BMJ Open

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

Wen-Yen Chiou,[1,2,3] Moon-Sing Lee,[1,2] Shih-Kai Hung,[1,2] Hon-Yi Lin,[1,2] Yuan-Chen Lo,[1] Feng-Chun Hsu,[1] Shiang-Jiun Tsai,[1] Chung-Yi Li[3,4]

To cite: Chiou W-Y, Lee M-S, Hung S-K, *et al*. Effectiveness of 23-valent pneumococcal polysaccharide vaccine on elderly long-term cancer survivors: a population-based propensity score matched cohort study. *BMJ Open* 2018;**8**:e019364. doi:10.1136/bmjopen-2017-019364

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-019364).

Received 31 August 2017
Revised 31 March 2018
Accepted 18 April 2018

[1]Department of Radiation Oncology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan
[2]School of Medicine, Tzu Chi University, Hualien, Taiwan
[3]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[4]Department of Public Health, China Medical University, Taichung, Taiwan

Correspondence to
Chung-Yi Li;
i54851345@gmail.com

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 sociodemographic 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 117.82 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=0.136).

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

Strengths and limitations of this study

- This study was a matched nationwide population-based cohort study using the National Health Insurance Research Database that left little room for selection bias, non-response or loss to follow-up, and used a propensity score matching strategy to select unvaccinated patients, which reduced confounding by indication.
- A person-years approach was used to determine incidence rate, reducing bias due to time of observation differences between vaccinated and unvaccinated groups, which is important because of the relatively short life expectancy of elderly long-term cancer survivors.
- This study adjusted several potential confounding factors, including influenza vaccination, vaccination period, anticancer treatments, comorbidities and socioeconomic status, reducing confounding by indication that vaccinated people may be more aware of the need for protection against pneumonia than unvaccinated people.
- This study follows a cohort postvaccination for only 2 years, which is the period repeatedly associated with highest vaccine effectiveness.
- Because the 'free vaccine' policy applies only to those over 75 years old, the conclusion of this population-based cohort study is limited to this age group rather than the more common 'over 65' group.

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.[1 2] There are currently more than 15.5 million cancer survivors in the USA—many of them are long-term

survivors, living 5, 10 or more years after receiving their diagnosis.[3] 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[4–7]; and a growing and ageing population.[2]

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.[8] Cancer treatment modalities (surgery, radiotherapy, chemotherapy and targeted therapies) can impair the immune system and thereby increase susceptibility to pneumonia.[9–11] 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.[12] 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.[13]

In general, older people are more susceptible to pneumonia and their immunosenescence may result in the low efficacy of vaccination.[14] 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 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 99% of Taiwanese people.[15] 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.[16] False diagnostic reports are liable to severe penalties from the NHIA.[17] Information obtained from NHIRD is considered both complete and accurate.[18] 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

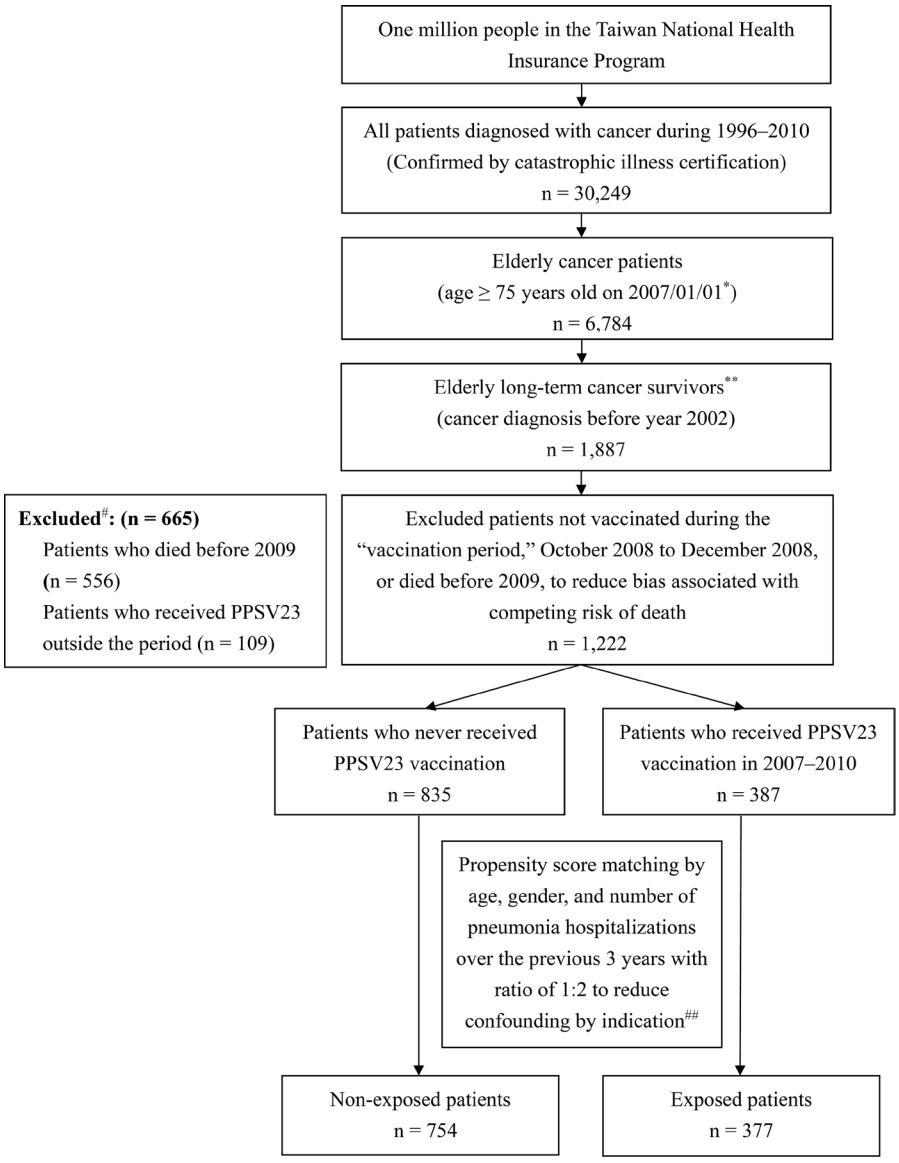

Figure 1 Study design flowchart. *Free 23-valent pneumococcal polysaccharide vaccine (PPSV23) policy started in 2007 in Taiwan for people aged ≥75 years. **Patients with cancer who survived at least 5 years after cancer diagnosis. #The 'vaccination period' is set to reduce the bias of competing risk 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.

Table 1 The distribution of people receiving 23-valent pneumococcal polysaccharide vaccine by vaccination period for all elderly long-term cancer survivors since 2007/01

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

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 hospitalisations over the previous 3 years. Unmatched patients or controls were excluded. Exactly 377 vaccinated patients and 754 unvaccinated patients were finally recruited (figure 1).

Measurements of endpoints and potential confounders

The primary outcome in the study was all-cause bacterial pneumonia hospitalisation (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for inpatient services: 481–482 and 485–486). All-cause pneumonia in this study included

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.[9–11] 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).[19] 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*.[20] We adjusted for urbanisation level because of the distinct urban–rural difference in medical care accessibility in Taiwan.[21]

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)

Table 2 Comparison of demographic characteristics and comorbidity between vaccinated and unvaccinated groups

Variables	Without PPSV23 vaccination n=754 n (%)	With PPSV23 vaccination n = 377 n (%)	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

Continued

Table 2 Continued

Variables	Without PPSV23 vaccination n=754 n (%)	With PPSV23 vaccination n = 377 n (%)	P values
Yes	215 (28.5)	96 (25.5)	
No	539 (71.5)	281 (74.5)	
Interstitial lung disease			1.000
Yes	6 (0.8)	3 (0.8)	
No	748 (99.2)	374 (99.2)	
COPD			0.141
Yes	405 (53.7)	185 (49.1)	
No	349 (46.3)	192 (50.9)	
Liver cirrhosis			0.585
Yes	57 (7.6)	32 (8.5)	
No	697 (92.4)	345 (91.5)	
Diabetes mellitus			0.304
Yes	312 (41.4)	144 (38.2)	
No	442 (58.6)	233 (61.8)	
Chronic renal failure (CKD)			0.204
Yes	113 (15.0)	46 (12.2)	
No	641 (85.0)	331 (87.8)	
Stroke			0.833
Yes	347 (46.0)	171 (45.4)	
No	407 (54.0)	206 (54.6)	
Dementia			0.043
Yes	92 (12.2)	31 (8.2)	
No	662 (87.8)	346 (91.8)	
Urbanisation level			0.152
Urban	226 (30.0)	103 (27.3)	
Suburban	281 (37.3)	163 (43.2)	
Rural	247 (32.8)	111 (29.4)	
Geographic region			0.036
North	397 (52.7)	176 (46.7)	
Central	141 (18.7)	73 (19.4)	
South	195 (25.9)	117 (31.0)	
East and remote islands	21 (2.8)	11 (2.9)	
Insurance premium (NTD)			0.656
≧30 000	9 (1.2)	4 (1.1)	
18 000–<30 000	201 (26.7)	108 (28.6)	
1–<18 000	211 (28.0)	113 (30.0)	
0*	333 (44.2)	152 (40.3)	

*Not actively employed.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NTD, New Taiwan Dollars; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

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

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 5). PPSV23 was a significant factor in both table 5 and online supplementary etable 3, with aIRR=0.695 (all covariates included, p=0.030), 0.697 (only univariate significant variates and influenza vaccination status adjusted, p=0.029) and 0.706 (only univariate significant variates adjusted, P=0.030), respectively. All covariates that were significant in table 5 remained significant in online supplementary etable 3 and the non-significance of influenza vaccination status in table 5 remained so in online supplementary etable 3 (online supplementary etable 3, aIRR=1.065, p=0.748).

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*.[22] Patients with HIV[23] or cancer are at a higher risk for developing *S. pneumonia* infection and invasive pneumococcal disease (IPD).[11 24] 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.[25] 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.[26] 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.[27] 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.[13] 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[28]; another had it at 30 per 1000 PYs for those aged ≥70 years.[29] 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.[13] 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 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		
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		
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		
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		
Yes	1.060	0.735 to 1.529	0.755	1.030	0.700 to 1.515	0.883
Cancer treatment modalities						
Chemotherapy (No, ref)	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		
Yes	1.961	1.440 to 2.669	<0.001*	1.771	1.280 to 2.450	<0.001*
Surgery (No, ref)	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		
Yes	4.345	2.611 to 7.231	<0.001*	2.943	1.584 to 5.468	<0.001*
Comorbidity						
Coronary heart disease (No, ref)	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		
Yes	3.088	2.356 to 4.045	<0.001*	2.013	1.494 to 2.713	<0.001*
Asthma (No, ref)	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		
Yes	1.342	0.333 to 5.401	0.679	0.661	0.161 to 2.716	0.566
COPD (No, ref)	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		
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		
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		
Yes	1.643	1.179 to 2.289	0.003*	1.230	0.868 to 1.744	0.245
Stroke (No, ref)	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		
Yes	2.363	1.706 to 3.275	<0.001*	1.962	1.397 to 2.756	<0.001*

Continued

Table 5 Continued

	Crude IRR			Adjusted IRR		
	IRR	95% CI	P values	aIRR	95% CI	P values
Sociodemographic characteristics						
Urbanisation (Urban, ref)	1			1		
Suburban	0.967	0.691 to 1.353	0.844	0.890	0.624 to1.268	0.517
Rural	1.154	0.822 to 1.620	0.409	0.890	0.579 to 1.368	0.596
Region (Northern, ref)	1			1		
Central	1.187	0.848 to 1.663	0.317	1.229	0.833 to 1.815	0.299
Southern	0.856	0.614 to 1.193	0.360	0.974	0.673 to 1.409	0.888
Eastern	0.700	0.258 to 1.899	0.484	0.490	0.175 to 1.369	0.174
Insurance premium (NTD)†	1			1		
18 000–<30 000	2.667	0.370 to 19.221	0.330	2.881	0.389 to 21.347	0.300
1–<18 000	2.703	0.376 to 19.457	0.323	2.340	0.318 to 17.241	0.404
0‡	2.009	0.279 to 14.444	0.488	2.603	0.354 to 19.144	0.347

*P<0.05.
†≧30 000 NTD as reference.
‡Not employed.
COPD, chronic obstructive pulmonary disease; NTD, New Taiwan Dollars; ref, reference.

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. 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 (ie, 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. pneumonia* 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 (ie, 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

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

Acknowledgements This study is partly based on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health in Taiwan and managed by National Health Research Institutes (registry number 99029). However, the interpretation and conclusions contained herein are not those of the Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

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.

Funding This study was supported by research grants of Buddhist Dalin Tzu Chi Hospital: DTCRD-105-I-09.

Disclaimer The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing interests None declared.

Patient consent Not required.

Ethics approval Institutional Review Board of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement 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 (NHRI), Taiwan.

REFERENCES

1. American Cancer Society. *Cancer treatment and survivorship facts & figures 2016–2017*. Atlanta: American Cancer Society, 2016.
2. Simon S. *ACS Report: number of US cancer survivors expected to exceed 20 million by 2026*. Atlanta: American Cancer Society, 2016.
3. Miller KD, Siegel RL, Lin CC, *et al*. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 2016;66:271–89.
4. Mandel JS, Bond JH, Church TR, *et al*. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota colon cancer control study. *N Engl J Med* 1993;328:1365–71.
5. Kapiteijn E, van de Velde CJ. The role of total mesorectal excision in the management of rectal cancer. *Surg Clin North Am* 2002;82:995–1007.
6. Tabár L, Fagerberg CJ, Gad A, *et al*. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the breast cancer screening working group of the Swedish National Board of Health and Welfare. *Lancet* 1985;1:829–32.
7. van Oortmarssen GJ, Boer R, Habbema JD. Modelling issues in cancer screening. *Stat Methods Med Res* 1995;4:33–54.
8. Semenov YR, Starmer HM, Gourin CG. The effect of pneumonia on short-term outcomes and cost of care after head and neck cancer surgery. *Laryngoscope* 2012;122:1994–2004.
9. Yen TT, Lin CH, Jiang RS, *et al*. Incidence of late-onset pneumonia in patients after treatment with radiotherapy for nasopharyngeal carcinoma: a nationwide population-based study. *Head Neck* 2015;37:1756–61.
10. Lee JY, Jin SM, Lee CH, *et al*. Risk factors of postoperative pneumonia after lung cancer surgery. *J Korean Med Sci* 2011;26:979–84.
11. Lee JO, Kim DY, Lim JH, *et al*. Risk factors for bacterial pneumonia after cytotoxic chemotherapy in advanced lung cancer patients. *Lung Cancer* 2008;62:381–4.
12. Gross PA, Gould AL, Brown AE. Effect of cancer chemotherapy on the immune response to influenza virus vaccine: review of published studies. *Rev Infect Dis* 1985;7:613–8.
13. Chiou WY, Hung SK, Lai CL, *et al*. Effect of 23-valent pneumococcal polysaccharide vaccine inoculated during anti-cancer treatment period in elderly lung cancer patients on community-acquired pneumonia hospitalization: a nationwide population-based cohort study. *Medicine* 2015;94:e1022.
14. Pritz T, Weinberger B, Grubeck-Loebenstein B. The aging bone marrow and its impact on immune responses in old age. *Immunol Lett* 2014;162:310–5.
15. Lu JF, Hsiao WC. Does universal health insurance make health care unaffordable? Lessons from Taiwan. *Health Aff* 2003;22:77–88.
16. Cheng TM. Taiwan's new national health insurance program: genesis and experience so far. *Health Aff* 2003;22:61–76.
17. Bureau of National Health Insurance Website. Methods for estimating false claims. 2000 http://www.nhi.gov.tw/ information/bulletin_file/421-0890036465-19.doc (accessed 1 Oct 2009).
18. Sun Y, Chang YH, Chen HF, *et al*. Risk of parkinson disease onset in patients with diabetes: a 9-year population-based cohort study with age and sex stratifications. *Diabetes Care* 2012;35:1047–9.
19. Cillóniz C, Polverino E, Ewig S, *et al*. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. *Chest* 2013;144:999–1007.
20. Liu CY, Hung YT, Chuang YL, *et al*. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. *J Health Manage* 2006:1–22.
21. Chen HF, Ho CA, Li CY. Age and sex may significantly interact with diabetes on the risks of lower-extremity amputation and peripheral revascularization procedures: evidence from a cohort of a half-million diabetic patients. *Diabetes Care* 2006;29:2409–14.
22. Centers for Disease Control and Prevention. Active bacterial core surveillance (ABCs) report, emerging infections program network. *Streptococcus pneumoniae, 2010*. Atlanta, GA: US Department of Health and Human Services, CDC, 2011.

23. Siemieniuk RA, Gregson DB, Gill MJ. The persisting burden of invasive pneumococcal disease in HIV patients: an observational cohort study. *BMC Infect Dis* 2011;11:314.
24. Wong A, Marrie TJ, Garg S, *et al*. Increased risk of invasive pneumococcal disease in haematological and solid-organ malignancies. *Epidemiol Infect* 2010;138:1804–10.
25. Addiego JE, Ammann AJ, Schiffman G, *et al*. Response to pneumococcal polysaccharide vaccine in patients with untreated hodgkin's disease. Children's cancer study group report. *Lancet* 1980;2:450–2.
26. Nordøy T, Aaberge IS, Husebekk A, *et al*. Cancer patients undergoing chemotherapy show adequate serological response to vaccinations against influenza virus and Streptococcus pneumoniae. *Med Oncol* 2002;19:71–8.
27. Berglund A, Willén L, Grödeberg L, *et al*. The response to vaccination against influenza A(H1N1) 2009, seasonal influenza and Streptococcus pneumoniae in adult outpatients with ongoing treatment for cancer with and without rituximab. *Acta Oncol* 2014;53:1212–20.
28. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, *et al*. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged ≥ 60 years: 3 years of follow-up in the CAPAMIS study. *Clin Infect Dis* 2014;58:909–17.
29. Garcia-Vidal C, Calbo E, Pascual V, *et al*. Effects of systemic steroids in patients with severe community-acquired pneumonia. *Eur Respir J* 2007;30:951–6.
30. Jackson ML, Neuzil KM, Thompson WW, *et al*. The burden of community-acquired pneumonia in seniors: results of a population-based study. *Clin Infect Dis* 2004;39:1642–50.
31. Bonten MJM, Huijts SM, Bolkenbaas M, *et al*. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med Overseas Ed* 2015;372:1114–25.
32. Pilishvili T, Lexau C, Farley MM, *et al*. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis* 2010;201:32–41.
33. Taiwan Press Release. Taiwan CDC announces this year's first pneumococcal death in infant and urges parents to get children meeting eligibility criteria for government-funded pneumococcal conjugate vaccine vaccinated. http://www.cdc.gov.tw/english/info.aspx?treeid=bc2d4e89b154059b&nowtreeid=ee0a2987cfba3222&tid=520647D35E5023F4 (accessed 26 Jan 2018).
34. Centers for Disease Control and Prevention. Active bacterial core surveillance (ABCs) report, emerging infections program network. *Streptococcus pneumoniae 2013*. Atlanta, GA: US Department of Health and Human Services, CDC, 2013.
35. Bennett NM, Whitney CG, Moore M, *et al*. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the advisory committee on immunization practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2012;61:816–9.