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LETTER TO THE EDITOR

Long-term antibiotic use and risk of hepatocellular carcinoma later in life: a nationwide cohort study of 9.8 million participants

Dear Editor,

Antibiotics are considered indispensable in numerous treatments against infectious diseases. However, their over-prescription and widespread use are emerging as important global issues, as they lead to resistant bacteria, reducing the efficacy of antibiotics[1]. The defined daily doses per 1,000 habitants per day for antibiotics in South Korea is 28, which is much higher than the average of Organization for Economic Co-operation and Development countries[1]. In animal studies, antibiotic tigecycline was found to inhibit the proliferation and induce apoptosis of hepatocellular carcinoma (HCC) cells[2]. In addition, isoprenoid antibiotic was found to suppress the growth and invasion of HCC by targeting the signal transducer and activator of the transcription 3 signaling cascade[3]. Despite evidence of the beneficial effects of antibiotics against HCC, evidence regarding their effects on the long-term development of HCC is limited. Introduction regarding the incidence of HCC is provided in the Supplementary file.

This nationwide population-based retrospective cohort study used data from the Korean National Health Insurance Service (NHIS)[4], comprising demographic information, health screening results, medical records related to inpatient and outpatient visits, and pharmaceutical prescriptions (Supplementary file). We identified 12,163,324 individuals aged ≥ 20 years who underwent health screening between 2005 and 2006 from the NHIS database for the adjusted analyses. Individuals were excluded if (1) died (n = 23,940), (2) had any cancer (n = 1,871,500), or (3) had missing values for covariates (n = 462,857) before the first day of follow-up. A total of 9,805,027 individuals were included (Supplementary Figure S1). They were followed up with a median of 15.0 years (mean, 14.2 years) from January 1, 2007, until the date of cancer event, death, or December 31, 2021, whichever came earliest.

Antibiotics were defined based on the World Health Organization Anatomical Therapeutic Chemical classification of drugs (Supplementary Table S1). The primary exposure was defined as cumulative days of antibiotic prescriptions within the first five years. Antibiotic cumulative days were categorized into none, 1-14, 15-59, 60-179, 180-364, and ≥365 days. The secondary exposure was the number of antibiotic classes, which were classified as none, 1, 2, 3, 4, and 5 or more.

The outcome was newly diagnosed HCC. HCC was identified using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code of C220 combined with the critical condition codes for cancer (V193-V194) of the NHIS.

Baseline characteristics and infection rates of the study population who underwent health screening between 2005 and 2006 are depicted in Supplementary Tables S2-S3. Long-term antibiotic users were likely to be older, never smokers, with a higher body mass index and Charlson comorbidity index. Increasing the cumulative days of antibiotic exposure was associated with a lower risk of HCC after the adjustments (P_{trend} < 0.001; Table 1). The long-term antibiotic use (≥ 365 days) group was associated with a lower risk of HCC (adjusted hazard ratio [aHR]: 0.64; 95% confidence interval [CI]: 0.61-0.67) in model 5 when compared to the antibiotic non-user group. HCC risk by cumulative days of antibiotics as a continuous variable is shown in Supplementary Table S4. These results were consistent regardless of men (Supplementary Table S5) and women (Supplementary Table S6). As compared with individuals who were not prescribed antibiotics, men (aHR: 0.62, 95% CI: 0.59-0.65) and women (aHR: 0.73, 95% CI: 0.63-0.83) who were prescribed antibiotics for ≥ 365 days had a significantly reduced risk of HCC in model 4, respectively.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NHIS, National Health Insurance Service.

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TABLE 1 Risk of hepatocellular carcinoma according to cumulative days of antibiotic use.

	Cumulative days antibiotics prescribed during 5 years before the index date						
Models	**None**	**1-14 days**	**15-59 days**	**60-179 days**	**179-364 days**	**≥ 365 days**	***P* for trend**
Participants, n	639,510	1,793,729	2,418,782	2,290,982	1,186,581	1,475,443	
Events, n	2,923	8,275	11,351	10,619	5,376	6,467	
Person-years	9,147,431	25,689,828	34,523,487	32,529,240	16,755,590	20,547,512	
Antibiotics non-user group as reference							
aHR (95% CI)							
Model 1	1.00 (ref.)	1.00 (0.96-1.05)	0.98 (0.94-1.02)	0.93 (0.89-0.97)	0.88 (0.84-0.92)	0.79 (0.75-0.82)	<0.001
Model 2	1.00 (ref.)	1.01 (0.97-1.05)	1.00 (0.96-1.04)	0.95 (0.92-0.99)	0.91 (0.87-0.95)	0.82 (0.79-0.86)	<0.001
Model 3	1.00 (ref.)	0.97 (0.93-1.02)	0.92 (0.88-0.95)	0.83 (0.79-0.86)	0.74 (0.71-0.78)	0.61 (0.59-0.64)	<0.001
Model 4	1.00 (ref.)	1.03 (0.99-1.08)	1.00 (0.95-1.04)	0.92 (0.87-0.96)	0.84 (0.79-0.88)	0.70 (0.66-0.73)	<0.001
Model 5	1.00 (ref.)	0.99 (0.95-1.04)	0.93 (0.89-0.97)	0.84 (0.80-0.88)	0.76 (0.72-0.80)	0.64 (0.61-0.67)	<0.001
Antibiotic use 1-14 days user group as reference							
aHR (95% CI)							
Model 1		1.00 (ref.)	0.98 (0.95-1.01)	0.93 (0.90-0.96)	0.88 (0.85-0.91)	0.79 (0.76-0.81)	<0.001
Model 2		1.00 (ref.)	0.99 (0.96-1.02)	0.95 (0.92-0.97)	0.90 (0.87-0.93)	0.82 (0.79-0.84)	<0.001
Model 3		1.00 (ref.)	0.94 (0.92-0.97)	0.85 (0.83-0.88)	0.77 (0.74-0.79)	0.63 (0.61-0.66)	<0.001
Model 4		1.00 (ref.)	0.97 (0.94-1.00)	0.89 (0.87-0.92)	0.82 (0.79-0.85)	0.68 (0.66-0.71)	<0.001
Model 5		1.00 (ref.)	0.94 (0.91-0.97)	0.85 (0.82-0.87)	0.77 (0.74-0.80)	0.65 (0.62-0.67)	<0.001
Model 6		1.00 (ref.)	0.97 (0.94-1.00)	0.90 (0.87-0.93)	0.83 (0.80-0.86)	0.71 (0.68-0.74)	<0.001

aHRs were calculated using Cox proportional hazards regression.

Model 1 was adjusted for age and sex.

Model 2 was adjusted for age, sex, household income, smoking status, alcohol intake, and physical activity.

Model 3 was adjusted for model 1 plus body mass index, total cholesterol, systolic blood pressure, and Charlson comorbidity index.

Model 4 was adjusted for model 2 plus acid suppressants use, statin use, non-steroidal anti-inflammatory drugs use, and aspirin use.

Model 5 was adjusted for model 3 plus chronic liver diseases, hepatitis B virus infection, hepatitis C virus infection, and type 2 diabetes.

Model 6 was further adjusted for model 3 plus infectious diseases (respiratory diseases, urinary tract infections, skin, soft tissue, bone and joint infections, intra-abdominal infections, intestinal infectious diseases, and other infectious diseases).

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; ref., reference.

In several sensitivity analyses, the findings were consistent with those of the primary analyses (Supplementary Table S7). First, when we washed out HCC events after the follow-up during the first 1, 3, or 5 years, overall trends remained unchanged. Second, after excluding the individuals who were diagnosed with chronic liver disease, hepatitis B virus infection (HBV), hepatitis C virus infection, and type 2 diabetes before the index date, the aHR of individuals who used antibiotics for ≥ 365 days was lower (aHR: 0.70) compared to antibiotic non-users. The risk of HCC was also lower after prolonging antibiotic exposure from 5 to 7 years compared to antibiotic non-users (aHR: 0.64, 95% CI: 0.60-0.68). The antibiotic use as the cumulative days during the last year of exposure period also showed that antibiotic use is associated with a lower risk of HCC ($P_{trend} < 0.001$).

Stratified analyses were performed to evaluate differences in HCC risk by covariates (Supplementary Table S8). The aHR of ≥ 365 days of antibiotic use was lower in participants with HBV infection (aHR: 0.59) compared to participants without HBV infection (aHR: 0.64). In the antibiotic user group with ≥ 365 days, patients with hepatitis B virus infection who did not receive antiviral treatment had an aHR of 0.57 (95% CI: 0.51-0.64), and patients with HBV infection who received antiviral treatment had an aHR of 0.83 (95% CI: 0.63-1.09; Supplementary Table S9). In addition, a greater number of antibiotic classes prescribed was associated with a reduced risk of HCC (Supplementary Table S10). Individuals who have been prescribed 5 or more classes of antibiotics were associated with a reduced risk of HCC compared to those who did not prescribe antibiotics (aHR: 0.65, 95% CI: 0.62-0.69, $P_{trend} < 0.001$). When we evaluated the association of any use of the category-specific antibiotics with the risk of HCC, no significant difference was found between never use versus any use of the category-specific antibiotics (Supplementary Table S11).

In this nationwide cohort study, we identified a dose-dependent association between cumulative days of antibiotics prescription and the risk of HCC. This association remained significant after adjusting for potential confounding factors. The results are noteworthy as previous

studies have found that antibiotics may be linked to a higher risk of certain diseases, such as cardiovascular disease, and the effects of antibiotics on the gut microbe-related metabolites are considered a major contributing factor[5, 6].

Since antibiotics may disrupt intestinal dysbiosis, which has been found to affect antitumor immune surveillance and contribute to the progression of liver disease toward cancer, antibiotics may be considered an unfavorable condition regarding the risk of HCC[7]. However, interestingly, gentamicin and amikacin antibiotics have been identified to decrease the deoxycholic acid concentration in liver tissues in a mouse model[8]. Deoxycholic acid, part of the enterohepatic circulation, has been shown to induce senescence-associated secretory phenotype in hepatic stellate cells, leading to the secretion of tumor-promoting and inflammatory factors in the liver and facilitating the development of HCC in mice[9]. Another possible explanation for the protective effects of antibiotics against HCC could be their anti-inflammatory properties, which are considered beneficial against non-bacterial infections[10]. Further rationale behind the proposed hypothesis is provided in the Supplementary file.

There are some underlying limitations that need to be considered when interpreting our results. First, cumulative days of antibiotics may not represent the actual doses of antibiotics. Second, the study could not account for other potential confounding factors, such as dietary habits, environmental factors, and genetic factors, which might influence the observed associations. Additionally, since gut microbiota and microorganisms within the liver may differ in different ethnicities, future studies from other regions are needed to generalize our results.

In conclusion, antibiotics were associated with a lower risk of HCC, and a negative relationship was observed between the cumulative days of antibiotics or the number of classes of antibiotics and the risk of HCC. Understanding the beneficial effects of antibiotics against HCC and exploring actionable approaches may provide novel insights to lower the incidence of HCC.

CONFLICT OF INTEREST DISCLOSURE

The authors declare no competing interests.

FUNDING INFORMATION

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Korean National Health Insurance Service, but restrictions apply to the availability of these data, which were used under license for the current study and are thus not publicly available. Data are, however, available from the Korean National Health Insurance Service (https://nhiss.nhis.or.kr) upon reasonable research proposal and with permission of the Korean National Health Insurance Service.

ETHICS APPROVAL STATEMENT

The institutional review board of Seoul National University Hospital approved this study (No. E-2108-136-1246). Informed consents were exempted because the NHIS database is strictly anonymized according to the Personal Data Protection Act.

PATIENT CONSENT STATEMENT

Not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CONSENT TO PUBLICATION

Not applicable.

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REFERENCES

1. Park J, Han E, Lee SO, Kim D-S. Antibiotic use in South Korea from 2007 to 2014: A health insurance database-generated time series analysis. Plos one. 2017;12(5):e0177435.
2. Tan J, Song M, Zhou M, Hu Y. Antibiotic tigecycline enhances cisplatin activity against human hepatocellular carcinoma through inducing mitochondrial dysfunction and oxidative damage. Biochemical and biophysical research communications. 2017;483(1):17–23.
3. Dai X, Ahn KS, Kim C, Siveen KS, Ong TH, Shanmugam MK, et al. Ascochlorin, an isoprenoid antibiotic inhibits growth and invasion of hepatocellular carcinoma by targeting STAT3 signaling cascade through the induction of PIAS3. Molecular oncology. 2015;9(4):818–33.
4. Cheol Seong S, Kim Y-Y, Khang Y-H, Heon Park J, Kang H-J, Lee H, et al. Data resource profile: the national health information database of the National Health Insurance Service in South Korea. International journal of epidemiology. 2017;46(3):799–800.
5. Heianza Y, Zheng Y, Ma W, Rimm EB, Albert CM, Hu FB, et al. Duration and life-stage of antibiotic use and risk of cardiovascular events in women. European Heart Journal. 2019;40(47):3838–45.
6. Jernberg C, Lofmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology. 2010;156(11):3216–23.
7. Schneider KM, Mohs A, Gui W, Galvez EJ, Candels LS, Hoenicke L, et al. Imbalanced gut microbiota fuels hepatocellular carcinoma development by shaping the hepatic inflammatory microenvironment. Nature Communications. 2022;13(1):3964.
8. Deng J, Yuan W, Tan Q, Wei X, Ma J. Non-absorbable antibiotic treatment inhibits colorectal cancer liver metastasis by modulating deoxycholic acid metabolism by intestinal microbes. Journal of Cancer. 2022;13(3):764–74.
9. Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, et al. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature. 2013;499(7456):97–101.
10. Poddighe D, Aljofan M. Clinical evidences on the antiviral properties of macrolide antibiotics in the COVID-19 era and beyond. Antiviral Chemistry and Chemotherapy. 2020;28:2040206620961712.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.