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Clinical Study

Chronic Diseases among Older Cancer Survivors

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Objective. To compare the occurrence of pre-existing and subsequent comorbidity among older cancer patients (≥ 60 years) with older non-cancer patients. *Material and Methods*. Each cancer patient ($n = 3835$, mean age 72) was matched with four non-cancer patients in terms of age, sex, and practice. The occurrence of chronic diseases was assessed cross-sectionally (lifetime prevalence at time of diagnosis) and longitudinally (incidence after diagnosis) for all cancer patients and for breast, prostate, and colorectal cancer patients separately. Cancer and non-cancer patients were compared using logistic and Cox regression analysis. *Results*. The occurrence of the most common pre-existing and incident chronic diseases was largely similar in cancer and non-cancer patients, except for pre-existing COPD (OR 1.21, 95% CI 1.06–1.37) and subsequent venous thrombosis in the first two years after cancer diagnosis (HR 4.20, 95% CI 2.74–6.44), which were significantly more frequent ($P < 0.01$) among older cancer compared to non-cancer patients. *Conclusion*. The frequency of multimorbidity in older cancer patients is high. However, apart from COPD and venous thrombosis, the incidence of chronic diseases in older cancer patients is similar compared to non-cancer patients of the same age, sex, and practice.

1. Introduction

With advances in early detection and cancer treatments, numbers of cancer survivors are rising [1], and with the ageing of the population, the number of older cancer survivors will continue to rise even if age-specific incidence rates remain constant [2]. Whereas cancer used to be a fatal disease, it is now developing towards a chronic or even curable disease [3, 4]. At present, more than 60% of older cancer patients suffer from one or more chronic diseases [5]. Because of the chronic character of cancer [6] and the high level of comorbidity [7], the role of general practitioners (GPs) in cancer aftercare will become more prominent [7, 8].

Studies among cancer survivors have shown that the consequences of cancer treatment are numerous and depend on the type of cancer and treatment characteristics [4, 9]. The most common sequelae are second malignancies (due to genetic or environmental risk factors shared with the first tumour and treatment-related factors) and cardiovascular diseases as myocardial infarction and cardiac insufficiency (due to radiotherapy as well as chemotherapy) [9]. Many other diseases, such as osteoporosis [10] and diabetes [11], have been related to cancer treatment also. These late effects are also common ageing-related diseases. Therefore, within primary care, which is characterized by a heterogeneous patient population and "only" 50 cancer patients per standard practice (of 2350 patients) [12], the late effects of cancer and its treatment could easily be mistaken for normal ageing and dismissed as such in older cancer survivors [13]. Given the GPs' expertise in dealing with multimorbidity, we believe that GPs could play an important role in aftercare for cancer survivors. Hence, primary care providers are in urgent need of more knowledge on the interaction between cancer, cancer treatment, and comorbidity in older cancer patients.

Therefore, we aim to examine from a generic GP perspective the occurrence of pre-existing (prevalent) and subsequent (incident) chronic diseases among cancer patients aged over 60, in comparison with non-cancer patients of the same age, sex, and practice in a large retrospective primary care-based cohort study.

2. Materials and Methods

2.1. The Registration Network Family Practices. This study was carried out within the context of the Registration Network Family Practices (RegistratieNet Huisartspraktijken, RNH) [14]. This is a continuously updated computerized primary care database, with a target population of about 135,000 people. All relevant health problems are routinely recorded using a computerized health information system. All participants were informed about the anonymous use of information about their health status when they registered as patients with the participating general practices (21 participating practices and about 65 general practitioners).

All relevant health problems—current as well as past—are recorded on a problem list. A health problem is defined as "anything that has required, does or may require health care management and has affected or could significantly affect a persons' physical or emotional well-being." Health problems are coded using the International Classification of Primary Care (ICPC), following the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2-defined) for diagnoses [14]. In the Netherlands, GPs have comprehensive information on the health status of their patients because GPs function as gatekeepers to other health care facilities, and it is compulsory for all Dutch residents to have health care insurance and to register with a GP. Hence, we can expect the registered population to be representative of the general population. In addition to medical information, the RNH database also contains background information on sex, date of birth, living arrangement, level of education, and the date and reason of removal. RNH registration only ends upon migration or death. The quality of the data is assured by instruction and training sessions, regional consensus groups, quality control experiments, and special software programs, such as an automated thesaurus and automated checking for erroneous or missing entries [14]. Reliability and completeness have been proved previously [15].

2.2. Design and Data Analysis. The design of this study is a retrospective cohort, including all patients who were members of the RNH database between 1 January 1998 and 31 December 2010, and aged 60 years and over. Patients with a previous cancer history (diagnosed before January 1998) were excluded. Neoplasms of the skin were excluded as well, as due to the ICPC coding we were unable to distinguish between benign and malign neoplasma of the skin. Each cancer patient, diagnosed between January 1998 and December 2010 ($n = 3835$), was matched with four non-cancer patients based on age, sex, and practice. For 239 cancer patients, we were unable to find an appropriate match. 337, 428, 429, and 3596 cancer patients were matched with one, two, three, and four non-cancer patients respectively. Matched non-cancer patients were assigned a reference date (the same as the date of the cancer diagnosis of their matched cancer patient).

Only ICPC codes that correspond to severe or chronic diseases were selected and categorized as previously described by Knottnerus et al. [16] (please see Table 1 in the Supplementary Material available online at doi:10.1155/-2012/206414).

Pre-existing chronic diseases were defined as all diagnoses established before the cancer diagnosis or reference date. Subsequent chronic diseases were defined as all diagnoses established after the cancer diagnosis or reference date. All diagnoses that were established within a 3-month period before removal from the RNH database were excluded, as these might reflect the palliative phase, in which the disease pattern might be different. Pre-existing chronic diseases were assessed by calculating the lifetime prevalence (per 1000 persons) cross-sectionally at the time of the cancer diagnosis or the reference date and were compared between cancer patients and their matched non-cancer patients using logistic regression analyses, adjusted for age and sex. Prevalence and odds ratios were calculated for all cancer patients together, and for breast, prostate, and colorectal cancer patients separately. The occurrence of subsequent chronic diseases was longitudinally assessed by calculating the incidence per 1000 person-years at risk, excluding patients with a previous diagnosis of the disease. Hazard ratios and their 95% confidence intervals (95% CIs) were calculated using multivariate Cox regression analyses, adjusted for age, sex, and presence of cardiovascular diseases, respiratory diseases, or diabetes at baseline (please see Table 1 in the Supplementary Material on the journal website for the precise cardiovascular and respiratory diseases which were included). Incidence and hazard ratios were computed for all cancer patients in comparison with their age, sex, and practice-matched controls and for all breast, prostate, and colorectal cancer patients separately, in comparison with their respective matched controls. The proportional hazards assumption was tested using Schoenfeld residuals. For venous thrombosis (K93+K94), limited mental function (P28), lipid disorders (T93), and other endocrine/metabolic/nutritional diseases (T99), proportional hazards assumption was violated. This was resolved by splitting the survival time.

Analyses were processed with the STATA statistical software package (StataCorp. 2009. Stata: Release 11. Statistical Software. College Station, TX: StataCorp LP). Throughout all analyses, a two-sided P-value <0.01 was used as the cut-off point for statistical significance.

3. Results

3.1. Population. In the thirteen-year study period (1998–2010), there were 3,835 patients with a first diagnosis of cancer who were 60 years or older at the time of their cancer diagnosis (see Table 1). These cases were matched to 11,973 controls.

Table 1: Characteristics of older cancer patients and non-cancer patients at time of cancer diagnosis or reference date.

	Cancer patients (N = 3835)		Non-cancer patients (N = 11973)	
	Mean	(SD)	Mean	(SD)
Age (years)				
Men	71.95	(7.35)	70.87	(7.13)
Women	73.22	(8.42)	72.90	(8.27)
Survival time (years)[1]				
Men	2.92	(3.06)	3.87	(3.15)
Women	3.32	(3.39)	4.17	(3.27)
	N	(%)	N	(%)
Sex				
Men	2163	(56)	6179	(52)
Women	1672	(44)	5794	(48)
Number of chronic diseases at baseline[2]				
0	846	(22)	2617	(22)
1	908	(24)	2916	(24)
2	752	(20)	2288	(19)
3	534	(14)	1682	(14)
≥4	795	(21)	2470	(21)
Five most common tumour sites				
Colon/rectum	675	(18)		
Prostate	573	(15)		
Bronchus/lung	550	(14)		
Breast	493	(13)		
Bladder	218	(7)		

[1] Survival time: time from date of diagnosis or reference date until death or end of follow-up.
[2] Number of chronic diseases excluding cancer.

3.2. Pre-Existing Chronic Diseases. The prevalence of pre-existing chronic diseases was high; 78% of all cancer patients had at least one disease additional to the malignancy at time of cancer diagnosis (see Table 1).

The most common pre-existing chronic diseases were the same for cancer patients and non-cancer patients. These were diabetes, lipid disorders, ischemic heart disease, myocardial infarction, and COPD. COPD was significantly more prevalent among cancer patients compared to non-cancer patients (OR 1.21, 95% CI 1.06–1.37). Furthermore, dementia (OR 0.48, 95% CI 0.36–0.64) and personality disorder (OR 0.53, 95% CI 0.33–0.84) were significantly less prevalent in cancer patients compared to non-cancer patients (see Table 2).

When stratified by cancer type (data not shown), we found no differences within breast cancer patients (n = 493) compared to their matched controls (n = 1675). For prostate cancer patients (n = 573) compared to their respective controls (n = 1604), we found a higher prevalence of benign prostatic hypertrophy (OR 1.44, 95% CI 1.09–1.88) and a lower prevalence of stroke (OR 0.40, 95% CI 0.25–0.65) and diabetes (OR 0.67, 95% CI 0.51–0.90). For colorectal cancer patients (n = 675) in comparison with their controls (n = 2063), we found a higher prevalence of blindness (OR 2.85, 95% CI 1.43–5.71) and a lower prevalence of stroke (OR 0.60, 95% CI 0.41–0.89), dementia (OR 0.26, 95% CI 0.12–0.56), and benign prostatic hypertrophy (OR 0.55, 95% CI 0.36–0.83).

3.3. Subsequent Chronic Diseases. Just as for pre-existing chronic diseases, risk of subsequent chronic diseases was similar among cancer survivors and non-cancer patients. The most common incident diseases in cancer patients were diabetes, venous thrombosis, osteoporosis, COPD, and heart failure. In non-cancer patients these were diabetes, benign prostatic hypertrophy, stroke, dementia, and COPD. In cancer survivors, the incidence of subsequent venous thrombosis was significantly higher compared to non-cancer patients during the first two years of survival (HR 4.20, 95% CI 2.74–6.44). Thereafter, this difference was no longer statistically significant (see Table 3). Furthermore, the incidence of hypertension with organ damage (HR 0.66, 95% CI 0.48–0.92), lipid disorders during the first two years after diagnosis (HR 0.49, 95% CI 0.29–0.82), and benign prostatic hypertrophy (HR 0.46, 95% CI 0.31–0.69) was significantly lower in cancer patients compared to non-cancer patients (see Table 3).

When stratified by cancer type (data not shown), we found no differences for breast cancer patients compared to their respective controls. In prostate cancer patients, the incidence of venous thrombosis (HR 7.10, 95% CI 2.25–22.40) was significantly higher compared to non-cancer patients, and the incidence of benign prostatic hypertrophy was significantly lower (HR 0.17, 95% CI 0.06–0.48). In colorectal cancer patients, the incidence of venous thrombosis (HR 2.43, 95% CI 1.22–4.81) was significantly higher compared to non-cancer patients.

4. Discussion

4.1. Principal Findings. The number of chronic diseases additional to cancer proved to be high and is probably associated with high age in the first place. Both prevalence at diagnosis and incidence, however, tend to be largely similar in older cancer and non-cancer patients. The latter is consistent with recent other studies [17, 18].

4.2. Pre-Existing Chronic Diseases. At time of cancer diagnosis, 78% of all cancer patients had at least one disease additional to the malignancy. This highlights the enormous burden of comorbidity in older cancer patients. However, from the perspective of a GP, it is also important that cancer and non-cancer patients were similar with respect to prevalence of chronic diseases. Still, there were some exceptions. In cancer patients, the prevalence of COPD was significantly higher compared to non-cancer patients. When stratified by cancer type, this difference remained significant, only within the group of lung cancer patients (OR 2.88, 95% CI 2.20–3.78) (data not shown). This is in line with previous reports [19] and is probably due to shared risk factors such as smoking [20]. Based on previous studies on the interaction between cancer and comorbidity, we would have expected an

Table 2: Pre-existing chronic diseases in men and women.

	Cancer patients		Non-cancer patients		P-value	OR[2]	(95% CI)
	N	Prev[1]	N	Prev[1]			
Ten most common pre-existing diseases in cancer patients							
Diabetes mellitus	586	152.80	1864	155.68	0.48	0.96	(0.87–1.07)
Lipid disorders	508	132.46	1559	130.21	0.60	1.03	(0.92–1.15)
Ischemic heart disease with angina	459	119.69	1326	110.75	0.73	1.02	(0.91–1.14)
Myocardial infarction	405	105.61	1162	97.05	0.86	1.01	(0.90–1.14)
Ischemic heart disease without angina	393	102.48	1151	96.13	0.98	1.00	(0.88–1.13)
Chronic obstructive pulmonary disease	382	99.61	944	78.84	**0.00**	**1.21**	**(1.06–1.37)**
Osteoarthrosis knee	312	81.36	1054	88.03	0.17	0.91	(0.80–1.04)
Benign prostatic hypertrophy	297	77.44	740	61.81	0.33	1.08	(0.93–1.25)
Back syndrome without radiating pain	281	73.27	888	74.17	0.70	0.97	(0.85–1.12)
Osteoarthrosis hip	272	70.93	885	73.92	0.47	0.95	(0.82–1.09)
Significant differences between cancer and non-cancer patients[3]							
Dementia	60	15.65	344	28.73	**0.00**	**0.48**	**(0.36–0.64)**
Personality disorder	21	5.48	127	10.61	**0.01**	**0.53**	**(0.33–0.84)**

[1] Prev: lifetime prevalence per 1000 persons.
[2] OR: odds ratio adjusted for sex and age.
[3] Please see Table 2 in the Supplementary Material on the journal website for all other diseases.

Table 3: Subsequent chronic diseases in men and women.

	Cancer survivors		Non-cancer patients		P-value	HR[2]	(95% CI)	
	N	Inc[1]	N	Inc[1]				
Ten most common subsequent diseases in cancer patients								
Diabetes mellitus[†]	133	13.46	589	14.79	0.31	0.91	0.75	1.09
Venous thrombosis								
Baseline—2 years	45	9.27	40	2.11	**0.00**	**4.20**	**2.74**	**6.44**
2 years—end of follow-up[†]	20	3.10	58	2.11	0.15	1.45	0.87	2.41
Osteoporosis	99	8.93	354	7.90	0.15	1.18	0.94	1.47
Chronic obstructive pulmonary disease	95	8.81	378	8.56	0.97	1.00	0.80	1.25
Heart failure[δ]	94	8.31	380	8.28	0.80	0.97	0.77	1.22
Stroke/cerebrovascular accident	92	8.27	435	9.81	0.08	0.82	0.65	1.03
Dementia[β]	83	7.16	417	8.93	0.07	0.81	0.64	1.02
Ischemic heart disease without angina[β]	71	6.76	308	7.17	0.50	0.92	0.71	1.19
Ischemic heart disease with angina	65	6.29	294	7.03	0.36	0.88	0.67	1.15
Osteoarthrosis hip	66	6.05	268	6.11	0.95	1.01	0.77	1.32
Significant differences between cancer and non-cancer patients[3]								
Hypertension with organ damage	41	3.67	250	5.55	**0.01**	**0.66**	**0.48**	**0.92**
Lipid disorders								
Baseline—2 years	16	3.66	129	7.62	**0.01**	**0.49**	**0.29**	**0.82**
2 years—end of follow-up	31	5.27	171	7.08	0.16	0.76	0.52	1.11
Benign prostatic hypertrophy	27	5.05	223	10.87	**0.00**	**0.46**	**0.31**	**0.69**

[1] Inc: incidence per 1000 person years at risk.
[2] HR: hazard ratio adjusted for sex, age, cardiovascular diseases, respiratory diseases, and diabetes.
[3] Please see Table 3 in the Supplementary Material on the journal website for all other diseases.
[†] Adjusted for age as time-varying coefficient.
[δ] Adjusted for sex and age as time-varying coefficient.
[β] Adjusted for cardiovascular diseases as time-varying coefficient.

increased prevalence of diabetes in colorectal cancer patients [21]. The point estimator was higher than one, but the absolute difference was small and not statistically significant.

We found a significant lower prevalence of dementia in cancer patients compared to non-cancer patients. This has been previously reported and is also known as inverse cancer comorbidity [22]. Probably, malignancies are not less frequently occurring, but less frequently diagnosed in patients with dementia. In line with Tabarés-Seisdedos et al., we also found inverse comorbidity for diabetes in prostate cancer patients [22], which may be related to diabetes treatment [23, 24]. Furthermore, we showed inverse comorbidity for stroke in both prostate and colorectal cancer patients. A negative association between prostate and colorectal cancer and stroke was also shown by others [17], however, a clear explanation is still lacking [25]. In this perspective Tabarés-Seisdedos et al. stated that "further research is needed as analyses of inverse cancer comorbidity can help us understand why some people are protected from certain cancers, and might help to uncover the mechanisms underlying malignancy" [22].

4.3. Subsequent Chronic Diseases. After cancer diagnosis we showed similar to pre-existing diseases that the most common new diseases in cancer survivors were also the most common ones in non-cancer survivors. In line, a recent and similar study by Khan et al. showed that long-term cancer survivors are a population at risk but that the absolute increase in disease burden is small [26].

For venous thrombosis we showed a significantly increased hazard ratio during the first two years of survival. This is in line with previous studies on consequences of cancer treatment [27] and was also confirmed for breast (P-value 0.03), prostate (P-value 0.00), and colorectal (P-value 0.01) cancer patients separately. Therefore, GPs should be alert for the occurrence of venous thrombosis in older cancer survivors, especially within the first two years after diagnosis.

Although it is not the scope of this study, we were unable to confirm a higher incidence of osteoporosis (due to hormone replacement therapy), hypothyroidism (due to radiotherapy), and heart failure (due to radiotherapy and chemotherapy) in specific groups of cancer survivors compared to non-cancer survivors [26]. This may result from small absolute differences and a lower power of our study. Furthermore, the time frame of our study does not enable us to study the occurrence of late effects of cancer therapy. As described by Hewitt et al. "late effects appear months to years after the completion of therapy" [4]. However, we continue our followup of the included patients and hope to come forward with late effect results at a later time.

Besides the increased risk for venous thrombosis, we found a lower incidence of hypertension with organ damage and lipid disorders (only during the first two years after cancer diagnosis) in cancer patients compared to non-cancer patients. In the first period after diagnosis, a decrease in food intake due to side effects of treatment and emotional factors, and later increased surveillance, and attention for healthy lifestyle might explain this lower incidence. A recent study showed, however, no obvious difference in lifestyle factors among short- and long-term cancer survivors compared to controls [28]. Furthermore, data on hyperlipidemia have been previously shown to be heterogeneous [21]. We also found a significant lower incidence of benign prostatic hypertrophy in all cancer patients compared to non-cancer patients. As expected, when stratified by cancer type, this difference only remained for prostate and bladder cancer patients (data not shown).

4.4. Strengths and Limitations. An important strength of this study was that the comprehensive registration of diseases was based on GPs' daily practice and that this data was analysed in a retrospective cohort design.

A shortcoming of this study was that information on cancer treatment and smoking status was incomplete. Therefore we were unable to analyse the risk of comorbidity according to treatment type and to consider smoking as a confounder. This is an important drawback because late effects in cancer survivors are treatment specific [4]. However, to assess the consequences of cancer treatment as such was beyond the scope of this study. The aim of this study was to assess the frequency of comorbidity in cancer patients from a GP perspective, who sees only a small number of cancer patients (about 50 per standard practice) with very diverse cancer types. Hence, we aimed to assess in a generic way the disease burden in older cancer patients, and we aimed to assess whether these cancer patients present to their GP with different diseases compared to non-cancer patients of the same age, sex, and practice.

Another limitation was that some associations may have occurred by chance (Type I error) due to multiple comparisons. The chance of Type I errors can be diminished by applying a Bonferroni correction. However, this would dramatically increase the chance for Type II errors. According to Rothman it is not necessary to correct for multiple comparisons as the underlying premise of research is that nature follows regular laws that may be studied through observation [29, 30]. Therefore, we decided not to formally correct for multiple comparisons and to use a P-value of 0.01 as cut-off for statistical significance. This does, however, not prohibit that some findings might have occurred due to chance, such as the increased prevalence of blindness, and the decreased prevalence of prostatic hypertrophy in colorectal cancer patients, and personality disorders in cancer patients in general. Furthermore, we showed that prostatic hypertrophy was more prevalent in prostate cancer patients, which is probably due to indication bias. Therefore, it is important that these results are validated in similar cohorts.

Because of the similarities between older cancer and non-cancer patients and the GPs' expertise in dealing with multimorbidity, we believe that GPs could play an important role in aftercare for cancer survivors. However, the participation of primary care in cancer care is still in its infancy. Hence, further research is needed. Future studies could focus on the coordination of aftercare between primary and secondary care, the development of guidelines for cancer

patients with comorbidity, and the use of patient goals in the determination of care planning in patients with complex care needs.

Conflict of Interests

The authors declared no conflict of interests.

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