Increasing Trends in the Prevalence of Prior Cancer in Newly Diagnosed Lung, Stomach, Colorectal, Breast, and Uterine Cancer Patients: A Population-Based Study

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Abstract

Background: Cancer survivors are frequently excluded from clinical research, resulting in their omission from the development of many cancer treatment strategies. Quantifying the prevalence of prior cancer in newly diagnosed cancer patients can inform research and clinical practice. This study aimed to describe the prevalence, characteristics, and trends of prior cancer in newly diagnosed cancer patients in Japan.

Methods: Using Osaka Cancer Registry data, we examined the prevalence, characteristics, and time trends of prior cancer in patients who received new diagnoses of lung, stomach, colorectal, female breast, or uterine cancer between 2004 and 2015. Site-specific prior cancers were examined for a maximum of 15 years before the new cancer was diagnosed. Time trends were evaluated using the Cochran-Armitage trend test.

Results: Among 275,895 newly diagnosed cancer patients, 21,757 (7.9%) had prior cancer. The prevalence of prior cancer ranged from 3.3% (breast cancer) to 11.1% (lung cancer). In both sexes, the age-adjusted prevalence of prior cancer had increased in recent years (P values for trend < 0.001), especially in newly diagnosed lung cancer patients. The proportion of smoking-related prior cancers exceeded 50% in patients with newly diagnosed lung, stomach, colorectal, and breast cancer.

Conclusions: The prevalence of prior cancer in newly diagnosed cancer patients is relatively high, and has increased in recent years. Our findings suggest that a deeper understanding of the prevalence and characteristics of prior cancer in cancer patients is needed to promote more inclusive clinical research and support the expansion of treatment options.

Introduction

Cancer survivors are at risk of developing second primary cancers, and their numbers are increasing worldwide [1–5]. A study from the US Surveillance, Epidemiology, and End Results Program reported that almost 20% of individuals with incident cancers between 2009 and 2013 had prior cancer [6]. The increasing incidence of second malignant cancers may be influenced by hereditary and familial risk, antecedent cancer therapy, lifestyle-related factors (e.g., tobacco and alcohol consumption), and environmental factors [7].

Cancer survivors require unique medical and psychosocial support with proactive assessments and follow-up care [4]. Several studies have reported that prior cancer did not adversely affect survival in lung and pancreatic cancer patients [8–11]. In contrast, another study noted that poorer survival was associated with some prior cancer types (e.g., colorectum, melanoma, and breast), but not others (e.g., esophagus, stomach, and lung) [12].

Despite the growing number of measures designed to support various aspects of cancer survivorship in patients, caregivers, and clinicians, further evidence-based resources are needed to improve the quality and effectiveness of cancer care. Identifying the occurrence and type of prior cancer in each newly diagnosed cancer patient can facilitate more accurate risk assessments in various clinical settings, including clinical cancer research. In addition, the frequent exclusion of cancer survivors from clinical research can lead to blind spots in the effectiveness and safety of treatment strategies for patients with metachronous cancers [13].

Insight into the prevalence and characteristics of prior cancer can inform research and clinical practice, but few studies have used population-based cancer registry data to examine these issues. In addition, most epidemiological evidence for the association between prior cancer and newly diagnosed cancer is derived from studies conducted in the US and Europe, with little evidence from Asian populations. The aim of this study was to provide globally comparable estimates of the prevalence, characteristics, and trends of prior cancer in newly diagnosed cancer patients using a long-term Japanese cancer registry database in order to aid further research and inform healthcare strategies.

Methods

Data source and study design

Data were obtained from the Osaka Cancer Registry (OCR), a population-based cancer registry founded in 1962 for the purpose of registering and monitoring all malignant tumors and benign intracranial tumors throughout Osaka prefecture (the third largest metropolitan area in Japan). The OCR covers a population of 8.8 million people, and allows the identification of prior cancers in individual patients [14].

Data on all cancer patients diagnosed between 1989 and 2015 were extracted for analysis. The various cancers were identified using the corresponding International Classification of Diseases, Tenth Revision (ICD-10) codes. The data also included each patient's age at diagnosis (hereinafter referred to as diagnostic age), sex, cancer detection method, cancer stage, treatment, month of diagnosis (diagnostic month), year of diagnosis (diagnostic year), inclusion in the registry through death certificate only, living status, and survival time.

We quantified the prevalence of prior cancer in patients who received new diagnoses of cancer of the following sites between 2004 and 2015: lung, stomach, colorectum, female breast (hereinafter referred to as breast), and uterus. These sites were selected as they are the target sites for cancer screening programs in Japan, and are associated with high incidence [15]. We then examined the occurrence and types of prior cancers within 15 years before the diagnostic month and year of each newly diagnosed cancer.

Definitions and study subjects

Index cancers were defined as cancers that were newly diagnosed between 2004 and 2015 in patients who met the following criteria: 1) diagnostic age of 15–99 years, 2) pathologically diagnosed cancer for any of the target sites (lung, stomach, colorectum, breast, and uterus), and 3) survived for three months or more after diagnosis. In Osaka prefecture, the percentage of cases registered from death certificate only fell below 10% from 2004 onward [16]. Therefore, data from 2004 and later were used to identify the index cancer cases. Patients were excluded if they were registered in the OCR through death certificate only. Cases of multiple cancers are recorded in the OCR in accordance with the guidelines of the International Agency for Research on Cancer and the International Association of Cancer Registries [17]. However, multiple cancers of the same site in an individual patient were combined as the “most common prior cancer” to avoid including the incomplete integration of multiple prior cancers or metastatic cancers [5].

Prior cancers were defined as cancers diagnosed during the 15-year period before the index cancer diagnosis. If two or more prior cancers had the same diagnostic month and year in a patient, the sequence of these cancers was randomly determined using a previously described method [6].

We identified the index and prior cancer sites using the following ICD-10 codes [18]: all sites (C00–C96.x), mouth and pharynx (C00–C14.x), esophagus (C15.x), stomach (C16.x), colon (C18.x), rectum (C19.x–C20.x), liver (C22.x), gallbladder and bile duct (C23.x–C24.x), pancreas (C25.x), larynx (C32.x), lung (C33–C34.x), melanoma of skin (C43.x), other skin (C44.x), mesothelioma (C45.x), breast (C50.x), uterus (C53.x–C55.x), cervix uteri (C53.x), corpus uteri (C54.x), ovary (C56.x), prostate (C61.x), bladder (C67.x), renal and urinary tract (C64.x–C66.x, C68.x), brain and central nervous system (C70.x–C72.x), thyroid (C73.x), Hodgkin lymphoma (C81.x), non-Hodgkin lymphoma (C82.x–C86.x, C96.x), immunoproliferative diseases (C88.x), myeloma (C90.x), lymphoid leukemia (C91.x), acute myeloid leukemia (C92.0), myeloid leukemia (C92.x–C94.x), and unspecified leukemia (C95.x).

Patient and index cancer characteristics

For each patient, we analyzed age group (15–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and 85–99 years), sex (male or female), method of cancer detection (screening and medical check-up, incidental detection during follow-up examination for another disease, and other or unknown; the last category generally involved cancer detection due to the occurrence of subjective symptoms)[19], cancer stage (localized, regional lymph nodes, regional extension, distant metastasis, and other or unknown), treatment (radiotherapy only, chemotherapy only, chemoradiotherapy, surgery only, surgery plus chemotherapy or radiotherapy, and other or unknown), and diagnostic year (2004–2005, 2006–2007, 2008–2009, 2010–2011, 2012–2013, or 2014–2015). Missing values were included in the “unknown” category for each factor.

Prior cancer characteristics

For patients with prior cancer, we calculated the number of prior cancers before the index cancer, as well as the diagnostic time interval between the index cancer and most recent prior cancer. In addition, we examined the stage, treatment, and site of each prior cancer. The prior cancer site was identified for the most recent prior cancer. We categorized the following prior cancers as smoking-related cancers based on previous studies [20–24]: mouth, pharynx, larynx, lung, esophagus, stomach, liver, pancreas, kidney, urinary bladder, colorectum, uterine cervix, and acute myeloid leukemia.

Statistical analysis

The main outcome measure was the prevalence of prior cancer in the study subjects. In order to account for the varying age structures of the cancer patient population over time, we examined the trends in the age-adjusted prevalence (measured every two years) of prior cancer for each index cancer site according to sex. First, we calculated the age-specific prior cancer prevalence for each age group according to sex and cancer site. To obtain the expected number of prior cancer cases, we multiplied the age-specific prior cancer prevalence by the number of patients for each age group according to sex in our subjects between 2004 and 2015, which we had set as the reference cancer population. We then totaled the expected number of prior cancer cases from all age groups. Finally, to calculate the age-adjusted prevalence, we divided the total expected number of prior cancer cases by the reference cancer population. We described the time trends in prior cancer prevalence from 2004 to 2015 using the Cochran–Armitage trend test [25]. The distributions of the above site-specific measurements were also examined according to sex.

Continuous variables were summarized as median values and interquartile ranges, and categorical variables were summarized as proportions. Proportions were compared using Pearson's chi-square test. The significance level was set at 5% (two-sided). All analyses were performed using STATA version 14 (Stata corporation, College Station, TX, USA).

Results

Prior cancer prevalence and patient characteristics

Figure 1 shows the subject selection process. We identified 275,895 index cancer patients that met the inclusion and exclusion criteria. Among these, 21,757 (7.9%) had prior cancer. As shown in Fig. 2, the age-adjusted prevalence of prior cancer had significantly increased over the study period for all index cancers in both male and female patients (all *P* values < 0.001). This prevalence was notably higher in lung cancer patients in both sexes.

The characteristics of the patients according to index cancer site are summarized in Table 1. The results for cervical cancer and corpus uterine cancer are described separately in Table A1 (Additional file). Among all patients, the prevalence of prior cancer was 11.1% in lung cancer patients, 9.5% in stomach cancer patients, 7.5% in colorectal cancer patients, 3.3% in breast cancer patients, and 4.5% in uterine cancer patients (cervix: 2.7%, corpus: 6.7%). Among

older patients aged 65 years or older, the prevalence of prior cancer was 12.1% in lung cancer patients, 10.5% in stomach cancer patients, 8.4% in colorectal cancer patients, 5.2% in breast cancer patients, and 6.2% in uterine cancer patients (cervix: 5.4%, corpus: 8.5%). Patients whose index cancers were incidentally detected during follow-up examination for another disease had a higher prevalence of prior cancer than other cancer detection methods for all index cancer sites. The prevalence of prior cancer was also higher in patients whose index cancer was in the localized stage. With the exception of other or unknown treatments, surgery was the most common treatment for lung cancer (16.9%), colorectal cancer (8.2%), breast cancer (4.6%), and uterine cancer (5.2%).

Table 1
Characteristics of newly diagnosed cancer patients according to index cancer site

Index Cancer Site	Lung			Stomach			Colorectum			Breast			Uterus		
	Total	Prior ^a		Total	Prior ^a		Total	Prior ^a		Total	Prior ^a		Total	Prior ^a	
N = 275,895	N	N	%	N	N	%	N	N	%	N	N	%	N	N	%
Total	56,930	6,309	11.1	78,092	7,382	9.5	77,032	5,757	7.5	47,860	1,588	3.3	15,981	721	4.5
Sex															
Male	39,040	4,628	11.9	54,479	5,800	10.6	44,535	3,841	8.6						
Female	17,890	1,681	9.4	23,613	1,582	6.7	32,497	1,916	5.9	47,860	1,588	3.3	15,981	721	4.5
Age, years															
Median (IQR)	70 (63–76)	73 (67–78)		71 (63–77)	74 (68–79)		70 (62–77)	73 (67–79)		60 (48–69)	69 (61–76)		57 (46–67)	63 (53–74)	
15–39	455	15	3.3	864	8	0.9	961	10	1.0	3,034	23	0.8	2,162	27	1.2
40–44	551	20	3.6	919	17	1.8	1,191	29	2.4	4,556	35	0.8	1,455	30	2.1
45–49	1,032	39	3.8	1,572	39	2.5	1,974	47	2.4	5,737	61	1.1	1,577	66	4.2
50–54	1,965	98	5.0	2,954	107	3.6	3,508	103	2.9	4,885	91	1.9	1,784	97	5.4
55–59	4,197	242	5.8	5,962	292	4.9	6,471	277	4.3	5,589	137	2.5	2,114	75	3.5
60–64	7,902	671	8.5	10,240	658	6.4	10,754	559	5.2	6,376	214	3.4	2,024	87	4.3
65–69	10,790	1,110	10.3	13,402	1,197	8.9	13,329	936	7.0	5,889	279	4.7	1,661	84	5.1
70–74	12,028	1,419	11.8	15,508	1,686	10.9	14,275	1,259	8.8	4,693	277	5.9	1,319	96	7.3
75–79	10,191	1,503	14.7	13,493	1,774	13.1	12,180	1,255	10.3	3,429	222	6.5	939	70	7.5
80–84	5,702	875	15.3	8,550	1,077	12.6	7,568	857	11.3	2,160	153	7.1	574	60	10.5
85–99	2,117	317	15.0	4,628	527	11.4	4,821	425	8.8	1,512	96	6.3	372	29	7.8
Method of cancer detection															
Screening and medical check-up	8,417	399	4.7	11,938	553	4.6	11,299	466	4.1	9,565	167	1.7	2,330	77	3.3
Incidental detection ^b	19,365	4,222	21.8	20,721	4,003	19.3	15,244	2,728	17.9	3,938	666	16.9	1,919	224	11.7
Other or unknown	29,148	1,688	5.8	45,433	2,826	6.2	50,489	2,563	5.1	34,357	755	2.2	11,732	420	3.6
Cancer stage															
Localized	17,540	2,986	17.0	43,352	5,027	11.6	35,289	3,152	8.9	28,498	1,087	3.8	8,960	444	5.0
Regional lymph nodes	7,112	785	11.0	9,327	725	7.8	15,269	1,036	6.8	11,856	343	2.9	656	21	3.2
Regional extension	8,188	782	9.6	8,477	509	6.0	9,034	581	6.4	2,179	44	2.0	4,134	158	3.8
Distant metastasis	20,480	1,388	6.8	12,500	688	5.5	12,838	659	5.1	2,340	48	2.1	1,275	49	3.8
Other or unknown	3,610	368	10.2	4,436	433	9.8	4,602	329	7.1	2,987	66	2.2	956	49	5.1
Treatment															
Radiotherapy only	3,116	471	15.1	48	14	29.2	93	6	6.5	214	3	1.4	899	44	4.9
Chemotherapy only	15,195	1,076	7.1	7,455	543	7.3	1,974	142	7.2	1,984	38	1.9	405	16	4.0
Chemoradiotherapy	7,394	515	7.0	166	38	22.9	184	13	7.1	185	4	2.2	1,200	35	2.9
Surgery only	15,772	2,665	16.9	29,975	2,514	8.4	40,687	3,331	8.2	16,277	741	4.6	6,765	350	5.2
Surgery plus chemotherapy or radiotherapy	6,839	634	9.3	13,618	772	5.7	23,206	1,176	5.1	24,665	639	2.6	5,390	201	3.7
Other or unknown	8,614	948	11.0	26,830	3,501	13.0	10,888	1,089	10.0	4,535	163	3.6	1,322	75	5.7
Diagnostic year															

Index Cancer Site	Lung			Stomach			Colorectum			Breast			Uterus		
2004–2005	7,288	538	7.4	9,969	635	6.4	9,151	498	5.4	5,650	143	2.5	1,992	83	4.2
2006–2007	8,407	803	9.6	11,542	892	7.7	11,295	743	6.6	6,913	206	3.0	2,193	84	3.8
2008–2009	8,880	856	9.6	12,498	1,048	8.4	11,833	825	7.0	7,297	244	3.3	2,323	96	4.1
2010–2011	10,240	1,195	11.7	13,806	1,373	9.9	13,565	1,052	7.8	8,596	270	3.1	2,965	140	4.7
2012–2013	10,641	1,379	13.0	15,047	1,661	11.0	15,074	1,252	8.3	9,050	337	3.7	3,173	153	4.8
2014–2015	11,474	1,538	13.4	15,230	1,773	11.6	16,114	1,387	8.6	10,354	388	3.7	3,335	165	4.9
Abbreviation: IQR, interquartile range.															
Categorical variables between cancer patients with and without prior cancer were compared using Pearson's chi-square test. Significant differences ($P \leq 0.05$) were found in all categories except for diagnostic year in uterine cancer patients. ^a Prior refers to newly diagnosed cancer patients with prior cancer of the specified site. ^b Incidental detection during follow-up examination for another disease.															

Prior cancer characteristics

The characteristics of male and female patients with prior cancer are shown in Table 2 and Table 3, respectively. Approximately 90% of these patients had only one prior cancer regardless of sex. The proportions of male patients with two prior cancers were 10.4% for lung cancer, 8.7% for stomach cancer, and 8.9% for colorectal cancer. In female patients, these proportions were 7.2% for lung cancer, 5.6% for stomach cancer, 6.1% for colorectal cancer, 5.0% for breast cancer, and 6.4% for uterine cancer (cervix: 7.3%, corpus: 5.4%). The cumulative proportions of the most recent prior cancers diagnosed within 5 years before the index cancer diagnosis were 69.4% (male) and 65.0% (female) for lung cancer, 75.0% (male) and 67.4% (female) for stomach cancer, 75.5% (male) and 65.3% (female) for colorectal cancer, 65.2% (female) for breast cancer, and 57.7% (female) for uterine cancer (cervix: 69.0%, corpus: 54.7%). The most common and least common prior cancer stages were localized and distant metastasis, respectively. Surgery only was the most common treatment for prior cancer across all index cancer sites in both sexes.

Table 2
Characteristics of newly diagnosed male cancer patients with prior cancer

Index Cancer Site	Lung		Stomach		Colorectum		Total	
	N	%	N	%	N	%	N	%
Total	4,628	100	5,800	100	3,841	100	14,269	100
Number of prior cancers before the index cancer								
1	4,100	88.6	5,256	90.6	3,457	90.0	12,813	89.8
2	481	10.4	507	8.7	343	8.9	1,331	9.3
3	44	1.0	35	0.6	39	1.0	118	0.8
4	2	0.0	2	0.0	1	0.0	5	0.0
5	1	0.0	0	0.0	1	0.0	2	0.0
Diagnostic time interval ^a								
< 3 months	741	16.0	1,687	29.1	1,240	32.3	3,668	25.7
3 months – 1 year	555	12.0	656	11.3	428	11.1	1,639	11.5
1–5 years	1,916	41.4	2,006	34.6	1,232	32.1	5,154	36.1
5–10 years	988	21.3	1,017	17.5	641	16.7	2,646	18.5
10–15 years	428	9.2	434	7.5	300	7.8	1,162	8.1
Stage of prior cancer ^b								
Localized	2,941	63.5	3,320	57.2	2,308	60.1	8,569	60.1
Regional lymph nodes	455	9.8	650	11.2	350	9.1	1,455	10.2
Regional extension	528	11.4	797	13.7	501	13.0	1,826	12.8
Distant metastasis	229	4.9	453	7.8	325	8.5	1,007	7.1
Other or unknown	475	10.3	580	10.0	357	9.3	1,412	9.9
Treatment of prior cancer ^b								
Radiotherapy only	185	4.0	265	4.6	152	4.0	602	4.2
Chemotherapy only	252	5.4	438	7.6	310	8.1	1,000	7.0
Chemoradiotherapy	148	3.2	296	5.1	141	3.7	585	4.1
Surgery only	1,986	42.9	2,246	38.7	1,468	38.2	5,700	39.9
Surgery plus chemotherapy or radiotherapy	631	13.6	893	15.4	535	13.9	2,059	14.4
Other or unknown	1,426	30.8	1,662	28.7	1,235	32.2	4,323	30.3
Site of prior cancer ^b								
Mouth and pharynx	209	4.5	254	4.4	137	3.6	600	4.2
Esophagus	236	5.1	646	11.1	172	4.5	1,054	7.4
Stomach	1,290	27.9	-	-	1,302	33.9	2,592	18.2
Colon	543	11.7	970	16.7	-	-	1,513	10.6
Rectum	342	7.4	602	10.4	-	-	944	6.6
Liver	234	5.1	570	9.8	278	7.2	1,082	7.6
Gallbladder and bile duct	40	0.9	75	1.3	56	1.5	171	1.2
Pancreas	45	1.0	69	1.2	35	0.9	149	1.0
Larynx	172	3.7	198	3.4	90	2.3	460	3.2

Values are expressed as the number of patients and column percentage.

^aInterval between the diagnostic dates of the most recent prior cancer and index cancer.

^bMost recently diagnosed prior cancer.

Index Cancer Site	Lung		Stomach		Colorectum		Total	
Lung	-	-	591	10.2	386	10.0	977	6.8
Melanoma of skin	4	0.1	7	0.1	4	0.1	15	0.1
Other skin	73	1.6	67	1.2	66	1.7	206	1.4
Mesothelioma	4	0.1	7	0.1	9	0.2	20	0.1
Prostate	687	14.8	924	15.9	646	16.8	2,257	15.8
Bladder	265	5.7	281	4.8	213	5.5	759	5.3
Renal and urinary tract	164	3.5	185	3.2	172	4.5	521	3.7
Brain and central nervous system	5	0.1	8	0.1	7	0.2	20	0.1
Thyroid	38	0.8	42	0.7	38	1.0	118	0.8
Hodgkin lymphoma	12	0.3	4	0.1	8	0.2	24	0.2
Non-Hodgkin lymphoma	118	2.5	142	2.4	97	2.5	357	2.5
Immunoproliferative diseases	1	0.0	1	0.0	0	0.0	2	0.0
Myeloma	18	0.4	19	0.3	17	0.4	54	0.4
Lymphoid leukemia	13	0.3	11	0.2	8	0.2	32	0.2
Myeloid leukemia	13	0.3	17	0.3	14	0.4	44	0.3
Leukemia unspecified	0	0.0	0	0.0	1	0.0	1	0.0
Others	102	2.2	110	1.9	85	2.2	297	2.1
Values are expressed as the number of patients and column percentage.								
^a Interval between the diagnostic dates of the most recent prior cancer and index cancer.								
^b Most recently diagnosed prior cancer.								

Table 3
Characteristics of newly diagnosed female cancer patients with prior cancer

Index Cancer Site	Lung		Stomach		Colorectum		Breast		Uterus		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	1,681	100	1,582	100	1,916	100	1,588	100	721	100	7,488	100
Number of prior cancers before the index cancer												
1	1,551	92.3	1,488	94.1	1,794	93.6	1,507	94.9	672	93.2	7,012	93.6
2	121	7.2	88	5.6	116	6.1	79	5.0	46	6.4	450	6.0
3	9	0.5	6	0.4	5	0.3	2	0.1	3	0.4	25	0.3
4	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	1	0.0
Diagnostic time interval ^a												
< 3 months	282	16.8	374	23.6	445	23.2	317	20.0	127	17.6	1,545	20.6
3 months – 1 year	188	11.2	151	9.5	173	9.0	177	11.1	67	9.3	756	10.1
1–5 years	623	37.1	541	34.2	634	33.1	548	34.5	222	30.8	2,568	34.3
5–10 years	373	22.2	324	20.5	421	22.0	357	22.5	193	26.8	1,668	22.3
10–15 years	215	12.8	192	12.1	243	12.7	189	11.9	112	15.5	951	12.7
Stage of prior cancer ^b												
Localized	979	58.2	917	58.0	1,155	60.3	882	55.5	393	54.5	4,326	57.8
Regional lymph nodes	285	17.0	233	14.7	275	14.4	232	14.6	147	20.4	1,172	15.7
Regional extension	185	11.0	174	11.0	202	10.5	212	13.4	71	9.8	844	11.3
Distant metastasis	66	3.9	100	6.3	117	6.1	112	7.1	31	4.3	426	5.7
Other or unknown	166	9.9	158	10.0	167	8.7	150	9.4	79	11.0	720	9.6
Treatment of prior cancer ^b												
Radiotherapy only	24	1.4	32	2.0	37	1.9	28	1.8	10	1.4	131	1.7
Chemotherapy only	65	3.9	97	6.1	123	6.4	88	5.5	38	5.3	411	5.5
Chemoradiotherapy	41	2.4	28	1.8	27	1.4	31	2.0	4	0.6	131	1.7
Surgery only	784	46.6	747	47.2	860	44.9	848	53.4	293	40.6	3,532	47.2
Surgery plus chemotherapy or radiotherapy	484	28.8	403	25.5	518	27.0	368	23.2	261	36.2	2,034	27.2
Other or unknown	283	16.8	275	17.4	351	18.3	225	14.2	115	16.0	1,249	16.7
Site of prior cancer ^b												
Mouth and pharynx	50	3.0	32	2.0	29	1.5	39	2.5	12	1.7	162	2.2
Esophagus	24	1.4	62	3.9	26	1.4	27	1.7	3	0.4	142	1.9
Stomach	239	14.2	-	-	445	23.2	250	15.7	61	8.5	995	13.3
Colon	203	12.1	320	20.2	-	-	252	15.9	72	10.0	847	11.3
Rectum	95	5.7	132	8.3	-	-	133	8.4	32	4.4	392	5.2
Liver	48	2.9	104	6.6	93	4.9	58	3.7	12	1.7	315	4.2
Gallbladder and bile duct	14	0.8	36	2.3	35	1.8	13	0.8	8	1.1	106	1.4
Pancreas	30	1.8	31	2.0	28	1.5	13	0.8	4	0.6	106	1.4
Larynx	13	0.8	2	0.1	4	0.2	2	0.1	3	0.4	24	0.3
Lung	0	0.0	96	6.1	151	7.9	155	9.8	38	5.3	440	5.9

Values are expressed as the number of patients and column percentage.

^aInterval between the diagnostic dates of the most recent prior cancer and index cancer.

^bMost recently diagnosed prior cancer.

Index Cancer Site	Lung		Stomach		Colorectum		Breast		Uterus		Total	
Melanoma of skin	1	0.1	3	0.2	3	0.2	3	0.2	1	0.1	11	0.1
Other skin	27	1.6	42	2.7	39	2.0	30	1.9	15	2.1	153	2.0
Mesothelioma	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0
Breast	485	28.9	378	23.9	528	27.6	-	-	311	43.1	1,702	22.7
Cervix uteri	72	4.3	61	3.9	62	3.2	100	6.3	-	-	295	3.9
Corpus uteri	66	3.9	45	2.8	108	5.6	132	8.3	-	-	351	4.7
Uterus	6	0.4	3	0.2	5	0.3	7	0.4	-	-	21	0.3
Ovary	46	2.7	25	1.6	56	2.9	60	3.8	49	6.8	236	3.2
Bladder	27	1.6	27	1.7	38	2.0	23	1.4	14	1.9	129	1.7
Renal and urinary tract	49	2.9	26	1.6	67	3.5	51	3.2	19	2.6	212	2.8
Brain and central nervous system	6	0.4	4	0.3	3	0.2	1	0.1	3	0.4	17	0.2
Thyroid	86	5.1	40	2.5	68	3.5	131	8.2	18	2.5	343	4.6
Hodgkin lymphoma	4	0.2	1	0.1	3	0.2	1	0.1	1	0.1	10	0.1
Non-Hodgkin lymphoma	38	2.3	56	3.5	50	2.6	48	3.0	23	3.2	215	2.9
Immunoproliferative diseases	0	0.0	0	0.0	1	0.1	1	0.1	0	0.0	2	0.0
Myeloma	2	0.1	9	0.6	12	0.6	7	0.4	4	0.6	34	0.5
Lymphoid leukemia	4	0.2	2	0.1	2	0.1	1	0.1	2	0.3	11	0.1
Myeloid leukemia	4	0.2	7	0.4	8	0.4	9	0.6	3	0.4	31	0.4
Others	41	2.4	38	2.4	52	2.7	41	2.6	13	1.8	185	2.5
Values are expressed as the number of patients and column percentage.												
^a Interval between the diagnostic dates of the most recent prior cancer and index cancer.												
^b Most recently diagnosed prior cancer.												

The most common sites of the most recent prior cancers were analyzed according to index cancer site in male patients (Table 2) and female patients (Table 3). The results for cervical cancer and corpus uterine cancer are described separately in Table A2 (Additional file). In male patients, smoking-related cancers accounted for approximately 70% of prior cancer. In female patients, smoking-related prior cancers were more common in index breast cancer patients than patients with other index cancers. Patients with cervical cancer had a significantly higher proportion of smoking-related cancers than those with corpus uterine cancer in Figure A1 (Additional file). The proportions of smoking-related prior cancers in male patients were significantly higher than in female patients for index lung, stomach, and colorectal cancer (Fig. 3).

Discussion

In this analysis of population-based cancer registry data from a major metropolitan area in Japan, we ascertained the prevalence, characteristics, and trends of prior cancer in patients newly diagnosed with one of five major cancer types. Even after accounting for the changes in age structure, the prevalence of prior cancer was found to have increased over time for all index cancer sites. These trends may be attributable to earlier detection (increase in localized cancer rates: 35.2% in 2004, 48.4% in 2015), longer survival (increase in relative survival: 42.3% in 2004, 56.2% in 2010), and expanded cancer registry coverage (decrease in the percentages of cases with death certificate notification or death certificate only) in more recently diagnosed cancer patients [15, 26, 27].

Among our subjects, patients with newly diagnosed lung cancer had the highest prevalence of prior cancer among the assessed index cancers. These differences in the prevalences of prior cancer may be indicative of underlying or shared risk factors (e.g., lifestyle habits such as smoking), and require further investigation.

Our analysis showed that the prevalence of prior cancer increased with age for all index cancers, with adolescents and young adults (aged 15–39 years) having a lower prevalence than older patients. However, our estimated prevalences of prior cancer in patients aged 65 years or older were lower than those reported in a previous study conducted in the US (lung: 18.7%, stomach: 17.8%, colorectum: 15.3%, breast: 7.4%, cervix: 13.6%, and corpus: 13.6%) [6]. This disparity may be influenced by an inherent difference in the age-standardized cancer incidence rates for all sites between the US (393.2 per 100,000 population) and Japan (285.9 per 100,000 population) [28]. In addition to variations in prior cancer prevalence, this may also be indicative of differences in genetic, lifestyle-related, and/or environmental risk factors. Differences in the prevalence of prior cancers among previous studies may also be explained in part by our non-inclusion of patients with carcinoma in situ, as this condition is generally curable and would not unduly affect survival. In addition, we did not use the recorded sequence numbers that indicate the order of cancer in individual cases, which may also have resulted in a lower apparent prevalence of

prior cancer. We had decided to exclude prior cancers at the same site as the index cancer to avoid potential double counting because we would be unable to determine if the index cancer was metastatic or primary.

The prevalence of prior cancer was found to be higher in index cancer patients with localized tumors, and prior cancers were generally diagnosed in the early localized stage across all index cancers. A possible explanation for the former observation is that patients with prior cancer would undergo regular follow-up examinations, which would support the prompt incidental detection of new tumors in the early stages. This may also contribute to the high prevalence of prior cancer for patients whose index cancers were incidentally detected during examinations for another disease. For the latter observation, we posit that patients with cancers diagnosed in the earlier stages would receive prompt treatment and have longer survival, thereby increasing the opportunities for other cancers to develop. Our results also showed that surgical treatment was often selected for prior cancer, which may be due to the high proportion of early-stage cancers.

In the present study, the prevalence of prior cancers in male patients was higher than in female patients. In particular, the proportion of male patients with two or more prior cancers was higher than female patients for new cases of lung cancer, stomach cancer, and colorectal cancer. The cumulative proportions of the most recent prior cancers diagnosed within 5 years before the index cancer diagnosis were higher in male patients (Table 2 and Table 3). These observations may be influenced by the higher incidence of cancers in men, lifestyle differences, and other sex-based differences [29].

While our data did not include information on tobacco consumption, smoking-related prior cancers were found to be less common in female patients newly diagnosed with lung, stomach, and colorectal cancer than their male counterparts. The proportions of smoking-related prior cancers were 73.1% in male patients and 53.0% in female patients among the general population of cancer patients ($P < 0.001$). This may indicate a biological difference in susceptibility to smoking-related cancer between the sexes [30, 31]. In addition, the proportion of smokers may be higher among male patients, which could have contributed to their higher prevalence of smoking-related prior cancers. Furthermore, female patients with index breast cancer had a higher proportion of smoking-related prior cancers than those with other index cancers. Although several studies have reported that smoking is associated with an increased risk of breast cancer [32–34], the evidence remains inconclusive and further research is needed to understand these findings. Patients with cervical cancer had a significantly higher rate of smoking-related cancers than those with corpus uterine cancer, likely because cervical cancer is a smoking-related cancer and has a common cause, such as smoking.

Our results also showed that patients with index breast cancer had a higher prevalence of prior corpus uterine cancer (8.3%) relative to the general cancer population (3.7%) in the OCR [15]. Similarly, patients with index corpus uterine cancer had a higher prevalence of prior breast cancer (46.6%) relative to the general cancer population (20.7%) in the OCR [15]. In addition, there was a slightly higher prevalence of prior ovary cancer in patients with index breast cancer (3.8%) than the general cancer population (2.4%) [15]. This may be indicative of hereditary cancers (such as hereditary breast and ovarian cancer syndrome, Lynch syndrome, and Li-Fraumeni syndrome) or the effects of previous treatments for prior cancers [35, 36].

Cases with prior cancer are frequently excluded from clinical research. However, the relatively high prevalence of prior cancer in newly diagnosed cancer patients suggests that their exclusion would have a substantial effect on research outcomes. Approximately 80% of previous clinical trials for lung cancer patients excluded those with prior cancer, and most trials employ a 5-year exclusion window [13, 37]. Patients with prior cancer are also sometimes excluded from observational studies due to concerns that they may affect outcome measurements [38, 39]. Our present study found that approximately 70% of lung, stomach, and colorectal cancer patients with prior cancer had a diagnostic interval of 5 years or less between the prior and index cancers. In addition, the most frequent diagnostic interval was 1–5 years for all index cancer sites. Even after excluding cancer patients with a diagnostic interval of 3 months or less, individuals who had a diagnostic interval of 5 years or less still accounted for more than 60% of patients with prior cancer. Accordingly, a considerable proportion of patients with prior cancer would not be eligible to participate in trials with a 5-year exclusion window. The impact of prior cancer on survival should be examined with scientific evidence, and cancer survivors should not be excluded from studies as a matter of course [40]. Quantifying the prevalence of prior cancer in newly diagnosed cancer patients can aid our understanding of these patients and support the formulation of comprehensive treatment strategies. For example, medical institutions, government agencies, and insurers may be able to design more efficient strategies to allocate health resources and develop treatment plans that account for cancer survivors [41–44].

This study has the following limitations. First, we created sequence numbers for multiple cancers in the OCR with the assumption that patients did not move outside of the cancer registry catchment area (i.e., Osaka prefecture). However, the number of prior cancers may be underestimated if there was substantial movement out of this area. Nevertheless, if the actual prevalence of prior cancer is actually higher, this would further reinforce our conclusions. Second, there were limitations to the types of information available in the registry, which prevented a more detailed analysis of patient background factors such as tobacco use, alcohol use, and obesity.

Our study has several strengths. Using a historic, large-scale cancer registry database, we were able to identify and characterize prior cancers in newly diagnosed cancer patients residing in a major metropolitan area in Japan. To the best of our knowledge, this is the first study to reveal recent trends in the age-adjusted prevalence of prior cancers stratified by sex.

Conclusions

This study provided globally comparable estimates of the prevalence and characteristics of prior cancer in newly diagnosed cancer patients using a long-term population-based cancer registry. The prevalence of prior cancer increased in recent years, and approximately 70% of prior cancers in male patients were potentially smoking-related. In light of the increasing number of cancer survivors worldwide, our findings suggest that a deeper understanding of the prevalence and characteristics of prior cancer in cancer patients is needed to promote more inclusive clinical research and support the expansion of treatment options.

Abbreviations

OCR: Osaka Cancer Registry

ICD-10: International Classification of Diseases, Tenth Revision

Declarations

Ethics approval and consent to participate:

This study was approved by the Research Ethics Committee of Osaka International Cancer Institute (Approval No. 18-0020; December 6, 2018) and the Kyoto University Graduate School of Medicine Ethics Committee (Approval No. R1808; December 18, 2018). The ethics committees waived the need for informed consent from the OCR-registered patients as the data were anonymized before being received by the authors. The study was performed in accordance with the ethical standards outlined in the Declaration of Helsinki.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

K. Kawakami has received research funds from Stella Pharma Corporation. The sponsor had no control over the interpretation, writing, or publication of this work. No potential conflicts of interest were disclosed by the other authors.

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Authors' contributions:

Conceptualization, data curation and methodology: A. Sato

Investigation and writing, review, and/or revision of the manuscript: A. Sato, K. Matsubayashi, T. Morishima, K. Nakata, K. Kawakami, I. Miyashiro

Supervision: K. Kawakami, I. Miyashiro

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Figures

Figure 1

Flow diagram of study subject selection

Figure 2

Trends in the age-adjusted prevalence of prior cancer between 2004 and 2015 The graphs show the age-adjusted prevalence of prior cancer in (A) male and (B) female patients according to index cancer site. P values for trend over the study period were calculated using the Cochran–Armitage test. The percentage of death certificate notification cases (DCN%) according to each diagnostic year was 26.2% in 2004–2005, 19.7% in 2006–2007, 16.5% in 2008–2009, 12.3% in 2010–2011, 9.0% in 2012–2013, and 6.0% in 2014–2015.

Figure 3

Proportions of smoking-related prior cancers according to index cancer site Smoking-related prior cancers included cancers of the mouth, pharynx, larynx, lung, esophagus, stomach, liver, pancreas, kidney, urinary bladder, colorectum, uterine cervix, and acute myeloid leukemia. Pearson’s chi-square test was used

to compare the proportions of smoking-related prior cancers between the sexes.

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