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Seasonal influenza vaccination among cancer patients: A systematic review and meta-analysis of the determinants

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ABSTRACT

Cancer patients are among high-risk individuals for whom seasonal influenza vaccine (SIV) is recommended, but rates of vaccination in this subpopulation remain suboptimal; even in jurisdictions with universal influenza vaccination programs. We sought to summarize the evidence to better understand the determinants of SIV uptake (vaccine receipt) among cancer patients. We searched MEDLINE, Embase, and CINAHL from 2000 to February 12, 2020, focusing on articles on the determinants of seasonal influenza vaccination among cancer patients, published in English. Study selection was conducted independently by 2 reviewers. One reviewer extracted data from the included studies and another reviewer checked the extracted data for errors. Outcomes were sociodemographic and health-related factors. We pooled adjusted results from studies using the inverse variance, random-effects method, and reported the odds ratios (OR) and their 95% confidence intervals (CI). Out of 2664 citations, 10 studies (mostly from USA and South Korea) met our eligibility criteria. Overall, being older (OR 2.23, 95% CI 1.46-3.38; I^2 92.3%, [6 studies]), a nonsmoker (1.43, 1.32-1.51; I^2 0%, [4 studies]), having a chronic illness (1.18, 1.07-1.29; I^2 15.7%, [5 studies]), having had a medical check-up in the past year (1.75, 1.65-1.86; I^2 0%, [2 studies]), and having health insurance (1.39, 1.13-1.72; I^2 21.8%, [3 studies]) were associated with increased SIV uptake. Compared with being African-American, being Caucasian was also associated with increased SIV uptake (1.79, 1.47-2.13;

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I^2 10.7%, [3 studies]). Limited evidence suggests seasonal influenza vaccination among cancer patients may be determined by some sociodemographic and health-related factors.

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Introduction

The impact of cancers on the body, and the immunosuppression caused by cancer treatments, put cancer patients at increased risk of infections and infection-related complications. Infections such as influenza can cause significant morbidity and mortality in this patient population. During seasonal influenza peaks, the rate of influenza-related pneumonia among cancer patients ranges from 21% to 80%, with associated fatality rate of 11%-38%.[1-4] These statistics may even be worse in seasons during which markedly drifted or highly virulent influenza viruses are in circulation. Influenza therefore places a substantial burden on the health of cancer patients.

Vaccination is the best form of prevention against influenza. However, while it has been shown to decrease the risk of influenza infection in individuals whose immune system is intact,[5] the effectiveness of influenza vaccination in immunosuppressed individuals such as cancer patients remains debatable.[6,7] Studies have demonstrated impaired influenza vaccine response in cancer and immunosuppressed patients compared with age-matched healthy controls.[8,9] In response to this finding, high-dose and adjuvanted influenza vaccines have been proposed and developed for vaccination of those with a suppressed immune system, including cancer patients.[10-12] Active influenza vaccination (adherence to vaccination) has also been shown to confer some protection on cancer patients at similar rates to healthy individuals[13]; thus, translating to reduced severity and duration of influenza infection among this subpopulation.

Various governments have implemented annual influenza vaccination programs. Influenza vaccination is mostly recommended for subpopulations at increased risk of complications, including cancer patients.[14,15] In some jurisdictions, vaccination has been made free-of-charge to all individuals 6 months old or older, irrespective of health status (universal vaccination). Despite availability of these programs, seasonal influenza vaccine (SIV) uptake among cancer patients has not been optimal in many populations.[16,17] The proportion of cancer patients who consistently receive SIV is likely even lower.

Knowledge, perceptions and attitudes are known to influence vaccine acceptance[18,19]; however, some sociodemographic and health-related factors may facilitate or hinder vaccine uptake. Knowledge of the impact of these factors on SIV uptake among cancer patients is vital for designing more effective public health intervention programs to optimize vaccination in this subpopulation. While published data on the effectiveness of influenza vaccine in cancer patients has been well-summarized,[6,20] we are not aware of any systematic review on the determinants of influenza vaccination in this important subpopulation. Currently, there is a gap in knowledge with regard to understanding the factors that may facilitate influenza vaccination among cancer patients.

To help decision-making regarding policy on influenza vaccination, we systematically identified, appraised and summarized findings from published studies on the determinants of SIV uptake in cancer patients.

Methods

We followed the Cochrane Handbook for Systematic Reviews of Interventions guidelines when undertaking the review,[21] and reported our findings following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).[22]

Literature search

A health sciences librarian (C.J.N.) designed a comprehensive search strategy for Ovid MEDLINE, based in part on the search strategy used in our previous similar publications (on older adults).[23,24] We limited the search results to publications in English since 2000. The decision to limit to 2000 was because a publicly funded influenza vaccination program was first introduced around the end of the 20th century; for example, in 1999 in Canada,[25] and 1993 in the United States of America.[26] The search strategy was peer reviewed by a second, independent librarian (Z.P.) using the Peer Review of Electronic Search Strategies checklist.[27] The finalized search strategy (Appendix Table A1) was executed on February 13, 2020, using the necessary adaptations for each of the three bibliographic databases searched: Ovid MEDLINE and Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily; Ovid Embase; and CINAHL with Full Text (EBSCO).

Study Selection

We were interested in only studies that reported data on sociodemographic and/or health-related factors that may determine SIV uptake among cancer patients. We excluded modeling studies and studies conducted in mixed patient populations (non-cancer and cancer patients) without reporting results separately on cancer patients. Identified citations from the searches were managed in EndNote software (version X9). Two reviewers in pairs (G.N.O./O.LT.L.; G.N.O./T.A.) independently screened the citations for eligibility using a 2-stage sifting approach to review the titles/abstracts and full-text articles. Citation sifting was conducted in a specially designed Microsoft (MS) Access 2016 database (Microsoft Corporation, Redmond, WA, USA). The number of ineligible citations was recorded at the abstract screening stage and both the number and reason for ineligibility were recorded at the full-text article screening stage. Disagreements were resolved by discussion and consensus or a third reviewer.

Data extraction

Data extraction was piloted on 5 articles by 2 reviewers in pairs (G.N.O./O.LT.L.; G.N.O./T.A.) using MS Excel 2016 (Microsoft Corporation, Redmond, WA, USA) spreadsheet. One reviewer (G.N.O. or O.LT.L.) extracted data from the included studies and a second reviewer (G.N.O. or T.A.) checked the extracted data for errors. Disagreements were resolved by discussion and consensus or a third reviewer. We extracted the name of each study's first author, the year of study, the year of study publication, the country and city of study, funding source, and population information such as size and average age of participants. We also extracted the sociodemographic and health-related factors assessed, the statistical measures used, and the multivariable adjusted results of the measures and their associated 95% confidence intervals (CI).

Study quality assessment

Study quality was assessed by one reviewer (G.N.O. or O.LT.L.) using the National Institutes of Health quality assessment tool for observational cohort and cross-sectional studies.[28] A second reviewer (G.N.O. or T.A.) checked the assessments for errors. Disagreements were resolved by

discussion and consensus, or a third reviewer. The National Institutes of Health quality assessment tool is made up of 14 assessed criteria to determine study quality. These include clarity of research questions/objectives; appropriateness of selection of study population/participants; justification for sample size; and quality of measurements and analysis of data. A study was judged to be of high quality if it satisfied all assessed parameters; of good quality if it satisfied all but 1 parameter; of moderate quality if it did not satisfy 2-4 parameters; and of poor quality if it did not satisfy more than 4 parameters.

Data synthesis and analysis

Data synthesis and analysis was by one reviewer (G.N.O.). We presented relevant study characteristics and quality assessments in a tabular form. We pooled adjusted odds ratios (OR) using the inverse variance, random-effects model implemented in STATA (version 13; StataCorp LP, Texas, USA) and we reported the pooled estimates and their 95% CI. We assessed and quantified statistical heterogeneity between pooled results using the I-squared statistic (I^2)[29] and, where appropriate, we assessed publication bias visually using funnel plots and, statistically, using Egger's regression test.[30] We reported publication bias only if detected. Where necessary, we flipped an OR (1/OR) and the associated CI (1/upper CI and 1/lower CI) for a reverse comparison and uniformity in the pooled analysis. For example, if a study reported results for more than 1 comparison of the same determinant; for example, the 25-29, 30-34, and 35-39 years age groups compared with the 18-24 years age group, results from the 3 comparisons were first pooled using a fixed-effects model before being pooled with other results for comparison of older against younger age groups using a random-effects model.[23,24]

Results

Search results and characteristics of included studies

From a total of 2664 retrieved citations after de-duplication, we included 10 articles (representing 8 cross-sectional and 2 retrospective cohort studies) that met our eligibility criteria (Fig 1).[31-40] Four studies were from the United States of America,[31,33,35,38] three from South Korea,[32,36,39] and 1 from each of Israel,[34] Germany,[37] and Spain[40] (Table 1). These studies were conducted from 2001 to 2017. Eight studies were in mixed cancer patient populations,[31,32,34-37,39,40] and one study in each of solid cancer,[33] and hematological malignancy (multiple myeloma)[38] patient populations. Study sample size ranged from 139 to 41,346 participants. No study was funded by industry. All of the studies reported ORs.

Study quality assessment

One study was judged to be of high quality having satisfied all assessed parameters (Appendix Table A2).[34] One study did not report on sample size justification and outcome measures were not defined clearly.[35] This study was judged to be of moderate quality. The other eight studies did not report on one assessed parameter (sample size justification) and were therefore judged to be of good quality.

Sociodemographic determinants

Overall, older age (in groups) was associated with a 123% increase in the odds of SIV uptake (95% CI 46%-238%; I^2 92.3%, 6 studies: 17,103 participants); however, with high heterogeneity between the included studies (Fig 2). A smaller associated increase in the odds of SIV uptake (36%)

Table 1
Characteristics of included studies (n = 10 studies).

Study	Year country (region)	Study type (Funding)	Sample size (% male) [age range]	Cancer type	Adjusted covariates (Number of covariates)
Stafford 2013[31]	2009 USA (National)	Cross-sectional (BVAMCGRECC, CDPOAIC, and CRCA)	41,346 (34.7%) [NR]	Mixed	Age, sex, marital status, education, health care coverage, having a health care provider, could not see a doctor due to cost in last 12 months, years since most recent cancer, smoking status (N=9)
Choi 2014[32]	2007-2011 South Korea (National)	Cross-sectional (Not funded)	943 (35.4%) [NR]	Mixed	Age, education, marriage, monthly household income, area of residence, smoking, alcohol, physical activity, health insurance,chronic disease, cancer type, time since cancer diagnosis (N=12)
Steele 2014[33]	2001-2006 USA (NR)	Retrospective cohort (NR)	9,737 (48.3%) [NR]	Colorectal	Race/ethnicity, Physician category, age at diagnosis, sex, comorbidities, number of primary cancers, SEER Registry, Number of follow-up years, poverty level, total number of physician visits (N=10)
Vinograd 2014[34]	2010-2011 Israel (Petah Tikva)	Cross-sectional (Young Researcher's Grant, Rabin Medical Centre, and Clalit Research Institute & Policy Planning)	806 (42.5%) [≥18 years]	Solid and Haematological malignancies	Age, born in Russia, number of influenza vaccines in past 5 years, H1N1 vaccine 2009-10, Past pneumococcal vaccine, high-risk malignancy (N=6)
Lowenstein 2015[35]	2003 USA (National)	Cross-sectional (National Institutes on Health)	1,882 (39.4%) [≥65 years]	Mixed	Age, gender, BMI, race, marital status, income, education, comorbidity, medicaid, HMO coverage, VES (N=11)
Oh 2015[36]	2007-2012 South Korea (National)	Cross-sectional (NR)	1,156 (35.8%) [≥19 years]	Mixed	Age, sex, marital status, household income, health insurance, smoking status, drinking frequency, physical activity, medical checkup, comorbid conditions, time since last diagnosis, cancer site (N=12)
Pettke 2017[37]	2010 Germany (Northwest)	Cross-sectional (Internal funding)	139 (NR) [1–18years]	Mixed	Age, recommendation from general practitioner/primary pediatrician (N=2)

(*continued on next page*)

Table 1 (*continued*)

Study	Year country (region)	Study type (Funding)	Sample size (% male) [age range]	Cancer type	Adjusted covariates (Number of covariates)
Giri 2019[38]	2008-2014 USA (Connecticut)	Retrospective cohort (Yale School of Medicine, Clinical and Translational Science Awards Grant from the National Center for Advancing Translational Science)	1,996 (46%) [Interquartile range 70–80 years]	Multiple Myeloma	Age, marital status, geographic region, Multiple Myeloma regimen, diagnosis year, Elixhauser comorbidity index, disability, socioecon status, education, medicaid dual coverage (N=10)
Kim 2020[39]	2005-2015 South Korea (NR)	Cross-sectional (Research grant of the Chungbuk National University Hospital in 2019)	2,210 (39%) [NR]	Mixed	Age, monthly household income, marital status, education level, occupation, residence, heavy alchol drinking, depressive symptoms, stress symtpoms, chronic diseases, cancer type, duration since cancer diagnosis, age at cancer diagnosis (N=13)
Martinez-Huedo 2020[40]	2017 Spain (NR)	Cross-sectional (FIS Health Research Fund, Instituto de Salud Carlos III & the European Union	335 (38.7%) [NR]	Mixed	Sex, nationality, number of chronic conditions (N=3)

NR, not reported; BVAMCGRECC, Baltimore VA Medical Center Geriatric Research, Educational and Clinical Center; CDPOAIC, Claude D. Pepper Older Americans Independence Center; CRCA, clinical research curriculum award; SEER, surveillance, epidemiology and end results; HMO, Health Maintenance Organization; VES, vulnerable elders survey; FIS, Fondo de Investigaciones Sanitarias.

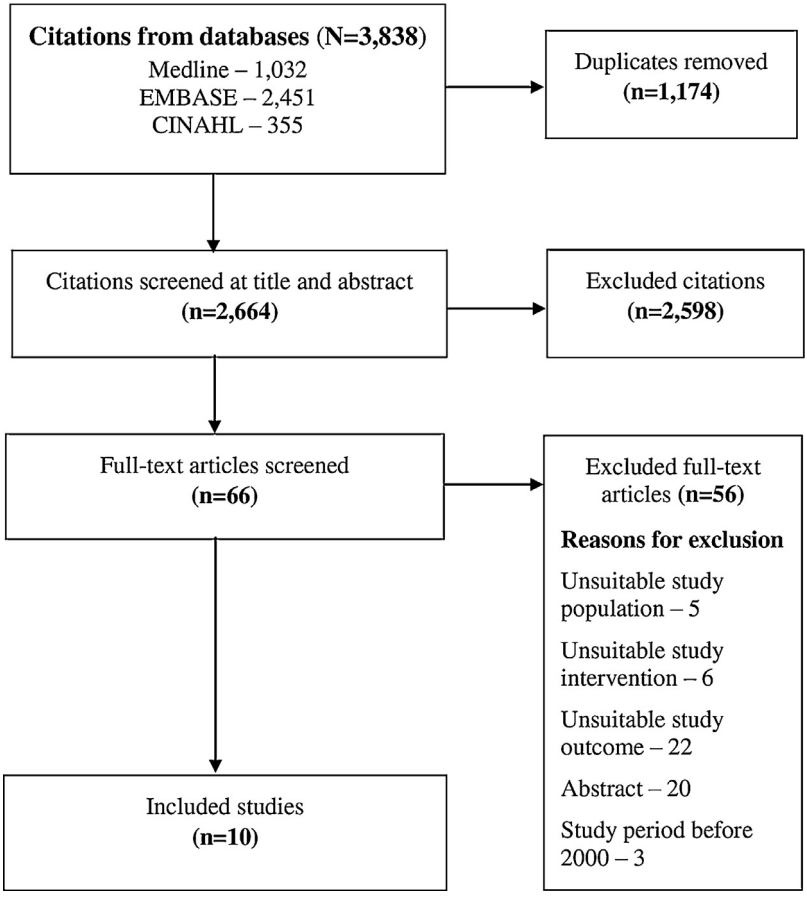

Fig. 1. Summary of literature search and screening process (Modified PRISMA flow diagram).

was found with regards to South Korea whereas a larger associated 246% increase in the odds of SIV uptake was found with regard to the United States of America (Table 2). Having had a medical check-up in the past year was associated with a 75% increase in the odds of SIV uptake (65%-86%; I^2 0%, 2 studies: 42,502 participants; Appendix Fig A1). When compared with being Caucasian, being an ethnic minority or Hispanic was not associated with SIV uptake, but being African-American was associated with a 44% decrease in the odds of SIV uptake (32%-53%; I^2 10.7%, 3 studies: 45,224 participants; Appendix Fig A2). Having health insurance was associated with a 39% increase in the odds of SIV uptake (13%-72%; I^2 21.8%, 3 studies: 44,384 participants; Appendix Fig A3). A similar associated 45% increase in the odds of SIV uptake was found with regard to the USA. Overall, there was no association found between sex, education, and area of residence, and SIV uptake; however, being male, and living in a rural area were both found to be associated with increase in the odds of SIV uptake with regard to South Korea (Appendix Figs A4 and A6, respectively), and having a higher education was found to be associated with increase in the odds of SIV uptake with regard to the USA (Appendix Fig A5). No association was found between marital status, and income, and SIV uptake (Appendix Figs A7 and A8, respectively). One study reported on the influence of previous influenza vaccination during the previous influenza season,[34] and another study reported on the influence of previous influenza vaccination any time in the past[37]; both reported associated increase in the odds of SIV uptake.

Table 2
Summary of results (by country of study) of meta-analysis of association between reported determinants and SIV uptake.

Determinants	Comparison	Continent	Number of studies	Study population size	Pooled Odds Ratio (95% CI)	I^2 Statistic (%)
Age	Older vs. Younger	Overall	6	17,103	**2.23 (1.46 – 3.38)**	92.3
		USA	3	13,615	**1.36 (1.07 – 1.74)**	77
		South Korea	2	3,153	**3.46 (1.92 – 6.23)**	72.3
		Spain	1	335	5.92 (3.03 – 11.56)*	NA
Ethnicity	African-Americans vs Caucasians	USA	3	45,224	**0.56 (0.47 – 0.68)**	10.7
	Hispanics vs. Caucasians	USA	2	3,878	0.72 (0.40 – 1.31)	63.8
	Ethnic minorities vs. Caucasians	USA	2	3,878	1.06 (0.76 – 1.48)	0
Marital status	Married vs Not married	Overall	5	8,187	1.05 (0.86 – 1.29)	26
		USA	2	3,878	1.18 (0.99 – 1.41)	0
		South Korean	3	4,309	0.86 (0.62 – 1.17)	5.1
Education	Higher vs Lower	Overall	5	47,537	1.05 (0.86 – 1.28)	63.2
		USA	2	43,228	**1.21 (1.09 – 1.35)**	18.5
		South Korea	3	4,309	0.84 (0.67 – 1.04)	0
Household income	High vs Low	Overall	4	6,191	0.93 (0.77 – 1.13)	0
		USA	1	1,882	0.91 (0.84 – 0.99)*	NA
		South Korea	3	4,309	0.99 (0.75 – 1.19)	0
Sex	Female vs Male	Overall	6	55,399	0.91 (0.82 – 1.00)	49.3
		USA	3	52,965	0.97 (0.93 – 1.00)	0
		South Korea	2	2,099	**0.53 (0.30 – 0.92)**	0
		Spain	1	335	1.04 (1.02 – 1.07)*	NA
Residence	Rural vs Urban	Overall	3	5,035	1.40 (0.87 – 2.25)	70.7
		USA	1	1,882	0.86 (0.55 – 1.37)*	NA
		South Korea	2	3,153	**1.78 (1.31 – 2.42)**	0
Comorbidity	Having vs Not having a chronic disease	Overall	5	16,768	**1.18 (1.07 – 1.29)**	15.7
		USA	3	13,615	**1.15 (1.06 – 1.25)**	0
		South Korea	2	3,153	1.34 (0.90 – 2.02)	58.1
Cancer type	Lung cancer vs Other cancers	South Korea	2	3,153	1.34 (0.70 – 2.56)	0
Smoking	Smoker vs. Non-smoker	Overall	4	45,655	**0.70 (0.66 – 0.76)**	0
		USA	1	41,346	0.71 (0.66 – 0.76)*	NA
		South Korea	3	4,309	**0.57 (0.39 – 0.83)**	0
Alcohol use	Nondrinker vs Drinker	South Korea	2	2,099	1.49 (0.99 – 2.24)	0
Medical checkup	Having a checkup within past year vs Not having a checkup	Overall	2	42,502	**1.75 (1.65 – 1.86)**	0
		USA	1	41,346	1.76 (1.66 – 1.87)*	NA
		South Korea	1	1,156	1.45 (0.99 – 2.11)*	NA
Health insurance	Having vs Not having health insurance	Overall	3	44,384	**1.39 (1.13 – 1.72)**	21.8
		USA	2	43,228	**1.45 (1.19 – 1.76)**	22
		South Korea	1	1,156	0.98 (0.48 – 2.01)*	NA

* = odds ratio (not pooled).NA = not applicable.

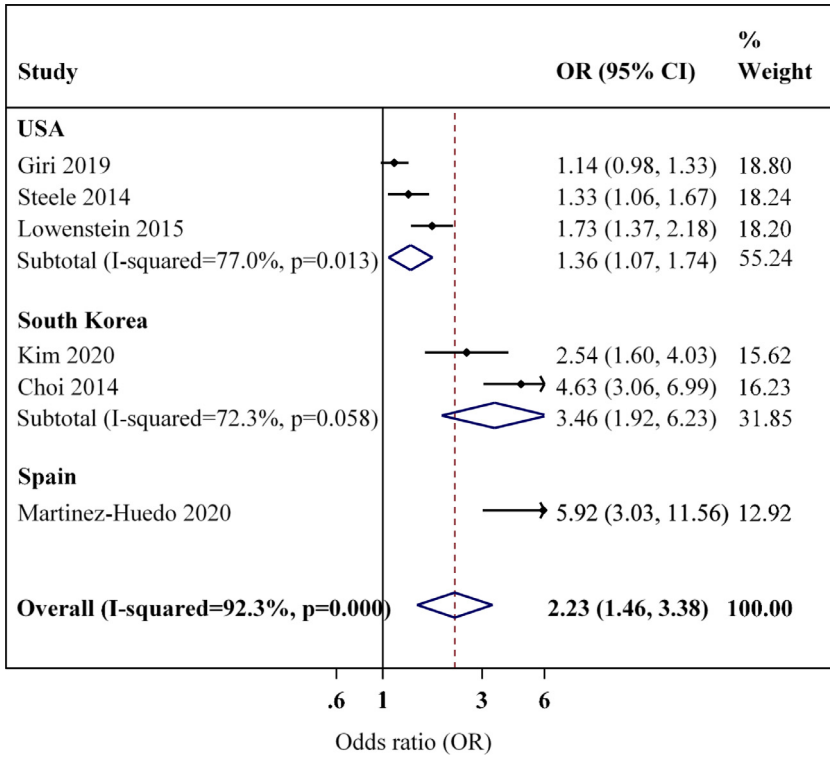

Fig. 2. Forest plot of the association between age and SIV uptake (older versus younger).

Health-related determinants

Overall, being a nonsmoker was found to be associated with a 43% increase in the odds of SIV uptake (32%-51%; I^2 0%, 4 studies: 45,655 participants; Fig 3). A larger associated 75% increase in the odds of SIV uptake was found with regard to South Korea. No association was found between alcohol consumption status and SIV uptake (Appendix Fig A9). Overall, having chronic disease(s) was associated with increased SIV uptake by 18% (7%-29%; I^2 15.7%, 5 studies: 16,768 participants) (Fig 4). A similar associated 15% increase in the odds of SIV uptake was found with regard to the United States of America.

Discussion

We sought to summarize the evidence on the association between sociodemographic and health-related factors, and SIV uptake among cancer patients. Overall, being older, a nonsmoker, having a chronic illness, having had a medical check-up in the past year, and having health insurance were all associated with increase in the odds of SIV uptake, whereas sex, marital status, level of education, level of income, area of residence, and alcohol consumption status all showed no association. However, when limited to South Korea, being male and living in a rural area were found to be associated with an increase in the odds of SIV uptake, and when limited to the United States of America, an increase in the odds of SIV uptake was found for having a higher education and for being Caucasian compared with being African-American. However,

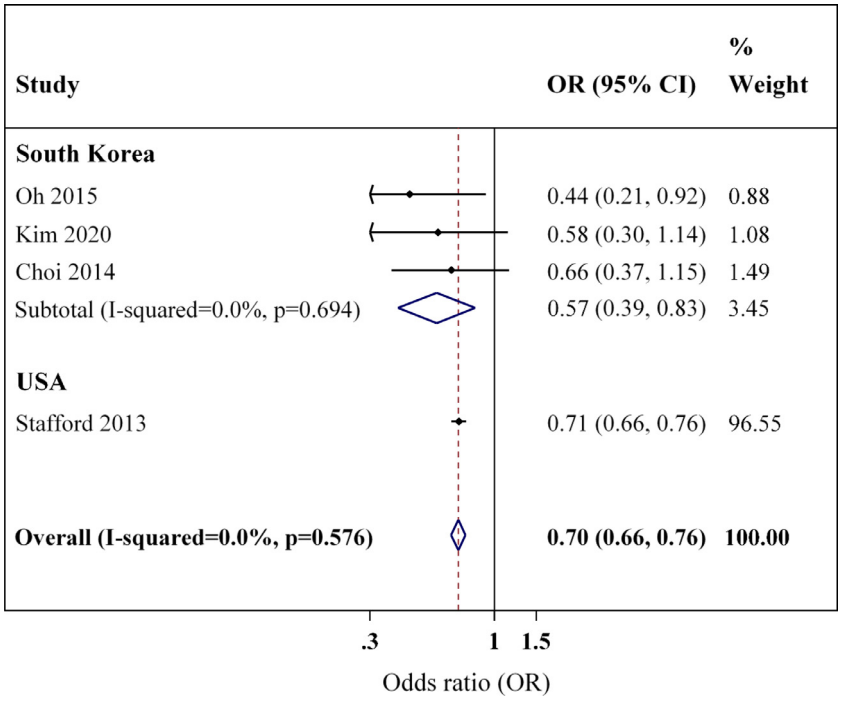

Fig. 3. Forest plot of the association between smoking status and SIV uptake (non-smokers versus smokers).

these findings may not be generalizable within and across jurisdictions due to the paucity of data.

Despite recommendation of annual seasonal influenza vaccination for cancer patients in many jurisdictions, vaccine hesitancy remains an issue that affects SIV acceptance. Even in poor health, skepticism influences acceptance of any health care. Generally, the decision to receive a vaccine is influenced by many factors, including complacency (low perceived risk/seriousness of an infectious disease), convenience (vaccine availability, accessibility, and affordability), and confidence (trust in vaccine effectiveness and safety).[41] The influence of these factors on both sociodemographic and health-related determinants of health, as well as on SIV uptake, could not be assessed in the included studies. In addition, most of the studies involved mixed cancer types with only 1 study each that focused on a solid cancer and on a hematological malignancy. Unfortunately, this meant that we could not explore the potential influence of cancer type on uptake of SIV. For example, hematological malignancy patients tend to undergo bone marrow transplant and intense immune suppression, and as such, may be more likely to be prescribed influenza vaccination. Furthermore, cancer stages differed significantly across studies. The method of confirmation of influenza vaccination also varied across studies; determined from electronic medical records in some studies and self-reported in others, with the potential for social desirability and recall biases. Categories of some of the determinants, for example, age and educational attainment, and covariates adjustments in multivariable logistic regression models differed across studies. These differences, in addition to the underlying differences in the studied populations, may explain the high heterogeneity in a few of the pooled analyses. Additionally, there are potential differences between the health systems of the countries where the studies were conducted, especially with regards to access to vaccination; and for this reason, we also reported country-specific pooled analyses.

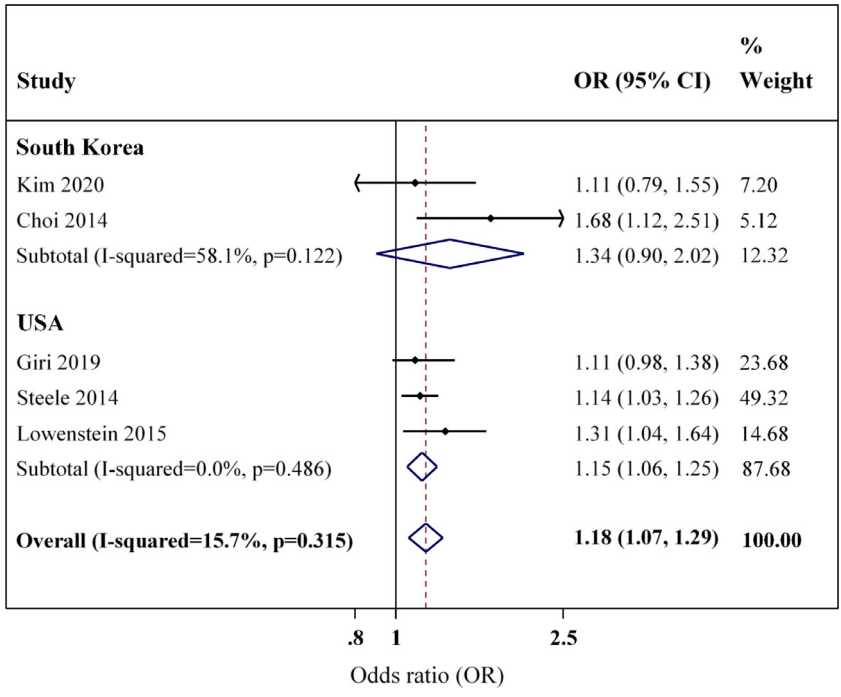

Fig. 4. Forest plot of the association between having a chronic disease and SIV uptake (having a chronic disease versus not).

Nonetheless, this review adds to the evidence base and provides more awareness to help clinicians assess and identify cancer patients that may be at increased risk of not receiving SIV and potentially not receiving other necessary preventive care. Considering that the available evidence is mainly from the United States of America and South Korea, in addition to the country-specific findings being potentially applicable to these countries, they may also be indicative of the determinants of SIV uptake among cancer patients in other jurisdictions with similar health system and population characteristics. This review also reveals the need for clinicians to engage more with, and to endeavour to recommend SIV and other preventive care to, younger cancer patients who may not be considered high-risk despite having cancer. However, in a country like the United States of America where healthcare is not offered free-of-charge, in addition to being employed, being educated and having health insurance also determine uptake of vaccination among cancer patients, as we have found; therefore, we recognize that SIV may not be accepted even if offered, due to cost implications to the patient. Our review findings could also aid public health experts and policy makers in designing targeted programs to help optimize influenza vaccination. Furthermore, the review reveals a lack of publications on the determinants of seasonal influenza vaccination among cancer patients, and suggests the need for consistency in definition and measurement of covariates across future studies.

We did not identify any previous similar meta-analysis in this patient population to compare our findings against. However, our findings are consistent with recent meta-analyses of the determinants of SIV uptake among older adults,[23,24] suggesting that the factors identified in this review may indeed play an important role in determining SIV uptake in different subpopulations. The observed increase in the odds of SIV uptake with older age may be a reflection of increased incidence of chronic diseases with aging.[42] This would lead to frequent contacts with healthcare providers,[43,44] and potentially increase the likelihood of being offered SIV. The observed increased odds of SIV uptake with having a chronic disease may be because seasonal

influenza vaccination is highly recommended for cancer patients as well as individuals who have other chronic disease(s) in the study jurisdictions; therefore, cancer patients who also have other chronic disease(s) are more likely to be offered and to have received SIV. Our findings with respect to ethnicity and education in the USA may be explained by previous literature which suggested that ethnicity is associated with educational achievement,[45,46] and employment status,[47,48] and that access and utilization patterns of healthcare services in the United States of America are influenced by ethnicity,[49,50] and education.[51,52] Furthermore, ethnicity and education, in addition to employment status and income, have been found to determine health insurance coverage in the United States of America,[53] and this may explain the observed associated increased odds of SIV uptake with having health insurance.

This review may not be an exhaustive assessment of all potentially relevant studies considering that we only included publications in English and studies conducted since 2000. However, due to a lack of resources, we could not support non-English language translations and limiting to publications since 2000 allowed us to focus on studies conducted after influenza vaccination became publicly funded in many jurisdictions. Inadequacy of data did not allow us to conduct some of the subgroup analysis that we planned a priori, and we could not examine publication bias for many of the assessed determinants. There are however many merits to this review. The search strategy was comprehensive and was developed and peer reviewed by professional health sciences librarians. We also conducted and reported the review in full compliance with known guidelines. To the best of our knowledge, this review is the first to provide a comprehensive quantitative summary of the available evidence on the sociodemographic and health-related determinants of seasonal influenza vaccination among cancer patients.

Conclusions

Limited evidence, mainly from the United States of America and South Korea, suggests that sociodemographic and health-related factors may determine seasonal influenza vaccination among cancer patients. The paucity of the data highlights the need for more high-quality studies.

Disclosures

No funding was attained for this study. S.M.M. is supported, in part, by funding from the Canada Research Chairs Program. G.N.O. is a recipient of the Manitoba Training Program Fellowship Award, the Centre on Aging Betty Havens Memorial Graduate Fellowship Award, and the Evelyn Shapiro Award, all for health services research.

Conflicts of Interest

S.M.M. has received unrestricted research grants from GlaxoSmithKline, Merck, Sanofi Pasteur, Pfizer and Roche-Assurex for unrelated studies, and fees as an advisory board member for Sanofi Pasteur. The other authors declare that they have no conflict of interest.

Acknowledgments

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Appendices

Tables A1 and A2, Figures A1-A9.

Table A1
Search strategy for Ovid MEDLINE(R) Epub Ahead of Print, In-process & Other Non-Indexed Citations and Daily <1946 to February 12, 2020>.

No.	Searches
1	Influenza Vaccines/
2	Influenza, Human/pc
3	("flu shot" or "flu shots").ti,ab,kf.
4	(Antiinfluenza or "anti influenza" or antiflu or "anti flu").ti,ab,kf.
5	or/1-4
6	Influenza, Human/
7	exp influenzavirus a/
8	exp influenzavirus b/
9	flu.ti,ab,kf.
10	Influenza*.ti,ab,kf.
11	or/6-10
12	Vaccines/
13	immunization/sn, td
14	exp Immunization Programs/
15	inoculat*.ti,ab,kf.
16	vaccin*.ti,ab,kf.
17	immuni*.ti,ab,kf.
18	or/12-17
19	5 or (11 and 18)
20	"Patient Acceptance of Health Care"/
21	patient compliance/
22	medication adherence/
23	exp Socioeconomic Factors/
24	Health Knowledge, Attitudes, Practice/
25	(Uptake or "up take").ti,ab,kf.
26	Adhere*.ti,ab,kf.
27	(Complian* or Comply or complied).ti,ab,kf.
28	accept*.ti,ab,kf.
29	Predict*.ti,ab,kf.
30	Factor*.ti,ab,kf.
31	Facilitat*.ti,ab,kf.
32	Enabl*.ti,ab,kf.
33	encourag*.ti,ab,kf.
34	motivat*.ti,ab,kf.
35	help*.ti,ab,kf.
36	(succeed or success*).ti,ab,kf.
37	Determinant*.ti,ab,kf.
38	characteristic*.ti,ab,kf.
39	indicator*.ti,ab,kf.
40	(demographic* or sociodemographic*).ti,ab,kf.
41	((improv* or increas* or rise or rais* or optimal* or optimi* or higher or influenc*) adj4 (level* or coverage or rate* or access*)).ti,ab,kf.
42	((improv* or increas* or rise or rais* or optimal* or optimi* or higher or influenc*) adj4 (probability or chance* or likelihood)).ti,ab,kf.
43	(barrier* or obstacle* or hinder* or hesitan* or hesitat* or refus* or noncomplian* or "non complian*" or deter* or discourag* or challeng*).ti,ab,kf.
44	or/20-43
45	exp Neoplasms/
46	cancer*.ti,ab,kf.
47	neoplas*.ti,ab,kf.

(*continued on next page*)

Table A1 (*continued*)

No.	Searches
48	tumo?r*.ti,ab,kf.
49	malignan*.ti,ab,kf.
50	metasta*.ti,ab,kf.
51	(carcinoma* or adenocarcinoma*).ti,ab,kf.
52	adenoma*.ti,ab,kf.
53	leuk?emia.ti,ab,kf.
54	lymphoma*.ti,ab,kf.
55	melanoma*.ti,ab,kf.
56	(sarcoma* or adenosarcoma* or gliosarcoma*).ti,ab,kf.
57	(blastoma* or retinoblastoma*).ti,ab,kf.
58	glioma*.ti,ab,kf.
59	meningioma*.ti,ab,kf.
60	(astrocytoma* or neurocytoma*).ti,ab,kf.
61	oncogen*.ti,ab,kf.
62	oncolog*.ti,ab,kf.
63	chemotherap*.ti,ab,kf.
64	radiotherap*.ti,ab,kf.
65	or/45-64
66	19 and 44 and 65
67	66 not (((exp animals/ or exp Models, Animal/) not humans/) or (mice or mouse or murine or rat or rats).ti.)
68	limit 67 to english language
69	remove duplicates from 68
70	limit 69 to yr="2000 -Current"

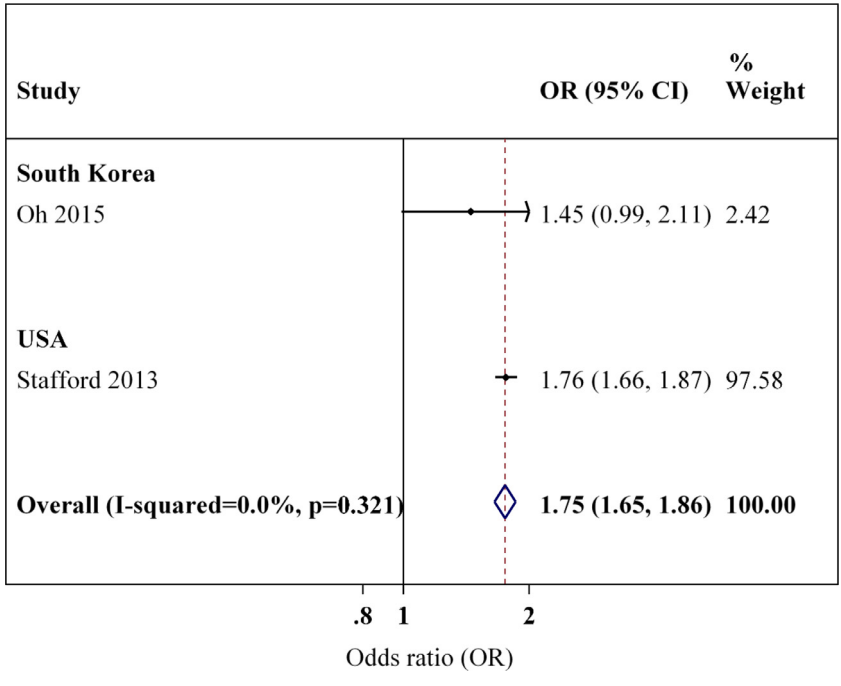

Fig. A1. Forest plot of the association between medical check-up and SIV uptake (having had versus not having had).

Table A2
Study quality assessment.

Study	Research objective stated	Study population specified	Participation rate ≥50%	Eligibility uniformly applied	Sample size justification	Exposures measured prior to outcomes	Sufficient study timeframe	Measured different levels of exposure	Consistent exposure measure across participants	Exposure assessed more than once over time	Outcome measures clearly defined	Blinding of outcome assessors	<20% Loss to follow-up	Confounders measured and adjusted
Stafford 2013[31]	✓	✓	NA	✓	✗	✓	NA	✓	✓	NA	✓	NA	NA	✓
Choi 2014[32]	✓	✓	NA	✓	✗	✓	NA	✓	✓	NA	✓	NA	NA	✓
Steele 2014[33]	✓	✓	NA	✓	✗	✓	NA	✓	✓	NA	✓	NA	NA	✓
Vinograd 2014[34]	✓	✓	NA	✓	✓	✓	NA	✓	✓	NA	✓	NA	NA	✓
Lowenstein 2015[35]	✓	✓	NA	✓	✗	✓	NA	✓	✓	NA	✗	NA	NA	✓
Oh 2015[36]	✓	✓	NA	✓	✗	✓	NA	✓	✓	NA	✓	NA	NA	✓
Pettke 2017[37]	✓	✓	NA	✓	✗	✓	NA	✓	✓	NA	✓	NA	NA	✓
Giri 2019[38]	✓	✓	NA	✓	✗	✓	NA	✓	✓	NA	✓	NA	NA	✓
Kim 2020[39]	✓	✓	NA	✓	✗	✓	NA	✓	✓	NA	✓	NA	NA	✓
Martinez-Huedo 2020[40]	✓	✓	NA	✓	✗	✓	NA	✓	✓	NA	✓	NA	NA	✓

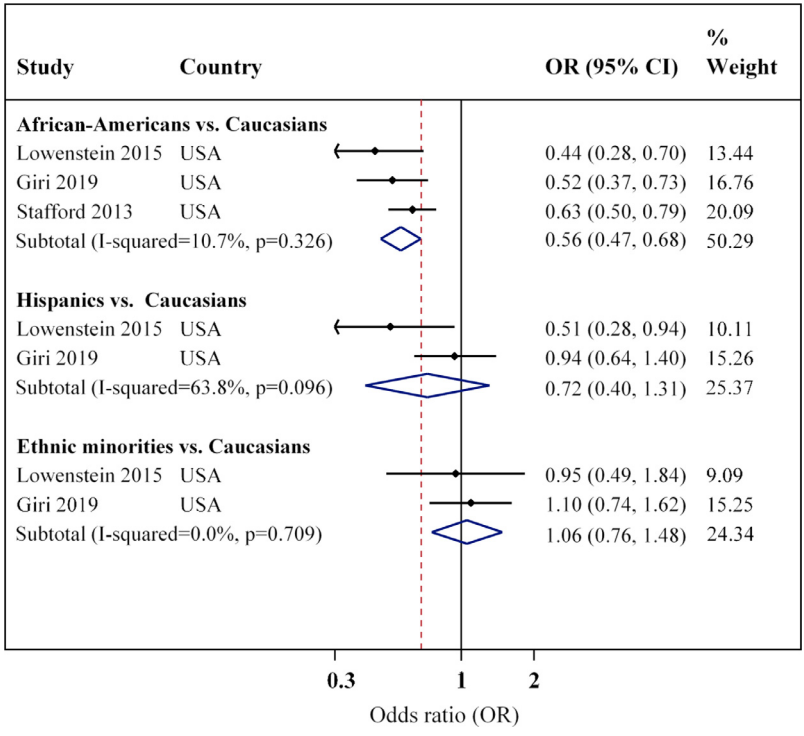

Fig. A2. Forest plot of the association between ethnicity and SIV uptake.

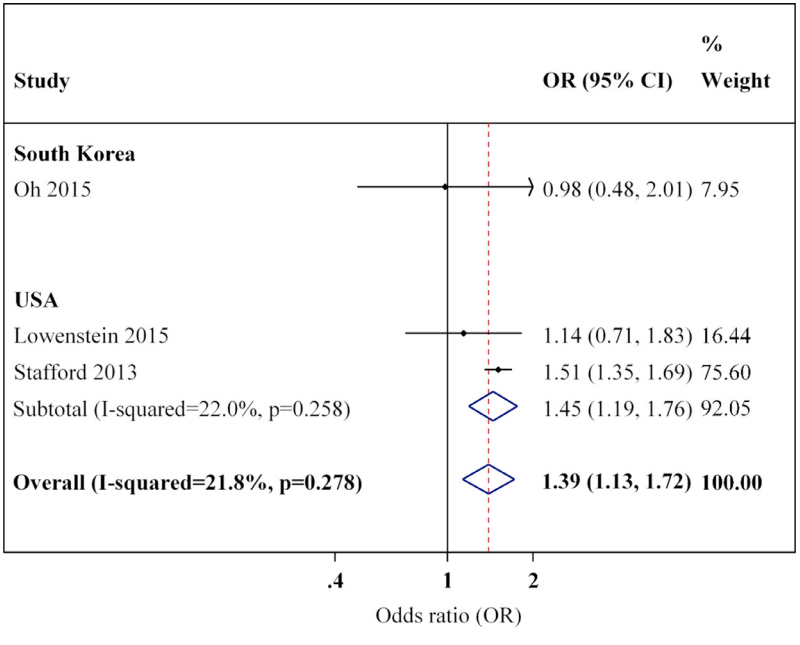

Fig. A3. Forest plot of the association between health insurance and SIV uptake (having vs not having).

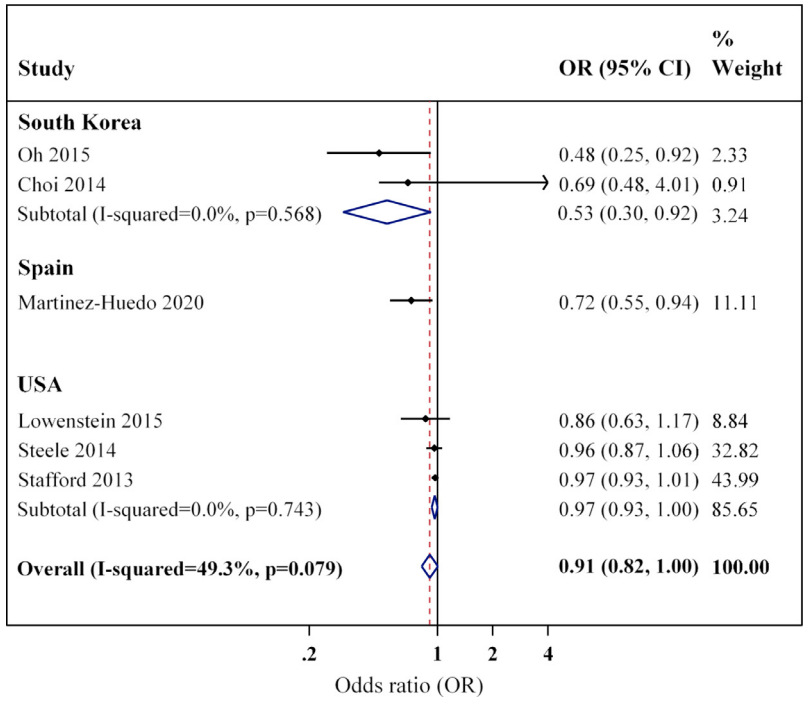

Fig. A4. Forest plot of the association between sex and SIV uptake (females vs males).

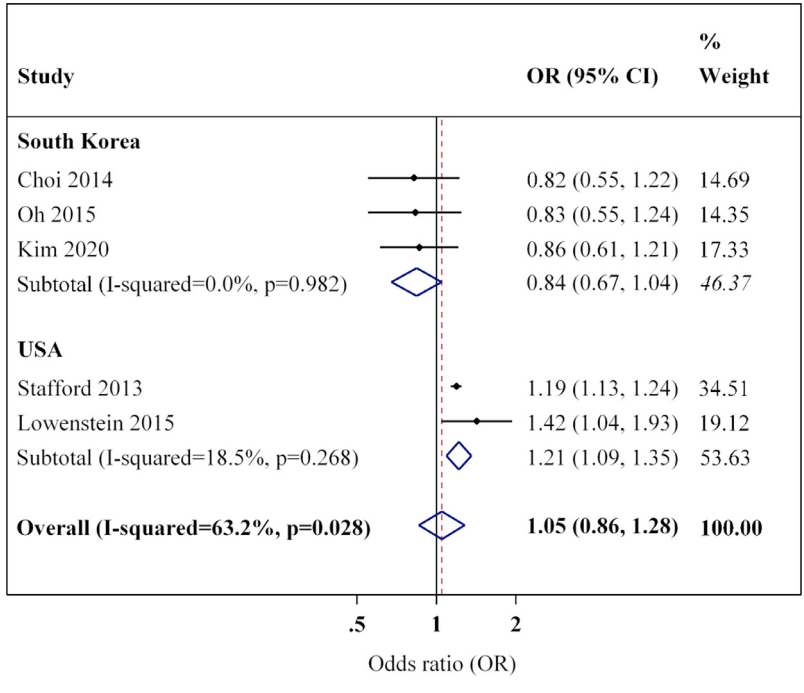

Fig. A5. Forest plot of the association between education and SIV uptake (higher vs lower education).

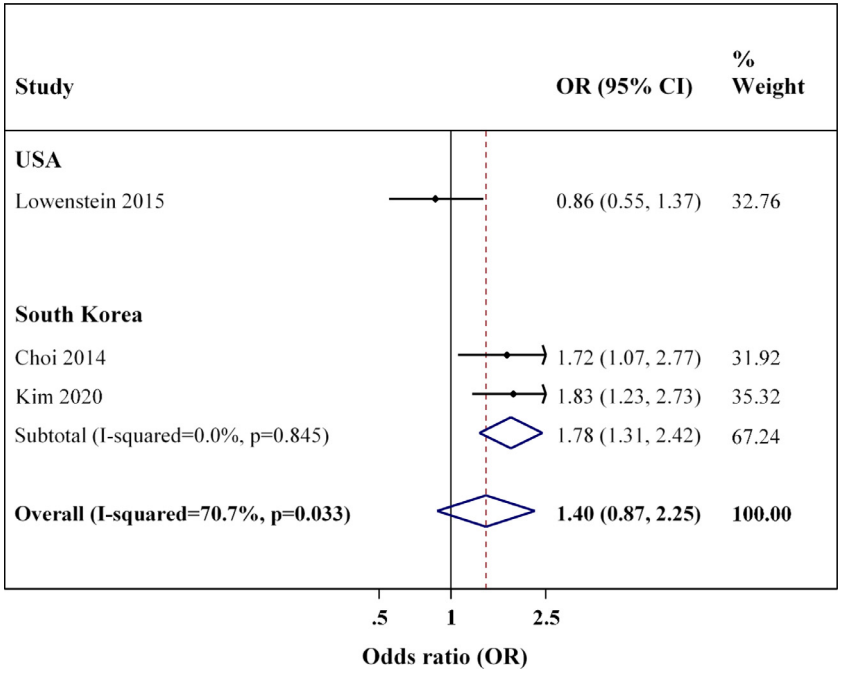

Fig. A6. Forest plot of the association between area of residence and SIV uptake (rural vs urban).

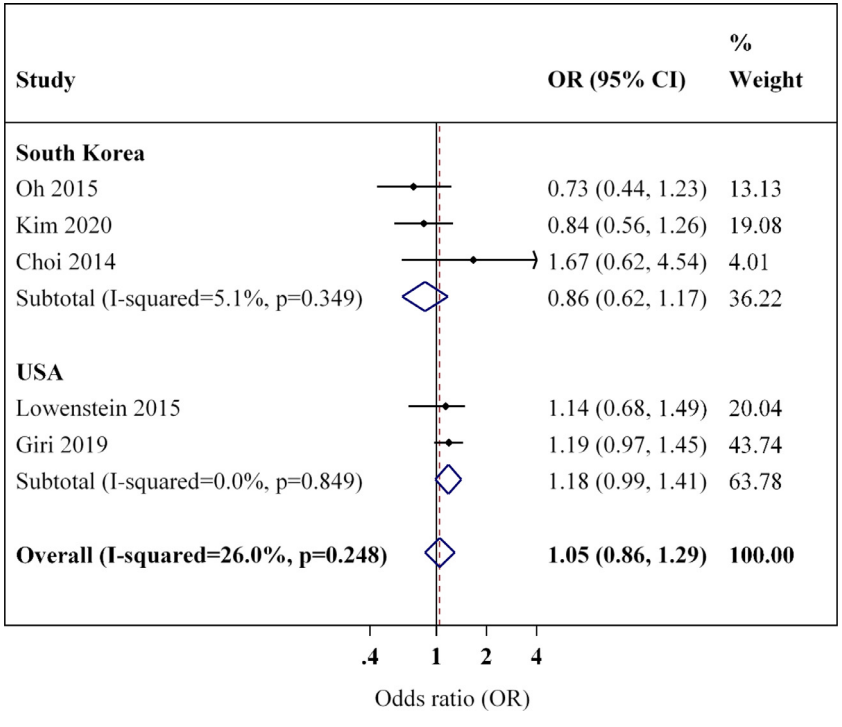

Fig. A7. Forest plot of the association between marriage and SIV uptake (married vs not married).

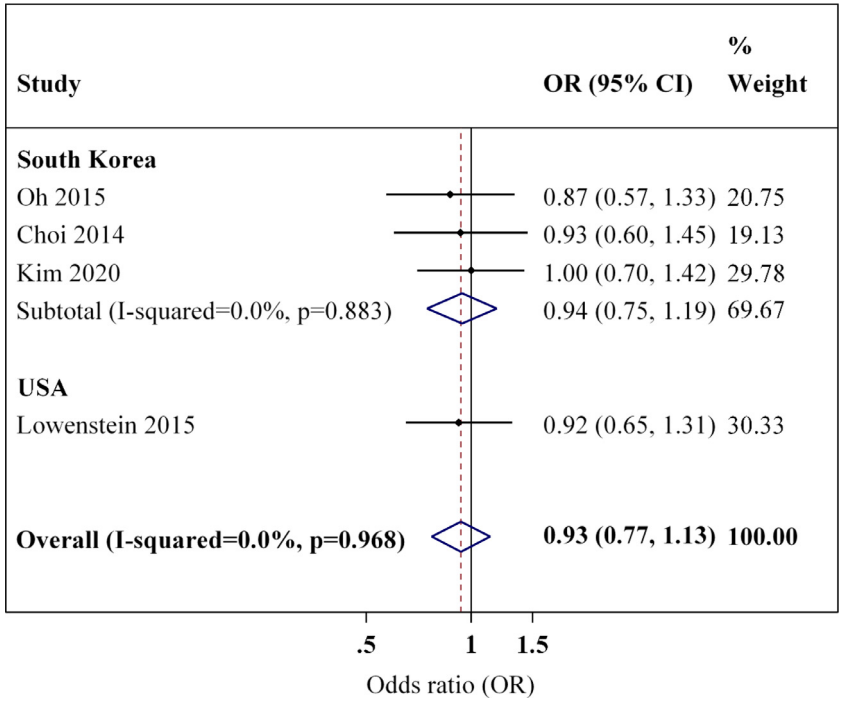

Fig. A8. Forest plot of the association between income and SIV uptake (higher vs lower income).

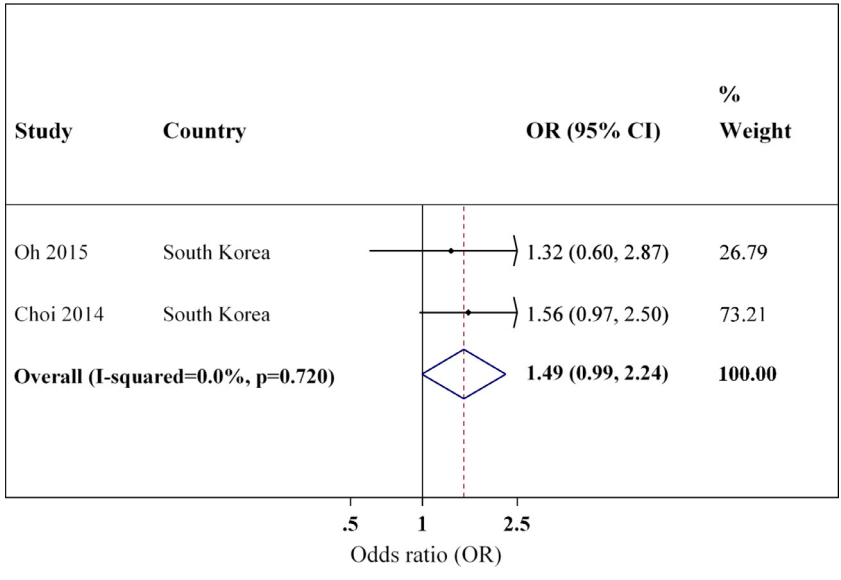

Fig. A9. Forest plot of the association between alcohol drinking and SIV uptake (nondrinker vs drinker).

References

1. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. *Lancet Infect Dis*. 2009;9:493–504.
2. Schnell D, Mayaux J, de Bazelaire C, et al. Risk factors for pneumonia in immunocompromised patients with influenza. *Respir Med*. 2010;104:1050–1056.
3. Dignani MC, Costantini P, Salgueira C, et al. Pandemic 2009 Influenza A (H1N1) virus infection in cancer and hematopoietic stem cell transplant recipients; a multicenter observational study. *F1000Res*. 2014;3:221.
4. Redelman-Sidi G, Sepkowitz KA, Huang CK, et al. 2009 H1N1 influenza infection in cancer patients and hematopoietic stem cell transplant recipients. *J Infection*. 2010;60:257–263.
5. Centers for Disease CPrevention. Surveillance for foodborne disease outbreaks — United States, 2007. *MMWR Morb Mortal Wkly Rep*. 2010;59:973–979.
6. Bitterman R, Eliakim-Raz N, Vinograd I, Zalmanovici Trestioreanu A, Leibovici L, Paul M. Influenza vaccines in immunosuppressed adults with cancer. *Cochrane Database Syst Rev*. 2018;2.
7. La Torre G, Mannocci A, Colamesta V, D'Egidio V, Sestili C, Spadea A. Influenza and pneumococcal vaccination in hematological malignancies: a systematic review of efficacy, effectiveness, and safety. *Mediterr J Hematol Infect Dis*. 2016;8.
8. Pollyea DA, Brown JM, Horning SJ. Utility of influenza vaccination for oncology patients. *J Clin Oncol*. 2010;28:2481–2490.
9. Chu CS, Boyer JD, Jawad A, et al. Immunologic consequences of chemotherapy for ovarian cancer: impaired responses to the influenza vaccine. *Vaccine*. 2013;31:5435–5442.
10. McManus M, Frangoul H, McCullers JA, Wang L, O'Shea A, Halasa N. Safety of high dose trivalent inactivated influenza vaccine in pediatric patients with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2014;61:815–820.
11. Tregoning JS, Russell RF, Kinnear E. Adjuvanted influenza vaccines. *Hum Vaccin Immunother*. 2018;14:550–564.
12. Manuel O, Pascual M, Hoschler K, et al. Humoral response to the influenza A H1N1/09 monovalent AS03-adjuvanted vaccine in immunocompromised patients. *Clin Infect Dis*. 2011;52:248–256.
13. Anderson H, Petrie K, Berrisford C, Charlett A, Thatcher N, Zambon M. Seroconversion after influenza vaccination in patients with lung cancer. *Br J Cancer*. 1999;80:219–220.
14. Zhao L, Young K, Gemmill I. Summary of the NACI seasonal influenza vaccine statement for 2019-2020. *Can Commun Dis Rep*. 2019;45:149–155.
15. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices - United States, 2019-20 influenza season. *MMWR Recomm Rep*. 2019;68:1–21.
16. Poeppl W, Lagler H, Raderer M, et al. Influenza vaccination perception and coverage among patients with malignant disease. *Vaccine*. 2015;33:1682–1687.
17. Shih YCT, Pan IW. Influenza vaccination among individuals with cancer and their family members. *Am J Prev Med*. 2010;38:61–69.
18. Kamimura A, Trinh HN, Weaver S, et al. Knowledge and perceptions of influenza vaccinations among college students in Vietnam and the United States. *J Prev Med Pub Health*. 2017;50:268–273.
19. Mytton OT, O'Moore EM, Sparkes T, Baxi R, Abid M. Knowledge, attitudes and beliefs of health care workers towards influenza vaccination. *Occup Med (Oxf)*. 2013;63:189–195.
20. Beck CR, McKenzie BC, Hashim AB, et al. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis from a public health policy perspective. *PLoS One*. 2011;6:e29249.
21. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10.
22. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8:336–341.
23. Okoli GN, Abou-Setta AM, Neilson CJ, Chit A, Thommes E, Mahmud SM. Determinants of seasonal influenza vaccine uptake among the elderly in the United States: a systematic review and meta-analysis. *Gerontol Geriatr Med*. 2019;5.
24. Okoli GN, Lam OL, Racovitan F, et al. Seasonal influenza vaccination in older people: a systematic review and meta–analysis of the determining factors. *PLoS One*. 2020;15.
25. Hilderman T, Katz A, Derksen S, et al. In: Health M, ed.. Winnipeg, Manitoba: Manitoba Centre for Health Policy; 2011.
26. Hinman AR, Orenstein WA, Rodewald L. Financing immunizations in the United States. *Clin Infect Dis*. 2004;38:1445–1451.
27. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016;75:40–46.
28. Quality assessment tool for observational cohort and cross-sectional studies. National Institute of Health. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
29. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
30. Sterne JAC, Egger M, Smith GD. Systematic reviews in health care - investigating and dealing with publication and other biases in meta-analysis. *Bmj-Brit Med J*. 2001;323:101–105.
31. Stafford KA, Sorkin JD, Steinberger EK. Influenza vaccination among cancer survivors: disparities in prevalence between blacks and whites. *J Cancer Surviv*. 2013;7:183–190.
32. Choi KH, Park SM, Lee K, Lee JH, Park JS. Influenza vaccination and associated factors among Korean cancer survivors: a cross-sectional analysis of the Fourth & Fifth Korea National Health and Nutrition Examination Surveys. *J Korean Med Sci*. 2014;29:1061–1068.
33. Steele CB, Townsend JS, Tai E, Thomas CC. Physician visits and preventive care among Asian American and Pacific Islander long-term survivors of colorectal cancer, USA, 1996-2006. *J Cancer Surviv*. 2014;8:70–79.

34. Vinograd I, Baslo R, Eliakim-Raz N, et al. Factors associated with influenza vaccination among adult cancer patients: a case-control study. *Clin Microbiol Infect*. 2014;20:899–905.
35. Lowenstein LM, Ouellet JA, Dale W, Fan L, Gupta Mohile S. Preventive care in older cancer survivors. *J Geriatr Oncol*. 2015;6:85–92.
36. Oh MG, Han MA, Yun NR, et al. A population-based, nationwide cross-sectional study on influenza vaccination status among cancer survivors in Korea. *Int J Environ Res Public Health*. 2015;12:10133–10149.
37. Pettke A, Jocham S, Wiener A, et al. Vaccination against influenza at a European pediatric cancer center: immunization rates and attitudes among staff, patients, and their families. *Support Care Cancer*. 2017;25:3815–3822.
38. Giri S, Zhu WW, Wang R, et al. Underutilization of guideline-recommended supportive care among older adults with multiple myeloma in the United States. *Cancer-Am Cancer Soc*. 2019;125:4084–4095.
39. Kim YS, Lee JW, Kang HT, Kim Y, You HS. Trends in influenza vaccination coverage rates among Korean cancer survivors: analysis of the Korea National Health and Nutrition Examination Survey III-VI. *Korean J Fam Med*. 2020;41:45–52.
40. Martinez-Huedo MA, Lopez-De-Andres A, Mora-Zamorano E, et al. Decreasing influenza vaccine coverage among adults with high-risk chronic diseases in Spain from 2014 to 2017. *Hum Vaccin Immunother*. 2020;16:95–99.
41. MacDonald NEHesitancy SWGV. Vaccine hesitancy: definition, scope and determinants. *Vaccine*. 2015;33:4161–4164.
42. Atella V, Piano Mortari A, Kopinska J, et al. Trends in age-related disease burden and healthcare utilization. *Aging Cell*. 2019;18:e12861.
43. Berglund BE, Westerlund I. Patient organizations and primary care development: reflections by patients with chronic diseases. *Patient Exp. J*. 2016;3:31–36.
44. Østbye T, Yarnall KSH, Krause KM, Pollak KI, Gradison M, Michener JL. Is there time for management of patients with chronic diseases in primary care. *Ann Fam Med*. 2005;3:209–214.
45. Maestri V. Can ethnic diversity have a positive effect on school achievement. *Educ. Econ*. 2017;25:290–303.
46. Sander W. The effects of ethnicity and religion on educational attainment. *Econ. Educ. Rev*. 1992;11:119–135.
47. Djamba YK, Kimuna SR. The influence of race on employment status and earnings of African immigrant men in the United States. *Int. J. Popul. Res*. 2011;2011.
48. Byars-Winston A, Fouad N, Wen Y. Race/ethnicity and sex in U.S. occupations, 1970-2010: Implications for research, practice, and policy. *J Vocat Behav*. 2015;87:54–70.
49. Race Egede LE, ethnicity culture. and disparities in health care. *J Gen Intern Med*. 2006;21:667–669.
50. Ashton CM, Haidet P, Paterniti DA, et al. Racial and ethnic disparities in the use of health services - bias, preference, or poor communication? *J Gen Intern Med*. 2003;18:146–152.
51. Fletcher JM, Frisvold DE. Higher education and health investments: does more schooling affect preventive health care use? *J Hum Cap*. 2009;3:144–176.
52. Zajacova A, Lawrence EM. The relationship between education and health: reducing disparities through a contextual approach. *Annu Rev Publ Health*. 2018;39:273–289.
53. Fox JB, Shaw FE. Office of Health System Collaboration, Office of the Associate Director for Policy, CDC. Relationship of income and health care coverage to receipt of recommended clinical preventive services by adults - United States, 2011-2012. *MMWR Morb Mortal Wkly Rep*. 2014;63:666–670.