Previous Infection Positively Correlates to the Tumor Incidence Rate of Patients with Cancer

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ABSTRACT

We conducted a 7-year case–control study of people ≥30 years of age on the prevalence of influenza, gastroenteritis, hepatitis, and pneumonia infections to indirectly examine whether these infections correlated to malignant cancer formation. Data were extracted from a large medical claims database of a Japanese social health insurance system; the case group included 2,354 people with their first cancer diagnosis in the 7th year of this study, and the control group included 48,395 people with no cancer diagnosis by the 7th year. The yearly prevalence rates of influenza, gastroenteritis, hepatitis, and pneumonia infections increased throughout the study period. Age-adjusted ORs and 95% confidence intervals (CI) in cases 1 year before cancer detection were significantly higher—for influenza 1.29 (95% CI, 1.14–1.46), for gastroenteritis 1.60 (95% CI, 1.41–1.82), for hepatitis 3.38 (95% CI, 2.12–5.37), for pneumonia 2.36 (95% CI, 1.79–3.13), and for any of these four diseases 1.55 (95% CI, 1.40–1.70). In influenza infections, significant ORs were found only in the 2nd and 6th years before cancer diagnosis. For each cancer site, an increased rate of infection prior to cancer diagnosis was observed. Here, we showed that increased infections during the precancerous stage, a possible surrogate for tumor-induced immune suppression, correlated to eventual cancer development.

Introduction

Immunity and inflammation status are involved in the oncogenesis (1–4). Infection with commonly acquired pathogens such as influenza, pneumonia, pharyngitis, and sinusitis can cause an inflammation that creates a tumorigenic cellular environment (5–13). Infection with specific carcinogen-related microorganisms such as human papillomavirus (HPV), *Helicobacter pylori*, and hepatitis may cause cancer; however, there are potentially immune variations that correlate with infection and later cancer development (14–18). Cancer can evolve and be confounded by chronic inflammation caused by carcinogen exposure such as from smoking and air pollution (18, 19). Cancer development can inhibit the immune system (1, 5, 16), thus in a precancerous state, the immune system could be suppressed, risking increased infection. Thus, signs of clinical inflammation, infection, and immunity before cancer development should be investigated as they may help to identify relevant factors for the early detection and the prevention of cancer.

We conducted a case–control study to estimate the prevalence of four major infectious diseases, influenza, gastroenteritis, hepatitis, and pneumonia, as possible surrogates for observing the immune status of patients during the precancer period. The study was based on a hypothesis that people live in the similar exposure areas to these community-acquired infections, thus suppressed immunity might appear in an elevated infection rate. We compared the prevalence rate of four infectious diseases over a 7-year period between patients who developed cancer and healthy controls using a large claims-based database from Japan.

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Materials and Methods

We used the claims-based database from 2005 to 2012 of Japan Medical Data Center (JMDC; ref. 20), which contains records of all medical claims of approximately 1.60 million individuals, based on a corporate social insurance system in Japan. The database comprises data of a wide range of employees nationwide, working in middle- to large-sized companies and their families, meaning the data incorporates the individuals who have a similar social economic status. The records of all inpatient and outpatient medical claims under anonymous individual codes were obtained from the JMDC, and the disease histories and records were reviewed using the diagnostic codes of the International Classification of Diseases, 10th Revision (ICD-10). Owing to the retrospective nature of the study, the need for informed consent was waived.

The study protocol was approved by the ethics committee of Kyoto University (Kyoto, Japan; registration number, R0133).

The case–control study

We set the study design to include people ≥30 years of age in a 7-year case–control study, with 6 years of observation of prevalence rate of infection, as a possible surrogate for tumor-induced immune suppression, before malignant cancer detection. The study objective was to investigate the precancer immunity trend of patients ≥30 years of age, thus the people who were ≥30 years of age as of the 7th year of this study were included. Then, the infection trend of 6 years onward was compared between cases and controls.

The case group was people who presented with malignant cancer detection in the 7th year of the study, between July 2010 and June 2011 (2010–2011). Then, by using ICD-10 codes that were input monthly as each individual diagnosis record, which was made by the diagnosis of clinical symptoms in the database, the prevalence rate in influenza, gastroenteritis, hepatitis, and pneumonia was calculated by epidemic seasons (July to June, a summer-to-spring epidemic season including one winter epidemic season) from 2004–2005 to 2009–2010 (6 years onward 2010–2011) before the malignant cancer detection.

As this study was intended to consider the correlation between previous infection and cancer formation, the population with chronic immune–related diseases (blood and blood-forming organ diseases and

Figure 1.
Flowchart for selecting the precancerous (case) and control patient data. The flow of data extraction from the JMDC database is described. Age was recorded in the 7th year of this study. *, Male patients with breast cancer ($n = 5$) were not included because of the limitation of the number of patients.

certain disorders involving the immune mechanism, congenital malformations, deformations and chromosomal abnormalities, renal failure, chronic hepatitis, rheumatoid arthritis, systemic lupus erythematosus, diseases of the spleen, and human immunodeficiency virus) were excluded from the case–control sample data (as this could exacerbate infections). Patients who had benign tumors were also excluded.

The control group was determined by people who presented with no cancer diagnosis between January 2005 and December 2012 (8 years), which contained data from the 7-year period of the case group plus another 1 year with no cancer status. The July-to-June epidemiologic period was set to monitor the winter-based infection trend of those infectious diseases (21). The study period for the case and control groups was matched as the prevalence of infectious diseases can be influenced by the year and season.

Gastroenteritis data included both bacterial and viral gastroenteritis, but not *Helicobacter pylori* for which a different ICD-10 code from the common infectious gastroenteritis was input. The major cause of infection of gastroenteritis is known to be norovirus, which also has an epidemic peak in the winter season, similarly for influenza and pneumonia (21). Hepatitis data, the majority of which was type A, included any viral hepatitis (22). Pneumonia data included any viral and bacterial pneumonia, including influenza-induced pneumonia. Because of the data limitations, the 2004–2005 season included only data between January and June (winter to spring) of 2005, including an influenza season (January–March) and only part of the infections of the other three diseases for that year. For influenza, the 2009–2010 season was accompanied by the emergence of Pandemic A (H1N1) virus, and for gastroenteritis, the 2006–2007 season included the largest norovirus epidemic brought by the new genotype GII.4 variant (21).

Prevalence rates for each group by year

We estimated the overall prevalence of infection by the rate of the number of infected patients for influenza, gastroenteritis, hepatitis, or pneumonia, and compared yearly trend of epidemic prevalence curves for cases and controls. If the patients had the record of the diagnosis of infection more than one time during the year, the frequency of infection was recorded as once for each infectious disease for the year to avoid counting a series of diagnoses. χ^2 analysis was used to compare the prevalence rate between the case and control groups. Because the single control group was compared repeatedly to each infection group at many time points, a Benjamini–Hochberg correction was applied to address multiplicity and adjust the P values. P values with adjusted significance <0.05 were considered statistically significant. Statistical analysis was performed using SPSS v21 (IBM Corporation).

ORs using logistic regression analysis

We estimated the overall yearly age-adjusted ORs before cancer detection by means of multivariate logistic regression analysis. Sex was not found to be significantly associated in the most of cancer sites (thus sex was not included in the multivariate regression models in most of the cancer sites.) The significance of age-adjusted ORs was tested for each year for all cancers, and also in the 6th year (1 year before the cancer detection) for cancer sites [head and neck, digestive and gastrointestinal (except stomach), stomach, liver, respiratory and thoracic, breast (female), germ cell (male/female), genitourinary, endocrine, hematologic, blood, bone, and bone marrow; unknown and other cancer (including skin and eye), and the control group]. Breast (female) and germ cell (female) were compared with the female

Table 1. Basic population characteristics.

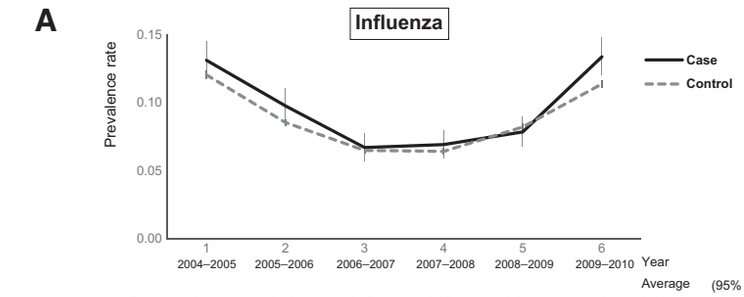
	Case group	Control group
N (men/women)	2,354 (1,843/511)	48,395 (37,779/10,616)
Average age (95% CI)	45.1 (44.8–45.4)	43.9 (43.8–43.9)
Median age (minimum–maximum)	45 (30–72)	43 (30–74)
SD	8.1	7.9

Note: Age was recorded in the 7th year of this study.
Abbreviation: CI, confidence interval.

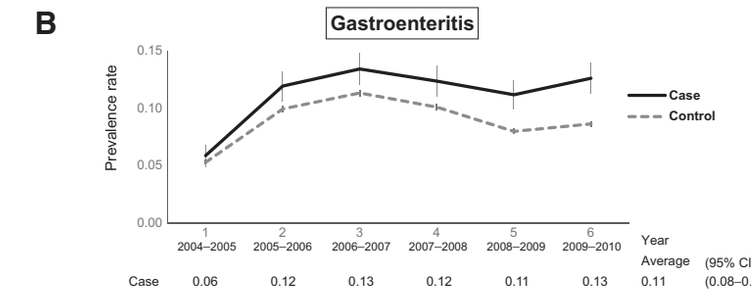
Table 2. Cancer site information.

Cancer site	*n* (men/women) (proportion)
Head and neck	399 (330/69) (0.169)
Digestive and gastrointestinal (except stomach)	583 (473/110) (0.248)
Stomach	346 (295/51) (0.147)
Liver	99 (85/14) (0.042)
Breast (female)	60 (0.025)
Respiratory and thoracic	288 (253/35) (0.122)
Germ cell	271 (169/102) (0.115)
Genitourinary	182 (142/40) (0.077)
Endocrine	30 (20/10) (0.013)
Hematologic, blood, bone, and bone marrow	41 (31/10) (0.017)
Unknown and other[a]	55 (45/10) (0.023)

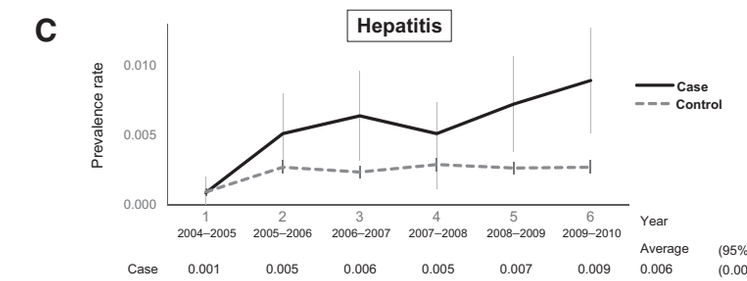
[a]Unknown and other, including eye and skin cancers.



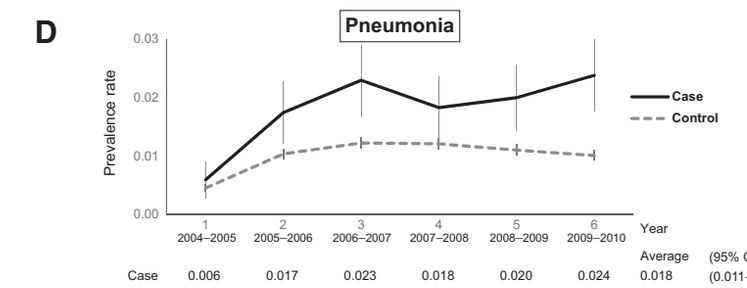
	2004–2005	2005–2006	2006–2007	2007–2008	2008–2009	2009–2010	Average	(95% CI)
Case	0.13	0.10	0.07	0.07	0.08	0.13	0.10	(0.08–0.13)
Control	0.12	0.09	0.07	0.06	0.08	0.11	0.09	(0.06–0.11)
Absolute increase (% increase) in prevalence rate in cases relative to controls	0.01 (8.3)	0.01 (11.7)	0 (0)	0.01 (15.6)	0 (0)	0.02 (17.6)	0.01 (9.47)	(0–0.02) (1.1–17.8)
Corrected *P*	0.238	0.118	0.679	0.505	0.637	*0.017*		



	2004–2005	2005–2006	2006–2007	2007–2008	2008–2009	2009–2010	Average	(95% CI)
Case	0.06	0.12	0.13	0.12	0.11	0.13	0.11	(0.08–0.14)
Control	0.05	0.10	0.11	0.10	0.08	0.09	0.09	(0.07–0.11)
Absolute increase (% increase) in prevalence rate in cases relative to controls	0.01 (11.1)	0.02 (20.2)	0.02 (18.5)	0.02 (22.4)	0.03 (40.0)	0.04 (46.1)	0.02 (26.4)	(0.01–0.04) (12.1–40.7)
Corrected *P*	0.215	*0.002*	*0.003*	*0.001*	*<0.001*	*<0.001*		



	2004–2005	2005–2006	2006–2007	2007–2008	2008–2009	2009–2010	Average	(95% CI)
Case	0.001	0.005	0.006	0.005	0.007	0.009	0.006	(0.003–0.009)
Control	0.001	0.003	0.002	0.003	0.003	0.003	0.003	(0.002–0.003)
Absolute increase (% increase) in prevalence rate in cases relative to controls	0 (0)	0.002 (74.5)	0.004 (171.3)	0.002 (104.4)	0.004 (152.4)	0.006 (223.4)	0.003 (121.0)	(0.001–0.006) (38.3–203.7)
Corrected *P*	0.925	*0.037*	*<0.001*	*0.032*	*<0.001*	*<0.001*		



	2004–2005	2005–2006	2006–2007	2007–2008	2008–2009	2009–2010	Average	(95% CI)
Case	0.006	0.017	0.023	0.018	0.020	0.024	0.018	(0.011–0.025)
Control	0.005	0.010	0.012	0.012	0.011	0.010	0.010	(0.007–0.013)
Absolute increase (% increase) in prevalence rate in cases relative to controls	0.001 (30.8)	0.007 (67.9)	0.011 (87.5)	0.006 (51.1)	0.009 (81.3)	0.014 (135.9)	0.008 (75.8)	(0.004–0.012) (38.0–113.5)
Corrected *P*	0.327	*0.002*	*<0.001*	*0.010*	*<0.001*	*<0.001*		

Figure 2.

Prevalence rate of infections over the 6 years prior to cancer detection. The yearly epidemic curves for the case and control groups depicted by the prevalence rates (calculated by the number of infected patients within each group) for influenza (**A**), gastroenteritis (**B**), hepatitis (**C**), and pneumonia (**D**). *P* values from χ^2 tests were adjusted for multiple comparisons using the Benjamini–Hochberg FDR correction. $P < 0.05$ was considered statistically significant (indicated in italic). The 2004 to 2005 season was from January to June 2005 due to the data availability that included an influenza season (January to March) and part of infections of the other three diseases for the year.

control, and germ cell (male) was compared with the male control. Statistical analysis was performed using SPSS v21 (IBM Corporation). The level of significance was set at 5%.

Results

Basic characteristics of the case and control groups

The case group included 2,354 (men/women: 1,843/511) and the control group included 48,395 (men/women: 37,779/10,616) subjects (**Fig. 1**; **Table 1**). The population characteristics showed that the age of each group was similar, although patients were slightly younger in the control group than in the case group.

In the case group, the three largest cancer sites were digestive and gastrointestinal (except the stomach; $n = 583$); head and neck ($n = 399$); and stomach ($n = 346$; **Table 2**). This was followed by respiratory and thoracic ($n = 288$); germ cell ($n = 271$, male/female: 169/102), genitourinary ($n = 182$); liver ($n = 99$); breast (female; $n = 60$); hematologic, blood, bone, and bone marrow ($n = 41$); endocrine ($n = 30$); and unknown/other (including eye and skin; $n = 55$).

Differences in the infection rate between the case and control groups

In 6 years before cancer detection, the yearly prevalence rates of influenza, gastroenteritis, hepatitis, and pneumonia infections in the case group were relatively higher than that of the control group (**Fig. 2**). The prevalence rate of the control group in hepatitis and pneumonia infections were similar in the study period, which suggested susceptible rates for these infections in a healthy cohort were similar over year.

The difference in the yearly prevalence rate between the case and control groups was largest in the 6th year, 1 year before cancer detection, suggesting that the largest change in immunity may occur just before cancer detection (**Fig. 2**). In the 6th year, the control group recorded a prevalence rate of 0.11 [95% confidence interval (CI), 0.11–0.12] for influenza, 0.09 (95% CI, 0.08–0.09) for gastroenteritis, 0.003 (95% CI, 0.002–0.003) for hepatitis, and 0.010 (95% CI, 0.009–0.011) for pneumonia infections. The case group recorded a prevalence rate of influenza infections in the 6th year, as 0.13 (95% CI, 0.12–0.15), with an absolute increase of 0.02 (18.0%) to that of the control group. In gastroenteritis infections, the prevalence rate in the 6th year was 0.13 (95% CI, 0.11–0.14) with an increase of 0.04 (46.1%) compared with the control group. The prevalence rate of hepatitis infections was 0.009 (95% CI, 0.005–0.013; 232.1% of the control rate) and of pneumonia infections was 0.024 (95% CI: 0.018–0.030; 135.9% of the control rate), which were also increased compared with the control group.

Logistic regression analysis revealed that the age-adjusted ORs in all cancers increased each year (**Table 3**). ORs for infection to any of the four infectious diseases were similar between the 2nd and 5th years and then increased in the 6th year (age-adjusted OR, 1.55; 95% CI, 1.40–1.70). In the 6th year, OR was significantly higher for infection to each of the four infectious diseases, with the highest OR for hepatitis infections (age-adjusted OR, 3.38; 95% CI, 2.12–5.37). In influenza infections, significances of ORs in cases were found in only the 2nd and the 6th years before cancer detection (**Table 3**).

In **Fig. 3**, the ORs of infection between the case and the control groups for each cancer site during the period 1 year before cancer detection are shown. In influenza infections, the OR was higher in germ cell (male) cancer (OR, 2.01; 95% CI, 1.31–3.09), compared with the ORs in the other cancer cites (**Fig. 3**). In gastroenteritis infections, the OR was relatively high for the most of cancer sites [OR: 2.03, 95% CI: 1.13–3.64 for germ cell (female); OR: 2.01, 95% CI: 1.54–2.62 for head and neck; and OR: 2.00, 95% CI: 1.59–2.52 for digestive and gastrointestinal (except stomach)]. Stomach cancer had a larger OR in pneumonia (OR, 3.59; 95% CI, 2.04–6.30) compared with other infectious diseases. In hepatitis infections, hematologic, blood, bone, and bone marrow cancers had the highest OR (OR, 19.04; 95% CI, 4.55–79.67), followed by liver, breast (female), and genitourinary (OR, 11.60; 10.57; and 6.32; respectively) in the subject period.

Discussion

This study considered the link between increases in infection prevalence and the formation of malignant cancer. Our study indicated a greater rate of infection for influenza, gastroenteritis, hepatitis, and pneumonia before malignant cancer detection. The four studied diseases showed increased rate of infections in eventual cancer patients occur from 6 to 7 years onwards. These findings suggested that the annual assessment of these four infectious diseases could potentially be useful in examining the precancerous status for adults. Likewise, an increase of infection could be a sign of cancer development and inclusion of clinical immune suppression assays may further help early cancer detection. ORs of any infection in the eventual cancer patients were similar between the 2nd and 5th years. These results suggested that better infection-based

Table 3. Yearly age-adjusted ORs for infection in all cancers over the 6 years prior to cancer detection.

Yearly OR (95% CI)	1st	2nd	3rd	4th	5th	6th
Any disease	1.16[a] (1.04–1.29)	1.31[a] (1.18–1.45)	1.31[a] (1.18–1.45)	1.27[a] (1.14–1.41)	1.34[a] (1.20–1.49)	1.55[a] (1.40–1.70)
Influenza	1.13 (1.00–1.28)	1.20[b] (1.05–1.39)	1.08 (0.91–1.27)	1.15 (0.98–1.36)	1.01 (086–1.17)	1.29[a] (1.14–1.46)
Gastroenteritis	1.16 (0.97–1.38)	1.29[a] (1.13–1.47)	1.26[a] (1.11–1.42)	1.30[a] (1.15–1.48)	1.52[a] (1.33–1.73)	1.60[a] (1.41–1.82)
Hepatitis	0.95 (0.23–3.91)	1.93[b] (1.07–3.50)	2.79[a] (1.63–4.79)	1.96[b] (1.11–3.46)	2.82[a] (1.70–4.69)	3.38[a] (2.12–5.37)
Pneumonia	1.25 (0.73–2.15)	1.67[a] (1.21–2.30)	1.89[a] (1.43–2.51)	1.51[a] (1.11–2.07)	1.80[a] (1.33–2.44)	2.36[a] (1.79–3.13)

[a]$P < 0.01$.
[b]$P < 0.05$.

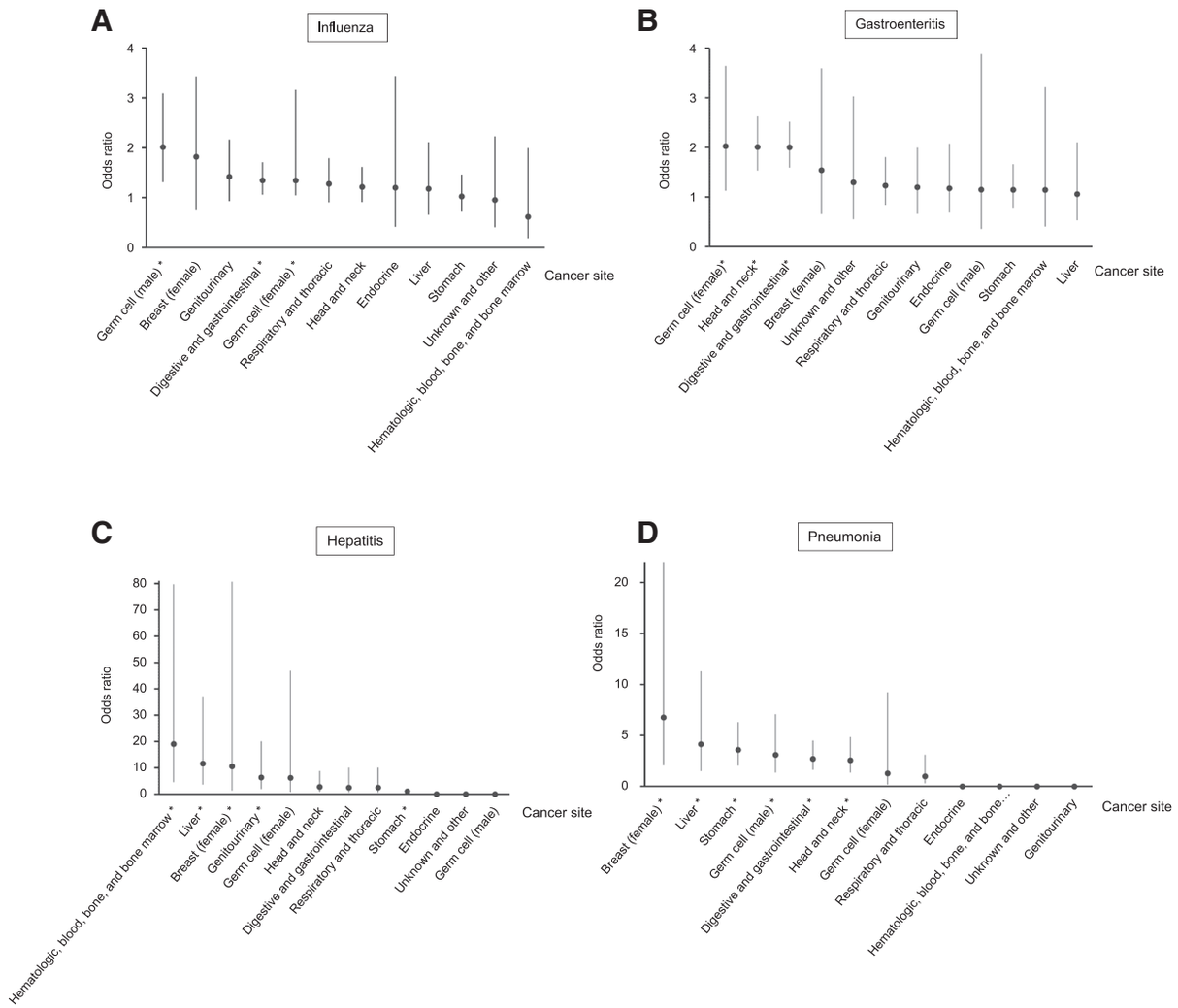


Figure 3.

ORs of infection by cancer site 1 year before cancer detection. ORs for the prevalence rate between the case (by each cancer site) and the control groups 1 year before cancer detection for influenza (**A**), gastroenteritis (**B**), hepatitis (**C**), and pneumonia (**D**) are shown. Breast (female) and germ cell (female) were compared with the female control group, and germ cell (male) was compared with the male control. ORs were adjusted by age, sex, or age and sex (or none of these) after checking the significance of each of these variables through univariate logistic regression analysis, that is, sex was included in the multivariate regression model for influenza and gastroenteritis infections for stomach, digestive, and gastrointestinal and respiratory and thoracic cancer sites. $P < 0.05$ was considered significant and indicated with *. There was no infection history of hepatitis for patients of endocrine, unknown and other, or germ cell (male) cancers in the 6th year. Similarly, for pneumonia infections, no infection history was found for patients of endocrine, hematologic, blood, bone, and bone marrow, unknown and other, or genitourinary cancers.

immune responses are linked to the prevention of cancer. Further study is needed to clarify these trends.

We used the infection status of patients as a surrogate for immune suppression. The patients here likely had equal exposure to common infectious agents; we hypothesized that becoming symptomatic after infection was dependent on an individual's immune status. The lack of change in the infection rate in the control group, for example, in hepatitis and pneumonia, suggested that the number of symptomatic people to each infection was consistent and the increase in the infection rate in eventual cancer patients was due to immune suppression compared with the healthy cohort.

In the 6th year of our study, there were higher ORs for all four infectious diseases in most of cancer sites, suggesting immune suppression during premalignancy for various cancer types. As the number of cases for each cancer site was limited, it was difficult to correlate the occurrence of cancer in a specific area to a specific infection. Infection to hepatitis B and C viruses may cause liver cancer (15); however our limited dataset could not reveal relationships between these infections and cancer at a specific site. For cancers that are relatively rare, such as endocrinal and hematologic, blood, bone, and bone marrow cancers, the calculation of prevalence rate of infection may have been less reliable for making a comparison; thus, further analysis is needed. However, the results suggest that cancer occurrence may be linked to immune suppression.

Larger increases and greater ORs were found in cases with gastroenteritis, hepatitis, and pneumonia infections compared with

those with influenza. This may have been because of the difference of infectivity between influenza and these three infectious diseases. Influenza is a common respiratory infection with a high rate of infection within only a few months, thus influenza generally has much larger sensitivity than gastroenteritis, hepatitis, and pneumonia. Thus, subjects tend to be more susceptible to influenza, even in the control group. Likewise, increased infection or increased sensitivity in eventual cancer patients might have been more obvious in gastroenteritis, hepatitis, and pneumonia infections compared with influenza infections. Similarly, less differences in the infection rate of influenza between the eventual cancer patients and healthy patients may appear during low epidemic seasons, for example, the 3rd to the 5th year in this study, when the prevalence of influenza in cases was lower than 0.10. In the 6th year (2009–2010 season), the epidemic of the new swine influenza virus [Pandemic A (H1N1)] occurred, thus the increase of infection might have been more visible than other influenza seasons. As pneumonia case could have been caused by influenza virus, the increased prevalence of pneumonia in cases may have indicated an increase of intensive influenza infections.

Few studies have addressed infection in the precancer period (5–13). Most consider infection in the precancer period of nonsolid tumors such as lymphoma, chronic lymphocytic leukemia (CLL), and myeloma; these studies discuss infection itself as the oncogenic trigger (3, 6–13). One study observed monoclonal (M-) protein, and changes in free and light chains (FLC) and γ-globulin, which are the immune-related compositions of blood and thought to be a byproduct of CLL, for 9.8 years before CLL diagnosis; up to 44% of 109 patients with CLL had M-proteins and different FLC ratios, and 3 years before the CLL diagnosis hypogammaglobulinemia was detected. Infection was suspected as a potential cause of this inflammatory response and associated with CLL formation (1). Respiratory infections, such as influenza and pneumonia, may be linked to oncogenic inflammation (9, 10). CLL was also diagnosed after pneumonia infection (OR, 1.4), and the OR increased to 1.6 during the 4 years before CLL diagnosis. Sinusitis, pharyngitis, bronchitis, cellulitis, tuberculosis, herpes zoster, and other community acquired infection induce tumorigenic inflammation (6, 7, 11–13); increased ORs were found prior to blood, bone, and lymphoma-related cancers. Therefore, further studies are needed for solid tumors to clarify our results.

Owing to the limitations of our data and the absence of any definitive index that could have been used in hematologic experiments and testing, whether infection or immunity is the most likely inflammatory cause for later tumorigenicity remains unclear. Cancer could occur when inflammation becomes chronic. For instance, although people can have HPV infection, the development of cervical cancer through inflammation post-HPV infection is thought to be dependent on immunity (18). Chronic infection only accounts for 20% of cancer causes, and overall, cell-mediated cancer development is still unclear (4). Any innate immunity disruption brought about by exposure to chemocarcinogens such as smoking, drug use, environmental pollution, and chronic or genetic conditions could be a factor that may induce cancerous inflammation (16–18). Our data provided limited information on other comorbidities, that is, exposure, genetics, or lifestyle. There are other possible precancerous indicators that might lead to oncogenesis, such as immune suppression which can be monitored by the composition of immunity-related cells such as Th, Toll-like receptor, and B cells (2, 23–26). In this precancer period, overall infection generally increases as a consequence of immune suppression (4, 5). In addition, aging is also a factor that causes immune suppression (4), which suggests the younger patients that eventually get cancer may potentially have differing levels of immune suppression compared with the healthy cohort.

One limitation of this study is that the disease trends were recorded using ICD-10 codes, thus these characteristics may have been dependent on the clinician's diagnosis for each cause (e.g., the differentiation between hepatitis A and C). We also only extracted the first cancer diagnosis for each patient, and as the observation period was limited to 8 years, we may have missed further cancer diagnoses. In this study, the precancer period was set before diagnosis of cancer; however, if there has been a delay in diagnosis, the precancer and cancer periods may have overlapped. The data also did not include information on the grade or stage of tumors, which might be potentially important to estimate each precancerous period. The study design was set to monitor the June-to-July infection trend to observe the winter-based infections; however, whether there had been any seasonal trend of each cancer formation or other setting of epidemiologic period is unknown. A series of diagnoses of infection over the years may have increased the prevalence rate of infection. Moreover, patients with infection who did not visit the hospital might have been overlooked. Influenza vaccination status may prevent infection, although a patient's influenza vaccination record was not available in our dataset. Patients who feel unwell, potentially because of cancerous status, tend to see doctors more often. Although our study considered four major infections, analysis of other infections and the timing of infection before malignant cancer detection, which can potentially be a factor for later cancer development, remains to be studied. Cancer can occur through a lifespan, thus a longer study is necessary to clarify the relationship between infections, immune suppression, and cancer formation. Our data suggest that immune suppression and increased infection could occur during the precancer period. Further studies are needed to clarify these precancer trends.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S. Inaida, S. Matsuno
Development of methodology: S. Inaida, S. Matsuno
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Inaida
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Inaida
Writing, review, and/or revision of the manuscript: S. Inaida
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Inaida
Study supervision: S. Inaida, S. Matsuno

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References

1. Tsai HT, Caporaso NE, Kyle RA, Katzmann JA, Dispenzieri A, Hayes RB, et al. Evidence of serum immunoglobulin abnormalities up to 9.8 years before diagnosis of chronic lymphocytic leukemia (CLL): a prospective study. Blood 2009;114:4928–32.

2. Khan AA, Khan Z, Warnakulasuriy S. Cancer-associated toll-like receptor modulation and insinuation in infection susceptibility: association or coincidence? Ann Oncol 2016;27:984–97.
3. Mackenzie JS, Houghton M. Influenza infections during pregnancy: association with congenital malformations and with subsequent neoplasms in children, and potential hazards of live virus vaccines. Bacreriol Rev 1974; 38:356–70.
4. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.
5. Kneale GW, Stewart AM. Pre-cancers and liability to other diseases. Br J Cancer 1978;37:448–57.
6. Anderson LA, Landgren O, Engels EA. Common community acquired infections and subsequent risk of chronic lymphocytic leukaemia. Br J Haematol 2009;147: 444–9.
7. Kristinsson SY, Gao Y, Björkholm M, Lund SH, Sjöberg J, Caporaso N, et al. Hodgkin lymphoma risk following infectious and chronic inflammatory diseases: a large population-based case-control study from Sweden. Int J Hematol 2015;101:563–8.
8. Titmarsh GJ, McMullin MF, McShane CM, Clarke M, Engels EA, Anderson LA. Community-acquired infections and their association with myeloid malignancies. Cancer Epidemiol 2014;38:56–61.
9. Landgren O, Rapkin JS, Caporaso NE, Mellemkjaer L, Gridley G, Goldin LR, et al. Respiratory tract infections and subsequent risk of chronic lymphocytic leukemia. Blood 2007;109:2198–201.
10. Fedrick J, Alberman ED. Reported influenza in pregnancy and subsequent cancer in the child. Br Med J 1972;5812:485–8.
11. Landgren O, Gridley G, Check D, Caporaso NE, Morris Brown L. Acquired immune-related and inflammatory conditions and subsequent chronic lymphocytic leukaemia (CLL). Br J Haematol 2007;139: 791–8.
12. McShane CM, Murray LJ, Engels EA, Landgren O, Anderson LA. Common community-acquired infections and subsequent risk of multiple myeloma: a population-based study. Int J Cancer 2014; 134:1734–40.
13. Goldin LR, Landgren O, Kristinsson SY, Björkholm M, Paltiel O. Infection in infancy and subsequent risk of developing lymphoma in children and young adults. Blood 2011;117:1670–2.
14. de Martel C, Franceschi S. Infections and cancer: established associations and new hypotheses. Crit Rev Oncol Hematol 2009;70:183–94.
15. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health 2016;4:e609–16.
16. Hagerling C, Casbon AJ, Werb Z. Balancing the innate immune system in tumor development. Trends Cell Biol 2015;254:214–20.
17. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44.
18. Eldridge RC, Pawlita M, Wilson L, Castle PE, Waterboer T, Gravitt PE, et al. Smoking and subsequent human papillomavirus infection: a mediation analysis. Ann Epidemiol 2017;27:724–30.
19. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med 2010;49:1603–16.
20. Kimura S, Sato T, Ikeda S, Noda M, Nakayama T. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. J Epidemiol 2010;20:413–9.
21. Inaida S, Shobugawa Y, Matsuno S, Saito R, Suzuki H. Delayed norovirus epidemic in the 2009–2010 season in Japan—potential relationship with intensive hand sanitizer use for pandemic influenza. Epidemiol Infect 2016; 144:2561–7.
22. Acute viral hepatitis, Japan. April-December 1999. Wkly Epidemiol Rec 2000;75: 190–2.
23. Balkwill FR, Mantovani A. Cancer-related inflammation: common themes and therapeutic opportunities. Semin Cancer Biol 2012;221:33–40.
24. Rakoff-Nahoum S, Medzhitov R. Toll-like receptors and cancer. Nat Rev Cancer 2009;9:57–63.
25. El-Omar EM, Ng MT, Hold GL. Polymorphisms in toll-like receptor genes and risk of cancer. Oncogene 2008;27:244–52.
26. Vijay K. Toll-like receptors in immunity and inflammatory diseases: past, present, and future. Int Immunopharmacol 2018;59:391–412.