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Full Paper

Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study

NF Khan*[,1], D Mant[1], L Carpenter[2], D Forman[3] and PW Rose[1]

[1]Department of Primary Care Health Sciences, University of Oxford, 2nd Floor, 23-38 Hythe Bridge Street, Oxford OX1 2ET, UK; [2]Department of Public Health, University of Oxford, Rosemary Rue Building, Old Road Campus, Oxford OX3 7LF, UK; [3]Cancer Information Section, International Agency for Research on Cancer, 150, Cours Albert Thomas, F-69372 Lyon Cedex 08, France

BACKGROUND: The community-based incidence of cancer treatment-related long-term consequences is uncertain. We sought to establish the burden of health outcomes that have been associated with treatment among British long-term cancer survivors.

METHODS: We identified 26 213 adults from the General Practice Research Database who have survived 5 years or more following breast, colorectal or prostate cancer. Four age-, sex- and general practice-matched non-cancer controls were selected for each survivor. We considered the incidence of treatment-associated health outcomes using Cox proportional hazards models.

RESULTS: Breast cancer survivors had an elevated incidence of heart failure (hazards ratio (HR) 1.95, 95% confidence interval (CI) 1.27–3.01), coronary artery disease (HR 1.27, 95% CI 1.11–1.44), hypothyroidism (HR 1.26, 95% CI 1.02–1.56) and osteoporosis (HR 1.26, 95% CI 1.13–1.40). Among colorectal cancer survivors, there was increased incidence of dementia (HR 1.68, 95% CI 1.20–2.35), diabetes (HR 1.39, 95% CI 1.12–1.72) and osteoporosis (HR 1.41, 95% CI 1.15–1.73). Prostate cancer survivors had the highest risk of osteoporosis (HR 2.49, 95% CI 1.93–3.22).

CONCLUSIONS: The study confirms the occurrence of increased incidence of chronic illnesses in long-term cancer survivors attributable to underlying lifestyle and/or cancer treatments. Although the absolute risk of the majority of late effects in the cancer survivors cohort is low, identifying prior risk of osteoporosis by bone mineral density scanning for prostate survivors should be considered. There is an urgent need to improve primary care recording of cancer treatment.

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More than 50% of adults with cancer in the UK will survive for at least 5 years following their initial diagnosis (Cancer Research UK, 2006). Recent improvements in cancer survival are largely due to earlier diagnosis and advancements in treatment. Despite having favourable effects on cancer survival, radiotherapy, hormone treatment and combination chemotherapy regimens can cause long-term organ damage and functional disabilities. These long-term toxicities, or late effects, defined as 'unrecognised toxicities that are absent or subclinical at the end of therapy' can manifest as new diagnoses months to years after the completion of primary cancer treatment (Hewitt *et al*, 2006). Late effects related to treatment are widely variable and are linked to characteristics of the cancer, the modality and intensity of treatment and the underlying health status of the individual experiencing cancer.

Some late effects are predictable, for example, the effect of radiotherapy treatment on adjacent organs. This may result in the increased incidence of hypothyroidism and heart failure in breast cancer patients (Clarke *et al*, 2005; Darby *et al*, 2005; Smith *et al*, 2008). The effects of hormonal treatments are also predictable; changes in bone physiology and increases in osteoporosis are increasingly found in patients treated with hormone therapy (Chen *et al*, 2005; Lopez *et al*, 2005; Shahinian *et al*, 2005; Saad *et al*, 2008; Brown *et al*, 2010). The late effects of chemotherapy are less easy to predict and are often drug specific. For example, cognitive impairment is a well-recognised late effect of chemotherapy (Hewitt *et al*, 2006). A conceptual framework of its aetiology proposes interactions between treatment effects on clotting in small blood vessels and endogenous hormones, in addition to chemotherapy mediating depression and fatigue through cytokine involvement leading to cognitive impairment (Heflin *et al*, 2005). Finally, some associations are difficult to explain with current knowledge. There is a reported association between diabetes mellitus and colorectal cancer: both diseases share common risk factors, but diabetes has also been shown to be a potential independent risk factor of several common cancers including colorectal cancer (Larsson *et al*, 2005). In addition to the effects of treatment, cancer patients are also at increased risk of developing subsequent disease because of the risk factors that led to the original cancer. Some of these risk factors are modifiable, for example, smoking and alcohol, and a cancer diagnosis may provide motivation for lifestyle change. Other factors, such as genetic mutations and polymorphisms, are currently immutable. A summary of common long-term and late effects of treatments for breast, colorectal and prostate cancer is shown in Table 1.

The prevalence of these late effects in a general population of adult cancer survivors is still uncertain; however, it is likely that with sophisticated and intense treatments long-term effects will become more common (Carver *et al*, 2007). The complicated

*Correspondence: Dr NF Khan; E-mail: nada.khan@phc.ox.ac.uk

Table 1 Examples of potential long-term and late effects of treatment amongst breast, colorectal and prostate cancer survivors

Surgery	Radiotherapy	Chemotherapy		Hormone therapy	
Breast					
Lymphoedema	Shoulder stiffening Lymphoedema Hypothyroidism Skin telangiectasia	Anthracyclines	Heart failure Left ventricular (LV) dysfunction (Hewitt *et al*, 2006)	Tamoxifen	Endometrial cancer Osteopenia Thromboembolic events (Hewitt *et al*, 2006)
	Cardiac damage Second malignancy Thyroid damage	Cyclophosphamide	Heart failure Pericarditis Premature menopause (Hewitt *et al*, 2006)	Aromatase inhibitors	Bone loss (Mincey *et al*, 2006) Possible increased risk of artherosclerosis (Senkus and Jassem, 2011)
		Trastuzumab	Heart failure LV dysfunction (Hewitt *et al*, 2006)		
		Bevacizumab	Hypertension Thromoembolic events Heart failure (Choueiri *et al*, 2011)		
		General effects	Weight gain Cognitive dysfunction (Partridge *et al*, 2001)		
Prostate					
Urinary incontinence Sexual dysfunction	Pelvic fibrosis Bowel fibrosis Bladder/bowel telangiectasia	Rarely used		LHRH analogues	Coronary artery disease (Saigal *et al*, 2007) Myocardial infarction (Taylor *et al*, 2009) Osteoporosis (Lopez *et al*, 2005; Taylor *et al*, 2009) Mild obesity (Hewitt *et al*, 2006) Sexual dysfunction (Schover, 2005)
				Bicalutamide	Breast enlargement (Hewitt *et al*, 2006)
Colorectal					
Stoma Bowel and urinary incontinence Sexual dysfunction	Pelvic necrosis Hip osteoporosis	Bevacizumab	Hypertension Thromoembolic events Heart failure (Hewitt *et al*, 2006)		
		5-Fluorouracil	Cardiac ischaemia (Keefe *et al*, 1993)		
		Oxaliplatin	Peripheral neuropathy (Hewitt *et al*, 2006)		
		General effects	Cognitive dysfunction (Heflin *et al*, 2005)		

Abbreviation: LHRH = lutenizing hormone-releasing hormone.

interaction of cancer, cancer treatment and risk factors means that community-based prevalence is difficult to predict. It is important to determine the burden of late effects in cancer survivors in order to provide guidance on long-term monitoring, case finding for disease, health promotion and planning service provision.

The main aim of the research reported here was to assess the size of this problem by documenting the incidence of late effects related to cancer treatment in a population-based cohort of cancer survivors in the UK. Our data, which were derived from comprehensive primary care records, also allowed us to explore the relative incidence of all health problems in cancer survivors compared with a control population.

MATERIALS AND METHODS

The source of data and participants

This paper reports a matched cohort analysis of longitudinal primary care records of cancer survivors and controls from the UK General Practice Research Database (GPRD) (Walley and Mantgani, 1997). The GPRD includes data on individual-level clinical diagnoses, test results, prescriptions, referrals and significant morbidity events in the patients' medical history (MHRA, 2004). All survivors of breast, colorectal and prostate cancer with more than 5 years follow-up post diagnosis were identified from the GPRD and matched to four control patients on the basis of age (within 1 year), gender and primary care practice. These matched groups were followed from the start of a 3-year analysis period beginning on 1 September 2003 and ending on 31 August 2006.

Outcomes

The main outcomes prespecified in the protocol were the late treatment effects suggested by previous studies, specifically radiotherapy and chemotherapy effects in breast cancer (hypothyroidism, heart failure, coronary artery disease, lymphoedema; Paskett and Stark, 2000; Bradbury *et al*, 2005; Darby *et al*, 2005; Carver *et al*, 2007; Smith *et al*, 2008) and in prostate and colorectal cancers (erectile dysfunction, incontinence), chemotherapy effects in colorectal cancer (dementia; Heflin *et al*, 2005) and hormonal effects in breast (osteoporosis) and prostate (osteoporosis and

coronary artery disease; Chen *et al*, 2005; Shahinian *et al*, 2005; Saad *et al*, 2008; Taylor *et al*, 2009). We also prespecified diabetes mellitus as an outcome because of its reported association with colorectal cancer (Larsson *et al*, 2005; Keating *et al*, 2006). We also considered long-term effects of treatment specific to each cancer, including lymphoedema (breast cancer), early menopause (breast cancer), non-infectious diarrhoea or constipation (colorectal cancer), erectile dysfunction (male colorectal and prostate cancer) and urinary incontinence (colorectal and prostate cancer). We focussed on outcomes that we could investigate within the GPRD by identifying incident events through Read or OXMIS codes for the clinical diagnosis, with the exception of osteoporosis – for which patients prescribed a bisphosphonate were included even if they did not have a clinical code for osteoporosis or osteoporotic fracture – and erectile dysfunction – for which we included new prescriptions for sildenafil (Viagra, Pfizer, NY, United States), apomorphone hydrochloride, vardenafil (Levitra, Bayer Healthcare Pharmaceuticals, New Haven, USA), alprostadil (an injectable treatment) and tadalafil (Cialis, Lilly, USA). Early menopause was defined as a clinical code for menopause or early menopause in the patient's electronic medical record before the age of 48 years. Clinical code lists are available on request. Only new diagnoses were included (i.e., diagnoses that were not present in the medical record before the cancer diagnosis) in any analyses of disease incidence.

Statistical analyses

We calculated the incidence rate for each outcome based on the number of events and cumulative person-years for each group of cancer survivors and controls within the analysis period. We used multivariate Cox proportional hazard models, stratifying for the matched groups, to compute hazard ratios (HRs) and 95% confidence intervals (95% CIs). This method allowed us to compare the incidence rates for matched groups of cancer survivors and controls. We only considered incidence of new diagnoses, and therefore excluded any patients with a previous diagnosis of the condition of interest before the start of the analysis period. To formally test the proportional hazards model assumption that the HR is proportional over time, we conducted post-estimation tests of the correlations between Schoenfeld residuals from each multivariate model and time (Cleves *et al*, 2006). In addition to incidence within the analysis period, we also report total prevalence from date of cancer diagnosis in the survivors and from date of matched survivor in the control population. All analyses were carried out using the Stata MP statistical software, version 10.1 (StataCorp LP, College Station, TX, USA).

Explanatory variables

To reduce confounding, we adjusted for smoking status and BMI in case–control comparisons of the incidence of heart failure, dementia, coronary artery disease, osteoporosis, diabetes and erectile dysfunction (Kanis *et al*, 2005). Recording of smoking status is high in the GPRD; however, data on former smoking status are lower than expected (Lewis *et al*, 2004). Smokers may be alternatively coded as ex, former or current smokers. Therefore, we classified individuals as ever smokers or never smokers. In addition, each patient was assigned a summary comorbidity score based on the Charlson index. This weighted and additive comorbidity score consists of 17 diagnostic categories and accounts for both the number and severity of comorbidity to provide a summary of disease burden for individual patients (Charlson *et al*, 1987). It has been adapted for use within the GPRD (Khan *et al*, 2010b).

Data on patient characteristics such as BMI and smoking status were not complete within the GPRD; however, coverage was high (Table 2). We compared three different approaches to dealing with the missing data in multivariate Cox proportional hazard models: multiple imputation, complete case analysis and use of a 'missing' category. As results for all three approaches were similar, we report the results from the complete case analysis.

RESULTS

Patient characteristics

Table 2 reports the age, gender, time since diagnosis and comorbidity score of 26 213 long-term survivors of breast, colorectal and prostate cancer and a matched control population of 104 486. The cohort was fairly elderly, and a high proportion of the population had at least one comorbid disease. It also shows that two of the most important confounding factors (smoking and BMI) were in fact very similar in prevalence among all survivors and controls, despite previous research showing a positive association between obesity and risk of cancer (Bianchini and Vainio, 2002).

Breast cancer survivors

Incidence rates and risk of new diagnoses related to late effects of treatment among breast cancer survivors and controls are shown in Table 3. Long-term survivors of breast cancer had an incident rate for heart failure of 5.73 per 1000 person-years compared with 4.40 in controls. This excess persisted in matched, multivariate models (adjusted HR 1.95, 95% CI 1.27–3.01). In addition, breast cancer survivors had a significantly elevated incidence of osteoporosis compared with controls (adjusted HR 1.26, 95% CI 1.13–1.40). We included use of bisphosphonates as indicative of a diagnosis of osteoporosis; however, some breast cancer survivors may be receiving prophylactic bisphosphonate treatment to prevent osteoporosis. To assess whether our case definition was affecting these results, we conducted a sensitivity analysis after excluding women receiving bisphosphonates from the analysis. The risk of developing a new diagnosis of osteoporosis was broadly similar (adjusted HR 1.38, 95% CI 1.19–1.60). A total of 260 breast cancer survivors were clinically coded with lymphoedema, which corresponded to an incidence rate of 6.73 per 1000 person-years (95% CI 5.95–7.59) and a substantially elevated rate of disease compared with controls (HR 18.12, 95% CI 13.6–24.1). There was evidence for a slight increase in the risk of early menopause among breast cancer survivors (adjusted HR 1.25, 95% CI 1.06–1.48).

Coronary artery disease and hypothyroidism crude incidence rates were similar in breast cancer survivors and controls. After accounting for matched groups and additional covariates, there was evidence for an increased rate of coronary artery disease (adjusted HR 1.27, 95% CI 1.11–1.44) and a marginal increase in the risk of hypothyroidism (adjusted HR 1.26, 95% CI 1.02–1.56) in breast cancer survivors. Coronary artery disease can affect heart muscle function, and ultimately is a leading cause of heart failure; however, because we have treated each outcome separately in the analysis, this causal effect is unlikely to affect the estimates for heart failure. Nevertheless, we compared the risk of heart failure among breast cancer survivors who only had a clinical code for heart failure (137 new diagnoses, HR 3.44, 95% CI 2.86–4.02) and among breast cancer survivors with a clinical code for CAD and heart failure (91 new diagnoses, HR 2.29, 95% CI 1.82–2.76).

Colorectal cancer survivors

Incidence rates of new diagnoses associated with surviving colorectal cancer are shown in Table 4. There was evidence for an increase in the incidence of dementia in colorectal cancer survivors compared with controls (adjusted HR 1.68, 95% CI 1.20–2.35) after adjusting for BMI and Charlson score. In addition, there was an increase of new diagnoses of diabetes among colorectal cancer survivors, and this risk remained after adjusting

Table 2 Characteristics of cancer survivors and matched controls (four patients of the same age and gender from the same primary care practice without a diagnosis of cancer) by cancer type

	Breast		Colorectal		Prostate	
	Survivor	**Control**	**Survivor**	**Control**	**Survivor**	**Control**
Gender						
Male	—	—	2569	10 178	4207	16 709
Female	16 938	67 649	2499	9950	—	—
Mean age[a] *(in years)*	66.9		74.1		76.1	
Standard deviation	12.3		10.9		8.1	
Mean years from diagnosis[a]	10.2	—	10.1	—	5.8	—
Standard deviation	7.5	—	7.9	—	3.6	—
Charlson comorbidity score > 0	7551	27 999	2942	10 343	2693	9345
%	44.6%	41.4%	58.1%	51.4%	64.0%	55.9%
Smoking status						
Ever smoked	5738	23 188	2238	8428	2139	9012
%	33.9%	34.3%	44.1%	41.9%	50.8%	53.9%
Never smoked	10 703	42 452	2662	10 889	1968	7044
%	63.2%	62.8%	52.5%	54.1%	46.8%	42.2%
BMI						
Underweight	583	2264	160	616	77	359
%	3.9%	3.8%	3.7%	3.6%	2.1%	2.5%
Normal weight	6046	23 651	1618	6654	1380	5651
%	41.2%	39.8%	37.8%	38.9%	37.3%	39.1%
Overweight	5030	20 169	1695	6781	1625	6355
%	34.3%	33.9%	39.6%	39.7%	43.9%	43.9%
Obese	3023	13 296	804	3033	623	2105
%	20.6%	22.4%	18.8%	17.8%	16.8%	14.6%

[a]The date used to calculate years from cancer diagnosis was 1 September 2003, and the year used to calculate age was 2003.

for BMI and smoking (adjusted HR 1.39, 95% 1.12–1.72). Colorectal cancer survivors also had a significantly higher incidence of osteoporosis (adjusted HR 1.41, 95% CI 1.15–1.73). Incidence, prevalence and risk of long-term effects including erectile dysfunction (adjusted HR 1.39, 95% CI 1.08–1.77), urinary incontinence (HR 1.79, 95% CI 1.40–2.30) and bowel dysfunction (HR 1.43, 95% CI 1.26–1.63) were significantly elevated in colorectal cancer survivors post diagnosis.

Prostate cancer survivors

Table 5 shows the incidence and risk of new diagnoses among prostate cancer survivors and controls. Prostate cancer survivors had a large increase in the rate of osteoporosis compared with matched controls (adjusted HR 2.49, 95% CI 1.93–3.22). Similar to the breast cancer analysis, we excluded men receiving bisphosphonates from the case definition for osteoporosis. The results were broadly similar (adjusted HR is 1.92, 95% CI 1.35–2.72). There were no differences in the incidence rate of heart failure or coronary artery disease between prostate cancer survivors and controls. Although the multivariate analysis showed no difference in the risk of developing erectile dysfunction among prostate cancer survivors, the incidence rate of erectile dysfunction was significantly higher among the prostate cancer group (23.5 new diagnoses per 1000 person-years, 95% CI 20.2–27.2). Prostate cancer survivors were significantly more likely to experience urinary incontinence, with a significantly higher total prevalence (Table 6) and long-term risk of new events (HR 3.20, 95% CI 2.45–4.16).

Total prevalence

In addition to new diagnoses during the analysis period, we also considered total prevalence of the long-term effects, including urinary incontinence, erectile dysfunction and bowel dysfunction (Table 6). The number of cancer survivors with a clinical record for these long-term effects significantly increased compared with the control population, and for the most part corresponded to the relative risks reported in the proportional hazards models with the exception of erectile dysfunction, which was recorded in almost twice as many prostate cancer survivors as controls.

DISCUSSION

Statement of principal findings

This large population-based matched cohort study has described the incidence and risk of new diagnoses related to late effects of treatment in long-term survivors of breast, colorectal and prostate cancer. We have confirmed previously reported associations between breast cancer and heart failure, coronary artery disease and hypothyroidism, and the increased risk of osteoporosis in all three cancers. We did not confirm the increase of coronary artery disease in prostate cancer; however, this analysis did show an association between colorectal cancer and diabetes mellitus, with an increased incidence of almost four new cases of diabetes per 1000 person-years. The incidence rate for osteoporosis was comparable between all cancer groups. Despite these associations, the absolute rise in incidence is very modest in this general population, with the exception of osteoporosis and urinary incontinence among prostate cancer survivors.

Comparison with other research

This is the first UK-based study to report the incidence and risk of new diagnoses related to late effects of treatment in an unselected population of cancer survivors. The study confirms most of the

Table 3 Incidence of new diagnoses related to treatment amongst breast cancer survivors

	Incidence			Hazard ratio[a]			
	n	**Incidence rate per 1000 person-years**	**95% CI**	**Unadjusted**	**95% CI**	**Adjusted**	**95% CI**
Heart failure							
Cancer survivors	228	5.73	5.0–6.5	1.80	1.51–2.13	1.95	1.27–3.01
Controls without cancer	760	4.40	4.1–4.7	—			
Coronary artery disease							
Cancer survivors	410	10.86	9.9–12.0	1.29	1.14–1.45	1.27	1.11–1.44
Controls without cancer	1726	10.60	10.1–11.1	—			
Dementia							
Cancer survivors	211	5.19	4.54–5.94	1.62	1.36–1.93	1.21	0.95–1.53
Controls without cancer	800	4.52	4.22–4.85				
Hypothyroidism							
Cancer survivors	437	11.76	10.7–12.9	1.18	1.05–1.32	1.26	1.02–1.56
Controls without cancer	1772	10.95	10.5–11.5	—			
Osteoporosis							
Cancer survivors	656	18.07	16.7–19.5	1.40	1.28–1.54	1.26	1.13–1.40
Controls without cancer	2305	14.57	13.9–15.2	—			
Lymphoedema							
Cancer survivors	260	6.73	5.95–7.59	18.12	13.6–24.1	—	—
Controls without cancer	77	0.34	0.34–0.54				
Early menopause[b]							
Cancer survivors	186	4.51	3.91–5.21	1.25	1.06–1.48	1.25	1.06–1.48
Controls without cancer	664	3.72	3.45–4.02				

Abbreviation: CI = confidence interval. [a]The hazard ratio in each case is based on individual comparison with controls matched for age, gender and primary care practice (i.e., the comparison for patients treated with radiotherapy is with controls individually matched to patients receiving radiotherapy rather than all controls); the adjusted hazard ratio takes account of the potential confounding effect of smoking and BMI (except for hypothyroidism which is adjusted for BMI and history of hormone therapy only, and early menopause which is adjusted for smoking only). [b]Defined as menopause before the age of 48 years.

Table 4 Incidence of new diagnoses related to treatment among colorectal cancer survivors

	Incidence			Hazard ratio[a]			
	n	**Incidence rate per 1000 person-years**	**95% CI**	**Unadjusted**	**95% CI**	**Adjusted**	**95% CI**
Dementia							
Cancer survivors	116	10.08	8.4–12.1	2.10	1.65–2.68	1.68	1.20–2.35
Controls without cancer	356	7.02	6.3–7.8	—			
Osteoporosis							
Cancer survivors	190	18.02	15.6–20.8	1.60	1.35–1.91	1.41	1.15–1.73
Controls without cancer	597	12.86	11.9–13.9	—			
Diabetes							
Cancer survivors	176	17.01	14.7–19.7	1.40	1.15–1.70	1.39	1.12–1.72
Controls without cancer	616	13.21	12.2–14.3	—			
Erectile dysfunction							
Cancer survivors	118	23.00	19.2–27.5	1.42	1.11–1.81	1.39	1.08–1.77
Controls without cancer	392	16.55	14.9–18.3				
Urinary incontinence							
Cancer survivors	252	14.49	12.8–16.4	1.79	1.40–2.30		
Controls without cancer	853	12.09	11.3–12.9				
Diarrhoea or constipation							
Cancer survivors	441	67.99	61.9–74.6	1.43	1.26–1.63		
Controls without cancer	1939	51.68	49.4–54.0				

Abbreviation: CI = confidence interval. [a]The hazard ratio in each case is based on individual comparison with controls matched for age, gender and primary care practice; the adjusted hazard ratio takes account of the potential confounding effect of comorbidity, BMI (and for osteoporosis and erectile dysfunction also for smoking).

Table 5 Incidence of new diagnoses related to treatment amongst prostate cancer survivors

	Incidence			Hazard ratio[a]			
	n	Incidence rate per 1000 person-years	95% CI	Unadjusted	95% CI	Adjusted	95% CI
Heart failure							
Cancer survivors	129	17.1	14.4–20.3	1.66	1.32–2.10	1.23	0.91–1.66
Controls without cancer	486	13.8	12.6–15.1	—			
Coronary artery disease							
Cancer survivors	173	27.95	24.1–32.4	1.27	1.05–1.56	1.17	0.94–1.46
Controls without cancer	863	29.15	27.3–31.2	—			
Osteoporosis							
Cancer survivors	120	15.38	12.9–18.4	2.39	1.89–3.00	2.49	1.93–3.22
Controls without cancer	292	7.98	7.1–8.9	—			
Erectile dysfunction							
Cancer survivors	163	23.51	20.2–27.4	1.22	0.96–1.55	1.17	0.91–1.49
Controls without cancer	563	16.13	14.8–17.5				
Urinary incontinence							
Cancer survivors	315	20.43	18.3–22.8	3.20	2.45–4.16		
Controls without cancer	677	12.45	11.5–13.4				

Abbreviation: CI = confidence interval. [a]The hazard ratio in each case is based on individual comparison with controls matched for age, gender and primary care practice (i.e. the comparison for patients treated with radiotherapy is with controls individually matched to patients receiving radiotherapy rather than all controls); the adjusted hazard ratio takes account of the potential confounding effect of comorbidity, smoking and BMI.

Table 6 Total prevalence of long-term effects in cancer survivors and controls

	Number of events	No event	Total patients
Urinary incontinence			
Prostate			
Survivor	411 (9.8%)[a]	3796 (90.2%)	4207
Control	525 (3.1%)	16 184 (96.9%)	16 709
Colorectal			
Survivor	324 (6.4%)[a]	4744 (93.6%)	5068
Control	1022 (5.1%)	19 106 (94.9%)	20 128
Erectile dysfunction			
Prostate			
Survivor	662 (15.7%)[a]	3545 (84.3%)	4207
Control	1394 (8.3%)	15 315 (91.7%)	16 709
Colorectal (men only)			
Survivor	344 (13.4%)[a]	2225 (86.6%)	2569
Control	931 (9.2%)	9247 (90.8%)	10 178
Diarrhoea or constipation			
Colorectal			
Survivor	2300 (45.4%)[a]	2768 (54.6%)	5068
Control	5792 (28.8%)	14 336 (71.2%)	20 128

[a]Significant at $P < 0.0001$ in Pearson's X^2-comparisons.

reported associations between treatment and outcomes drawn from cross-sectional studies and specialist databases. The risk of heart failure, hypothyroidism and osteoporosis among breast cancer survivors in this cohort was similar to previously reported research (Mincey *et al*, 2006; Pinder *et al*, 2007; Smith *et al*, 2008). However, rates of osteoporosis among prostate cancer survivors in this cohort were substantially higher compared with the results from a meta-analysis assessing the risk of androgen deprivation therapy-related osteoporosis (Taylor *et al*, 2009). We did not identify any non-reported outcomes from this study. Low-level incontinence can develop in some patients many years after radical prostatectomy. Previous research on the incidence of pelvic late effects has documented a substantial increase in the risk of bowel and urinary incontinence, which was mirrored in this cohort where the incidence of long-term effects such as urinary incontinence, erectile dysfunction and bowel dysfunction was substantially higher among the cancer survivors in this population (Farnell *et al*, 2010; Henson *et al*, 2011). These may affect cancer survivors closer to diagnosis; however, we did not have longitudinal follow-up data on this cohort before 2 years post diagnosis (Chen *et al*, 2009).

Strengths and limitations

This analysis uses data from a large, representative database, and quantified new diagnoses in a community-based group of cancer survivors with a robust comparison population. Although large data repositories such as the GPRD offer the opportunity to access information on a large number of patients, there are several limitations inherent to conducting research in a data set that has not been collected primarily for research purposes. The main drawback of this observational research is that it is not possible to explore the relationships between specific treatments and new diagnoses. A lack of detailed treatment information from the GPRD prevented analysis of treatment effects among the entire cohort. We attempted to gain additional treatment data by linking this GPRD data set with National Cancer Intelligence Network (NCIN); however, historical treatment data have not been consistently recorded across the different national cancer registries. A summary of treatment data that was available for this study is shown in Appendix. There is a strong need for improvements in capturing cancer treatment at cancer registries, and more importantly cancer treatment data need to be incorporated into patient electronic medical records in primary care. Read coding of radiotherapy, chemotherapy and surgery is weak in primary care, which needs to improve before general practitioners (GPs) can identify individual cancer treatment histories and assess risk for late effects among long-term cancer survivors. In addition, because

individual-level data are limited, we have only taken a small proportion of potentially confounding baseline patient characteristics into account.

The results need to be interpreted with caution, as the mechanisms underlying these new diagnoses have not been fully elucidated, disease definitions are not standardised in the GPRD and incident diseases may result from shared risk factors with the initial cancer (Wefel and Meyers, 2005). Although conducting a comparison between cancer survivors and a control population minimises bias due to misclassification or failure to record clinical data, it is possible that the raised risks of disease are partly due to increased follow-up and clinical contact among the cancer survivors group. In addition, we have conducted numerous statistical tests, but have not adjusted for multiple comparisons.

Case definition is an important issue to consider when using administrative databases for research purposes (Khan *et al*, 2010a). Previous validation studies of the GPRD have suggested that prescribing data can be used to capture additional cases when the prescribed drug is specific to the diagnosis of interest (Hansell *et al*, 1999). Accordingly, we included bisphosphonates in the case definition for osteoporosis among the cancer survivors and control population, which was supported by sensitivity analyses. Use of prophylactic bisphosphonates for prevention of osteoporosis is not currently recommended among cancer survivors receiving aromatase inhibitors; however, it is possible that this may occur in practice. It is also possible that prostate cancer survivors receiving bisphosphonates as treatment for skeletal metastases were wrongly attributed as osteoporotic. It is a potential limitation of these analyses that it has not been possible to specifically identify those patients with secondary disease; however, only 14 of the 120 prostate cancer survivors who were identified as osteoporotic solely on the basis of a new prescription of a bisphosphonate had a PSA level suggestive of secondary disease (defined as at least one PSA reading over $50\,ng\,ml^{-1}$), which suggests that misclassification bias is minimal in this instance. Furthermore, results of a sensitivity analysis excluding those patients receiving bisphosphonates show broadly similar relative results for risk of osteoporosis among cancer survivors compared with matched controls.

Implications of the study

Although this study has shown that long-term cancer survivors are a population at risk, the absolute increase in disease burden is small apart from the risk of osteoporosis. Most cancer survivors readjust to their disease and do not have long-term physical or psychological sequelae. These findings support the approach of the UK National Cancer Survivors Initiative to develop risk stratification tools to manage cancer survivors post treatment (National Cancer Survivorship (NSCI) Research Workstream, 2010). Most of these patients will be cared for in primary care, and GPs will need an awareness of the increased risks in individual patients. Our findings certainly suggest a substantially increased risk of osteoporosis among prostate cancer survivors, and adequate surveillance systems are required to manage this risk. Guidelines developed by the National Institute for Health and Clinical Excellence recommend baseline dual energy X-ray absorptiometry scans to women with breast cancer; however, no current guidelines exist for the management of bone loss among prostate cancer survivors (National Collaborating Centre for Cancer, 2009). General practitioners will also need to pay special attention to the presence of risk factors in this population that may have led to the original cancer diagnosis, as well as managing long-term treatment effects.

Although large, prospective cohort studies have described late effects among childhood cancer survivors (Oeffinger *et al*, 2006; Reulen *et al*, 2007), there is a strong need for similar work among survivors of adult cancer. In order to better elucidate the relationships between treatment and late effects, future research needs to involve detailed and individual-level treatment data; this will allow an assessment of risk stratified by treatment. This may involve further research using existing databases, as recording of treatment improves within cancer registries and primary care, or long-term follow-up of participants of treatment clinical trials where detailed information on treatment and individual-level patient characteristics will have been collected at baseline.

Conclusion

This research has confirmed the increased incidence of previously reported late effects of treatment in long-term survivors of cancer in an unselected population. Although the absolute increase of most late effects is small, clinicians will need an awareness of these risks.

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Author contributions

PWR, NFK and DM were responsible for the study design. NFK, DM, LC and PWR planned the data analysis, and NFK conducted all statistical analyses, prepared tables and drafted the manuscript. DF assisted with NCIN data provision and interpretation of treatment data. PWR is the principal investigator of the study. All authors revised and commented on the manuscript and approved the final draft.

Ethics approval

The GPRD Group has obtained ethical approval for all observational research using GPRD data. This study has been approved by the Independent Scientific Advisory Committee (ISAC) of the GPRD (ISAC protocol No. 06_051R).

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Appendix

Treatment data available in GPRD-NCIN-linked database

	Yes	No	Total	% Of total patients
Radiotherapy				
Breast	4509	2539	7048	41.6
Colorectal	322	1111	1433	28.3
Prostate	717	974	1691	40.2
Total	5548	4624	10 172	38.8
Chemotherapy				
Breast	2677	3352	6029	35.6
Colorectal	684	1010	1694	33.4
Prostate	171	1187	1358	32.3
Total	3532	5549	9081	34.6
Surgery				
Breast	4980	1574	6554	38.7
Colorectal	1421	501	1922	37.9
Prostate	1053	812	1865	44.3
Total	7454	2887	10 341	39.4
Hormone therapy				
Breast	13 304	716	14 020	82.8
Colorectal	231	1214	1445	28.5
Prostate	3197	369	3566	84.8
Total	16 732	2299	19 031	72.6