



Association between aspirin use and lung cancer incidence depends on high-frequency use, bodyweight, and age in U.S. adults

Xuesi Dong^{1,2,3,4#}, Jieyu He^{1,3#}, Lijuan Lin^{1,2,3#}, Ying Zhu^{1,3}, Chao Chen^{1,3}, Li Su^{2,5}, Yang Zhao^{1,2,3,6}, Ruyang Zhang^{1,2,3,6}, Yongyue Wei^{1,2,3,7}, Feng Chen^{1,3,8,9*}, David C. Christiani^{2,5*}

¹Department of Biostatistics, Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, China; ²Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA; ³Key Laboratory of Biomedical Big Data of Nanjing Medical University, Nanjing, China; ⁴Department of Epidemiology and Biostatistics, School of Public Health, Southeast University, Nanjing, China; ⁵Pulmonary and Critical Care Division, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; ⁶Department of Medical Oncology, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, China; ⁷China International Cooperation Center for Environment and Human Health, Nanjing Medical University, Nanjing, China; ⁸State Key Laboratory of Reproductive Medicine, Nanjing Medical University, Nanjing, China; ⁹Jiangsu Key Lab of Cancer Biomarkers, Prevention and Treatment, Cancer Center, Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing Medical University, Nanjing, China

Contributions: (I) Conception and design: X Dong, R Zhang, Y Wei; (II) Administrative support: F Chen, DC Christiani; (III) Provision of study materials or patients: Y Zhu; (IV) Collection and assembly of data: X Dong, Y Zhu; (V) Data analysis and interpretation: X Dong, J He, L Lin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work.

*These authors contributed equally to this work as senior authors.

Correspondence to: Ruyang Zhang, PhD. SPH Building Room 406, 101 Longmian Avenue, Nanjing 211166, China; Email: zhangruiyang@njmu.edu.cn; Yongyue Wei, PhD. SPH Building Room 418, 101 Longmian Avenue, Nanjing 211166, China. Email: ywei@njmu.edu.cn; Feng Chen, PhD. SPH Building Room 410, 101 Longmian Avenue, Nanjing 211166, China. Email: fengchen@njmu.edu.cn.

Background: Chemoprevention of cancer with aspirin is controversial as a primary prevention strategy. We sought to investigate the association between aspirin frequency and risk of lung cancer in The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Methods: Using data from 101,722 participants in PLCO, we used a Cox regression model coupling with propensity score to detect the association between aspirin frequency and lung cancer risk.

Results: High-frequency aspirin use significantly increased risk of lung cancer by 28% compared to no use (HR =1.28; 95% CI, 1.14–1.45; $P=3.37\times 10^{-5}$), especially for current smoker (HR =1.30; 95% CI, 1.07–1.57; $P=6.82\times 10^{-3}$). However, the increased lung cancer risk due to high-frequency aspirin use significantly decreased with increasing bodyweight (HR_{interaction} =0.96; 95% CI, 0.94–0.99; $P=1.26\times 10^{-2}$). Further, for participants with bodyweight <80 kg, high-frequency aspirin use showed an elevated risk at <76 years of age (HR_{age<76} =1.47; 95% CI, 1.25–1.73; $P=3.81\times 10^{-6}$). Our study used propensity score under various confounding and stratification analyses by cardio-cerebrovascular status, which all presented similar evidences.

Conclusions: High-frequency aspirin use is associated with the increased risk of lung cancer. Current smoker or people with age <76 years and bodyweight <80 kg should be more cautious to high-frequency aspirin use for lung cancer chemoprevention. This study provides a new insight for lung cancer chemoprevention.

Keywords: Aspirin; lung cancer; risk; bodyweight; age

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Introduction

Aspirin, one of the most frequently used medications worldwide, is effective for treatment of pain, inflammation, and fever (1). Recently, chemoprevention of cancer with aspirin has become of particular interest as a primary prevention strategy (2). This function may be due to the role of aspirin in inhibiting both non-selectively inactivating cyclooxygenase (COX)-1 and COX-2 enzymes, resulting in restoration of normal apoptosis and reduction of angiogenesis (3).

However, the practice of using aspirin for primary prevention of cancer remains controversial. A recent large-scale cohort study shown that long-term aspirin use was associated with a modest reduced risk for overall cancer, especially gastrointestinal tract tumors; regular aspirin use may prevent a substantial proportion of colorectal cancers and complement the benefits of screening (4). Consistently, United States Preventive Services Task Force recommends low-dose aspirin use for colorectal cancer chemoprevention in adults ages 50 to 59 years and 60 to 69 years, with grade level B and C respectively (5). However, a recent study demonstrated that risk of death from any cause is higher in aspirin users, with cancer a major contributor to higher mortality in the aspirin-using group (6). The American Cancer Society recommends against aspirin use for colorectal cancer prevention in the general population (7), except for persons with Lynch syndrome (8). Additionally, another study showed a slight promotion of brain tumors with aspirin use (9). These negative reports raise public concern over aspirin chemoprophylaxis.

For lung cancer, several meta-analyses demonstrate varied results and interpretations. Some studies show that aspirin users have significantly lower risk, while others report no significant difference (10-14). With adequate adjustment for demographic, dietary, and ethological factors, analysis of a cohort of women in the U.S. showed a 55% increased risk of lung cancer with high-frequency aspirin use (≥ 15 tablets per week) (15). On the other hand, evidences shown that the effect of aspirin use on chemoprevention can be modified by bodyweight and age (16,17). Thus, adequate adjustment for covariates (e.g., demographic, diet, cardio-cerebrovascular disease history) in a statistical model and comprehensive consideration of modifiers (e.g., bodyweight, age) may account for varied reported results. Further, the modified effect of high-frequency aspirin use on lung cancer risk by both bodyweight and age remains largely unclear.

Therefore, we analyzed data from participants enrolled in the Prostate, Lung, Colorectal and Ovarian (PLCO)

study to evaluate the association between aspirin use and lung cancer with the modifier roles of bodyweight and age as well as adjustment for demographic, dietary, and ethological factors. The results of our study provide new insight into the use of aspirin for chemoprevention of lung cancer.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-414>).

Methods

Experimental design

The study design of PLCO has been described previously (18). Briefly, 154,897 participants aged 55–74 years were enrolled during November 1993–July 2001, and data were collected up to December 31, 2009, with median follow-up of 11.9 years. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent, and the study was approved by both the National Cancer Institute and local Institutional Review Boards (ClinicalTrials.gov registration numbers: NCT01696968). We extracted Diet History Questionnaire (DHQ) data from PLCO, which was offered to both arms of the trial (screening and control) starting in 1998. In total, 77% of all participants in both arms of the trial completed the DHQ, screening arm complete 78%, and control arm 75%, respectively. Data for demographic and dietary variables were collected through epidemiological questions in a baseline questionnaire (BQ). We sequentially excluded unqualified samples for the following reasons: missing BQ; incomplete DHQ; invalid DHQ [missing ≥ 8 food items or extreme energy intake values (i.e., lowest or highest 1%)]; cancer diagnosed before study entry. After these exclusions, 101,722 participants remained in the study, [Figure S1](#).

Ascertainment of lung cancer

Participants in screening arm undergo a chest X-ray (one postero-anterior view) at baseline and annually for 2 years; Participants in control arm receive standard medical care. During the follow-up, participants with histologically confirmed lung cancers will be regard as cases. As per the PLCO protocol (NCT01696968), lung cancer diagnosis was confirmed through medical records abstraction and subsequent mortality (from lung cancer or otherwise) was confirmed through a death review committee if available,

otherwise by death certificate. The ICD codes used in this study is International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3): adenocarcinoma (AD), squamous cell carcinoma (SQ), other non-small cell carcinoma (OTH) and small cell carcinoma (SM). An Annual Study Update was mailed to each participant annually for 13 years to identify all new lung cancers among both screened and control subjects during the trial.

Aspirin use

The BQ included two questions that pertained to aspirin use. (I) “During the last 12 months, have you regularly used aspirin or aspirin-containing products, such as Bayer, Bufferin, or Anacin?” (Specific instruction was provided to not count aspirin-free products, such as Tylenol or Panadol). (II) “During the last 12 months, how many pills of aspirin or aspirin-containing products did you usually take per day, per week, or per month?” Possible responses were: none, <2 pills per month, 2–3 pills per month, 1 pill per week, 2 pills per week, 3–4 pills per week, 1 pill per day, or ≥ 2 pills per day. For this study, we categorized aspirin dose as: (I) no use: no history of aspirin use; (II) irregular use: <1 pill per week; (III) low use: 1–4 pills per week; and (IV) high use: ≥ 1 pill per day.

Covariate data

Information regarding the following patient characteristics was obtained from BQ responses: age at time of lung cancer diagnosis (in years), gender, ethnicity, PLCO trial arm, body mass index (BMI), smoking pack-years, family history of cancer (yes or no), and history of diabetes/heart/stroke disease (yes or no). Other intake variables previously reported to have a potential relationship with lung cancer incidence were extracted from DHQ: alcohol (19), total energy (20), vitamin C (21), vitamin E (22), folate (23), calcium (24), red meat (25), processed meat (26), lycopene (27), alpha-carotene (28), fruit (29), vegetables (30), and fat (31).

Statistical analysis

Age-adjusted incidence rates of lung cancer were determined for categories of aspirin use. Hazard ratio (HR) and 95% confidence interval (95% CI) were defined as the ratio of rate in each category of use compared with rate for no use. We used Cox proportional hazards models to adjust simultaneously for age, smoking characteristics, and other

potential confounders. We adjusted the level of age in Age-adjusted analysis (Model 1). In the smoking-adjusted analysis (Model 2), additional covariates were included in Cox models, including pack-years of smoking, gender, race, screening arm, BMI, diabetes, and heart disease and stroke history. Further, dietary factors, which were previously reported to affect lung cancer risk, were also taken into consideration in Dietary-adjusted analysis (Model 3), which additionally adjusted for intake of alcohol, total energy, vitamin C, vitamin E, folate, calcium, red meat, processed meat, lycopene, alpha-carotene, fruit, vegetables, and fat. The association between aspirin frequency and lung cancer risk was further evaluated among participants with different smoked (Never, former, current), and cardiac-cerebral vascular status. The BQ included two questions that pertained to cardiac-cerebral vascular disease. (I) “Did the participant ever have coronary heart disease or a heart attack?” and (II) “Did the participant have a stroke?”. Participants with/without cardiac-cerebral vascular disease were analyzed separately, because of the different purpose of aspirin use between two groups (32). Interaction term was incorporated into Cox models to describe synergetic or antagonistic effects among categories of aspirin use, bodyweight, and age. We adopted the propensity score method, which is qualified to adequately adjust for a series of covariates in the Cox proportional hazards regression model (33). Statistical analyses were performed using R program version 3.4.2. Two-sided P value of <0.05 was considered statistically significant.

Results

Detailed characteristics of the study population are shown in *Table 1*, by category of regular aspirin use over the follow-up period. Results are shown as mean \pm SD for continuous variables and as number (percent) for categorical variables.

High-frequency aspirin use was associated with lung cancer incidence

Age-adjusted analysis (Model 1) showed a linear trend between aspirin use and lung cancer incidence, with modest positive association (HR =1.07; 95% CI, 1.03–1.11; $P=2.02 \times 10^{-4}$) (*Table 2*). High-frequency of aspirin use was significantly associated with higher risk of lung cancer (HR =1.28; 95% CI, 1.14–1.44; $P=5.11 \times 10^{-5}$). However, effects among irregular and low-frequency aspirin users were not significant when compared with non-users.

In the smoking-adjusted analysis (Model 2), additional

Table 1 Cohort characteristics, stratified by level of aspirin use

Characteristics	Aspirin use in past 12 months			
	No use, n=51,870	Irregular use (<1 pill per week), n=99,46	Low use (1–4 pills per week), n=13,477	High use (≥1 pill per day), n=26,429
Lung cancer event	670 (1.29)	143 (1.44)	167 (1.24)	448 (1.70)
Age, years	65.28±5.69	64.81±5.68	65.51±5.71	66.25±5.76
Female (%)	29,171 (56.35)	4820 (48.82)	6,669 (49.77)	11,451 (43.32)
BMI (kg/m ²)	27.13±4.87	27.26±4.78	26.94±4.48	27.79±4.87
Bodyweight (kg)	78.15±16.67	79.39±16.78	78.76±15.86	81.87±16.88
Pack-years	15.91±25.22	18.46±26.29	17.52±26.27	21.55±29.34
Alcohol intake (g/day)	8.74±23.89	10.17±26.47	10.52±24.97	10.35±27.42
Screening arm	26,451 (51.09)	4,800 (48.62)	6,838 (51.04)	13,625 (51.55)
White (non-Hispanic)	46,443 (89.71)	8,724 (88.38)	12,570 (93.82)	24,555 (92.90)
Total energy intake (kcal/day)	1,705.20±726.83	1,778.54±767.42	1,769±718.41	1,773.87±748.97
Vitamin C (mg/day)	356.84±381.84	351.86±375.01	390.84±375.87	416.61±406.33
Vitamin E (mg/day)	137.62±170.60	138.72±172.19	163.79±171.95	180.34±186.46
Folate (mcg/day)	559.12±256.96	564.2±260.01	592.47±252.15	605.01±262.67
Calcium (mg/day)	998.02±519.87	976.35±511.89	1,027.53±502.17	1,023.27±527.32
Red meat (g/day)	59.29±50.85	65.3±55.3	63.3±51.43	63.65±54.49
Processed meat (g/day)	16.37±18.49	17.71±19.27	17.06±18.41	18.04±19.49
Lycopene (mcg/day)	6,265.31±6664.72	6,556.27±7034.22	6,625.05±6,869.4	6,766.95±7,517.76
Alpha-carotene (mcg/day)	841.38±925.09	830.13±908.79	857.8±908.66	830.38±899.78
Fruit (g/day)	271.6±218.81	271.22±217.94	274.47±204.38	279.01±222.09
Vegetables (g/day)	280.16±185.3	286.1±190.86	287.08±178.74	289.46±190.38
Fat (g/day)	61.46±33.22	64.68±34.96	63.74±32.78	62.96±34.09
Family cancer history	29,280 (56.56)	5,496 (55.67)	7,552 (56.37)	14,369 (54.36)
Complication (%)				
Heart disease	1,670 (3.22)	243 (2.46)	638 (4.76)	5,866 (22.19)
Stroke	605 (1.16)	86 (0.87)	144 (1.07)	1,205 (4.55)
Diabetes	2,977 (5.75)	559 (5.66)	659 (4.91)	2,595 (9.81)
Hypertension	14,637 (28.27)	2,682 (27.17)	4,126 (30.79)	11,523 (43.59)

BMI, body mass index.

covariates were included in Cox models, including pack-years of smoking, gender, race, screening arm, BMI, diabetes, and heart disease and stroke history. HRs for lung cancer incidence were still not significant for irregular-frequency and low-frequency aspirin use compared to non-users, although high-frequency aspirin use remained

significantly associated with the increased risk of lung cancer (HR =1.29; 95% CI, 1.15–1.46; P=3.37×10⁻⁵).

Further, dietary factors, which were previously reported to affect lung cancer risk, were also taken into consideration in Model 3, which additionally adjusted for intake of alcohol, total energy, vitamin C, vitamin E, folate, calcium,

Table 2 Relationship between aspirin use and lung cancer incidence among all participants

Aspirin frequency	N	Lung cancer event	Crude incidence (%)	HR _{Model 1} [*]	HR _{Model 2} [†]	HR _{Model 3} [‡]
Linear trend	101,722	1,428	1.41	1.07 (1.03–1.11), P=2.02×10 ⁻⁴	1.08 (1.04–1.12), P=1.73×10 ⁻⁴	1.08 (1.03–1.12), P=1.91×10 ⁻⁴
No use	51,870	670	1.29	Ref	Ref	Ref
Irregular-frequency	9,946	143	1.44	1.17 (0.97–1.4), P=0.10	1.11 (0.92–1.32), P=0.27	1.10 (0.92–1.32), P=0.28
Low-frequency	13,477	167	1.24	0.96 (0.81–1.14), P=0.62	0.96 (0.81–1.13), P=0.59	0.95 (0.8–1.13), P=0.57
High-frequency	26,429	448	1.72	1.28 (1.14–1.44), P=5.11×10 ⁻⁵	1.29 (1.15–1.46), P=3.37×10 ⁻⁵	1.28 (1.14–1.45), P=3.01×10 ⁻⁵

^{*}, Model 1: Cox regression model adjusted for age; [†], Model 2: Cox regression model adjusted for propensity score calculated using age, pack-years of smoking, gender, race, screening arm, body mass index, diabetes, and heart disease and stroke history; [‡], Model 3: Cox regression model adjusted for propensity score calculated using age, pack-years of smoking, gender, race, screening arm, body mass index, diabetes, heart disease and stroke history, and intake of alcohol, total energy, vitamin C, vitamin E, folate, calcium, red meat, processed meat, lycopene, alpha-carotene, fruit, vegetables, and fat. Irregular use: 1 pill per week; Low use: 1–4 pills per week; High use: ≥1 pill per day. HR, hazard ratio.

Table 3 Relationship between aspirin use and lung cancer incidence among participants without cardiac-cerebral vascular disease

Aspirin frequency	N	Lung cancer event	Crude incidence (%)	HR _{Model 1} [*]	HR _{Model 2} [†]	HR _{Model 3} [‡]
Linear trend	89,994	1,219	1.35	1.05 (1.01–1.1), P=0.02	1.05 (1.01–1.1), P=0.01	1.05 (1.01–1.1), P=0.01
No use	48,971	623	1.27	Ref	Ref	Ref
Irregular-frequency	9,346	138	1.48	1.20 (1.00–1.44), P=0.05	1.13 (0.94–1.36), P=0.17	1.13 (0.94–1.36), P=0.18
Low-frequency	12,406	154	1.24	0.97 (0.81–1.16), P=0.74	0.97 (0.81–1.15), P=0.71	0.97 (0.81–1.15), P=0.69
High-frequency	19,271	304	1.58	1.21 (1.05–1.39), P=6.45×10 ⁻³	1.22 (1.06–1.40), P=5.03×10 ⁻⁵	1.22 (1.06–1.41), P=4.47×10 ⁻³

^{*}, Model 1: Cox regression model adjusted for age; [†], Model 2: Cox regression model adjusted for propensity score calculated using age, pack-years of smoking, gender, race, screening arm, body mass index, diabetes, and heart disease and stroke history; [‡], Model 3: Cox regression model adjusted for propensity score calculated using age, pack-years of smoking, gender, race, screening arm, body mass index, diabetes, heart disease and stroke history, and intake of alcohol, total energy, vitamin C, vitamin E, folate, calcium, red meat, processed meat, lycopene, alpha-carotene, fruit, vegetables, and fat. Irregular use: 1 pill per week; Low use: 1–4 pills per week; High use: ≥1 pill per day. HR, hazard ratio.

red meat, processed meat, lycopene, alpha-carotene, fruit, vegetables, and fat. Model 3 showed no obvious change in the consequence of aspirin frequency on lung cancer risk. As shown in *Table 2*, high-frequency aspirin use increased the risk of lung cancer by 28% (HR =1.28; 95 % CI =1.14–1.45; P=3.01×10⁻⁵). We evaluated the association between high-frequency aspirin use and lung cancer risk among different smoking status. As shown in *Table S1*, high-frequency aspirin use significantly associated with increased risk of lung cancer for current cigarette smoker (HR =1.30; 95% CI, 1.07–1.57; P=6.82×10⁻³).

High-frequency aspirin users without cardiac-cerebral vascular disease are susceptible to lung cancer

Participants with cardiac-cerebral vascular disease had a higher likelihood of high aspirin use (*Table 1*). Therefore, we stratified the population into two groups according to participants' cardiac-cerebral vascular status and recalculated the association between high-frequency aspirin use and lung cancer risk. For participants without cardiac-cerebral vascular disease, high-frequency aspirin use was significantly associated with the increased risk of lung cancer (*Table 3*). After adjustment for smoking/

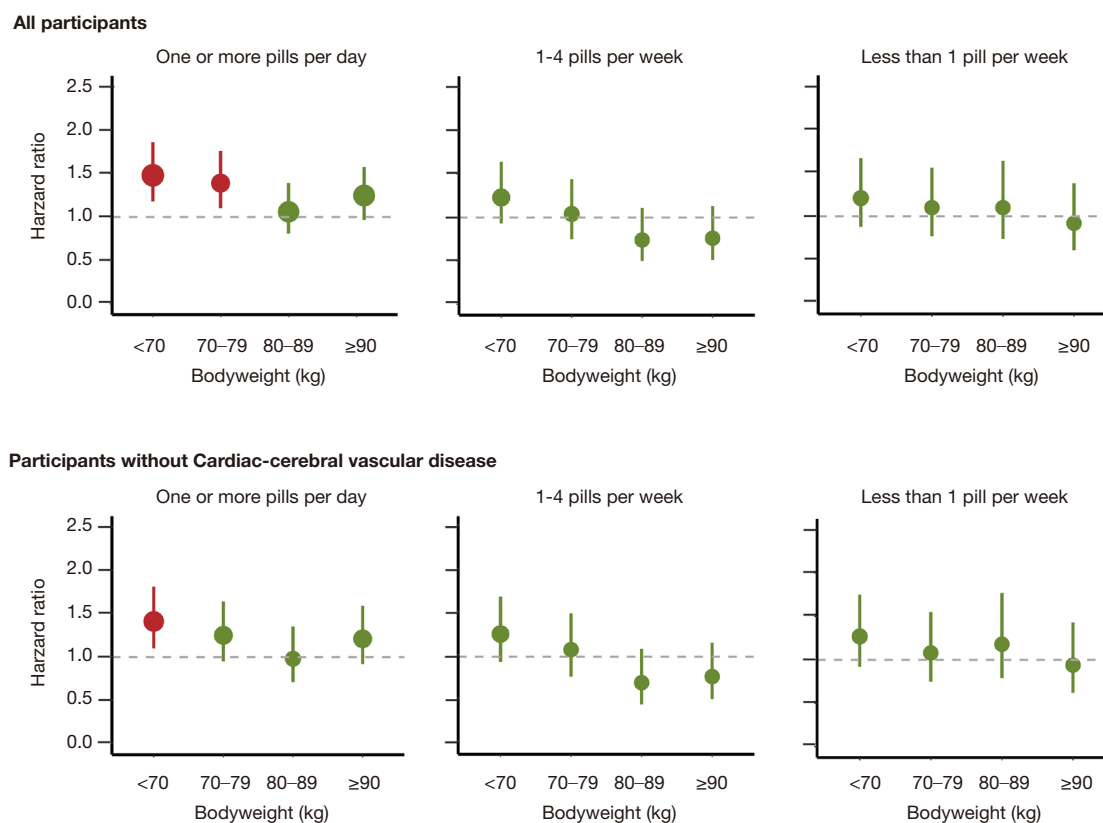


Figure 1 Effect of aspirin use on risk of lung cancer according to bodyweight, compared to no aspirin use, for all participants and for participants without cardiac-cerebral vascular disease. Size of circles representing point estimates of hazard ratios is proportional to inverse of variance of the estimate.

dietary factors, high-frequency aspirin use showed a stably positive association with lung cancer risk (HR =1.22; 95% CI, 1.06–1.41; $P=4.47 \times 10^{-3}$) compared with aspirin non-users. Irregular and low-frequency aspirin use did not have a significant association. For participants with cardiac-cerebral vascular disease, no significant association with lung cancer risk was observed at any frequency of aspirin use, even if covariates were well-adjusted (Table S2).

Bodyweight modifies the adverse effect of high aspirin use

To investigate whether the association between aspirin use and lung cancer was modified by bodyweight, we divided participants into bodyweight categories of <70, 70–79, 80–89, and >90 kg. The association between high-frequency aspirin use and lung cancer risk decreased with increasing bodyweight (HR_{interaction} =0.96; 95% CI, 0.94–0.99; $P=1.26 \times 10^{-2}$) in linear model. High-frequency aspirin use and bodyweight of <80 kg had a significantly adverse effect

for lung cancer risk (Figure 1, Table S3).

For participants without cardiac-cerebral vascular disease, compared with no-users, high-frequency aspirin use among bodyweight of <70 kg had a positive association with lung cancer risk (Figure 1 and Table S4), although the linear interaction term (treat aspirin frequency as continuous variable) was not significant (HR_{interaction} =0.97; 95% CI, 0.92–1.01; $P=0.18$). The association between aspirin use and lung cancer incidence was not significant for participants with cardiac-cerebral vascular disease (Figure S2 and Table S5).

Older age alleviates the adverse association between high-frequency aspirin use and lung cancer incident among individuals with lower bodyweight

We further evaluated whether high-risk groups of (I) high aspirin users with bodyweight <80 kg and (II) high aspirin users without cardiac-cerebral vascular disease and

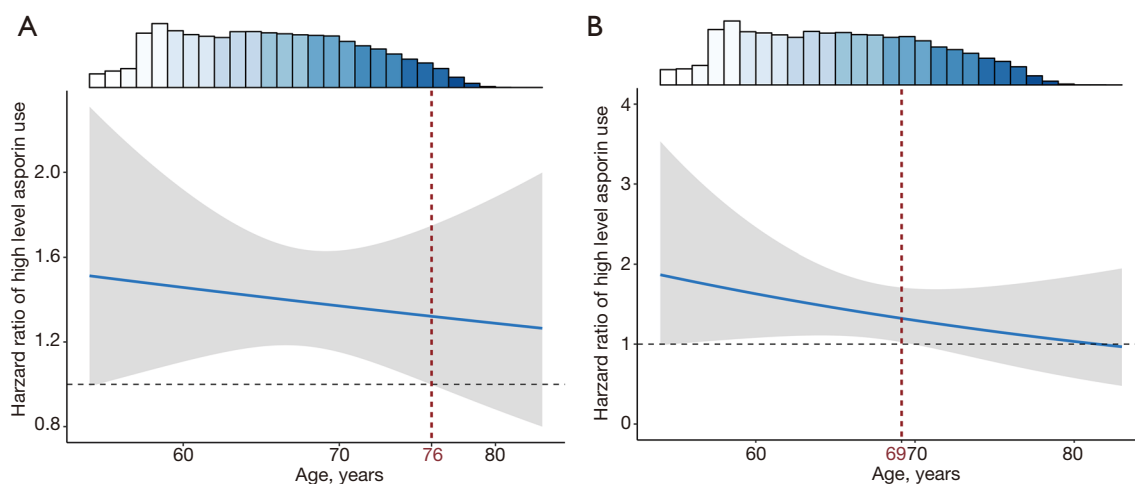


Figure 2 Effect of high-frequency aspirin use (≥ 1 pill per day) compared to no use on risk of lung cancer according to age for (A) all participants and (B) participants without cardiac-cerebral vascular disease. Red dashed lines represent significant cutoff from age; gray dashed lines represent no effect.

bodyweight <70 kg had with a “safe age band”. Among participants with bodyweight <80 kg, high aspirin use was associated with decreasing lung cancer risk with increasing age, and the adverse effect of high aspirin use disappeared at ≥ 76 years of age ($HR_{\text{age}<76} = 1.47$; 95% CI, 1.25–1.73; $P = 3.81 \times 10^{-6}$; $HR_{\text{age} \geq 76} = 1.13$; 95% CI, 0.46–2.69; $P = 0.80$) (Figure 2A).

The age modification of adverse association between high-frequency aspirin use and lung cancer incident was also observed among participants without cardiac-cerebral vascular disease. High-frequency aspirin users, without cardiac-cerebral vascular disease and bodyweight <70 kg, had increased lung cancer risk when age was <69 years old ($HR_{\text{age}<69} = 1.45$; 95% CI, 1.05–1.95; $P = 0.022$) (Figure 2B). However, participants with high-frequency aspirin use and age of ≥ 69 years were not classified as a risk group ($HR_{\text{age} \geq 69} = 1.38$; 95% CI, 0.99–1.93; $P = 0.054$), despite relatively low bodyweight (<70 kg) and no cardiac-cerebral vascular disease.

Discussion

In this study, a cohort of 101,462 participants from PLCO was used to assess the relationship between aspirin use and lung cancer risk. After comprehensive adjustment for covariates, high-frequency aspirin use was associated with the increased risk of lung cancer, especially for current smoker, and higher bodyweight and older age tended to alleviate this relationship. The results of this study provide

new insight for chemoprevention of lung cancer with aspirin.

Aspirin irreversibly and non-selectively inactivates COX, inhibiting both COX-1 and COX-2 enzymes (3,34). However, there is evidence that this inactivating mechanism requires a megadose of aspirin (≥ 2 aspirin tablets per week for 10 years), which indicates that daily regular aspirin use may have no effect on cancer prevention (35–37). On this basis, low aspirin use maybe not be feasible to lower cancer incidence, which has been hinted by the inconsistent results of previous studies.

Bodyweight, instead of BMI, was taken into consideration in this study. Because high-frequency of aspirin should overcome any reduced drug concentration with increasing body size, but might be excessive in patients with low bodyweight because of reduced endothelial prostacyclin production due to high systemic levels of aspirin or possibly because of increased salicylate levels (38). If the effectiveness of lower frequency decreases, and the effectiveness of higher frequency increases, with increasing body size, then weight-dose interactions could explain why low-dose aspirin appears to prevent stroke only in women (39), and high doses only in men (40), despite them having similar BMIs. Even so, BMI was also adjusted in Cox analysis. The increased lung cancer risk with high-frequency aspirin use tended to be smaller at higher bodyweight and older age. In other words, there seems to be a dangerous window of aspirin use that is related to bodyweight and age. Consistently, high aspirin use is reported to be an independent factor

contributing to lung cancer risk in a cohort of U.S. women (15). Our study extends it to a whole-population scale. Our study used propensity score under various confounding and stratification analyses by cardio-cerebrovascular status, which all presented similar evidence. Thus, we have reason to think that our conclusions are reliable.

Despite its strengths, we acknowledge some limitations of our study. (I) Physical activity was not included in this study, which is also important for lung cancer risk. However, measurement of physical activity is more difficult than daily nutrient intake, so quantitative accuracy is difficult to guarantee. (II) Further, we did not focus on lung cancer subtypes. Because nearly 90% of lung cancer patients in the PLCO trial were diagnosed as non-small cell lung cancer, small sample sizes of other types of lung cancer did not allow robust statistical analysis. (III) Due to the small sample size of the non-cardiac-cerebral vascular disease population, the effect of aspirin use on lung cancer incidence needs further evaluation in future studies. (IV) The underlying biological mechanism, high-frequency aspirin biologically associated with increased the risk of lung cancer, is remain not quite specific. This study just provides a statistical clue for further biological research.

In conclusion, our study provides evidence of interactions among aspirin use, bodyweight, and age for lung cancer risk in U.S. adults. Aspirin should be used carefully for two higher-risk groups of people: (I) individuals with bodyweight <80 kg and age <76 years; and (II) cardiac-cerebral vascular disease patients with bodyweight <70 kg and age <69 years.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent, and the study was approved by both the National Cancer Institute and local Institutional Review Boards (ClinicalTrials.gov registration numbers: NCT01696968).

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