Effectiveness of 23-valent pneumococcal polysaccharide vaccine on elderly long-term cancer survivors: a population-based propensity score matched cohort study

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ABSTRACT

Objective The Advisory Committee on Immunization Practices in 2012 recommended the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for adults with high risk of pneumonia. However, its effectiveness in cancer survivors has not been investigated. Our aim was to investigate the effectiveness of PPSV23 in these patients.

Design Population-based matched cohort study.

Setting Claim data were obtained from 1 million people registered with the National Health Insurance Research Database in 1996, and followed to 2010. People aged ≥75 years are eligible for receiving PPSV23 vaccination in Taiwan since 2007.

Participants Among the 30 249 patients with cancer, 6784 patients were 75 years or older eligible for PPSV23 vaccination. Among them, 1887 survived 5 or more years (ie, cancer survivors) after cancer diagnosis. We identified 377 cancer survivors who received PPSV23. A total of 754 propensity score matched unvaccinated patients were randomly selected.

Intervention PPSV23 vaccination.

Primary outcome measures The primary outcome was pneumonia hospitalisation. Potential confounders include influenza vaccination, vaccination period, cancer treatment modalities, comorbidities and socioeconomic variables.

Results After 2 years of follow-up, vaccinated patients had a significantly lower incidence rate of pneumonia hospitalisation at 73.66 per 1000 person-years (PYs), compared with 111.32 per 1000 PYs for unvaccinated patients. Additionally, the prevalence for pneumonia hospitalisation frequency of >0–1, >1–2, >2–3 and >3 times per PY was all consistently lower in the vaccinated group (6.63% vs 9.28%, 1.86% vs 2.52%, 0.80% vs 1.59% and 0.27% vs 0.53%, respectively). After adjustment for covariates, PPSV23 vaccine was significantly associated with reduced pneumonia hospitalisation risk, with an adjusted incidence rate ratio of 0.695 (p = 0.030). While the cumulative pneumonia incidence was also significantly lower in the vaccinated patients (p = 0.027), the overall survival time was similar (p = 0.138).

Conclusions PPSV23 vaccination was associated with a significantly reduced rate of pneumonia hospitalisation in long-term cancer survivors.

INTRODUCTION

A recent report by the American Cancer Society, in collaboration with the National Cancer Institute, revealed that the number of cancer survivors is growing. There are currently more than 15.5 million cancer survivors in the USA—many of them are long-term survivors.
survivors, living 5, 10 or more years after receiving their diagnosis. In fact, the majority of survivors received their diagnosis 5 or more years ago. The report also found that 47% of cancer survivors, almost half, are 70 years old or older, and only 5% are younger than 40. This is due partly to improved treatments that help people with cancer live longer; improvements in early detection, like faecal occult blood test screening, Pap smear screening and mammography screening, which allow physicians to find cancer earlier when it is easier to treat; and a growing and ageing population.

One of the major causes for mortality in patients with cancer is pneumonia. Pneumonia is associated with increased mortality, number and severity of complications, length of hospitalisation and hospital-related costs in patients with cancer. Cancer treatment modalities (surgery, radiotherapy, chemotherapy and targeted therapies) can impair the immune system and thereby increase susceptibility to pneumonia. Anticancer therapies may also affect the immune response to vaccination, with their ability to prevent development of an adequate immune response to influenza or pneumococcal pneumonia vaccine remaining controversial. A previous study showed a significantly weaker serum antibody response to influenza virus vaccine in patients receiving cancer chemotherapy. However, our previous study demonstrated the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in patients with lung cancer even when given during the active anticancer treatment period.

In general, older people are more susceptible to pneumonia and their immunosenescence may result in the low efficacy of vaccination. In some long-term cancer survivors with chronic comorbid liver and renal dysfunction caused by previous cancer treatments, such as repeat radiotherapy to the liver, there is the added risk of long-term neutropaenia. Because of the high mortality rate associated with some cancers and the low cost–benefit ratio of vaccination in patients newly diagnosed with cancer, if they die early due to cancer, our aim in this study was to investigate the effectiveness of PPSV23 in elderly patients who survived cancer for at least 5 years after initial cancer diagnosis.

**MATERIALS AND METHODS**

**Sources of data**

The data were obtained from the National Health Insurance Research Database (NHIRD) and released for research purposes by the National Health Research Institutes (NHRI), Taiwan. The NHIRD contains medical claims data for approximately 90% of Taiwanese people. To ensure the accuracy of the claims, the National Health Insurance Administration (NHIA) performs quarterly expert reviews on every 50 to 100 ambulatory and inpatient claims filed by each medical institution. False diagnostic reports are liable to severe penalties from the NHIA. Information obtained from NHIRD is considered both complete and accurate. The PPSV23 vaccine code used in this study is a drug code rather than diagnosis code.

All the claims data of one million people (approximately 4% of the total Taiwanese population) who registered with the National Health Insurance Program in 1996 were obtained for the period 1996–2010. The database contained ambulatory care claims, inpatient hospitalisation claims, a registry of beneficiaries which recorded socioeconomic data and a registry of catastrophic illness. In Taiwan, the NHIA issues catastrophic illness certificates to all patients with pathologically confirmed malignant tumours.

**Patient and public involvement**

This is a database study using NHIRD. No patients or public were involved in setting out the research question or developing the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients or public were asked to advise on interpretation or writing up of results, nor was the burden of the interventions on patients assessed. The results of the research were not disseminated to those study patients.

**Patients and the study groups**

Between 1996 and 2010, a total of 30 249 patients with cancer were identified from inpatient or outpatient claims and validated in the catastrophic illness registry. In Taiwan, the policy of administering PPSV23 free of charge started in 2007 for people ≥75 years of age. Therefore, we limited our sample to those over 75 years old. The flow chart of study subjects’ enrolment is presented in figure 1. Additionally, to include only long-term survivors (subjects who survived at least 5 years after cancer diagnosis), we excluded patients with cancer diagnosed after 2002.

In all, 1887 patients were elderly long-term survivors and 507 received PPSV23. The number of patients receiving PPSV23 vaccination during specific periods is shown in table 1. Most patients (387 patients, 76.3%) received PPSV23 from October 2008 to December 2008. We defined the ‘vaccination period’ as October 2008 to December 2008, to reduce bias associated with the competing risk of death, that is, people dying too early to receive the vaccination. All patients and controls survived to the end of the vaccination period, that is, 1 January 2009, at least. Therefore, we excluded 556 patients and controls who died before 2009 and 109 patients who received PPSV23 outside this vaccination period (figure 1). The follow-up period for both the vaccinated and unvaccinated groups started on 1 January 2009 and ended on the date of withdrawal from the NHI programme, death or study termination (31 December 31 2010).

Considering the relatively low vaccination rate, self-selection for vaccination may exist. To reduce the bias of confounding by indication that people with a history of frequent pneumonia would have a greater tendency...
to receive vaccination than the general population, we propensity score matched each vaccinated patient to two unvaccinated patients. The propensity score was calculated from the age on 1 January 2009, gender, and number of pneumonia hospitalizations over the previous 3 years with ratio of 1:2 to reduce confounding by indication.

Figure 1 Study design flowchart. *Free 23-valent pneumococcal polysaccharide vaccine (PPSV23) policy started in 2007 in Taiwan for people aged ≥75 years. **Patients with cancer who survived at least 5 years after cancer diagnosis. #The ‘vaccination period’ is set to reduce the bias of competing risk of death, that is, by excluding people who did not receive vaccination because they died too early to receive vaccination. All cases and controls survived at least until the end of the defined vaccination period, 1 January 2009. ##To reduce confounding by indication, propensity score matching was used. Non-matched cases or controls were excluded.

| Vaccination period    | Number of vaccination | Percentage |
|-----------------------|-----------------------|------------|
| October 2007 - December 2007 | 43                    | 8.5        |
| January 2008 - March 2008   | 2                     | 0.4        |
| April 2008 - June 2008     | 1                     | 0.2        |
| October 2008 - December 2008 | 387                 | 76.3       |
| October 2009 - December 2009 | 52                   | 10.3       |
| October 2010 - December 2010 | 22                   | 4.3        |
| Total                  | 507                   | 100        |
both invasive pneumonia and non-invasive pneumonia and excluded viral pneumonia, pneumonia due to bacteria other than Streptococcus pneumoniae and influenza. Clinically, patients with a pneumonia patch or positive sputum culture would be diagnosed as having pneumonia and receive treatment. In the database of our study, less than 5% of the all-cause pneumonia cases were invasive. The pneumonia in most of our hospitalised patients was non-invasive, and this finding was the subject of previous controversy regarding the vaccine’s effectiveness. The potential confounders in this study were age, gender, influenza vaccination, vaccination period, cancer treatment modalities, comorbidity and sociodemographic variables (table 2). Cancer treatment modalities were adjusted, including surgery, radiotherapy, chemotherapy and targeted therapy. Additionally, because most patients received both the PPSV23 and influenza vaccines, the influenza vaccination status was also considered as a potential confounder and adjusted in the analysis.

A number of major illnesses that could affect susceptibility to pneumonia were included in our analysis, including coronary heart disease, congestive heart failure (CHF), asthma, interstitial lung disease, chronic obstructive pulmonary disease (COPD), liver cirrhosis, diabetes mellitus (DM), chronic renal failure, stroke and dementia (see online supplementary etable 1). These data were obtained from both ambulatory care and inpatient hospitalisation claims for the period 1996–2008.

To reduce confounding by indication, as people with higher health awareness would be more likely to be vaccinated than the general population, we also adjusted for several socioeconomic variables, including urbanisation level, geographic region and the monthly income-based insurance premium. We grouped patients on the basis of urbanisation level (ie, urban, suburban and rural) according to the proposed classification scheme of Liu et al. We adjusted for urbanisation level because of the distinct urban–rural difference in medical care accessibility in Taiwan.

Statistical analysis
We first compared characteristics between the two study groups. The incidence rate of pneumonia hospitalisation was calculated as the ratio of the number of pneumonia hospitalisations to the number of person-years (PYs) of follow-up, to reduce bias that different observation time among patients, that is, patients died early due to any cause and had no or less chance to have a pneumonia. The follow-up period for both study groups started on 1 January 2009, and ended on either the date of withdrawal from the NHI programme, death or study termination (31 December 2010). Since the incidence rate followed a Poisson distribution, we used a multivariate log-linear Poisson regression model to calculate the incidence rate ratios (IRRs) with all covariates included. We also performed multivariate analyses with only significant covariates in the univariate model included, and with/without influenza vaccination status included (influenza vaccination status was not significant in the univariate analysis model), and these results were listed in the online supplementary data. The Kaplan-Meier method was used to estimate cumulative incidence of pneumonia hospitalisation and overall survival time. Two statistical packages (SAS (V.9.2; SAS Institute, Cary, North Carolina, USA) and SPSS (V.12, SPSS, Chicago, Illinois, USA)) were used to analyse the data. A two-sided p value of <0.05 was considered statistically significant.

RESULTS
Distribution of demographic characteristics and comorbidities, including pneumonia hospitalisation history, for the two groups is shown in table 2. PPSV23 (vaccinated) and PPSV23 (unvaccinated) long-term cancer survivors had similar mean±SD age, which was 82.69±4.08 and 82.54±4.20 years, respectively, and distribution of cancer sites, which commonly were the colon, prostate, rectum, uterine cervix, stomach, bladder, breast, lung and liver (see online supplementary etable 2).

A total of 214 episodes of pneumonia hospitalisation occurred over an observation period of 2080.98 PY in 1131 patients. The pneumonia incidence rate was significantly lower in vaccinated patients (73.66 per 1000 PY; 95% CI 53.64 to 93.68) than unvaccinated patients (117.82 per 1000 PY; 95% CI 99.68 to 135.96; table 3), and a higher proportion of vaccinated than unvaccinated patients had no pneumonia hospitalisation (90.45% vs 86.07%; table 4). On the other hand, proportions of patients who had 0–1, 1–2, 2–3 and >3 pneumonia hospitalisations per PY were all consistently lower in the vaccinated than unvaccinated group (6.63% vs 9.28%, 1.86% vs 2.52%, 0.80% vs 1.59% and 0.27% vs 0.53%, respectively).

Our analysis after adjustment for confounders shows that PPSV23 vaccination significantly reduced pneumonia hospitalisation risk, with an IRR of 0.695 (p=0.030; table 5), and that adjusted IRR (aIRR) was higher in men (1.389, p=0.053) than women. The incidence rate of pneumonia hospitalisation was increased by certain cancer treatment modalities such as radiotherapy (aIRR=1.771, p<0.001) and targeted therapy (aIRR=2.943, p<0.001) and was not affected by other modalities such as surgery and chemotherapy.

PPSV23 and influenza vaccinations were given from around October to December every year in Taiwan. There was no difference in the periods of both vaccine administrations between PPSV23 vaccinated and PPSV23 unvaccinated groups (table 2). In both univariate and multivariate analysis, all covariates adjusted, influenza vaccination had no significant effect on pneumonia hospitalisation (IRR=1.060, p=0.755; aIRR=1.030, p=0.883; table 5).

The only comorbidities to affect the pneumonia hospitalisation incidence rate were CHF (aIRR=2.013, p<0.001), asthma (aIRR=1.592, p=0.003), COPD (aIRR=2.090, p<0.001) and dementia (aIRR=1.962, p<0.001). None of the sociodemographic variables (ie, urbanisation, region of residence and wages)
| Variables                                      | Without PPSV23 vaccination n=754 | With PPSV23 vaccination n = 377 | P values |
|------------------------------------------------|----------------------------------|---------------------------------|----------|
| Age (years)                                    |                                  |                                 | 0.879    |
| 75–80                                          | 253 (33.6)                       | 121 (32.1)                      |          |
| 81–85                                          | 297 (39.4)                       | 153 (40.6)                      |          |
| >=86                                           | 204 (27.1)                       | 103 (27.3)                      |          |
| Gender                                         |                                  |                                 | 0.410    |
| Male                                           | 463 (61.4)                       | 241 (63.9)                      |          |
| Female                                         | 291 (38.6)                       | 136 (36.1)                      |          |
| No. of hospitalisations for pneumonia between years 2005 and 2007 |                                  |                                 | 0.930    |
| 0                                              | 703 (93.2)                       | 356 (94.4)                      |          |
| 1                                              | 39 (5.2)                         | 17 (4.5)                        |          |
| 2                                              | 6 (0.8)                          | 3 (0.8)                         |          |
| >=3                                            | 6 (0.8)                          | 1 (0.3)                         |          |
| PPSV23 vaccination period                      |                                  |                                 |          |
| January–March                                  | –                                | 0                               |          |
| April–June                                     | –                                | 0                               |          |
| July–September                                 | –                                | 0                               |          |
| October–December                               | –                                | 377 (100)                       |          |
| Influenza vaccination                          |                                  |                                 | <0.001   |
| Yes                                            | 566 (75.1)                       | 371 (98.4)                      |          |
| No                                             | 188 (24.9)                       | 6 (1.6)                         |          |
| Influenza vaccination period                   |                                  |                                 | 0.355    |
| January–March                                  | 6 (1.1)                          | 2 (0.5)                         |          |
| April–June                                     | 0                                | 0                               |          |
| July–September                                 | 103 (18.2)                       | 57 (15.4)                       |          |
| October–December                               | 457 (80.7)                       | 312 (84.1)                      |          |
| Chemotherapy                                   |                                  |                                 | 0.251    |
| Yes                                            | 67 (8.9)                         | 26 (6.9)                        |          |
| No                                             | 687 (91.1)                       | 351 (93.1)                      |          |
| Radiotherapy                                   |                                  |                                 | 0.185    |
| Yes                                            | 127 (16.8)                       | 52 (13.8)                       |          |
| No                                             | 627 (83.2)                       | 325 (86.2)                      |          |
| Surgery                                        |                                  |                                 | 0.797    |
| Yes                                            | 306 (40.6)                       | 156 (41.4)                      |          |
| No                                             | 448 (59.4)                       | 221 (58.6)                      |          |
| Target therapy                                 |                                  |                                 | 0.082    |
| Yes                                            | 20 (2.7)                         | 4 (1.1)                         |          |
| No                                             | 734 (97.3)                       | 373 (98.9)                      |          |
| Coronary heart disease                         |                                  |                                 | 0.038    |
| Yes                                            | 452 (59.9)                       | 250 (66.3)                      |          |
| No                                             | 302 (40.1)                       | 127 (33.7)                      |          |
| Congestive heart failure                       |                                  |                                 | 0.375    |
| Yes                                            | 159 (21.1)                       | 71 (18.8)                       |          |
| No                                             | 595 (78.9)                       | 306 (81.2)                      |          |
| Asthma                                         |                                  |                                 | 0.279    |

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showed any significant effect on the IRR of pneumonia hospitalisation.

The cumulative pneumonia incidence was significantly lower in PPSV23-vaccinated than unvaccinated patients (see online supplementary eFigure 1, p=0.027) and overall survival time was similar between the two groups (see online supplementary eFigure 2, p=0.136).

The results of multivariate analysis including significant covariates in the univariate model (see online supplementary etable 3) were almost the same as the above results.
DISCUSSION

*S. pneumoniae* infection is a serious public health issue. It has been estimated that around 4000 (mostly adults) die in the USA each year because of *S. pneumoniae*. Patients with HIV or cancer are at a higher risk for developing *S. pneumonia* infection and invasive pneumococcal disease (IPD). However, few studies have investigated the effectiveness of PPSV23 on health outcomes in patients with cancer. One study reported an adequate antibody response to PPSV in children with untreated Hodgkin’s disease regardless if the vaccine was given before or after splenectomy. In a single-institution study in Norway, PPSV23 vaccination elicited adequately protective pneumococcal IgG antibody levels without significant difference, except for serotype 4 in both 35 patients with cancer who had just received chemotherapy and 38 control patients who had not. In another study, Berglund et al found that 49% of adult patients with cancer with ongoing chemotherapy treatment could respond to at least 50% of serotypes. Our pneumonia study in patients with lung cancer conducted earlier in Taiwan showed that PPSV23 inoculated during the active anticancer treatment period could effectively reduce risk of hospitalised pneumonia. In this study, our results confirmed that PPSV23 can protect elderly long-term cancer survivors against pneumonia. Because the cost of PPSV23 is low, it can be considered a feasible strategy for coping with the high risk of pneumonia in elderly cancer survivors.

Elderly patients are at a higher risk of pneumonia. One study had the incidence rate of community-acquired pneumonia (CAP) at 7.51 per 1000 PYs for the general population aged ≥60 years; another had it at 30 per 1000 PYs for those aged ≥70 years. The study by Chiou et al reported a much higher incidence of 444 per 1000 PYs in patients with lung cancer aged ≥75 years, which they attributed to much older age, immunocompromised status during cancer treatment and poor pulmonary function. In the present study, the incidence rate in long-term cancer survivors aged ≥75 years was 117.82 per 1000 PYs. These data highlight the importance of pneumonia vaccination in the elderly population.

In the present study, influenza vaccination had no effect on the number of pneumonia hospitalisations, even though previous influenza infection may predispose some patients to bacterial pneumonia. There are three possible reasons for this finding: (1) our endpoint outcome was strictly bacterial pneumonia, not virus pneumonia and influenza; (2) not all the virus strains circulating were covered by the influenza vaccine; and (3) our endpoint was hospitalised pneumonia, which is more severe than CAP.

In our study, targeted therapy and radiotherapy were associated with higher risk of pneumonia hospitalisation. Radiotherapy and target therapy may increase susceptibility to pneumonia in patients with a history of more complex, combined cancer therapies or in those who had more advanced cancer stage before treatment.

### Table 3  Pneumonia hospitalisation incidence rate in vaccinated and unvaccinated groups

|                   | PYs  | No. of subjects with pneumonia hospitalisation | No. of pneumonia hospitalisations | IR     | 95% CI         |
|-------------------|------|-----------------------------------------------|-----------------------------------|--------|----------------|
| With PPSV23       | 705.98 | 36                                             | 52                                 | 73.66  | 53.64 to 93.68 |
| Without PPSV23    | 1375.00 | 105                                            | 162                                | 117.82 | 99.68 to 135.96 |
| Total             | 2080.98 | 141                                            | 214                                | 102.84 | 89.06 to 116.61 |

IR, incidence rate, calculated as the ratio of the number of pneumonia hospitalisations per 1000 PYs of follow-up; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PY, person-year.

### Table 4  Distribution of pneumonia hospitalisation incidence rate in elderly long-term cancer survivors with and without PPSV23

|                   | No. of pneumonia hospitalisations per PY (%) |
|-------------------|---------------------------------------------|
|                   | 0       | >0–1   | >1–2   | >2–3   | >3     |
| Patients with PPSV23 |  341 (90.45) |  25 (6.63) |  7 (1.86) |  3 (0.80) |  1 (0.27) |
| Patients without PPSV23 |  649 (86.07) |  70 (9.28) |  19 (2.52) |  12 (1.59) |  4 (0.53) |
| Total             |  990 (87.53) |  95 (8.40) |  26 (2.30) |  15 (1.33) |  5 (0.44) |

PPSV23, 23-valent pneumococcal polysaccharide vaccine; PY, person-year.
Table 5  Crude and adjusted incidence rate ratio (aIRR) of pneumonia hospitalisation in association with 23-valent pneumococcal polysaccharide vaccine (PPSV23) vaccination in univariate and multivariate analysis (all covariates included)

|                          | Crude IRR | Adjusted IRR |                  |
|--------------------------|-----------|--------------|------------------|
|                          | IRR       | 95% CI       | P values         | aIRR       | 95% CI       | P values         |
| PPSV23 (Without, ref)    | 1         |              | 1                | 1          |              | 1                |
| With                     | 0.625     | 0.457 to 0.854 | 0.003*          | 0.695     | 0.501 to 0.965 | 0.030*          |
| Age (75–80, ref)         | 1         |              | 1                | 1          |              | 1                |
| 80–85                    | 1.148     | 0.837 to 1.577 | 0.392           | 1.105     | 0.794 to 1.538 | 0.554           |
| 85+                      | 1.056     | 0.741 to 1.505 | 0.763           | 1.085     | 0.749 to 1.572 | 0.666           |
| Gender (Female, ref)     | 1         |              | 1                | 1          |              | 1                |
| Male                     | 1.590     | 1.180 to 2.142 | 0.002*          | 1.389     | 0.996 to 1.937 | 0.053           |
| Influenza vaccination (No, ref) | 1     |              | 1                | 1          |              | 1                |
| Yes                      | 1.060     | 0.735 to 1.529 | 0.755           | 1.030     | 0.700 to 1.515 | 0.883           |
| Cancer treatment modalities |          |              |                  | 1          |              | 1                |
| Chemotherapy (No, ref)   | 1         |              | 1                | 1          |              | 1                |
| Yes                      | 2.481     | 1.741 to 3.536 | <0.001*         | 1.433     | 0.929 to 2.210 | 0.104           |
| Radiotherapy (No, ref)   | 1         |              | 1                | 1          |              | 1                |
| Yes                      | 1.961     | 1.440 to 2.669 | <0.001*         | 1.771     | 1.280 to 2.450 | <0.001*         |
| Surgery (No, ref)        | 1         |              | 1                | 1          |              | 1                |
| Yes                      | 0.908     | 0.689 to 1.196 | 0.491           | 0.872     | 0.654 to 1.162 | 0.350           |
| Targeted therapy (No, ref) | 1     |              | 1                | 1          |              | 1                |
| Yes                      | 4.345     | 2.611 to 7.231 | <0.001*         | 2.943     | 1.584 to 5.468 | <0.001*         |
| Comorbidity              |          |              |                  | 1          |              | 1                |
| Coronary heart disease (No, ref) | 1   |              | 1                | 1          |              | 1                |
| Yes                      | 1.617     | 1.198 to 2.182 | 0.002*          | 1.122     | 0.817 to 1.542 | 0.477           |
| Congestive heart failure (No, ref) | 1   |              | 1                | 1          |              | 1                |
| Yes                      | 3.088     | 2.356 to 4.045 | <0.001*         | 2.013     | 1.494 to 2.713 | <0.001*         |
| Asthma (No, ref)         | 1         |              | 1                | 1          |              | 1                |
| Yes                      | 2.838     | 2.170 to 3.710 | <0.001*         | 1.592     | 1.178 to 2.150 | 0.003*          |
| Interstitial lung disease (No, ref) | 1   |              | 1                | 1          |              | 1                |
| Yes                      | 1.342     | 0.333 to 5.401 | 0.679           | 0.661     | 0.161 to 2.716 | 0.566           |
| COPD (No, ref)           | 1         |              | 1                | 1          |              | 1                |
| Yes                      | 3.936     | 2.801 to 5.532 | <0.001*         | 2.090     | 1.420 to 3.074 | <0.001*         |
| Liver cirrhosis (No, ref) | 1         |              | 1                | 1          |              | 1                |
| Yes                      | 1.396     | 0.906 to 2.152 | 0.131           | 1.245     | 0.799 to 1.942 | 0.333           |
| Diabetes mellitus (No, ref) | 1     |              | 1                | 1          |              | 1                |
| Yes                      | 1.581     | 1.209 to 2.066 | <0.001*         | 1.038     | 0.783 to 1.377 | 0.795           |
| Chronic kidney disease (No, ref) | 1   |              | 1                | 1          |              | 1                |
| Yes                      | 1.643     | 1.179 to 2.289 | 0.003*          | 1.230     | 0.868 to 1.744 | 0.245           |
| Stroke (No, ref)         | 1         |              | 1                | 1          |              | 1                |
| Yes                      | 1.892     | 1.437 to 2.491 | <0.001*         | 1.077     | 0.802 to 1.447 | 0.621           |
| Dementia (No, ref)       | 1         |              | 1                | 1          |              | 1                |
| Yes                      | 2.363     | 1.706 to 3.275 | <0.001*         | 1.962     | 1.397 to 2.756 | <0.001*         |

Continued
In this study, certain comorbidities affected the risk of pneumonia hospitalisation. Previously, Jackson et al identified CHF, asthma, COPD, DM, stroke, dementia and lung cancer as risk factors for CAP in people aged ≥65 years old in the general population, and CHF, asthma, COPD and dementia as risk factors in elderly patients with cancer.30 Another study also singled out CHF and asthma as risk factors in patients with lung cancer.13 Unlike our study, the Community-Acquired Pneumonia immunisation Trial in Adults (CAPiTA) reported the effectiveness of PCV13 (13-valent pneumococcal conjugate vaccine) in preventing vaccine-type CAP and vaccine-type IPD but not all-cause CAP in healthy people older than 65 years old.31 There are several differences in design between our study and the CAPiTA trial. First, the primary endpoint in our study was bacterial pneumonia (ICD-9-CM 481–482 and 485–486) rather than all-cause pneumonia. We excluded viral pneumonia, pneumonia due to organisms other than S. pneumoniae and influenza. We excluded viral pneumonia, pneumonia due to organisms other than S. pneumoniae and influenza. Second, we included only patients with hospitalised pneumonia, which is more severe than CAP. The CAPiTA trial collected data from 101 temporary community-based sites throughout the Netherlands. Third, the population in our study was older (≥75 years old), weaker and more susceptible to pneumonia than that in the CAPiTA trial. Fourth, our study subjects were all cancer survivors post anticancer treatment. Fifth, our study analysed not only the cumulative pneumonia incidence, but also the incidence rate of pneumonia hospitalisations (i.e., the number of patients with hospitalised pneumonia per PY of follow-up).

Other vaccines, such as the PCV, can have indirect effects. For example, introduction of routine infant 7-valent PCV immunisation in 2000 in the USA reduced pneumococcal infections in unvaccinated persons of all ages.32 The PCV7 vaccine has been available free of charge for childhood vaccination in Taiwan since 2009. However, S. pneumoniae serotype 19A was the major serotype in Taiwan and was not covered by the PCV7. The PCV13 vaccine was introduced in Taiwan in 2011 and has been provided free to children since 2013.33 Since our study ended at the end of 2010, an indirect effect of other vaccines would not be expected.

Though the immune response is greater to PCV than to PPSV23, PPSV23 protects against 23 serotypes of S. pneumoniae bacteria. PPSV23 contains 12 of the serotypes in PCV13 plus 11 additional serotypes. In 2013, 38% of IPD among adults aged ≥65 years was caused by serotypes unique to PPSV23.34 Given the high burden of IPD caused by serotypes in PPSV23 but not in PCV13, broader protection could be provided through use of both pneumococcal vaccines. PPSV23 was recommended by the Advisory Committee on Immunisation Practices in 2012 for prevention of IPD in all adults aged ≥65 years, and high-risk adults aged 19–64 years (i.e., immunocompromised patients (e.g., patients with cancer)).35 However, neither the PPSV23 nor PCV has ever been investigated for effectiveness in long-term cancer survivors.

### Study strengths

This study had several strengths. First, it was a nationwide population-based study using data from the NHIRD, which included a representative sample of long-term cancer survivors in Taiwan that left little room for non-response or loss to follow-up. Second, this study used propensity score matching to select unvaccinated patients,
which reduced confounding by indication. Third, a PY approach was used to determine incidence rate, reducing bias due to difference in observation time between the vaccinated and unvaccinated groups, which is important because of the relatively short life expectancy of elderly long-term cancer survivors. Fourth, this study adjusted several confounding factors (including influenza vaccination, vaccination period, anticancer treatments, comorbidities and personal socioeconomic status), reducing confounding by indication that vaccinated people may be more aware of the need for protection against pneumonia than unvaccinated people.

Study limitations
Our study also had several limitations. First, this study did not collect cancer stage information, and it is impossible to combine all kinds of cancer staging covariates into one covariate. Further studies of individual cancer types with larger sample size may be needed in the future. Second, it is observational, not randomised and is limited to routinely collected data, that is, does not include relevant data that are not routinely collected. Third, this study follows a cohort postvaccination for only two years, which is the period repeatedly associated with highest vaccine effectiveness. Fourth, because the ‘free vaccine’ policy applies only to those over age 75 years old, the conclusion of this population-based cohort study applies to this age group rather than the more common ‘age over 65’ group.

CONCLUSION
PSV23 vaccination was associated with a significantly reduced rate of pneumonia hospitalisation in long-term cancer survivors.

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Contributors
MSL, SKH and HYL acquired the data and supervised the project. WYC and CYL conceived and designed the study, with input from the other authors. WYC, CYL, FCH and SJT performed statistical analyses. WYC and CYL wrote the first draft of the manuscript. All authors interpreted the data and contributed to the writing of the paper. All authors revised and approved the final version.

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We, as the authors of this original research article, state that there are no additional, unpublished data available from this study. Raw data sharing of National Health Insurance Research Database is prohibited according to policy of National Health Research Institutes (NHR), Taiwan.

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