Factors associated with influenza vaccination among adult cancer patients: a case–control study

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Abstract

Influenza vaccination is recommended for cancer patients; however, adherence is low. We aimed to identify predictive factors for vaccination among cancer patients. We conducted a case–control analysis of a patient cohort in the 2010–2011 influenza season. We included adult cancer patients with solid malignancies undergoing chemotherapy, and haematological patients with active disease. Patients who died between October and November 2010 (N = 43) were excluded from analysis. Cases received the 2011 seasonal influenza vaccine, and controls did not. Data were obtained from patients' records, and validated through personal interviews. We collected socio-demographic information, and data on the malignancy and co-morbidities and triggers for vaccination and non-vaccination. We performed bivariate and multivariable analyses, in which vaccination status was the dependent variable. Of 806 patients included in analysis, 387 (48%) were vaccinated. Variables associated with vaccination on bivariate analysis were older age, higher socio-economic status, lower crowding index, marital status (widowed > married > single), malignancy type (haematological > solid tumours) and time from diagnosis, low-risk malignancy, diabetes, past vaccination, country of birth (non-Russian origin), and physicians' recommendations. Predictive factors found to be independently associated with vaccination on multivariable analysis were past vaccinations, low-risk malignancy, and country of birth. In the analysis conducted among interviewees (N = 561), recommendations from the oncologist (OR 10.7, 95% CI 5.4–21.2) and from the primary-care physician (OR 3.35, 95% CI 2.05–5.49) were strong predictors for vaccination. We conclude that 'habitual vaccinees' continue influenza vaccinations when ill with cancer. Physicians' recommendations, especially the oncologist's, have a major influence on patients' compliance with influenza vaccination.

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Introduction

Annual vaccination against influenza is the most effective way to avoid influenza and related complications [1]. Vaccination of immunosuppressed patients, including cancer patients, is universally recommended [2–6]. Among patients with cancer admitted to hospital with respiratory symptoms during influenza epidemics, 21–33% test positive for influenza, and fatality rates in those with confirmed influenza range between 11% and 33% [7]. However, influenza vaccination rates among cancer patients are low [7,8].

The most common predictors for vaccination in the general population are older age and the presence of chronic diseases [9]. Other determinants include influenza vaccination in the past, free-of-charge vaccination, higher education, and recommendations from physicians, family, or friends [9]. The most

common reasons for non-vaccination in the population are misconceptions concerning vaccine safety, lack of faith in vaccine efficacy, and the absence of recommendations for vaccination from healthcare providers [9].

Clinical data on influenza among cancer patients are scarce and mostly based on small studies [7,10–12]. Current influenza vaccination guidelines for cancer patients are not based on actual evidence, and are thus less likely to be followed. Studies assessing compliance with influenza vaccination and factors that influence the acceptance or non-acceptance of the vaccine in oncology patients are lacking. We have previously shown that influenza vaccination is associated independently with lower all-cause mortality in cancer patients [13]. In the current study, we aimed to identify factors associated with influenza vaccination, considering factors that cannot be modified, and modifiable factors that can be targeted for future interventions.

Materials and Methods

Study design and settings

This study was a case–control analysis of cohort members. The study was conducted in the 2010–2011 influenza season (October 2010 to April 2011) at Davidoff Centre, Rabin Medical Centre, a primary-care and tertiary-care university-affiliated hospital comprising oncology, haemato-oncology and bone marrow transplantation wards. The hospital belongs to the largest health maintenance organization (HMO) in Israel, which insures 52.3% of its population [14]. We obtained local research ethics committee approval for the study, requesting oral informed consent for telephone/personal interviews.

Participants

Cases were defined as all cohort patients who received the 2011 seasonal trivalent inactivated influenza vaccine ('vaccinated'). Controls were cohort patients who did not receive a seasonal influenza vaccine ('unvaccinated'). Administration and receipt of the vaccine were according to physicians' and patients' decisions. Data on seasonal influenza vaccination were fully recorded in patients' electronic health records. No matching procedure was performed to allow the study of all potential factors. The cohort included adult cancer patients (>18 years of age) with solid and haematological malignancies treated with chemotherapy, and patients who had received autologous (up to 6 months after transplantation) or allogeneic (at any time) haematopoietic stem cell transplantation and who were alive on December 2010 (thus having had the opportunity to be vaccinated). We excluded patients with untreated solid malignancies, haemato-oncological patients at least 1 year in remission post-therapy, and patients insured through other HMOs [13]. The viral strains included in this season were A/Perth/16/2009 (H3N2), A/California/7/2009 (H1N1), and B/Brisbane/60/2008.

Variables and data sources

We collected a range of variables that might affect patients' decisions on whether to be vaccinated. These included socio-demographic factors, and information on the oncological disease and comorbidities. Owing to the complexity of risk classification of different cancers, we defined two broad categories: high-risk malignancy, which included metastatic solid tumours, leukaemia, including myelodysplastic syndromes, and all haematopoietic stem cell transplantation recipients; and low-risk malignancy, which included non-metastatic solid cancer, lymphoma, and multiple myeloma. Data were collected from hard copy and electronic medical records, including inpatient and outpatient records. Information on recommendations for vaccination, reasons for vaccination and non-vaccination, attitudes towards vaccination, vaccine-related adverse events and a few socio-economic factors was obtained through telephone or personal interviews conducted during May–June 2011. The questionnaire had previously been assessed for content validity in a pilot study among a small group of lay volunteers, to ensure clarity and understandability, and revised where necessary. We validated exposure to vaccination reported in interviews by crossing it with data from electronic sources.

Study size

The final sample size provided a power of >70% to detect a statistically significant OR of >1.45 for influenza vaccination ($\alpha = 0.05$).

Statistical methods

We conducted a bivariate analysis to compare factors predicting vaccination between vaccinated and unvaccinated patients. Dichotomous data were compared by use of a chi-square test or Fisher exact test, and continuous data by use of the *t*-test or the Mann–Whitney *U*-test, as appropriate. We carried out a multivariable analysis with vaccination as the dependent variable. The covariates included factors associated with vaccination that resulted in a statistically significant association ($p < 0.05$) in the bivariate analysis. We excluded variables that were clinically related to each other and significantly correlated. Variables were entered into the logistic regression model by forward stepwise inclusion. Goodness-of-fit was measured with Hosmer and Lemeshow and –2 log-likelihood tests, and the predictive ability of the

model was evaluated from the area under the receiver operating characteristic (ROC) curve. ORs with 95% CIs are reported. Data were analysed with SPSS version 20.0.

Results

Participants

We included 806 cancer patients who were actively treated during the period of routine influenza vaccination (October–November), of whom 387 (48%) were vaccinated. At the time of vaccination, one of 363 (0.3%) were neutropenic (<500/μL) and 65 of 363 (17.9%) were lymphopenic (<900/μL). The kappa statistic for vaccination status between records and self-reporting was 0.87 (standard error of 0.0021, $p < 0.001$). Interviews were conducted with 561 patients. The most common reason for not performing an interview was patient death (Fig. 1).

Factors associated with vaccination on bivariate analysis

Vaccinated patients were older than unvaccinated patients (66 ± 13 vs. 60 ± 15 years). Marital status was associated with vaccination, and a significantly lower percentage of patients born in Russia was observed among vaccinated (32/387, 8.3%) than among unvaccinated (62/419, 14.8%) patients. A crowding index of >1 person/room was associated with non-vaccination (68/269 (25.2%) vs. 91/246 (37%), respectively). The percentage of patients in lower socio-economic clusters [15] was also higher among unvaccinated patients (35/383 (9.1%) vs. 67/418 (16%), respectively). There were no significant associations between vaccination and sex, ethnicity, or years of education (Table 1).

There was no association between vaccination and Eastern Cooperative Oncology Group performance status, body mass index, smoking and hospitalization in the previous year. No association was found with the Charlson comorbidity index or specific comorbidities, with the exception of diabetes (97/387 (25.1%) among vaccinated patients vs. 81/419 (19.3%) among unvaccinated patients, p 0.05). Vaccinated patients more frequently received an influenza vaccine in the 10 years prior to the studied winter (300/387 (77.5%) among vaccinated patients vs. 136/419 (32.5%) among unvaccinated patients; bivariate OR 7.1, 95% CI 5.2–9.8), more frequently received the seasonal influenza vaccine in 2009 (258/387 (66.7%) vs. 85/419 (20.3%); OR 7.9, 95% CI 5.7–10.8), more frequently received the H1N1 vaccine in 2009 (124/387 (32%) vs. 35/419 (8.4%); OR 5.2, 95% CI 3.4–7.8), and were more frequently vaccinated against *Streptococcus pneumoniae* in the past (260/387 (67.2%) vs. 117/419 (27.9%); OR 5.3, 95% CI 3.9–7.1).

The type of cancer was significantly associated with vaccination status; a higher percentage of haematological cancer patients and a lower percentage of breast cancer patients were found among vaccinated patients (Table 2). Differences with regard to radiation therapy probably reflected the cancer type distribution. A longer time since cancer diagnosis was associated with vaccination. High-risk malignancy was inversely associated with vaccination. There was no association between vaccination and steroid treatment, active chemotherapy and documented neutropenia or lymphopenia at the time of vaccine administration or during the winter.

Among 561 interviewed patients, a significant association was found between vaccination and recommendations

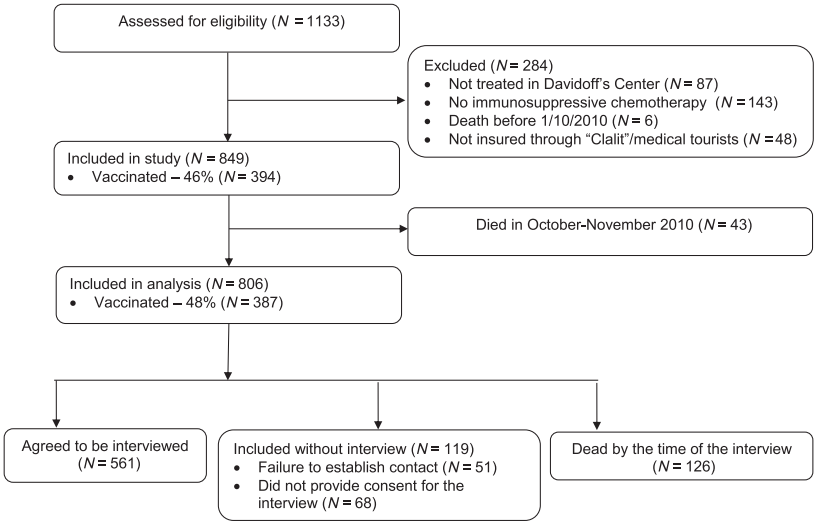

FIG. 1. Patients' flow chart and reasons for exclusion from the preliminary cohort.

TABLE 1. Demographics and background conditions

Variable	Vaccinated (*N* = 387) (%)	Unvaccinated (*N* = 419) (%)	p
Demographic and socio-economic characteristics			
Age (years), mean ± SD	66 ± 13	60 ± 15	<0.001
Sex (female)	213 (55)	251 (59.9)	0.163
Ethnicity	No. evaluated = 387	No. evaluated = 418	0.279
Arab	19 (4.9)	28 (6.7)	
Jew	368 (95.1)	390 (93.3)	
Country of birth			
Russia	32 (8.3)	62 (14.8)	0.004
Other[a]	355 (91.7)	357 (85.2)	
Socio-economic cluster[b]	No. evaluated = 383	No. evaluated = 418	0.003
1–4	35 (9.1)	67 (16)	
5–10	348 (90.9)	351 (84)	
Crowding-index (persons per room)	No. evaluated = 269	No. evaluated = 246	0.004
≥1	68 (25.2)	91 (37)	
<1	201 (74.8)	155 (63)	
Years of education			
≤12	213 (55)	219 (52.3)	0.127
>12	103 (26.6)	99 (23.6)	
Unknown	1 (18.3)	101 (24.1)	
Marital status			
Married	290 (74.9)	307 (73.3)	0.012
Single/divorced/separated	41 (10.6)	70 (16.7)	
Widowed	56 (14.5)	42 (10)	
ECOG grade	No. evaluated = 353	No. evaluated = 394	0.081
0–1	323 (91.5)	345 (87.6)	
2–4	30 (8.5)	49 (12.4)	
Medical background and comorbidities			
BMI, mean ± SD	26.20 ± 4.55	26.55 ± 5.31	0.314
Charlson Index, mean ± SD	4.65 ± 2.37	4.74 ± 2.28	0.597
Congestive heart failure	38 (9.8)	28 (6.7)	0.105
Chronic pulmonary disease	22 (5.7)	21 (5)	0.671
Diabetes	97 (25.1)	81 (19.3)	0.05
Smoking	120 (31)	128 (30.5)	0.89
Hospitalization in the previous year	265 (68.5)	297 (70.9)	0.457
Past vaccinations			
No. of influenza vaccines in the past 5 years, median (range)[c]	3 (0–5)	0 (0–5)	<0.001
Past influenza vaccine (in the last 10 years)	300 (77.5)	136 (32.5)	<0.001
Influenza vaccine last year	258 (66.7)	85 (20.3)	<0.001
H1N1 vaccine 2009–2010	124 (32)	35 (8.4)	<0.001
Past pneumococcal vaccine	260 (67.2)	117 (27.9)	<0.001

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.
[a]Comparison with patients born in Israel (*N* = 339), eastern Europe (*N* = 137), North Africa and elsewhere (*N* = 236). No differences were observed among patients included in the 'other category'.
[b]Socio-economic cluster according to the Israeli Central Bureau of Statistics clustering [15].
[c]Mann–Whitney *U*-test.

to receive the vaccine from the treating oncologist or primary-care physician (Table 3). Of vaccinated patients, 33.8% (99/293) reported that their oncologist recommended influenza vaccination, as compared with only 5.2% (14/268) of unvaccinated patients. Of vaccinated patients, 0.3% (1/293) perceived that their oncologist actively recommended against vaccination, as compared with 5.6% (15/268) of unvaccinated patients. Similar results were obtained for the recommendations of the primary-care physician (Table 3). Compliance with oncologists' recommendations for vaccination was higher than compliance with the primary physicians' recommendations: 87.8% (99/113) of patients reporting that their oncologist recommended vaccination were vaccinated, as compared with 67.3% (136/202) of patients reporting having received a recommendation from their primary-care physician (p 0.001). A 'regular habit' and a healthcare provider recommendation were more frequently stated as reasons for than as reasons against vaccination. The minority of triggers for or against vaccination were accessibility issues (e.g. comfortable access to clinics; shortage of vaccines). Of the vaccinated interviewees, 95 of 293 (32.4%) reported 'avoiding influenza morbidity' as the trigger to be vaccinated. Of the unvaccinated interviewees, 63 of 268 (23.5%) reported concerns about side effects as a reason not to be vaccinated.

Factors associated with vaccination on multivariable analysis

We used two multivariable models for factors independently associated with vaccination: the first for the entire cohort (*N* = 806), and the second for patients who were interviewed (*n* = 561) (Table 4). In the first model, variables independently associated with vaccination were non-Russian origin, number of influenza vaccines in the last 5 years, H1N1 vaccine in the 2009–2010 influenza season, past pneumococcal vaccination, and high-risk malignancy. Marital status, diabetes, influenza vaccine in the past 10 years, type of cancer, radiation therapy and time since diagnosis of cancer were available in the model, but were not included in the final model. The area under the ROC curve for the model was 0.82 (95% CI 0.80–0.85). The association between vaccination and the identified independent factors remained similar in stratified analysis of three

TABLE 2. Oncological disease characteristics

Variable	Vaccinated (*N* = 387) (%)	Unvaccinated (*N* = 419) (%)	p
Cancer type[a]			
Breast	84 (21.7)	126 (30.1)	0.001
Colon	64 (16.5)	68 (16.2)	
Lung	27 (7)	33 (7.9)	
Other solid malignancies	98 (25.3)	116 (27.7)	
Haematological	114 (29.5)	76 (18.1)	
Months since diagnosis	No. evaluated = 380	No. evaluated = 418	<0.001
<6	130 (34.2)	197 (47.1)	
≥6	257 (65.8)	22 (52.9)	
Radiation therapy	172 (44.4)	218 (52)	<0.001
Steroid treatment[b]	103 (26.6)	131 (31.3)	0.146
Active chemotherapy in winter 2010[c]	264 (68.2)	273 (65.2)	0.357
High-risk malignancy[d]	186 (44.4)	233 (55.6)	0.032
Neutropenia during winter[e]	47 (12.1)	49 (11.7)	0.844
Severe neutropenia during winter[e]	25 (6.5)	20 (4.8)	0.297
Lymphopenia during winter[e]	207 (53.5)	245 (58.5)	0.154
Severe lymphopenia during winter[e]	95 (24.5)	122 (29.1)	0.144

[a]Defined as the active cancer, as some patients had other types of cancer in the past.
[b]Defined as 20 mg of prednisone-equivalent daily for ≥14 days.
[c]Defined as chemotherapy given between November 2010 and February 2011.
[d]High-risk malignancy included metastatic solid tumours, leukaemia including myelodysplastic syndromes, and HSCT. Low-risk malignancy included non-metastatic solid cancer, lymphoma, and multiple myeloma without HSCT.
[e]Cytopenias were defined as at least one measurement below the cut-off: neutropenia, <500 cells/μL; severe neutropenia, <100 cells/μL; lymphopenia, <900 cells/μL; and severe lymphopenia, <400 cells/μL. Also on comparison of the total number of days with documented cytopenia, there were no significant differences between groups in any of the blood counts.

TABLE 3. Questionnaire data: healthcare provider recommendations and triggers for vaccination decision

Variable	Vaccinated (*N* = 293) (%)	Unvaccinated (*N* = 268) (%)	p
Recommendation by oncologist	No. evaluated = 293	No. evaluated = 267	<0.001
Not to receive	1 (0.3)	15 (5.6)	
To receive	99 (33.8)	14 (5.2)	
No recommendation	191 (65.2)	235 (88)	
Don't remember	2 (0.7)	3 (1.1)	
Recommendation by primary-care physician	No. evaluated = 293	No. evaluated = 267	<0.001
Not to receive	0	12 (4.5)	
To receive	136 (46.4)	66 (24.7)	
No recommendation	155 (52.9)	186 (69.7)	
Don't remember	2 (0.7)	3 (1.1)	
Recommendation by other	No. evaluated = 293	No. evaluated = 267	0.046
Not to receive	0	3 (1.1)	
To receive	24 (8.2)	32 (12)	
No recommendation	269 (91.8)	230 (86.1)	
Don't remember	0	2 (0.7)	
Trigger for decision			
Primary disease	90 (30.7)	66 (24.6)	0.108
Regular habit	87 (29.7)	58 (21.6)	0.03
Accessibility	4 (1.4)	7 (2.6)	0.29
Healthcare provider recommendation	90 (30.7)	54 (20.15)[a]	<0.001

[a]Of these, 22 (8.2%) received a recommendation not to vaccinate and 32 (11.9%) received no recommendation.

patient subgroups (solid cancer without metastases, metastatic solid cancers, and haematological patients).

In the second model, vaccination history remained significantly associated with vaccination, and the recommendations of the oncologist (OR 10.7, 95% CI 5.4–21.2) and of the primary-care physician (OR 3.35, 95% CI 2.05–5.49) were strong predictors for vaccination. The crowding index was not included in the final model. The area under the ROC curve for this model was 0.88 (95% CI 0.85–0.91).

Discussion

We assembled a cohort of actively treated oncological patients during the winter of 2010–2011 to analyse factors associated with influenza vaccination, both modifiable and non-modifiable. The vaccination rates in our cohort were 46% (394/849) among all patients and 48% (387/806) among patients alive on 1 December 2010. Reported vaccination data were in excellent agreement with those obtained from patients' electronic files (kappa statistic of 0.87, p <0.001) [16], indicating good validity of the data sources. According to the Israel Centre for Disease Control data, vaccination rates in Israel in the studied winter were 15.7% in the entire population and 57.2% in persons >65 years of age.

Predictive factors found to be independently associated with vaccination on multivariable analysis were younger age, country of birth (non-Russian origin), past pneumococcal and influenza vaccinations, H1N1 vaccine in 2009–2010, and low-risk malignancy. Although these factors cannot be changed, they can be used to identify patients at high risk for non-compliance with vaccination, and increased awareness will allow interventions targeting these groups. The strongest association was observed with previous influenza vaccination. Non-compliance with influenza vaccination in the past can be easily identified, and these patients should be targeted for increased efforts to promote vaccination. In the multivariable model for interviewed patients, the most prominent factors associated with vaccination were physicians' recommendations: the oncologist's recommendation was associated with vaccination with an OR of 10.7 (p <0.001), and the primary-care physician's recommendation was associated with vaccination with an OR of 3.35 (p < 0.001). Regrettably, of 561 interviewees, only 113 (20.1%) remembered that their oncologist recommended influenza vaccination, and the majority (87.6%) of these were vaccinated. An explanation about vaccine safety also seems to be important, as 23.5% of unvaccinated interviewees gave fear of adverse effects as the reason for not being vaccinated.

Vaccination rates (46%) were slightly higher in our cohort of a mixed adult cancer population in 2010 than previously reported. Rates of influenza vaccination were 33% among patients receiving chemotherapy in London in 2002 [17], 30% among patients with solid cancers, 73% of whom had

TABLE 4. Significant factors in the multivariable regression model for vaccination.

	All patients (N = 806, included in model N = 798)[a]				Interviewed patients (N = 561, included in model N = 515)[b]			
			95% CI for OR				95% CI for OR	
	p	OR	Lower	Upper	p	OR	Lower	Upper
Variable								
Age[c]	NS				0.020	0.98	0.96	0.996
Born in Russia	0.040	0.58	0.34	0.98	NS			
Influenza vaccine last year	0.014	1.84	1.13	2.99	NS			
No. of influenza vaccines in the past 5 years[d]	0.000	1.47	1.28	1.68	.000	1.74	1.49	2.03
H1N1 vaccine 2009–2010	0.016	1.82	1.12	2.95	.015	2.25	1.17	4.32
Past pneumococcal vaccine	0.000	2.27	1.58	3.26	.000	3.02	1.79	5.09
High-risk malignancy	0.005	0.61	0.43	0.86				
Recommendation by oncologist	NA				0.000	10.70	5.40	21.23
Recommendation by primary-care physician	NA				0.000	3.35	2.05	5.49
Test performance								
Hosmer and Lemeshow test	0.39	χ^2 = 8.45			0.381	χ^2 = 8.56		
−2 log-likelihood	<0.001	χ^2 = 276.36, d.f. = 6			<0.001	χ^2 = 251.3, d.f. = 6		
Area under the ROC curve	<0.001	AUC = 0.82	0.79	0.85	<0.001	AUC = 0.88	0.85	0.91

d.f., degrees of freedom; NA, not assessed; NS, non-significant; ROC, receiver operating characteristic.
[a]Variables available in the regression that were not statistically significant and not included in the final model were: age, marital status, diabetes, influenza vaccine in the past 10 years, type of cancer, radiation therapy, and time since diagnosis of cancer.
[b]Variables available in the regression that were not statistically significant and not included in the final model were: country of birth, influenza vaccine in the past 10 years, influenza vaccine in the previous year, type of cancer, house crowding, and recommendation from sources other than the oncologist/primary-care physician.
[c]OR per 1 year.
[d]OR per one vaccine.

metastases, in Paris in 2008 [18], and 43% among colorectal cancer patients in the USA in 1998 [12]. The association between physicians' recommendations and vaccine uptake among cancer patients has not been previously reported, to our knowledge, although the importance of this factor was stressed in a French study reporting that 72% of unvaccinated cancer patients claimed that lack of a recommendation by the treating physician was the main reason for their decision [18], and in a study in the USA, in which only 7% of patients reported having received a recommendation for influenza vaccination from their oncologist [19]. Also in the general population, lack of recommendations was identified as a barrier to adult immunization against influenza [20]. In the general population, it has been recognized that previous vaccination leads to continued vaccination. It is interesting that this remains true after cancer diagnosis, as shown in our study [21,22]. As in our study, studies in the general population have not found an association between influenza vaccination and education level [19,23,24]. We focused on Russian immigrants, as lower vaccination rates have been previously shown among Israeli patients born in Russia [25,26] and among Russian immigrants in the USA [27]. As there was no association between Russian origin and socio-economic status (data not shown), we believe that the association between Russian origin and vaccination reflect cultural beliefs and habits.

Our study has several limitations. Data dealing with patient views and triggers for vaccination were obtained from a subgroup of responders who were interviewed. This subgroup probably consisted of 'less ill' patients (better performance status and better prognosis) who were alive at the end of the influenza season and accessible (Fig. 1). Data on recommendations relied on patients' reports. Patients might have reported their interpretations or perceptions regarding physicians' recommendations rather than the actual recommendations, which could bias the results in favour of an association between the perceived recommendation and vaccination status. A recall bias might have influenced the patients' reported triggers to vaccinate. Another limitation is that the study was conducted in a single teaching hospital and included patients from a specific HMO, which might limit the generalizability of the results. However, the hospital belongs to the largest HMO in Israel, which insures 52.3% of its population [14].

In summary, we identified several non-modifiable factors and a single modifiable factor (physicians' recommendations) that were associated with influenza vaccination among cancer patients. The most prominent findings are the tendency of 'habitual vaccinees' to continue influenza vaccination when ill with cancer, and the major influence of physicians' recommendations, especially those of the oncologist, on patients' behaviour. The first factor can be easily used to target interventions promoting influenza vaccination, and the second factor should be improved, as rates of perceived clinicians' recommendations were low in our study, as in previous studies. The strong association between vaccination and the oncologist's recommendation highlights the faith and confidence of the patient in their treating oncologists. Influenza vaccine might offer, to some degree, protection in immunocompromised patients [7], was associated with lower all-cause

mortality in the current cohort [13], and has no potential to cause influenza; thus, we believe that all cancer patients should be vaccinated. Future studies should focus on characterizing the 'patients who vaccinate out of habit', and explore ways to encourage and inculcate a standard of influenza vaccine recommendation by physicians.

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Transparency Declaration

The authors declare no conflicts of interest.

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