 (1.60-5.20)	1.30 (0.36-4.72)	0.32 (0.09-1.14)

[a]Model includes exposure to metformin, sulphonylurea derivatives (SUs), insulin and other GLDs and are additionally adjusted for age at BC diagnosis, diabetes duration (years) before BC, year of BC diagnosis, BC treatment (surgery, radiotherapy, chemotherapy, chemotherapy and hormone therapy within 6 months after BC diagnosis), hormone replacement therapy prior to BC diagnosis (yes/no) and comorbidity (stroke, chronic pulmonic pulmonary disease, congestive heart disease, diabetes with complications, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease) prior to BC diagnosis (yes/no)

[b]Exposure to metformin, SUs, insulin and other GLDs were modelled as time varying covariates, where patients become exposed after the first prescription of the respective drug (i.e. ever/never analysis)

[c]Model includes exposure to metformin, SUs, insulin and other GLDs and are additionally adjusted for age at BC diagnosis, year of BC diagnosis, BC treatment (surgery, radiotherapy, chemotherapy and hormone therapy within 6 months after BC diagnosis), hormone replacement therapy prior to BC diagnosis (yes/no) and comorbidity (stroke, chronic pulmonary disease, congestive heart disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease) prior to BC diagnosis (yes/no)

[d]OR and 95% CIs are presented. Among cases (n=149), 76 (51%) used metformin, 77 (52%) used SUs, 28 (19%) used insulin and 24 (16%) used other GLDs. Among controls (n=1373), 752 (55%) used metformin, 587 (43%) used SUs, 201 (15%) used insulin and 189 (14%) used other GLDs.

Discussion

This study showed some evidence of lower breast cancer-specific and all-cause mortality rates in breast cancer patients with diabetes who were treated with metformin, especially among longer term users (≥2 years exposure), but these associations were attenuated in sensitivity analyses. In contrast, SU use was associated with substantially increased breast cancer-specific and all-cause mortality, however there was no dose response association, and these associations were most marked in short-term users, and in patients who developed diabetes after their breast cancer diagnosis.

Only one previous study[11] has provided data relating to the potential effects of metformin, SUs, insulin and other GLDs on breast cancer-specific mortality, and adjusted for the use of other GLDs. This study, revealed no significant association between metformin use and mortality[11]. However, we observed some evidence of an association for long-term use of metformin on mortality. Also, Lega et al. did not find an association between SU use versus non-use and breast cancer-specific (HR=0.97; 95%CI:0.86-1.16) or all-cause mortality (HR=0.98; 95%CI:0.94-1.04), nor for SU use modelled per year of exposure[11]. In contrast, we observed increased breast cancer-specific and all-cause mortality for short-term SU use among those with prevalent diabetes at breast cancer diagnosis. Among those with incident diabetes we found a more pronounced increased mortality among SU users in all the analyses. Lega et al. did not assess short- and long-term SU use and they did not include patients who developed diabetes after their breast cancer diagnosis[11].

The observed reduction in cancer-specific mortality in longer term metformin users is consistent with findings from preclinical studies suggesting that metformin may have anti-tumor properties. Metformin may directly suppress breast cancer cell growth via activation of the AMP-activated protein kinase, resulting in downstream signaling of the protein kinase, MTOR, which regulates cell growth[22,23]. Moreover, due to the activation of the AMP-activated protein kinase and inhibition of MTOR, metformin might act synergistically with chemotherapeutic agents[24] and positively influence response to adjuvant chemotherapy in diabetic breast cancer patients[25]. Metformin may also work through an indirect mechanism by improving insulin sensitivity, thereby reducing insulin levels[26] and decreasing activation of IGF-1 receptors[27]. Deactivation of IGF-1 may inhibit Cyr61, and thereby suppress breast cancer growth and invasion[28]. On the other hand, the observed reduction in breast cancer-specific mortality rates in metformin users could also be due to residual confounding or reflect chance, particularly as the association was most apparent among long-term users of metformin. Further evidence will be provided by an ongoing randomized controlled trial of metformin versus placebo in over 3,500 women with breast cancer, although results will not be reported until the end of 2016[29,30].

Previous studies reported increased mortality rates in cancer patients using SUs but of less magnitude than associations seen in our study[16,31]. We believe that the increased cancer-specific mortality in SU users apparent in our data should be interpreted cautiously

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for various reasons. First, we did not have a prior hypothesis regarding the association between SUs and mortality. Second, the association with SUs did not follow a dose-response, which is counterintuitive. Third, although strong associations were seen in those with incident diabetes, the risk estimates were based on small numbers of deaths. Fourth, a proportion of the diabetes occurring after a breast cancer diagnosis might partly be due to treatment for advanced/recurrent disease (e.g. steroids), which is often a transient condition. Finally, in patients with advanced cancer it has been recommended that SUs are used in preference to metformin due to the gastro-intestinal side effects of metformin[32], and consequently these drugs may be spuriously associated with increased cancer-specific mortality.

From a physiological point of view, it is possible that SUs detrimentally affect breast cancer progression/metastasis, possibly mediated through hyperinsulinemia, as SUs increase insulin secretion[33] and preclinical studies have shown that hyperinsulinemia may promote breast cancer metastasis to the lung[34]. Moreover, observational studies have shown that hyperinsulinemia is associated with increased cancer-specific mortality[35]. Despite the caveats mentioned above, the associations we have seen between SU use and mortality in breast cancer patients are worthy of further investigation.

This study used data from a large population-based database which is of validated high quality[17,18]. Importantly, time-dependent analyses were performed to avoid immortal time bias[14], and we accounted for cumulative exposure to GLDs and conducted sensitivity analyses to investigate the robustness of our findings. In addition, GLDs are not available 'over the counter' in the UK, so it is likely that we captured all GLD use in our study, apart perhaps from use during care within hospital or a hospice. However, this study also has several limitations. We do not have data on patients' compliance with prescribed medications. Cancer stage at diagnosis was missing in 60% of our study population, although stage distribution appeared similar in metformin users and non-users. Additional adjustments for stage attenuated observed hazard ratios, but this appeared to result from the restriction of the dataset to those with available stage, rather than an effect of adjustment for stage per se. We did not have data on disease progression, while GLD use may have changed following cancer recurrence, although associated biases should be reduced in lagged analyses. Moreover, there may have been some misclassification regarding the cause of death.

In conclusion, this study provides some support for an inverse association between metformin exposure and (breast cancer-specific) mortality among breast cancer patients. In addition, an increased breast cancer-specific mortality was observed among SU users. This finding should be interpreted cautiously, as it could reflect selective prescribing in advanced cancer patients, but merits further investigation.

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CHAPTER 9

THE EFFECT OF GLUCOSE LOWERING DRUG USE ON OVERALL MORTALITY AMONG BREAST CANCER PATIENTS

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Abstract

Aims
This study assesses the effect of glucose lowering drug (GLD) use, i.e. metformin, sulfonylurea derivatives (SUs), insulin and other GLDs, started after breast cancer diagnosis, on overall mortality.

Methods
All female breast cancer patients diagnosed between January 1st, 1998 and December 31st, 2011 who started using GLDs after breast cancer diagnosis, were included. Clinical characteristics were derived from the Netherlands Cancer Registry, drug dispensing data from the PHARMO Database Network and data on overall mortality from the Dutch municipal personal records database. Time-dependent Cox regression analyses, with cumulative exposure to GLDs were conducted to assess effects on overall mortality.

Results
In total, 407 breast cancer patients were included. Most women (n=335, 82%) used metformin at some point during follow-up, followed by SUs (n=202, 50%), insulin (n=58, 14%) and other GLDs (n=41, 10%). The average follow-up was 7.7 ± 3.6 years and 107 (26%) patients died during follow-up. Adjusted analyses showed that metformin users had a lower overall mortality (HR=0.47; 95%CI:0.29-0.74), while insulin users had a higher overall mortality (HR=1.85; 95%CI:1.09-3.15) compared to non-users. However, when assessing dose-response effects no association was found between cumulative use of metformin, SU, insulin or other GLDs and mortality.

Conclusions
No association between cumulative exposure to metformin, SU, insulin and other GLDs and overall mortality was found. However, metformin users did have a lower, while insulin users had a higher overall mortality risk which is likely to be a result of different patient characteristics.

Introduction

Both cancer and diabetes belong to the most common chronic diseases worldwide, and both diseases are among the leading causes of death with 8.2 million and 1.5 million deaths in 2012, respectively[1]. Among women, breast cancer is the most common cancer and in 2012 there were 1.7 newly diagnosed breast cancer patients worldwide[2]. As both breast cancer and diabetes are common, they often co-occur; diabetes is prevalent in 16% of breast cancer patients[3,4]. Previous studies showed higher mortality rates among cancer patients with diabetes compared to those without diabetes[4-6], with increased mortality rates of up to 40% for women with postmenopausal breast cancer[6].

Numerous studies observed an association between diabetes and an increased risk of breast cancer among postmenopausal women[7-9]. In part, this association might be the result of high serum insulin levels, which are known to have a direct mitogenic effect on normal mammary cells[9]. In addition, insulin receptors, which are overrepresented on breast cancer cells, have been associated with increased tumor size and grade at cancer diagnosis and increased mortality[9]. This insight resulted in major attention for the potential anti-mitogenic effect of the glucose lowering drug (GLD) metformin, as metformin improves insulin sensitivity of the peripheral tissue by increasing insulin-stimulated glucose uptake in skeletal muscle tissue and adipocytes and lowering the hepatic glucose output[10,11].

Most recent research focused on the protective effect of metformin on breast cancer incidence[12], while the effects of metformin on tumor progression and mortality are less well understood. A few studies indicated that metformin might reduce tumor cell growth[13,14]. However, inconsistent results regarding the effect of metformin and other GLDs on mortality were found in observational studies[15-23]. The majority of studies included patients with diabetes at breast cancer diagnosis and found no association between metformin use and mortality[15,17,18,20,21], but four studies did observe reduced mortality rates ranging between 24% and 53% among metformin users[16,19,22,23]. Furthermore, several studies assessed the effect of other GLDs on mortality, but also reported inconsistent results[16-18,21,23]. Other studies, showed that sulfonylurea derivative (SU)[18,23] or insulin use[18,21] was associated with increased mortality while one study showed that thiazolidinediones were associated with lower mortality[16]. Contrasting results were found in another study that reported no association between metformin, SU, insulin or other GLD use and mortality[17]. Comparison of previous results is complex as these studies included different disease subtypes (i.e. HER2+[16], triple-receptor negative[15] or all types of breast cancer patients[17-23]), used varying definitions of GLD exposure and applied different statistical techniques. Moreover, only one study included patients who developed diabetes after breast cancer and reported those results separately[23]. To accurately assess a dose-response relationship, the study sample should be restricted to those with incident diabetes. Moreover, as diabetes has been associated with cancer

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incidence[12], GLD use prior to cancer diagnosis might influence patients prognosis as patients with diabetes might present with a more advanced cancer stage at diagnosis[24].

Therefore, the aim of this study is to assess the effect of GLD use after breast cancer diagnosis on overall mortality. Based on the results of previous studies, we hypothesize that (cumulative) exposure to metformin after breast cancer diagnosis will result in a lower, while exposure to SU and insulin will result in higher overall mortality.

Methods

Data sources

Data were collected from the Netherlands Cancer Registry (NCR) and linked to the PHARMO Database Network (PHARMO), covering a demographic region in the South-East of the Netherlands of approximately one million inhabitants. The linkage between PHARMO and the NCR was performed for cancer patients diagnosed from 1998 onwards. The construct and validity of the linkage between the NCR and PHARMO is described in detail elsewhere[25].

The NCR records all newly diagnosed cancer patients, for this study data from an area with 2.4 million inhabitants, 10 hospitals, 6 pathology departments and 2 radiotherapy institutions in the South of the Netherlands was used. Trained registrars routinely collect data on cancer diagnosis, stage, primary treatment, receptor status and comorbidity at time of cancer diagnosis. The PHARMO Database Network is a population-based network of healthcare databases and combines data from different healthcare settings in the Netherlands. These different data sources, including general practitioner, in- and out-patient pharmacy, clinical laboratory, hospitals, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. In the Netherlands, studies with anonymized patient records do not fall under the scope of the Medical Research Involving Human Subjects Act. This study is therefore exempt from medical ethics review.

Study population

All female breast cancer patients diagnosed in the South of the Netherlands between January 1st, 1998 and December 31st, 2011 were selected from the NCR and linked to PHARMO. All incident users of GLDs (i.e. with Anatomical Therapeutic Chemical (ATC)-code A10) after breast cancer diagnosis were selected. Incident users of GLDs were defined as patients who had at least six months of history prior to breast cancer diagnosis and did not use GLDs in these months.

Exposure and outcome

The ATC classification code was used for selection of metformin (A10BA02), SUs (A10BB), insulin (A10A) and other GLD (all other A10 codes) use[26]. The number of cumulative days of exposure to GLDs since the start of GLD use, was calculated from the dispensing data available from PHARMO. For insulin, the duration of use was not recorded and was set to 90 days for each dispensing. In periods of non-use the cumulative exposure up to the last prescription remained unchanged. Overall mortality was obtained from the municipal personal records database. Follow-up time was measured from breast cancer diagnosis until death, loss to follow-up, or until the end of the study period at 31 December 2012, whichever occurred first.

Covariates

Age at breast cancer diagnosis, primary cancer treatment (i.e. surgery, radiotherapy, chemotherapy and/or hormone treatment), TNM stage , hormone receptor status, and comorbidity at breast cancer diagnosis were retrieved from the ECR. The first date of statin and aspirin use after cancer diagnosis was retrieved from PHARMO and both statin and aspirin were modelled as time-dependent dichotomous variables. The calendar year of breast cancer diagnosis was included as a covariate as well.

Statistical analyses

Baseline characteristics of metformin, SU, insulin and other GLD users were presented. Time dependent Cox regression models were constructed, in which the time between breast cancer diagnosis and end of follow-up was the underlying time scale. Patients started using GLDs at different times after breast cancer diagnosis, which might impose survivorship bias (i.e. patients who die shortly after cancer diagnosis are missed in these analyses), therefore, the data was left truncated at the time of GLD initiation. To assess differences between users and non-users of GLDs a model was used that included time dependent ever/never terms for the use of metformin, SU, insulin and other GLDs (i.e. a GLD user was, and remained, classified as exposed after the first prescription of the respective drug). The main Cox regression analysis to study a possible dose response effect of GLD use, included cumulative exposure to GLDs (per year) modeled as time varying covariates. This model additionally included the time varying binary variables terms for all GLDs (ever/never use), to distinguish between the exposed and unexposed groups as has been previously recommended[27]. To further explore dose-response associations, we modelled all GLDs in categories of short (<2 years) and long-term (≥2 years) use. Results of unadjusted models as well as models adjusted for age at breast cancer diagnosis, calendar year of breast cancer diagnosis, cancer stage, cancer treatment (i.e. surgery, radiotherapy, chemotherapy or hormone therapy) and statin and aspirin use (i.e. modelled as time-dependent binary terms for ever/never use) were reported.

Sensitivity analyses

To assess the robustness of our findings, several sensitivity analyses were performed. As breast cancer patients with a positive hormone receptor status (Estrogen Receptor (ER)

and Progesterone Receptor (PR)) have a better prognosis, we conducted a sensitivity analysis among those with positive ER and/or PR status. In addition, we additionally adjusted for comorbidity at breast cancer diagnosis; this model did not include adjustments for aspirin and statin use. Moreover, the adjusted model was analyzed using a 6 month time lag, as has been recommended previously[28]. In this lagged analysis all GLD dispensings in the 6 months prior to the end of study or death were not taken into account as this possibly reflects end of life care. The last sensitivity analysis was restricted to patients with the first GLD prescription >6 months after breast cancer diagnosis, as diabetes might be a result of breast cancer treatment[29]. A P-value <0.05 was regarded as statistically significant and all analyses were performed using SAS software (version 9.3, SAS institute, Cary, US).

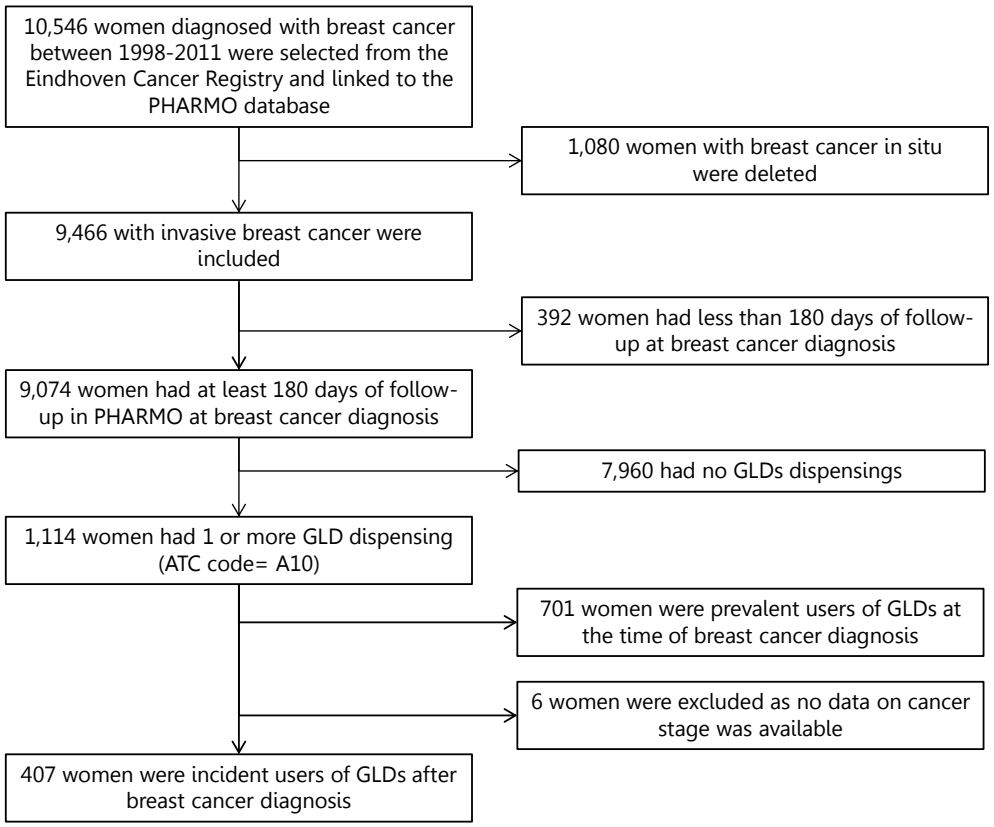

Figure 1 Flowchart of the patient selection method

Results

Study population

In total, for 10,546 women with breast cancer diagnosed between 1998 and 2011 data on drug use was available, of whom 407 were incident users of GLDs after breast cancer diagnosis (Figure 1). Of them 82% (n=335) used metformin, 50% (n=202) used SUs, 14% (n=58) used insulin and 10% (n=41) used other GLDs at some point in time during follow-up (Table 1). Patients were on average 64.6 years old (SD=11.4) at cancer diagnosis. Insulin users were slightly more often diagnosed with cancer stage II (62%) as compared to metformin (48%), SU (47%) and insulin users (44%). Seventy percent of the included patients had a positive ER status, and 54% had a positive PR status, which did not differ between the different GLD users. In addition to GLD use, patients also often used statins and aspirins. Other GLD users used statin most often at some time during follow-up (83%) which was slightly higher compared with metformin (72%), SU (65%), and insulin users (59%). Aspirin was used by 30% of the included patients at some time during follow-up. Patients started with GLDs on average 3.5 years (SD=2.8) after cancer diagnosis, the mean follow-up time (i.e. between breast cancer diagnosis and end of follow-up) was 7.7 years (SD=3.6) and 26% (n=107) died during the study period.

GLD use and overall mortality - ever/never use of GLDs

The ever/never analysis adjusted for age, calendar year, cancer stage, cancer treatment (i.e. surgery, radiotherapy, chemotherapy and hormone therapy), statin and aspirin use, showed that ever use of metformin and insulin was significantly associated with overall mortality with a HR of 0.47 (95%CI:0.29-0.74) and HR of 1.85 (95%CI:1.09-3.15), respectively (Figure 2). No effects of SU and other GLD use on mortality was observed with HR=1.09 (95%CI:0.71-1.68) and HR=0.34 (95%CI:0.11-1.10), respectively. In sensitivity analyses (Table 2) these results were attenuated after restricting the sample to those with a positive ER or PR status (HR metformin=0.59; 95%CI:0.29-0.98, HR insulin=1.53; 95%CI:0.76-3.09) and after the analysis was lagged with 6 months (HR metformin=0.63; 95%CI:0.35-1.14, HR insulin=1.18; 95%CI:0.57-2.46). After adjustment for comorbidity, or the restriction to patients with a first GLD prescription >6 months after breast cancer diagnosis, similar results as in the main analyses were found.

GLD use and overall mortality - cumulative exposure to GLDs

Dose-response effects of GLDs were addressed in time-dependent Cox regression models that included cumulative exposure, modeled per year of use (Figure 3). Fully adjusted models showed no associations between metformin (HR=0.98; 95%CI:0.84-1.15), SU (HR=0.94; 95%CI:0.80-0.11), other GLD (HR=1.18; 95%CI:0.53-2.62) and insulin use (HR=0.83; 95%CI:0.62-1.11) and mortality. After modelling GLD use in categories of short and long-term use we found that short-term (<2 years) SU and insulin use was associated with an increased mortality with HR=3.12 (95%CI:1.98-4.91) and HR=4.00 (95%CI:2.32-6.90), respectively, while long-term use (≥2 years) was not (results not shown). No effects for either short (<2 years) or long-term (≥2 years) metformin use were found. Similar to the ever/never analyses, results were mainly attenuated in analyses

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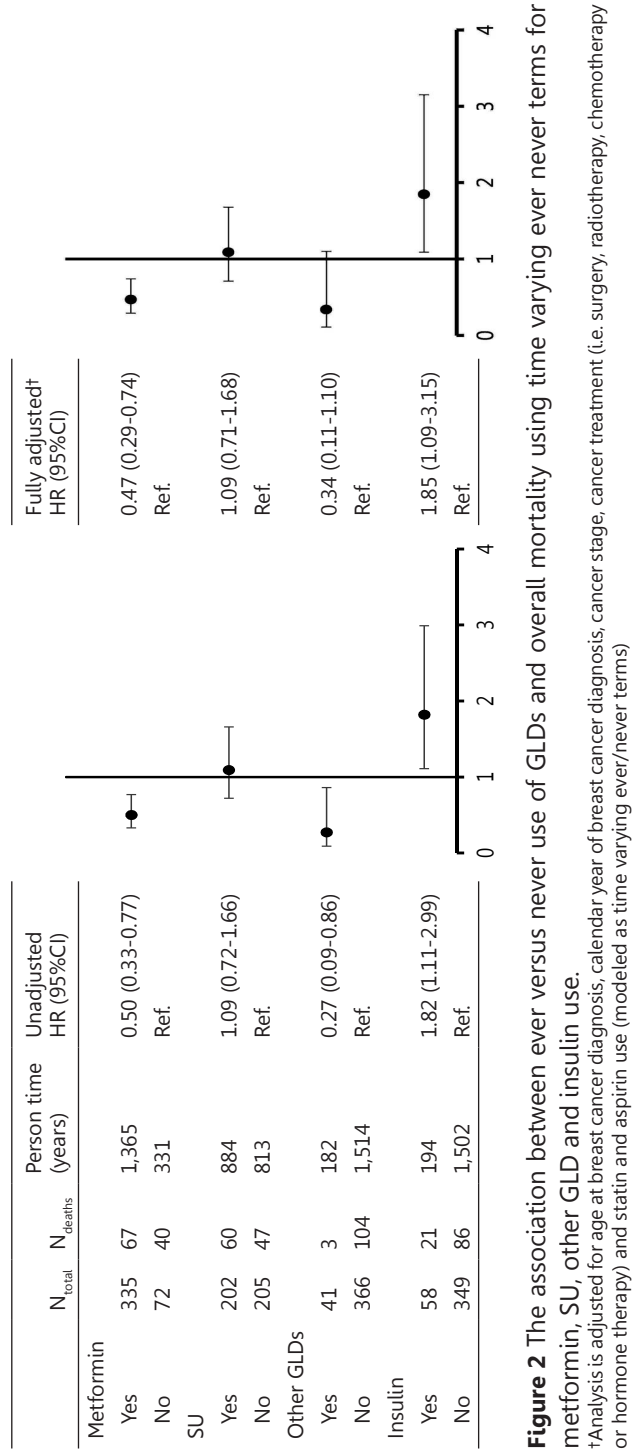
restricted to those with positive ER or PR status and in the lagged analysis, however all associations remained non-significant (Table 2).

Table 1 Baseline characteristics of the study population

Mean ± SD or n(%)	Total N=407	Metformin[a] N=335	SU[a] N=202	Insulin[a] N=58	Other GLDs[a] N=41
Patient characteristics					
Age at cancer diagnosis (years)	64.6±11.4	64.5±10.7	65.3±12.0	63.0±12.5	62.2±7.9
Time between cancer diagnosis and start on GLDs in years (years)	3.5±2.8	3.6±2.9	2.9±2.3	2.3±2.0	2.8±2.1
Comorbidity					
Lung disease	22 (6)	18 (6)	10 (5)	6 (11)	4 (11)
Cardiovascular disease	71 (19)	60 (19)	38 (20)	12 (22)	7 (19)
Liver disease	3 (1)	3 (1)	0 (0)	0 (0)	0 (0)
Renal disease	1 (0)	1 (0)	1 (1)	1 (2)	1 (3)
Stroke	10 (3)	9 (3)	2 (1)	1 (2)	0 (0)
Missing	28 (7)	24 (7)	12 (6)	4 (7)	5 (12)
Cancer characteristics					
Cancer stage					
I	157 (39)	129 (39)	78 (38)	14 (24)	19 (46)
II	191 (47)	161 (48)	94 (47)	36 (62)	18 (44)
III	45 (11)	35 (10)	24 (12)	7 (12)	3 (7)
IV	14 (3)	10 (3)	6 (3)	1 (2)	1 (2)
Cancer treatment					
Surgery	386 (95)	319 (95)	190 (94)	56 (97)	40 (98)
Radiotherapy	273 (67)	226 (67)	135 (67)	37 (64)	29 (71)
Chemotherapy	100 (25)	80 (24)	47 (23)	19 (33)	10 (24)
Hormone therapy	205 (50)	172 (51)	94 (47)	31 (53)	16 (39)
Estrogen receptor					
Negative	41 (10)	35 (10)	21 (10)	5 (9)	2 (5)
Positive	284 (70)	239 (71)	141 (70)	39 (67)	29 (71)
Missing	82 (20)	61 (18)	40 (20)	14 (24)	10 (24)
Progesterone receptor					
Negative	74 (18)	64 (19)	39 (19)	6 (10)	4 (10)
Positive	220 (54)	183 (55)	109 (54)	32 (55)	22 (54)
Missing	113 (28)	88 (26)	54 (27)	20 (34)	15 (37)
GLD use[a]					
Metformin	335 (82)	335 (100)	145 (72)	41 (71)	37 (90)
Sulfonylurea derivatives	202 (50)	145 (43)	202 (100)	34 (59)	31 (76)
Other GLDs	41 (10)	37 (11)	31 (15)	14 (24)	41 (100)
Insulin	58 (14)	41 (12)	34 (17)	58 (100)	14 (34)
Co-medication[a]					
Statin use	266 (65)	241 (72)	132 (65)	34 (59)	34 (83)
Aspirin use	123 (30)	104 (31)	63 (31)	13 (22)	8 (20)

[a]Ever use of the respective drug during follow-up



	N_{total}	N_{deaths}	Person time (years)	Unadjusted HR (95%CI)
Metformin				
Yes	335	67	1,365	0.50 (0.33-0.77)
No	72	40	331	Ref.
SU				
Yes	202	60	884	1.09 (0.72-1.66)
No	205	47	813	Ref.
Other GLDs				
Yes	41	3	182	0.27 (0.09-0.86)
No	366	104	1,514	Ref.
Insulin				
Yes	58	21	194	1.82 (1.11-2.99)
No	349	86	1,502	Ref.

Figure 2 The association between ever versus never use of GLDs and o
metformin, SU, other GLD and insulin use.
†Analysis is adjusted for age at breast cancer diagnosis, calendar year of breast cancer diagnos
or hormone therapy) and statin and aspirin use (modeled as time varying ever/never terms)

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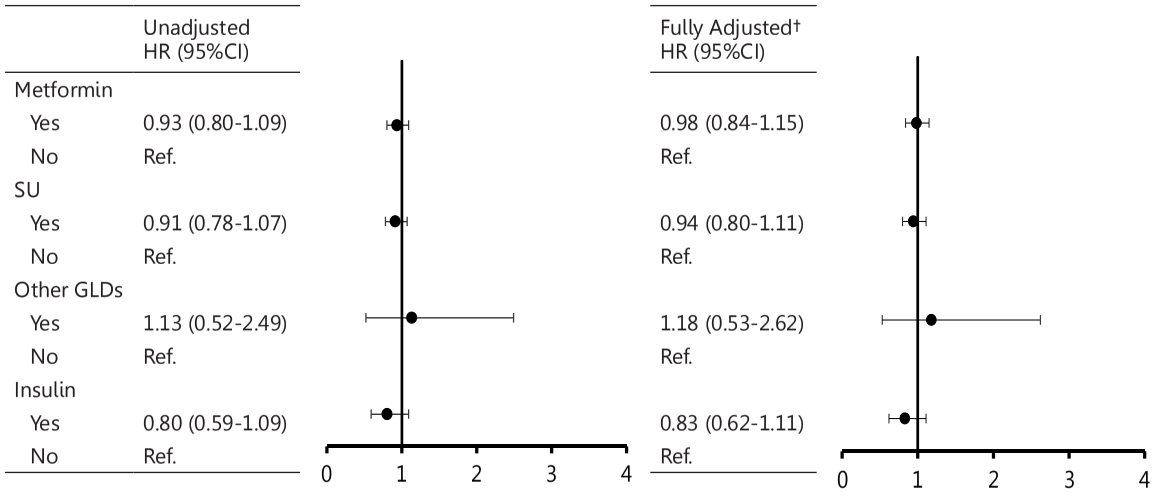

Figure 3 The association between GLD use and overall mortality using time varying covariates for cumulative exposure (per year) to metformin, SU, other GLD and insulin.

†Analysis includes time varying ever/never terms for metformin, SU, other GLD and insulin use and is adjusted for age at breast cancer diagnosis, calendar year of breast cancer diagnosis, cancer stage, cancer treatment (i.e. surgery, radiotherapy, chemotherapy or hormone therapy) and statin and aspirin use (modeled as time varying ever/never terms)

Table 2 Sensitivity analyses assessing the effect of GLDs on mortality in adjusted models

	N_{total}	N_{deaths}	Metformin (yes vs. no) HR (95%CI)	SU (yes vs. no) HR (95%CI)	Other GLDs (yes vs. no) HR (95%CI)	Insulin (yes vs. no) HR (95%CI)
Ever never analyses - main results (Figure 2)[a]	407	107	0.47 (0.29-0.74)	1.09 (0.71-1.68)	0.34 (0.11-1.10)	1.85 (1.09-3.15)
With positive ER and/or PR [a]	287	66	0.53 (0.29-0.98)	1.09 (0.62-1.91)	0.44 (0.11-1.85)	1.53 (0.76-3.09)
Additionally adjusted for comorbidity at BC diagnosis[b]	379	101	0.40 (0.25-0.64)	1.19 (0.75-1.88)	0.21 (0.05-0.87)	1.93 (1.12-3.33)
Analysis lagged with 6 months [a]	359	72	0.63 (0.35-1.14)	0.83 (0.49-1.39)	0.51 (0.16-1.66)	1.18 (0.57-2.46)
Restricted to those with the first GLD Prescription >6months after BC diagnosis [a]	368	93	0.49 (0.30-0.80)	0.98 (0.61-1.57)	0.35 (0.11-1.12)	1.90 (1.05-3.45)
Cumulative exposure per year - main results (Figure 3)[c]	407	107	0.98 (0.84-1.15)	0.94 (0.80-1.11)	1.18 (0.53-2.62)	0.83 (0.62-1.11)
With positive ER or PR status[c]	287	66	1.01 (0.83-1.23)	1.04 (0.85-1.28)	1.21 (0.54-2.70)	0.88 (0.64-1.21)
Additionally adjusted for comorbidity at BC diagnosis[d]	379	101	0.95 (0.81-1.13)	0.91 (0.77-1.07)	1.41 (0.63-3.18)	0.81 (0.60-1.10)
Analysis lagged with 6 months[c]	359	72	1.05 (0.88-1.24)	1.08 (0.90-1.29)	0.94 (0.37-2.43)	1.04 (0.77-1.41)
Restricted to those with the first GLD Prescription >6months after BC diagnosis[c]	368	93	0.95 (0.79-1.14)	0.94 (0.78-1.15)	1.22 (0.55-2.73)	0.91 (0.60-1.37)

[a]Analyses include time varying ever/never terms for metformin, SU, other GLDs and insulin use and are adjusted for age at breast cancer diagnosis, calendar year of breast cancer diagnosis, cancer stage, cancer treatment (i.e. surgery, radiotherapy, chemotherapy or hormone therapy) and statin and aspirin use (modeled as time varying ever/never terms)

[b]Analyses include time varying ever/never terms for metformin, SU, other GLDs and insulin use and are adjusted for age at breast cancer diagnosis, calendar year of breast cancer diagnosis, cancer stage and cancer treatment (i.e. surgery, radiotherapy, chemotherapy or hormone therapy)

[c]Analyses include cumulative exposure to metformin, SU, other GLDs and insulin and are adjusted for time varying ever/never terms for metformin, SU, other GLD and insulin use, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, cancer stage, cancer treatment (i.e. surgery, radiotherapy, chemotherapy or hormone therapy) and statin and aspirin use (modeled as time varying ever/never terms)

[d]Analyses include cumulative exposure to metformin, SU, other GLDs and insulin and are adjusted for time varying ever/never terms for metformin, SU, other GLD and insulin use, age at breast cancer diagnosis, calendar year of breast cancer diagnosis, cancer stage and cancer treatment (i.e. surgery, radiotherapy, chemotherapy or hormone therapy)

Discussion

This study showed that breast cancer patients who used metformin after cancer diagnosis have a 53% lower overall mortality compared to breast cancer patients on other GLD's. However this might be a result of selection bias, as no effect of cumulative exposure to metformin on overall mortality was observed. This suggests that metformin users might have different characteristics that are associated with a better prognosis and that there is no true protective drug effect on mortality of metformin itself. Similarly, women with breast cancer who used insulin after cancer diagnosis seem to have a higher overall mortality as compared to other GLD users, but again no dose-response effect was observed. No significant association between SU or other GLD use and mortality was observed.

The majority of previous studies included breast cancer patients who used GLDs prior to breast cancer diagnosis and results regarding the effect of metformin have been inconsistent. Several studies reported no association between metformin use and mortality[15,17,18,20,21], while some did observe reduced mortality rates among metformin users[16,19,22,23]. An American study among 1,983 HER2+ patients reported a 48% decrease in all-cause mortality for users versus non-users of metformin[16]. But as metformin users were classified as exposed from cancer diagnosis on and not from initial drug initiation[16], immortal time bias may have confounded the observation[30,31]. Another study among 1,013 breast cancer patients with and 4,621 without diabetes showed that metformin-treated patients had the highest 5 year overall survival as compared to non-metformin treated diabetes patients and people without diabetes[19]. But as no dose-response effect was studied this could be due to selection bias, with metformin users having prognostically better characteristics. In a study among 1,058 breast cancer patients with diabetes at breast cancer diagnosis, metformin use was associated with a lower overall mortality (HR=0.74; 95%CI:0.58-0.96) but not breast cancer-specific mortality (HR=0.88; 95%CI:0.59-1.29)[22]. Moreover, a dose-response effect was observed where a higher number of metformin prescriptions (i.e. 21-30 and ≥30 prescriptions) resulted in lower mortality, but results for other GLDs than metformin were not separately reported[22]. All these previous studies included breast cancer patients with diabetes prior to breast cancer diagnosis, and drug use was only taken into account from cancer diagnosis onwards, and thus dose-response relationships could not be assessed accurately.

Only one previous study, conducted by us using data from the UK, included 706 patients who started using GLDs after breast cancer diagnosis. In this study we applied time-dependent Cox regression models to avoid immortal time bias, reported results for separate GLDs and assessed cumulative drug exposure, however, data on cancer stage was limited and no information regarding receptor status was available[23]. In that study, cumulative exposure to metformin (per year of exposure) was associated with a lower breast cancer specific mortality with a HR of 0.73 (95%CI:0.56-0.96) but, similar to our results, not with overall mortality[23]. However, in line with this study an increased mortality

risk among short-term SU users (HR=3.51; 95%CI:2.04-6.06) was found[23]. This result is counterintuitive and it is likely that other factors that were not adjusted for might have confounded the findings. Possibly more patients with advanced cancer might have switched to SUs, as SUs are often preferred in the palliative phase instead of metformin due to possible gastro-intestinal side effects[32].

Although we did not observe a statistically significant association between cumulative metformin use and mortality, several pre-clinical studies show that metformin suppresses breast cancer cell growth[33,34]. Metformin is suggested to directly inhibit cell growth due to activation of the AMPK protein kinase, which results in activation of the MTOR protein kinase and a decreased translation initiation[33,34]. In addition, metformin might inhibit breast cancer cell growth indirectly, due to reduced insulin levels and deactivation of IGF-1 receptors[35], which is possibly associated with lower mortality[36]. Finally, lower IGF-1 levels might inhibit the signaling protein Cyr61 which in turn, suppresses breast cancer cell growth and invasion[37].

In this study we observed lower mortality among metformin users and higher mortality among insulin users, however, this is likely to be a result of selection bias, i.e. the different patient characteristics of different GLD users. The choice to prescribe a certain drug is depending on other factors that were not taken into account such as Body Mass Index (BMI), contra-indications for the drugs, HbA1c levels, diabetes complications etcetera. Thus more studies are needed to understand differences in characteristics of patients who start on the different GLDs. Before more observational studies are undertaken, it is important to reveal why patients are allocated to the specific drugs as these characteristics are likely to influence their mortality risk.

Strong points of this study include its detailed information on cancer characteristics, including hormone receptor status, and drug dispensing, including duration of the dispensing. Furthermore, we performed time-dependent analyses to rule out time-related biases. In addition, this study is one of the first that focused on patients who develop diabetes after cancer diagnosis which rules out the possible effect of diabetes, and its medication on the development of breast cancer. Despite the large population-based sample of breast cancer patients, the final selected study population was relatively small and no information regarding cancer-specific deaths was available. In addition, we did not have information on BMI and diabetes characteristics, including Hba1c levels and the presence of complications. Moreover our follow-up period is relatively short for a study involving breast cancer patients, who generally have a good prognosis. Longer follow-up is necessary to assess the association between metformin and other GLDs and mortality in the long run in future studies.

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In conclusion, GLDs were not associated with mortality among patients who started using GLDs after breast cancer diagnosis. We did observe a lower mortality among those using metformin and higher mortality among those using insulin, however, this might be a result of differences in patient characteristics that we could not adjust for. Larger studies with longer follow-up among patients who start using GLDs after cancer diagnosis are needed to establish our findings. Moreover, differences in patient characteristics between those allocated to different GLDs should be identified to distinguish a potential true drug effect.

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CHAPTER 10

GENERAL DISCUSSION

Summary of results

This thesis aimed to assess the dual impact of having both cancer and diabetes on Patient Reported Outcomes (PROs) and mortality. The main objectives of this thesis were:

- To assess the impact of comorbidity, with a main focus on cancer and diabetes, on PROs, including Health-Related Quality of Life (HRQoL) and symptoms (Part I)
- To assess the impact of cancer and diabetes, and the role of lifestyle factors, on mortality rates (Part II)
- To assess the effect of Glucose Lowering Drug (GLD) use on mortality rates among breast cancer patients (Part II)

As an introduction to **Part I** of this thesis, we started with a systematic literature review on the impact of cancer and diabetes on PROs in **Chapter 2**. Besides providing a systematic review of the literature in this largely neglected research area, we also proposed a research agenda to direct future research. A broad search strategy was used which identified a total of 3,553 eligible studies. After selection, only 10 studies were included that studied the impact of cancer and diabetes on PROs, of which 8 focused on HRQoL, functioning or symptoms, and 2 studies assessed the effects of cancer on diabetes self-management among patients with both cancer and diabetes. Results indicated that patients with both cancer and diabetes reported mainly lower general health, lower physical functioning and lower sexual functioning while prostate cancer patients with diabetes reported lower urinary function and lower vitality as compared to patients with either one or none of the diseases. Moreover, more problems with diabetes self-management were reported among patients with both diseases. However, no firm conclusions could be drawn, this was mainly due to the low number and heterogeneity of the included studies. We identified several important research topics for future research. For example, we suggest that more research is needed on the impact of having both diseases on mental health, as depression is highly prevalent among both cancer and diabetes patients. Moreover, as the occurrence of multiple chronic diseases poses important constraints on a person's life and their health care, future research should focus on the self-management of both diseases. Patients need to be able to manage the treatment, symptoms, and psychological consequences of having both diseases.

Research shows that the presence of comorbidity is associated with decreased HRQoL among cancer patients. However, its relative impact on HRQoL as compared with sociodemographic and clinical characteristics is rarely studied. Therefore, we assessed the variance in HRQoL explained by comorbidity as compared with sociodemographic and clinical characteristics in **Chapter 3**. To determine whether results are similar for different cancer types we investigated this among colorectal cancer, thyroid cancer and (non-) Hodgkin's lymphoma patients. We found that the number of comorbid conditions explained more of the variance in physical functioning (11-17%), emotional functioning (7-17%), pain (7-20%) and fatigue (11-13%) compared with both sociodemographic and cancer characteristics (0-4%) among all studied cancer types. Assessing the effect

of individual comorbidities on HRQoL showed that particularly heart disease and back pain explained most variance in physical function (ranging between 2 and 4%), while depression explained most variance in emotional functioning (12 and 8%) among colorectal and non-Hodgkin's lymphoma patients, respectively.

Previous studies among cancer patients showed that these patients experience worse HRQoL as compared with a healthy population, and also, sexual problems are highly prevalent. Similar results are found among diabetes patients. Thus, both cancer and diabetes are independently associated with worse HRQoL and sexual dysfunctioning. However, we hypothesized that having both cancer and diabetes may result in even worse outcomes. Therefore, we assessed the individual and combined effects of colorectal cancer and diabetes on HRQoL and sexual functioning in **Chapter 4**. Data from a colorectal cancer population with (CRC+DM+) and without diabetes (CRC+DM-) and a normative population, with (CRC-DM+) and without diabetes (CRC-DM-) aged ≥60 years were used. In general, CRC-DM- patients reported highest functioning and lowest symptoms followed by CRC-DM+, CRC+DM- and CRC+DM+ patients. No interaction between colorectal cancer and diabetes was observed, indicating that having both diseases did not result in worse outcomes than the sum of the individual effects of colorectal cancer and diabetes, contrary to our expectation. Colorectal cancer seemed to be stronger associated with worse outcomes, as it was independently associated with the majority of HRQoL subscales. However, diabetes was also independently associated with lower physical functioning and more symptoms of dyspnea.

Next, to investigate whether treatment-related toxicities were more prevalent among cancer patients with versus without diabetes, we assessed differences in neuropathic symptoms between CRC+DM+ patients and age and sex-matched CRC+DM- patients, using cross-sectional data (**Chapter 5**). As results of previous research suggest that cancer patients with diabetes are often less aggressively treated with chemotherapy than those without diabetes, we additionally aimed to investigate whether there were differences in type of cancer treatment. CRC+DM+ patients experienced more mild to severe neuropathic symptoms including tingling fingers or hands (Odds Ratio (OR)=1.40; 95% confidence interval (CI): 1.00-1.94), tingling toes or feet (OR=1.47; 95%CI: 1.04-2.07), numbness in toes or feet (OR=1.83; 95%CI: 1.28-2.62) and erection problems among men (OR=1.83; 95%CI: 1.11-3.03) as compared to CRC+DM- patients. However, no differences in cancer treatment were found between both groups.

As cancer and diabetes share several lifestyle-related risk factors, including a high Body Mass Index (BMI), low physical activity, smoking and excessive alcohol consumption, in **Chapter 6** we investigated whether lifestyle factors differed between cancer patients with and without diabetes. We also studied whether these lifestyle factors could explain the differences in HRQoL between CRC+DM+ and CRC+DM- patients. We used longitudinal data collected in 2010, 2011 and 2012 for this purpose. At baseline, CRC+DM+ patients had a higher BMI (29.1±4.2 vs. 26.4±3.7 kg/m2), moreover, the number of alcohol users

was lower (50 vs 70%) as compared to CRC+DM- patients. No differences in moderate-to-vigorous physical activity (MVPA) and smoking were observed between the two groups. Adjusted analyses of the longitudinal data showed that CRC+DM+ patients reported significantly lower physical function (beta-5.76; SE=1.67), global QoL (beta-4.31; SE=1.48) and more symptoms of fatigue (beta=5.38; SE=1.95) as compared to CRC+DM- patients. However, these effects disappeared after adjustments for lifestyle factors; BMI, MVPA, smoking and alcohol use were all significant predictors of HRQoL. The association between diabetes and HRQoL was further attenuated after additional adjustments for comorbidity.

In **Part II** of this thesis we studied the potential dual impact of having both cancer and diabetes on mortality. As only a few previous studies that adjusted for lifestyle factors found an increased mortality risk for CRC patients with versus without diabetes, we aimed to assess whether lifestyle factors, including BMI, MVPA, smoking, and alcohol consumption, explain the increased mortality rates among CRC patients with diabetes (**Chapter 7**). Independent effects of lifestyle factors as well as effects of different lifestyle clusters were identified and associated with mortality. Four different lifestyle clusters were identified which were labeled as (1) healthy, (2) moderately healthy, (3) overweight and (4) smoking. CRC+DM+ patients had a 29% higher mortality risk as compared to CRC+DM- patients. After adjustments for BMI, MVPA, smoking and alcohol use, this effect was slightly attenuated to non-significance (Hazard ratio (HR)=1.24; 95%CI: 0.98-1.56), but remained after adjustments for the lifestyle clusters (HR=1.29; 95%CI: 1.02-1.61). Alcohol use, MVPA and being overweight were all independently associated with a decreased mortality risk, while smoking was associated with an increased mortality risk. Moreover, the lifestyle cluster with patients who smoke, with low MVPA and low BMI had a 3.7 fold increased mortality risk as compared with those with a healthy lifestyle.

Recent literature shows that metformin, a GLD used as first-line treatment among diabetes patients, potentially decreases the risk of cancer and possibly improves outcomes among patients with both cancer and diabetes. We aimed to assess the effect of GLDs, including metformin, sulfonylurea derivatives, insulin and other GLDs, on mortality among breast cancer patients from the United Kingdom (UK) and the Netherlands in **Chapter 8** and **Chapter 9**, respectively. In **Chapter 8**, we included women who started using GLDs prior to breast cancer as well as women who started using GLDs after breast cancer diagnosis. This study showed some evidence of lower breast cancer-specific and all-cause mortality for metformin users among breast cancer patients who started GLDs prior to breast cancer diagnosis. Results were mainly apparent among patients with long-term (i.e. ≥2 years) metformin use, with HR=0.47 (95%CI:0.26-0.82) and HR=0.70 (95%CI:0.49-0.99) for breast cancer-specific and all-cause mortality, respectively. Among patients who started using GLDs after breast cancer diagnosis, cumulative metformin use was also associated with lower overall mortality, while sulfonylurea derivative use was associated with substantial higher breast cancer-specific and all-cause mortality. As in the UK sample no (complete) data on breast cancer stage and other clinical details such as estrogen or progesterone receptor status were available, we conducted these analyses also within a sample from the Netherlands that included information on stage and receptor status (**Chapter 9**). As relatively little is known on mortality risk among patients who start using GLDs after breast cancer diagnosis, only those patients were included. Using time-dependent Cox regression analyses, this study found a lower mortality among patients using metformin (HR=0.47; 95%CI: 0.29-0.74) and a higher mortality among patients using insulin (HR=1.85; 95%CI:1.09-3.15) as compared to non-users. However, no clear association between cumulative use of any GLD on overall mortality was observed. Thus the found effects are likely to result from factors other than GLDs, such as BMI, glycemic control, diabetes complications and differences in diabetes severity, as metformin is prescribed earlier in the disease course.

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General discussion

As a result of the aging of the population, the prevalence of both cancer and diabetes is rapidly increasing[1,2]. Subsequently, an increasing number of individuals will have both cancer and diabetes. The number of cancer patients with diabetes at cancer diagnosis in the Netherlands was expected to drastically increase from 5,500 in 2000 to 10.000 in 2015[3]. Up to now, the dual impact of cancer and diabetes on Patient Reported Outcomes (PROs) has rarely been studied. PROs are used as an umbrella term and include a wide range of different measurements that reflect patients' perspectives, and include for example Health-Related Quality of Life (HRQoL), perceived symptoms and satisfaction with health care. Moreover, as previous research shows that cancer patients with diabetes have a 40% higher mortality risk[4], it is important to study which factors contribute to this increased mortality. This information may guide future interventions that help to improve HRQoL and reduce mortality. Thus, in order to improve outcomes among patients with both cancer and diabetes, this thesis aimed to assess the dual impact of cancer and diabetes on PROs and mortality.

The dual impact of cancer and diabetes on PROs and mortality

In this thesis we showed that the impact of cancer and diabetes on PROs is largely neglected in current literature. The studies that did assess PROs primarily focused on HRQoL, while other PROs such as symptoms of pain and fatigue and emotional functioning including anxiety and depression were neglected. In our own research, we observed that having both cancer and diabetes results in worse HRQoL, more neuropathic symptoms and an increased mortality risk as compared to having only cancer, only diabetes and/or neither of both diseases. In the following paragraphs we will present possible explanations for the worse outcomes found among cancer patients with concurrent diabetes.

The influence of cancer stage at diagnosis, treatment and disease progression on deteriorated outcomes

Previous research suggests that cancer patients with diabetes present with a higher cancer stage at diagnosis[5-7], possibly as a result of the underuse of screening[8]. This was mainly found among breast cancer patients[5-7] while the evidence was less convincing among colorectal cancer patients[7,9]. However, in our colorectal cancer sample, cancer patients with diabetes did not present with a more advanced cancer stage at diagnosis, while we did observe deteriorated outcomes among patients with both diseases. A more plausible explanation for the deteriorated outcomes among patients with both cancer and diabetes may lie within the received cancer treatment. Research showed that esophageal, colon, breast and ovary cancer patients with diabetes often received less aggressive treatment[7]. However, in our study described in the present thesis we did not find differences in the receipt of chemotherapy, radiotherapy and surgery in the six months after cancer diagnosis between cancer patients with and without diabetes. We also observed that colorectal cancer patients with diabetes reported more

neuropathic symptoms, which is in accordance with previous studies that found more toxicities related to radiotherapy or chemotherapy among cancer patients with versus without diabetes[6,10]. It is possible, that among cancer patients with diabetes, the doses for certain chemotherapeutic agents have been adjusted or that patients were switched to a different type of chemotherapeutic agent as a result of these treatment-related toxicities. Especially taxanes and platinum derived chemotherapeutic agents such as oxaliplatin are known to induce these neuropathic symptoms[11]. Unfortunately, we had no data regarding the type and dose of chemotherapeutic agent used. Thus it remains possible that cancer patients with diabetes are less aggressively treated by alterations in the dose and type of agents, which might result in an increased risk for cancer progression and recurrence. At the same time, the higher prevalence of neuropathic symptoms and treatment-related toxicities may have resulted in worse HRQoL. Previous research concluded that neuropathic symptoms are common up to 11-years after cancer diagnosis and having these symptoms results in worse HRQoL[12]. Further research should assess whether differences in dose and type of chemotherapeutic agents explain the deteriorated outcomes (i.e. both PROs and mortality) among cancer patients with diabetes as compared to patients without diabetes. And if so, it should be assessed whether these alterations in chemotherapeutic schedule outweigh the risk for cancer progression and mortality.

The influence of lifestyle on deteriorated outcomes

Cancer and diabetes share several lifestyle-related risk factors including overweight and obesity, physical inactivity, poor dietary habits and smoking[13]. Besides influencing the risk of developing both diseases, lifestyle-related risk factors may also impact negatively on outcomes among patients with both diseases. Previous studies showed that overweight and obesity, physical inactivity, smoking and excessive alcohol consumption are all independently associated with worse HRQoL[14-20] and increased mortality[21-28] among both cancer and diabetes patients. In this thesis we observed that lifestyle factors did explain the worse HRQoL found among patients with both cancer and diabetes. The lower physical functioning and HRQoL and higher levels of fatigue found among colorectal cancer patients with diabetes disappeared after adjustments for BMI, MVPA, smoking and alcohol use in longitudinal analyses. Thus, in order to improve HRQoL among patients with both diseases, lifestyle improvements seem to be crucial, yet further experimental research is needed to test this hypothesis.

In contrast, we also showed that the increased mortality rates found among cancer patients with diabetes could not be explained by lifestyle factors. Even after adjustments for BMI, MVPA, smoking and alcohol use, colorectal cancer patients with diabetes had a 29% higher mortality risk as compared to those without diabetes. Thus, the increased mortality found among cancer patients with diabetes is not fully explained by lifestyle and therefore it is likely that other factors are involved. As previously discussed, the increased mortality could be due to clinical factors including the underuse of screening, less aggressive cancer treatment, and more treatment-related toxicities among cancer

patients with diabetes. Moreover, as previous research shows that cancer patients with diabetes perform less diabetes related self-management activities[29], cancer patients with diabetes may prioritize their cancer care over there diabetes care. In turn, this may lead to more diabetes-related complications resulting in worse prognostic outcomes. Although differences in mortality between cancer patients with and without diabetes were not (fully) explained by lifestyle, individual factors such as being overweight, high MVPA, and moderate alcohol use were associated with lower mortality while smoking was associated with higher mortality. Thus, regardless of having diabetes, lifestyle improvements might reduce mortality among cancer patients.

The effect of glucose lowering drugs on mortality after breast cancer

Currently, the evidence regarding the effects of metformin and other GLDs on mortality among breast cancer patients is inconclusive. Some previous studies reported a protective effect of metformin on mortality[30-32] while others found no effect[33-37]. Several of these studies may have been influenced by different types of bias which are discussed later in this chapter. Only one previous study[35] used a time-dependent analysis to adjust for immortal time bias, included a measure of cumulative exposure and reported results for different GLDs similar to the analyses in this thesis. This Canadian study observed that metformin and any of the other GLDs was not associated with mortality rates in breast cancer patients[35]. In the study that is described in the present thesis, based on a large UK dataset, we observed a protective effect of metformin on mortality, mainly among patients who developed diabetes after their cancer diagnosis and among long-term users of metformin. However, these results were not confirmed in similar analyses among a Dutch sample, although this can possibly be explained by a small sample size and a possible lack of power. In order to obtain a definite answer regarding the potential effects of metformin on mortality among breast cancer patients, there is still a need for additional, large and well-designed observational studies. One way to achieve this is by combining different data sources. Furthermore, although laboratory studies and observational studies show potential beneficial effects on cancer prevention and prognosis, the mechanism of action of metformin needs to be further elucidated. Currently numerous randomized controlled trials (RCTs) are being conducted among breast cancer patients and the majority focus on the efficacy of metformin during cancer treatment[38]. Another ongoing RCT among breast cancer patients without diabetes administers daily metformin till 5 years after cancer diagnosis[39,40]. This study assesses the effect of metformin use versus placebo on cancer free survival, of which the results are expected at the end of 2017[39,40].

Methodological considerations

Bias and confounding

Selection bias

The lower PRO scores among persons with both cancer and diabetes may have been influenced by selection bias. Even though participants were selected from a population-based sample and initial response rates in the studies presented in this thesis were relatively high (i.e. ranged between 67 and 73%), selection bias could have occurred. To explore the representativeness of the data, we compared data on sociodemographic and clinical characteristics between respondents and non-respondents. We found that in general more males responded and that respondents were younger. Moreover, it is possible that non-respondents had more complications at cancer diagnosis, had a poorer general health to start with or may have deceased prior to the study as patients were selected between 1 and 10 years after cancer diagnosis. Furthermore, our findings may also have been biased by attrition bias as a result of loss to follow-up. By comparing colorectal cancer patients who completed 1 versus 2 or more questionnaires, we showed that, as expected, those who completed 1 questionnaire had a lower educational level, engaged less in physical activity and reported worse overall HRQoL and physical functioning[17]. It remains a challenge to maintain high response rates and minimize loss to follow-up. A more personal invitational approach, for example via telephone contact, could possibly improve response rates in future studies, although these strategies are time consuming and more expensive. Moreover, future studies should also focus on the reasons for participants drop-out to identify barriers for participation. In addition, the difference in disease progression and survival between respondents and non-respondents should be compared in order to gain more insight into the degree of selection bias.

Immortal time bias

One of the most criticized biases among research on the effect of metformin and other GLDs on mortality is immortal time bias[41]. Several of the previous observational studies that found a remarkably decreased mortality, ranging between 34 and 62%, among metformin users appear to have been influenced by immortal time bias[30,41-44]. These studies classified metformin users as users from cancer diagnosis onwards and not from the time of actual drug initiation. Thus in the period between cancer diagnosis and drug initiation, death could not occur; a period of 'immortal time' was initiated as the patient stayed alive at least until the first drug dispensing. This bias is known to result in a higher protective effect than the true drug effect[45]. A more optimal statistical analysis that can avoid immortal time bias is a time-dependent Cox regression analysis in which the exposure to the drug remains zero until the first drug dispensing. These time-dependent analyses have been applied in this thesis.

Confounding by disease severity

The studies that assessed the effects of different drugs on mortality among diabetes patients may have been confounded by disease severity. Currently in the Netherlands, metformin is used as a first choice in the treatment of type 2 diabetes[46] and is therefore used earlier in the disease course than other GLDs. Thus, patients who are treated with metformin only, generally have a lower diabetes severity and often a better glycemic control. Subsequently these patients may have better outcomes than those who received add-on treatments or switched to other GLDs such as insulin. These differences in

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the allocation of GLDs may be (partly) responsible for the found protective effects of metformin in previous studies that used a dichotomous variable for metformin use versus non-use[30,42,43]. We confirmed that confounding by disease severity had occurred in this thesis as we observed a lower mortality among metformin users as compared to non-users, while no effect of cumulative exposure to metformin was observed. This indicates that metformin users had more favorable characteristics at baseline as compared to users of other GLDs.

To avoid confounding by disease severity it is essential to consider cumulative exposure to the drugs as was done in this thesis. The cumulative drug exposure represents the daily or monthly drug use and thus we modelled the effect of each additional day or month of use on mortality. These analyses were adjusted for the difference between the users and non-users of the drugs. Although we included cumulative exposure to the drugs, we did not take the dosage of the drugs into account. As the dosage of GLDs can vary strongly during the course of disease, this asks for far more complex statistical analyses. Moreover, datasets with detailed and accurate information regarding the dosage need to be available. However, even after considering cumulative exposure and dosage of GLDs in observational studies, residual confounding remains. Therefore ongoing trials could provide more insight into the dose-response effect of metformin. The majority of ongoing trials on the effect of metformin among cancer patients use conventional doses of metformin, while preclinical studies that report a beneficial effect for metformin use considerably higher doses[47,48]. Thus results of these ongoing trials should be awaited to see whether conventional doses of metformin are also associated with decreased tumor progression and mortality. At the same time several current ongoing trials that test the effect of metformin during cancer treatment on tumor response, activity or time to cancer progression are studying the maximum tolerable dose of metformin[49].

Strengths and limitations of the data sources

Netherlands Cancer Registry

The studies that are described in this thesis are based on different data sources, which have several methodological strengths and weaknesses. The majority of studies were based on routinely collected data from the Netherlands Cancer Registry (NCR) on all newly diagnosed cancer patients in the South of the Netherlands (formerly known as the Eindhoven Cancer Registry (ECR)). This area comprises an area of 2.4 million inhabitants served by 10 community hospitals[50]. Detailed clinical data regarding cancer diagnosis, stage and primary treatment are available. Since 1995, the ECR registers comorbidity at cancer diagnosis[51], which is unique as compared to other cancer registries in the world. Although data regarding comorbidity including diabetes were collected, no information regarding diabetes type, complications, blood glucose levels and diabetes severity were available. Moreover, data on systemic primary cancer therapy were available, but we had no details on the type of agent, dosage and treatment regimen used. Although we did not observe differences in cancer treatment between cancer patients with and without diabetes, it is possible that doses were adjusted or treatments were ended early. These

modifications in dosage and treatment regimen may have influenced the differences found in neuropathic symptoms, HRQoL or mortality between cancer patients with and without diabetes, as investigated in this thesis.

PROFILES registry

PROs were collected using the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) registry[52]. For our analyses we mainly used longitudinal data from a cohort of colorectal cancer patients diagnosed between 2000 and 2009. Thus at the time of the first data collection in 2010, patients were between 1 and 10 years after cancer diagnosis. A strength of this dataset is the relatively large population-based sample that results in large statistical power. Moreover, the data is linked to clinical data from NCR. Furthermore, longitudinal data on HRQoL, symptoms, and lifestyle were collected in 2010, 2011 and 2012 which enabled us to look at changes over time. In addition, the response rates were relatively high, with a 73% response rate at the first wave in 2010. This is much higher than the 40% average response rate for mailed cross-sectional surveys found in an earlier meta-analysis[53]. After the initial data collection, the response rates dropped to 55% and 49% for the second wave in 2011 and third wave in 2012, respectively, with mainly the healthiest patients continuing to participate in the study. The invitation letter for the study was sent from the hospital by the (ex-) attending specialist of the patient, which may have resulted in the high initial response rate. Patients may have developed a good relationship with their specialist and may have felt more motivated to participate. Nevertheless, it remains a challenge to encourage patients to participate continuously in longitudinal studies. Recently our research group investigated whether a monetary incentive can increase the response rate (results have not been published yet). In this study, patients who were asked to complete a third questionnaire in a longitudinal study received a 10 euro gift card which increased the overall response from 66% to 90%. In addition, patients who received the monetary incentive responded quicker. Thus sending a monetary incentive may outweigh the cost of sending reminders.

However, one of the main limitations of the data used in this thesis is that the collection of PROs started shortly or even up to years after cancer diagnosis and treatment, so no information on PROs before cancer diagnosis was available. Without a measure prior to the cancer treatment it is unknown whether the found deteriorated outcomes are a result of the studied predictors, the cancer treatment, or whether they can be explained by differences in patient characteristics that existed prior to cancer diagnosis. Moreover, cancer patients may have adjusted several lifestyle behaviors shortly after cancer diagnosis, they might have improved their dietary habits, quitted smoking and/or increased their physical activity as has been seen in a previous study[54]. This could have influenced the findings in this thesis. Currently our research group is planning to start a new prospective PRO data collection in the fall of 2015 among colorectal cancer patients in 4 hospitals in the south of the Netherlands. This study will assess PROs directly after cancer diagnosis and prior to cancer treatment which will help to explore changes

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in PROs and lifestyle behaviors around cancer diagnosis. At the same time the impact of cancer treatment on PROs can be evaluated. Another limitation in our data is that misclassification regarding diabetes status may have occurred as having diabetes was self-reported in the majority of studies presented in this thesis. However, in community dwelling elderly self-reports on several chronic diseases were fairly accurate with an accordance of 98% between the self-reports and records of the general practitioner for diabetes[55]. Moreover, undiagnosed or untreated diabetes patients may have been missed. Misclassification also could have occurred as cancer treatment can result in transient diabetes. A previous study among colorectal cancer patients observed that 12% of the patients developed diabetes, during or shortly after chemotherapy treatment, of whom 17% returned to normal blood glucose levels during follow-up[56]. Finally, no information regarding the type of diabetes, complications or severity of diabetes was available.

Data on glucose lowering drugs

In this thesis, data regarding GLD use in the Netherlands were retrieved from the out-patient pharmacy database from the PHARMO database network. PHARMO has previously been linked to clinical data from the NCR covering a demographic area of approximately 1 million inhabitants in the south-east of the Netherlands. For the linkage a validated algorithm that used multiple variables for matching, including patients' initials, last name and their most recent zipcode, was used[57]. The outpatient pharmacy database comprises information regarding type of product, date of dispensing, dosage, and quantity. The linkage between PHARMO and the NCR provides us with unique information, and the linkage is annually updated, resulting in longer follow-up of existing cancer patients each year. Although we had detailed information regarding dispensed products, we cannot ascertain whether the dispensed products were actually ingested by the patients. A previous study compared pharmacy records with a home inventory and interview and showed that 85% of the drugs in use based on the pharmacy records were also in use at the home inventory[58]. The misclassification that does occur is likely to result in an underestimation of the true intake[58]. Thus pharmacy records seem to be fairly reliable data sources to estimate drug use. Moreover, the sample size for this study type was relatively low but currently an expansion of the linkage is pursued by means of geographic coverage as well as increasing follow-up time. The expansion of this linkage will result in an overlapping area of approximately 4 million inhabitants in the Netherlands. Furthermore, as PHARMO is also linked with other databases including in-patient pharmacies, general practitioner databases, and clinical laboratory databases, this provides unique opportunities for further research.

Implications of the main findings and directions for the future

The research conducted in this thesis provides several insights in the dual impact of cancer and diabetes on PROs and mortality. In this section we will discuss the implications of our main findings for future research and clinical practice.

Implications for future research

Intervening on self-management

Due to the aging of the population the number of patients with multiple chronic diseases, including cancer and diabetes is rapidly increasing. To maintain good health in the long-term, self-management is becoming more important. Self-management can be defined as a person's ability to manage symptoms, treatment, physical and psychosocial consequences and lifestyle changes following a chronic disease[59]. To achieve good self-management, patients need to be educated and supported on, for example, medication use, the prevention, detection and treatment of complications, and personal skills such as solving problems and dealing with psychological consequences. Current evidence on effective self-management interventions mainly focus on information provision, symptom management and improving lifestyle behaviors[59]. Among cancer as well as diabetes patients, self-management interventions have been found to reduce distress, improve HRQoL and increase knowledge and self-efficacy[60-62]. As poor lifestyle behaviors are a risk factor for developing cancer as well as diabetes, intervening on lifestyle will be discussed in more detail.

Intervening on lifestyle behaviors

In this thesis we showed that cancer patients with diabetes had a poorer lifestyle than those without diabetes. These poor lifestyle habits were independently associated with worse HRQoL and increased mortality. Moreover, unhealthy lifestyle habits among cancer patients have previously been associated with more chronic conditions including diabetes[63]. Therefore, among this group of patients, there is a need for effective lifestyle interventions that may improve HRQoL and lower the risk of mortality. Current evidence on the effectiveness of lifestyle interventions among cancer patients often focuses on only one component, such as enhancing weight loss, increasing physical activity or improving dietary quality[64]. However, according to the results presented in this thesis, lifestyle behaviors often cluster together. Thus an intervention focused on multiple components is possibly more effective. Among cancer patients, only a few previous intervention studies focused on multiple lifestyle components and showed positive results. A telephone-based health coaching intervention among colorectal cancer patients that focused on physical activity, dietary habits, weight management, smoking and alcohol use showed that the intervention resulted in increased physical activity, lower BMI, and improved dietary quality at 12 months follow-up as compared to a control group that received usual care[65]. Similar results were found from the FRESH START trial that randomly assigned breast and prostate cancer patients to a 10-month program or to a control group that received non-tailored general health education[66]. The program aimed to promote fruit and vegetable consumption, reduce fat intake and increase physical activity via tailored mailed print materials. Results showed that after 1 year of follow-up the intervention group significantly lowered fat intake, increased fruit and vegetable consumption and increased physical activity[66]; these results remained at 2 years of follow-up[67,68]. Although the majority of studies among both cancer and diabetes patients report short-term effects of lifestyle interventions, recently the results of a

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large intervention study among diabetes patients with a median follow-up of 10 years were presented[69]. This study randomized over 5000 obese diabetes patients to either an intensive lifestyle intervention focused on diet and physical activity or to a diabetes education program[69]. Patients in the intervention lost significantly more weight than the control group; differences were largest at 1 year (8.6 versus 0.7% weight loss), directly after the intervention, but remained during the next 9 years of follow-up[69].

Although the evidence on the effectiveness of previous lifestyle interventions is promising, studies that assess sustainable long-term changes remain scarce. Possibly these sustainable changes can be reached by interventions that intervene on lifestyle but additionally focus on several other aspects of self-management. If patients gain more confidence in their own abilities, are able to set goals and learn strategies to deal with the consequences of their diseases, patients may adhere better to an intervention program and the lifestyle changes may sustain for a longer period of time.

Targeting patients with both cancer and diabetes in interventions
Although the provision of self-management and lifestyle interventions seem to be effective among patients with cancer or diabetes only, it is questionable whether these interventions are also effective among patients with both cancer and diabetes as in previous intervention studies often patients with multiple chronic diseases have been excluded[70]. Patients with multiple chronic diseases are likely to have poor general health, lower health literacy and, are older and more often cognitively impaired which may limit the effectiveness of self-management interventions[70]. On the other hand, as their health is poor, they may benefit most from these interventions. Thus, future research should establish whether self-management interventions among patients with both cancer and diabetes can improve self-efficacy, lifestyle behaviors and knowledge. The effectiveness of these interventions on improving HRQoL and symptom management in the long run, and decreasing the risk of complications and mortality should also be studied.

The need for well-designed observational studies on the effect of GLDs
In this thesis we did not find convincing evidence that GLDs, including metformin, are associated with mortality among breast cancer patients. Currently the evidence from well-designed studies that account for time-related biases among breast cancer patients is scarce. In order to establish the effect of the use of different GLDs on mortality there is a need for large well-designed observational studies while the results of ongoing RCTs are awaited. We did observe a difference in patient characteristics, with metformin users having characteristics that are associated with lower mortality. More research is needed to assess which factors explain this prognostic difference. These factors may include co-medication, complications, hospitalizations, lifestyle behaviors and glycemic control.

Implications for clinical practice
Both oncologists and primary care physicians will encounter an increasing number of patients with (a history of) both cancer and diabetes, and need to become aware that these patients have an increased mortality risk and report worse PROs. As lifestyle behaviors were independently associated with both HRQoL and mortality, these patients should be informed about the consequences of poor lifestyle behaviors and should be encouraged to improve their health behavior. However, specialists often have to deal with time constraints which is an important barrier for providing this crucial information. A possible solution is to increase referrals to rehabilitation programs where patients receive help from physiotherapists, dieticians and medical psychologists or health psychologists, when necessary. Moreover, during the active cancer treatment phase, treatment regimens for both diseases should be considered. Previous research shows that around cancer diagnosis patients with co-occurring diabetes seem to prioritize their cancer care over their diabetes care which affects blood glucose monitoring activities, exercise and the ability to eat and drink[29]. This may lead to more diabetes-related complications and poorer outcomes. Clinical care for patients with both cancer and diabetes is often fragmented and usually involves primary care and multiple secondary care specialists. As such, there is a need for close collaboration and integrated care to monitor the treatment and progression of both diseases. Moreover, primary care physicians need to be involved more in the follow-up care of cancer survivors. Primary care physicians will attend to a growing group of patients with (a history of) both cancer and diabetes and should be educated about self-management strategies and provide the necessary information to patients to maintain good health in the long-term.

Concluding remarks
The number of patients with both cancer and diabetes is rapidly increasing. In this thesis we showed that this growing group of patients reports worse HRQoL, more neuropathic symptoms and have an increased mortality risk as compared to patients with cancer only. Currently the factors underlying these worse outcomes are not (fully) known. Further research should focus on self-management, including lifestyle behaviors as we showed that healthy lifestyle behaviors are associated with better HRQoL and decreased mortality. Finally, we did not found convincing evidence for an association between GLDs, including metformin, on mortality. More evidence from well-designed observational studies is needed and the results of ongoing trials should be awaited. The results of this thesis highlight the need to increase awareness among physicians on the association between cancer and diabetes and their negative impact on outcomes. Endocrinologists, oncologists and primary care physicians should work closely together as treatment regimens of both diseases may interfere with each other. Moreover, due to aging of the population, primary care physicians may play an increasingly important role in providing information and self-management strategies to ensure good health outcomes in the long-term for patients with multiple chronic conditions.

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10

NEDERLANDSE SAMENVATTING

(DUTCH SUMMARY)

Inleiding

Door de vergrijzing van de bevolking en de verhoogde levensverwachting neemt het aantal mensen dat één of meerdere chronische ziekten heeft toe. In Nederland heeft ongeveer 34% van de bevolking minstens 1 chronische ziekte en deze prevalentie ligt hoger onder ouderen (≥75 jaar) waar 84% minstens 1 chronische ziekte heeft. Zowel kanker als diabetes behoren tot de meest voorkomende chronische ziekten en behoren daarnaast tot de meest levensbedreigende ziekten wereldwijd.

Kanker
Kanker is een veel voorkomende ziekte die gekenmerkt wordt door de ongecontroleerde deling van lichaamscellen. Iedere dag vinden er miljoenen celdelingen plaats in het lichaam en tijdens deze celdelingen kan er schade ontstaan. Normaal gesproken zorgen reparatiegenen voor het herstel van deze schade. Wanneer deze genen niet werken kan een cel zich ongecontroleerd delen wat kan leiden tot een gezwel die omliggend weefsel binnendringt; een kwaadaardige tumor. De meest voorkomende kankersoorten zijn huid-, dikkedarm-, borst-, long- en prostaatkanker. In het algemeen wordt kanker behandeld met chirurgie, radiotherapie en/of chemotherapie. Dit proefschrift is gericht op zowel dikkedarmkanker als borstkanker.

Diabetes
Diabetes, ook wel suikerziekte genoemd, is een chronische ziekte die gekenmerkt wordt door een te hoge glucose, of bloedsuiker, spiegel. Bij gezonde mensen zorgt insuline, wat gemaakt wordt door de alvleesklier, ervoor dat het overschot aan glucose door de lever en spieren wordt opgenomen. Bij diabetes is de glucosespiegel te hoog en ervaart men klachten zoals dorst, vermoeidheid, wazig zicht en veel plassen. Op langere termijn kunnen er ernstigere gevolgen optreden zoals blindheid, nierfalen of hartproblemen. Er worden twee typen diabetes onderscheiden waarvan type 1 diabetes het minst voorkomt (in 5-10% van alle gevallen). Type 1 diabetes ontwikkelt zich tijdens de kindertijd en hierbij zijn cellen in de alvleesklier beschadigd waardoor er geen insuline gemaakt kan worden. Bij het veel frequenter voorkomende type 2 diabetes reageert het lichaam niet meer goed op insuline waardoor de bloedglucose waarden te hoog blijven. Type 2 diabetes ontwikkelt zich vaak op hogere leeftijd en ontstaat vaak door ongezonde leefgewoonten zoals weinig fysieke activiteit en ongezonde voeding. Bij type 2 diabetes wordt eerst leefstijladvies gegeven om de bloedglucose waarden te controleren. Wanneer dit niet werkt wordt er overgeschakeld op medicatie. Sinds 2006 wordt metformine als eerste behandeling gegeven en dit kan eventueel aangevuld worden met sulfonylureum derivaten, andere glucose verlagende middelen of uiteindelijk het spuiten van insuline.

De relatie tussen kanker en diabetes
Door de vergrijzing van de bevolking, maar ook door de betere detectie en behandelingsmethoden neemt zowel het aantal kankerpatiënten als diabetespatiënten toe. Doordat beide ziekten vaker voorkomen, komen ze ook steeds vaker samen voor.

Daarnaast toont eerder onderzoek aan dat diabetes geassocieerd is met een hoger risico op het ontwikkelen van verschillende typen kanker. Hierdoor wordt verwacht dat het aantal patiënten met zowel kanker als diabetes de komende jaren sterk zal toenemen. Uit gegevens van de Nederlandse Kankerregistratie blijkt dat inmiddels bijna 1 op de 5 oudere kankerpatiënten ook diabetes heeft ten tijde van de diagnose kanker.

Momenteel is het precieze mechanisme dat ten grondslag ligt aan de associatie tussen kanker en diabetes nog niet bekend. Mogelijk verklaren de verschillende gedeelde risicofactoren voor zowel kanker als diabetes een deel van de associatie. Zo zouden bijvoorbeeld een hogere leeftijd en etniciteit een rol kunnen spelen, maar ook modificeerbare factoren zoals overgewicht, fysieke inactiviteit, roken, overmatig alcoholgebruik en een ongezond voedingspatroon. Daarnaast geeft de huidige literatuur ook een aantal mogelijke biologische verklaringen. In een vroeg stadium van diabetes gaat de alvleesklier meer insuline produceren om te compenseren voor de slechte reactie van het lichaamsweefsel op insuline. Deze hoge insulinewaarden in het bloed zouden mogelijk de tumorcelgroei stimuleren.

De duale impact van kanker en diabetes op patiënt gerapporteerde uitkomstmaten en overlijden
Voorgaand onderzoek over de associatie tussen kanker en diabetes richt zich vooral op harde uitkomstmaten zoals de ontwikkeling van de ziekten en het overlijdensrisico, terwijl patiënt gerapporteerde uitkomstmaten nauwelijks onderzocht zijn. Patiënt gerapporteerde uitkomstmaten weerspiegelen het perspectief van de patiënt en omvatten verschillende uitkomsten zoals kwaliteit van leven, symptomen, en tevredenheid met de zorg. Eerder onderzoek naar het effect van kanker en diabetes op patiënt gerapporteerde uitkomstmaten, richt zich vooral op kwaliteit van leven en laat zien dat patiënten met beide ziekten een slechtere kwaliteit van leven rapporteren. Doordat er weinig onderzoek is gedaan, er een beperkte populatie is onderzocht (vooral prostaatkankerpatiënten) en er verschillende meetinstrumenten gebruikt zijn, is er meer onderzoek nodig om het effect van beide ziekten op patiënt gerapporteerde uitkomsten vast te stellen.

Eerder onderzoek laat zien dat patiënten met kanker en diabetes een 40% hoger overlijdensrisico hebben ten opzichte van kankerpatiënten zonder diabetes. En hoewel de exacte verklaring van dit verhoogde risico nog onbekend is, zijn er wel een aantal mogelijke verklaringen in de literatuur. Zo wordt de kankerdiagnose bij patiënten met daarnaast diabetes mogelijk in een later stadium gesteld dan bij patiënten zonder diabetes, waardoor de kanker vaak verder gevorderd is. Dit is mogelijk een gevolg van een lager gebruik van screening bij diabetespatiënten. Daarnaast zijn er indicaties dat kankerpatiënten met diabetes minder agressief behandeld worden voor hun kanker, zij krijgen bijvoorbeeld minder vaak chemotherapie en/of radiotherapie. Ook zouden hier de slechtere leefgewoonten zoals overgewicht, fysieke inactiviteit, roken, overmatig alcoholgebruik en een ongezond voedingspatroon een rol kunnen spelen.

Glucoseverlagende geneesmiddelen en overleving
In 2005 ontstond grote interesse in de associatie tussen kanker en diabetes nadat er een onderzoek werd gepubliceerd waaruit bleek dat metformine, een geneesmiddel dat gebruikt wordt voor de behandeling van diabetes, was geassocieerd met een lager risico op kanker. Hierna werden vele studies gepubliceerd naar het effect van glucoseverlagende middelen op het risico op kanker en op het overlijdensrisico. Omdat patiënten met diabetes vaak verschillende soorten geneesmiddelen gelijktijdig of afwisselend gebruiken is het erg moeilijk om het effect van glucoseverlagende middelen op het overlijdensrisico in kaart te brengen. Vele voorgaande studies hadden dan ook methodologische tekortkomingen en vaak werd er geen rekening gehouden met de gebruikte dosis. Daarom is het belangrijk om het effect van glucoseverlagende middelen op het overlijdensrisico van kankerpatiënten verder te onderzoeken in studies met een goede onderzoeksopzet.

Doel van dit proefschrift

In dit proefschrift wordt de duale impact van kanker en diabetes op patiënt gerapporteerde uitkomstmaten en het overlijdensrisico onderzocht. De belangrijkste doelstellingen van dit proefschrift zijn als volgt:

- Evalueren van het effect van kanker en diabetes op patiënt gerapporteerde uitkomstmaten zoals kwaliteit van leven en symptomen (Deel I)
- De impact van kanker en diabetes, en de rol van leefstijlfactoren, op het overlijdensrisico onderzoeken (Deel II)
- Het effect van glucoseverlagende middelen op het overlijdensrisico van borstkankerpatiënten onderzoeken (Deel II)

Belangrijkste bevindingen

De impact van kanker en diabetes op patiënt gerapporteerde uitkomsten
In **Deel I** van dit proefschrift is middels een literatuuroverzicht bekeken wat er tot nu toe bekend is over het effect van kanker en diabetes op patiënt gerapporteerde uitkomstmaten (**Hoofdstuk 2**). In eerste instantie leverde de zoekactie 3.553 mogelijke studies op, maar na selectie bleken er slechts 10 studies de impact van zowel kanker als diabetes op patiënt gerapporteerde uitkomsten te onderzoeken. Het merendeel was gericht op kwaliteit van leven, functioneren of symptomen. Patiënten met kanker en diabetes rapporteerden voornamelijk een lagere algemene kwaliteit van leven, een lager fysiek functioneren en een lager seksueel functioneren ten opzichte van patiënten met alleen kanker, alleen diabetes en/of patiënten zonder beide ziekten. Omdat er beperkt literatuur over dit onderwerp beschikbaar is, hebben we een aantal belangrijke onderwerpen voor vervolgonderzoek aangedragen. Mentale problemen komen bijvoorbeeld bij zowel kanker als diabetes patiënten veelvuldig voor en mogelijk zijn deze klachten erger bij mensen met beide ziekten. Daarnaast leidt het hebben van meerdere chronische ziekten tot beperkingen in het dagelijkse leven. Het is daarom belangrijk om aandacht te besteden aan zelfmanagement. Door bijvoorbeeld informatie te verzamelen, symptomen te monitoren en actief in gesprek te gaan met de behandelaar kunnen patiënten meer grip krijgen op hun ziekten.

Eerder onderzoek laat zien dat het hebben van andere chronische ziekten, ook wel comorbiditeiten genoemd, naast kanker geassocieerd is met een lagere kwaliteit van leven. In **Hoofdstuk 3** bekeken we wat de relatieve impact van deze comorbiditeiten in vergelijking met sociaal demografische kenmerken en klinische karakteristieken op de kwaliteit van leven van kankerpatiënten is. We vonden dat het hebben van comorbiditeiten een grotere invloed op de kwaliteit van leven heeft dan sociaal demografische kenmerken waaronder leeftijd en geslacht en klinische kenmerken, waaronder het kanker stadium en behandeling. Dit resultaat vonden we voor patiënten met dikkedarmkanker, (non-) Hodgkin lymfoom en schildklierkanker. We vonden dat vooral hartziekten en rugpijn het fysiek functioneren negatief beïnvloedde terwijl depressie voornamelijk een negatieve invloed op het mentaal functioneren had.

Het is bekend dat zowel kankerpatiënten als diabetespatiënten een slechtere kwaliteit van leven rapporteren dan de gezonde populatie. Daarnaast worden er in beide groepen ook veel problemen met het seksueel functioneren gerapporteerd. Het is echter niet bekend of patiënten met zowel kanker als diabetes een slechtere kwaliteit van leven en seksueel functioneren rapporteren dan mensen met één van beide ziekten. In **Hoofdstuk 4** lieten we zien dat de groep met zowel kanker als diabetes inderdaad de laagste kwaliteit van leven en het laagste seksueel functioneren rapporteerde, gevolgd door patiënten met alleen kanker en alleen diabetes. De groep zonder kanker en diabetes rapporteerde de hoogste kwaliteit van leven. Kanker in vergelijking met diabetes leek de sterkste voorspeller van de lagere kwaliteit van leven en seksueel functioneren.

Bij zowel kanker als diabetespatiënten komen vaak neuropathische klachten voor, zoals het tintelen van handen en voeten. Bij kankerpatiënten ontstaan deze klachten vaak als gevolg van de chemotherapie terwijl bij diabetes beschadigingen van zenuwuiteinden ontstaan door de te hoge bloedsuikerspiegel. In **Hoofdstuk 5** hebben we bekeken of er verschillen zijn in neuropathische klachten tussen kankerpatiënten met en zonder diabetes en of dit een mogelijk gevolg is van verschillen in de behandeling met chemotherapie. Eerder onderzoek liet zien dat kankerpatiënten met diabetes minder vaak chemotherapie krijgen en minder agressief behandeld worden voor hun kanker. Zoals verwacht vonden we dat kankerpatiënten met diabetes meer klachten rapporteerden, voornamelijk tintelende vingers of handen, tintelende tenen of voeten, doofheid in tenen of voeten en erectieproblemen bij mannen. Er werden voornamelijk milde klachten gerapporteerd en relatief weinig ernstige klachten. Daarnaast leken deze verschillen niet verklaard te kunnen worden door de kankerbehandeling.

In **Hoofdstuk 6** onderzochten we of de eerder gevonden verschillen in kwaliteit van leven tussen kankerpatiënten met en zonder diabetes verklaard konden worden door

leefstijlfactoren, zoals, fysieke inactiviteit, roken en overmatig alcoholgebruik, en overgewicht. Dikkedarmkankerpatiënten met diabetes bleken een hogere body mass index (BMI) te hebben en minder vaak alcohol te drinken. Er werden geen verschillen in fysieke activiteit en rookgedrag gevonden. Verdere analyses lieten zien dat het slechte fysieke functioneren, de lagere kwaliteit van leven en de hogere vermoeidheidsklachten die patiënten met zowel kanker als diabetes rapporteerden, gedeeltelijk verklaard werden door de verschillen in leefstijlfactoren.

De impact van kanker en diabetes op het overlijdensrisico

In **Deel II** van dit proefschrift hebben we onderzocht wat de duale impact van kanker en diabetes op het overlijdensrisico is. In **Hoofdstuk 7** hebben we bekeken of leefstijlfactoren het verhoogde overlijdensrisico in kankerpatiënten met of zonder diabetes kunnen verklaren. In dit hoofdstuk lieten we zien dat leefstijl sterk geassocieerd is met het overlijdensrisico: (matig) alcoholgebruik, fysieke activiteit en overgewicht waren geassocieerd met een lager overlijdensrisico terwijl roken geassocieerd was met een hoger overlijdensrisico. Daarnaast hebben we ook gekeken naar leefstijlclusters omdat slechte leefstijlgewoonten vaak samen voorkomen. Hieruit bleek dat patiënten die roken, weinig fysiek actief zijn en een laag BMI hebben (ondergewicht), een ruim 3 keer hoger overlijdensrisico hadden in vergelijking met de mensen met een gezond leefstijlpatroon. Na correctie voor deze leefstijlfactoren bleken de patiënten met zowel kanker als diabetes nog steeds een hoger overlijdensrisico te hebben dan kankerpatiënten zonder diabetes.

In **Hoofdstuk 8** en **9** hebben we onderzocht of er een verschil is in het overlijdensrisico tussen borstkankerpatiënten met diabetes die verschillende geneesmiddelen voor diabetes gebruikten. Dit naar aanleiding van eerder onderzoek waarin metformine mogelijk een verlaagd en insuline mogelijk een verhoogd overlijdensrisico met zich mee brengt. In **Hoofdstuk 8** hebben we gegevens vanuit het Verenigd Koninkrijk gebruikt en vonden we dat borstkankerpatiënten die voor langere tijd (>2 jaar) metformine gebruiken mogelijk een lager overlijdensrisico hebben. Daarnaast vonden we dat borstkankerpatiënten die sulfonylureum derivaten gebruiken mogelijk een hoger overlijdensrisico hebben. In een soortgelijke studie waarbij we gebruik hebben gemaakt van Nederlandse data vonden we geen overtuigende verschillen in overlijdensrisico tussen de verschillende geneesmiddelen (**Hoofdstuk 9**). In zowel **Hoofdstuk 8** als **Hoofdstuk 9** hebben we gebruik gemaakt van geavanceerde statistische analyses om bias te voorkomen. Dit type analyses blijft echter erg gecompliceerd omdat het type geneesmiddel dat een diabetespatiënt voorgeschreven krijgt vaak samenhangt met de ernst van de ziekte. Zo wordt metformine in een vroeg stadium van de ziekte voorgeschreven en zouden deze patiënten daarom dus mogelijk een lager overlijdensrisico hebben.

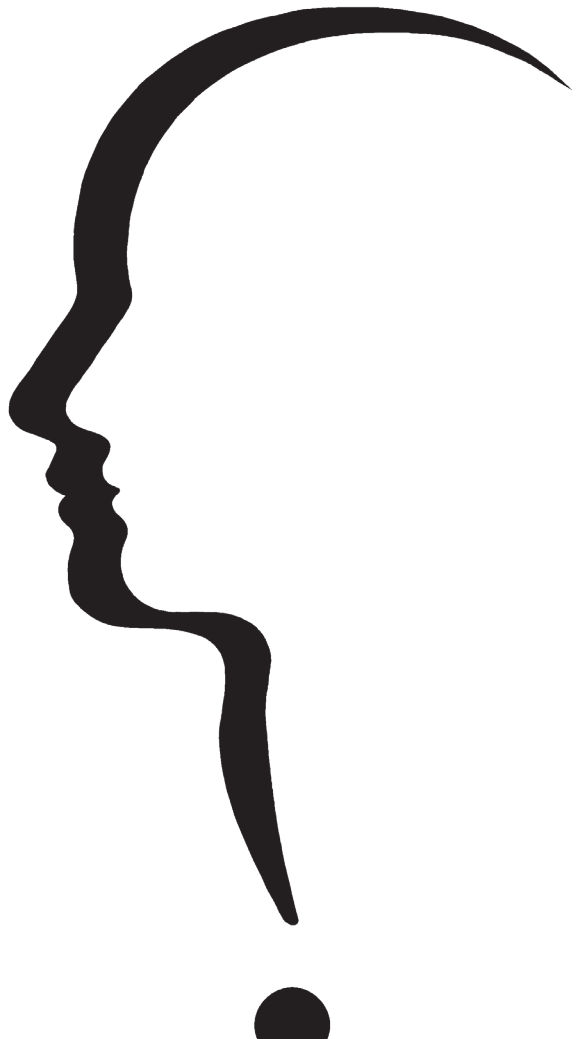
Concluderende opmerkingen

In dit proefschrift lieten we zien dat de groeiende groep patiënten met zowel kanker als diabetes een slechtere kwaliteit van leven en meer neuropathische klachten rapporteert en een hoger overlijdensrisico heeft dan kankerpatiënten zonder diabetes. Daarnaast vonden we geen overtuigend effect van verschillende geneesmiddelen voor diabetes op het overlijdensrisico bij borstkankerpatiënten. Er is echter meer bewijs nodig van grote en methodologisch goed opgezette studies om hier een eenduidige conclusie over te trekken.

In vervolgonderzoek moet er aandacht zijn voor zelfmanagement. Zelfmanagement houdt in dat patiënten leren omgaan met hun chronische ziekten en zich capabel voelen om bijvoorbeeld informatie in te winnen over de ziekten, tijdig symptomen of complicaties op te merken en daarop actie te ondernemen, maar ook leren omgaan met de psychologische consequenties van de ziekten. Daarnaast is het belangrijk om verder onderzoek te doen naar de verbetering van leefstijlgewoonten omdat leefstijlfactoren een grote invloed hebben op zowel de kwaliteit van leven als het overlijdensrisico van patiënten met zowel kanker als diabetes. Vanuit de literatuur zijn er effectieve interventies bekend die leefstijlfactoren op de korte termijn verbeteren, maar er is weinig bekend over de lange termijn effecten van deze interventies.

Ook in de klinische praktijk moet er aandacht besteed worden aan de groeiende groep van patiënten met zowel kanker als diabetes. Er zijn verschillende zorgverleners betrokken bij patiënten met kanker en diabetes in zowel de eerste lijn (huisartsen) als in de tweede lijn (internisten, chirurgen, en radiotherapeuten). Deze specialisten zullen samen moeten werken om bijvoorbeeld de behandeling van beide ziekten op elkaar af te stemmen. Daarnaast zal ook de huisarts een steeds belangrijkere rol krijgen in de nazorg van patiënten met kanker en diabetes. Zij zouden bijvoorbeeld informatie of training kunnen geven over zelfmanagementstrategieën zodat patiënten ook op de langere termijn in goede gezondheid verder kunnen leven.

DANKWOORD



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Pauline
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LIST OF PUBLICATIONS

Publications included in this thesis

1. **Vissers PAJ**, Falzon L, van de Poll-Franse LV, Pouwer F, Thong MSY. The impact of having both cancer and diabetes on patient-reported outcomes: A systematic review and directions for future research. *Journal of Cancer Survivorship.* 2015.

2. **Vissers PAJ**, Thong MSY, Pouwer F, Zanders MMJ, Coebergh JWW, van de Poll-Franse LV. The impact of comorbidity on health-related quality of life among cancer survivors: Analyses of data from the PROFILES registry. *Journal of Cancer Survivorship.* 2013;7(4):602-613.

3. **Vissers PAJ**, Thong MSY, Pouwer F, den Oudsten BL, Nieuwenhuijzen GAP, van de Poll-Franse LV. The individual and combined effect of colorectal cancer and diabetes on health-related quality of life and sexual functioning: Results from the PROFILES registry. *Supportive Care in Cancer.* 2014;22(11):3071-3079.

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5. **Vissers PAJ**, Thong MSY, Pouwer F, Creemers GJ, Slooter GD, van de Poll-Franse LV. Prospectively measured lifestyle factors and BMI explain differences in health-related quality of life between colorectal cancer patients with and without comorbid diabetes. *Submitted.*

6. **Vissers PAJ**, Thong MSY, Pouwer F, Pruijt HFM, Wasowicz DK, van de Poll-Franse LV. The effect of lifestyle clusters on mortality among colorectal cancer patients with and without diabetes: Results from the PROFILES registry. *Submitted.*

7. **Vissers PAJ**, Cardwell CR, van de Poll-Franse LV, Young IS, Pouwer F, Murray LJ. The association between glucose-lowering drug use and mortality among breast cancer patients with type 2 diabetes. *Breast Cancer Research and Treatment.* 2015;150(2):427-437.

8. **Vissers PAJ**, Zanders MMJ, Voogd AC, van Herk-Sukel MPP, Ruiter R, Hollestein LM, Herings RMC, Stricker BHC, van de Poll-Franse LV. The effect of glucose lowering drug use on overall mortality among breast cancer patients. *Submitted.*

Other publications

1. Zanders MMJ, van Herk-Sukel MPP, **Vissers PAJ**, Herings RMC, Haak HR, van de Poll-Franse LV. Are metformin, statin and aspirin use still associated with overall mortality among colorectal cancer patients with diabetes if adjusted for one another? *British Journal of Cancer.* 2015;113(3):403-410.

2. Verhaar S, **Vissers PAJ**, Maas H, van de Poll-Franse LV, van Erning FN, Mols F. Treatment-related differences in health related quality of life and disease specific symptoms among colon cancer survivors: Results from the population-based PROFILES registry. *European Journal of Cancer.* 2015;51(10):1263-1273.

3. Zanders MMJ, **Vissers PAJ**, van Herk-Sukel MPP, Haak HR, van de Poll-Franse LV. Effect van metformine op de overleving van patienten met een colorectaal carcinoom in de dagelijkse praktijk. *Nederlands Tijdschrift voor Oncologie.* 2015;12(2):58-65.

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5. Horevoorts NJE, **Vissers PAJ**, Mols F, Thong MSY, van de Poll-Franse LV. Response rates for patient-reported outcomes using web-based versus paper questionnaires: Comparison of two invitational methods in older colorectal cancer patients. *Journal of Medical Internet Research.* 2015;17(5):e111.

6. Zanders MMJ, **Vissers PAJ**, van de Poll-Franse LV. Association between metformin use and mortality in patients with prostate cancer: Explained by confounding by indication? *Journal of Clinical Oncology.* 2014;32(7):701.

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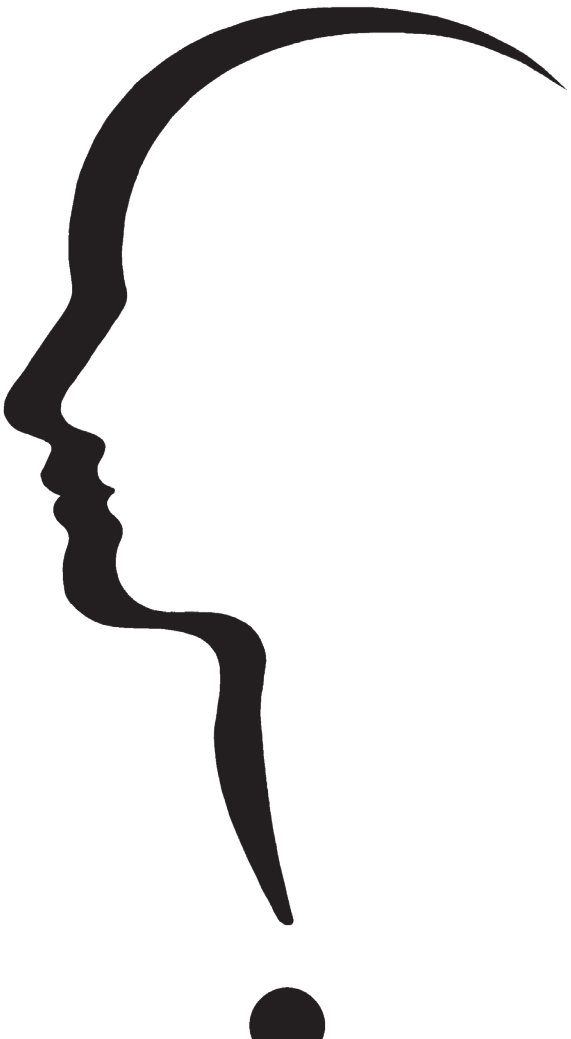
ABOUT THE AUTHOR

About the author

Pauline Vissers was born on September 3, 1987 in 's-Hertogenbosch, the Netherlands. She finished her pre-university education at Ds. Pierson college in 's-Hertogenbosch in 2005. In 2008, she obtained her Bachelor's degree in Nutrition and Health at Wageningen University and Research centre (WUR). Subsequently she started her Master's degree in Nutritional and Public Health Epidemiology at the same institution. After conducting a 4 month internship at the University of East Anglia, Norwich, in the United Kingdom, she graduated in 2010. After working as a junior researcher at WUR, she started her PhD project at Tilburg University and the Netherlands Comprehensive Cancer Organisation (IKNL) in 2011. Her research focused on the effect of having both cancer and diabetes on patient reported outcomes and mortality. During her PhD, in 2014, she joined the Centre for Public Health at Queen's University in Belfast, Northern-Ireland for a 3 month period. Currently she is working as a post-doctoral researcher at IKNL where she studies the effect of centralization of cancer surgery, among elderly patients, on complication rates, mortality and quality of life.

DOUBLE TROUBLE?

THE DUAL IMPACT OF CANCER AND DIABETES ON PATIENT REPORTED OUTCOMES AND MORTALITY



PAULINE VISSERS