Journal of the National Cancer Center 3 (2023) 279–285

Contents lists available at ScienceDirect

Journal of the National Cancer Center

journal homepage: www.elsevier.com/locate/jncc

Full Length Article

Interplay between oral health and lifestyle factors for cancer risk in rural and urban China: a population-based cohort study

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ARTICLE INFO

Keywords:
Oral health
Lifestyle factors
Cancer risk
Rural-urban disparities
Cohort study

ABSTRACT

Background: Although poor oral health and several lifestyle factors have been found to be associated with cancer risk, their joint relationship has rarely been studied.

Methods: We prospectively examined the associations of oral health and healthy lifestyle factors with cancer risk among 0.5 million rural and urban residents from the China Kadoorie Biobank (2004–2015). Oral health status was assessed from self-reported baseline questionnaires. A healthy lifestyle index comprising non-smoking, non-drinking, ideal body shape, physical activity and healthy diet was calculated for each participant, and categorized into favorable, intermediate and unfavorable lifestyle behavior. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) relating oral health and healthy lifestyle index to cancer risk using Cox proportional hazards models. We estimated the population attributable risk percent (PAR%) and 95% CIs using multivariate models.

Results: During a median follow-up of 9 years, 23,805 new cancer cases were documented, with 52% from rural areas and 48% from urban areas. Compared with those with good oral health and favorable lifestyle, participants with poor oral health and unfavorable lifestyle had a higher risk of developing cancer in both rural (adjusted HR, 1.55 [95% CI, 1.39–1.74]; P for trend < 0.001) and urban areas (adjusted HR, 1.44 [95% CI, 1.24–1.67]; P for trend < 0.001). A significant multiplicative interaction between oral health and healthy lifestyle index on cancer risk was found in rural residents (P for interaction = 0.004) rather than in urban residents (P for interaction = 0.973). Assuming poor oral health as an additional risk factor, the PAR% of total cancer increased by 3.0% and 1.1% for participants with intermediate lifestyle and unfavorable lifestyle, respectively.

Conclusions: These findings suggest a joint effect of oral health and common lifestyle factors on cancer risk. Promotion of healthy lifestyle by integration of good oral health would be beneficial to consider in cancer prevention strategies.

1. Introduction

Primary prevention plays a pivotal role in reducing cancer burden globally.[1] Lifestyle modifications, such as tobacco cessation,[2-4] diet intervention[5] and intentional weight loss[6] can substantially reduce the risk of developing or dying from cancer. Results from population-based studies also suggested common lifestyle factors, including cigarette smoking, obesity, physical activity, alcohol intake and diet quality, independently predicted cancer incidence and mortality.[7-9]

As a part of overall health, oral health is often neglected from conventional lifestyle factors globally, partly because the overlooked underlying causes of disease in high-income countries and unaffordable dental care in low-income and middle-income countries.[10] Moreover, oral disease may have complex interactions with common lifestyle factors. Tobacco smoking and obesity could be two potential modifiers in the association between poor oral health and cancer risk.[11-15] In a health professional cohort study, although an increased cancer risk was recorded in men who reported having severe tooth loss or periodontal diseases, the association between the number of teeth and the total cancer risk was attenuated after adjusting for smoking.[14] Therefore, to elucidate the role of poor oral health and cancer-associated lifestyle behaviors in cancer development, the association of oral health in regard to interactions

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https://doi.org/10.1016/j.jncc.2023.10.004
Received 20 March 2023; Received in revised form 23 October 2023; Accepted 24 October 2023

with specific lifestyle factor and different cancer types requires further investigation. Moreover, it remains unknown the quantification of cancer attributable risk to poor oral health when considering conventional lifestyle factors simultaneously.

Using prospective data from a large contemporary population-based cohort, we aimed to investigate the combined association of oral health and conventional lifestyle factors on cancer risk in rural and urban areas in China. We also estimated cancer attributable risk to poor oral health in different populations when considering conventional lifestyle factors simultaneously.

2. Materials and methods

2.1. Study population

This is a prospective, population-based cohort study of participants enrolled in China Kadoorie Biobank (CKB). The study design, data management and long-term follow-up of CKB have been described previously.[16,17] In brief, CKB recruited 512,726 participants aged 30 to 79 years between 2004 and 2008 from ten geographically diverse areas (five rural counties and five urban districts) across China. At the assessment centers, participants completed an interviewer-administered electronic questionnaire, physical measurements and provided blood spot tests and non-fasting blood samples. Data have been linked with several electronic registries for ongoing follow-up on health status. The CKB study was approved by the ethics committees of the University of Oxford and the China National Center for Disease Control and Prevention.[16] All participants provided written informed consent.

In the present study, we excluded 2,578 participants who reported a medical history of cancer at baseline. We further excluded 2 participants with missing information on body weight. All participants reported their oral health status and other lifestyle factors of interest on the baseline questionnaire. After exclusions, a total of 510,146 participants remained for the current analysis.

2.2. Measurements

Oral health status was assessed using baseline questionnaire at assessment centers. In CKB, we determined oral health status by the question “How often do your gums bleed when you brush your teeth?” Participants who rarely brushed their teeth or always had gum bleeding were considered to have poor oral health, which is consistent with our previous study.[18]

From the baseline questionnaire, we identified five lifestyle factors (smoking, alcohol consumption, physical activity, body shape, and diet) that have been proved to be closely related to cancer risk.[19,20] For each lifestyle factor, a binary score was used to distinguish healthy or unhealthy behaviors (Supplementary Table 1). We generated a healthy lifestyle index with all these five lifestyle factors, ranging from 0 (least healthy) to 5 (most healthy). As only a small proportion of participants had an index of 0 (1.98 %) or 5 (3.94 %), the lifestyle behaviors of participants were further categorized into three groups according to the scores of the healthy lifestyle index: favorable (score 4 or 5), intermediate (score 2 or 3), and unfavorable (score 0 or 1) lifestyle behaviors.

Anthropometry data, including body weight, standing height, and waist circumference (WC) were measured using standard instruments and protocols and were regularly calibrated.[16] Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and classified into four categories: underweight (< 18.5 kg/m^2), normal (18.5 to < 24 kg/m^2), overweight (24 to < 28 kg/m^2), and obese (≥ 28 kg/m^2). WC was measured in centimeters and classified into a high or low category with 85 cm for women and 90 cm for men as the cutoff value. Both indices of general obesity and central obesity were utilized to assess body shape. Questions about smoking and alcohol intake were self-reported, capturing information on frequency, type, amount, age first began and age stopped.[21] Based on their smoking history, participants were categorized as never, occasional, ex-regular and regular smokers. Based on their past and current drinking history, participants were classified as abstainers, ex-regular drinkers, occasional drinkers and current regular drinkers.[22] Validation studies in this cohort using biomarkers (such as carbon monoxide and genetic variants) as references indicated a good accuracy for smoking and alcohol consumption estimation from the baseline questionnaire.[22,23] Consumption of fresh vegetables, fruits and red meat during the past 12 months was asked and categorized as daily, 4–6 days per week, 1–3 days per week, monthly and never/rarely. The questions on a range of physical activities were adapted from validated questionnaires used in several other studies, with some additional modifications after a CKB pilot study.[24] In the present study, we used metabolic equivalent task hours per day (MET-h/d) to quantify activity levels.

Long-term outcome data were obtained through active follow-up, as well as by electronic linkages to mortality and morbidity registries for cancer and the new nationwide health insurance system. During the follow-up, a range of health-related outcome data were collected, including cause-specific mortality, morbidity for major diseases, and any episode of hospitalization. Information on cancer incidence was collected through linkages with established disease registries and electronic linkages with the national health insurance system. Detailed information about each hospital admission, including dates of admission and discharge, the description and the International Classification of Disease 10th Revision (ICD-10) code of the conditions, and detailed procedure codes, was collected and processed.[16]

The primary outcome of our study was the incidence of total cancer (ICD-10 codes C00-97). Secondary endpoints were the main cancer types in CKB,[25] including lung (C33-C34), female breast (C50), stomach (C16), esophageal (C15), liver (C22), colorectal (C18-C20), cervix uteri (C53), pancreas (C25), head and neck (C00-C14), leukemia (C91-C95) and lymphoma (C81-C85).

2.3. Statistical analysis

We calculated person-years from baseline until the date of primary cancer diagnosis, death, loss to follow-up, or the end of the study period (31 December 2015), whichever occurred first. To examine the association between exposures and cancer risk, we performed crude and multivariable Cox proportional hazards regression analyses and estimated unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) using follow-up time as the time scale. In multivariable Cox regression models, we adjusted for age (continuous), sex (male and female), region (rural and urban), education level (illiterate and primary school, middle school, or university and college degree), annual household income ($<$ 10,000 CNY /year, 10,000–19,999 CNY /year, 20,000–34,999 CNY /year, and $>$ 35,000 CNY /year), marital status (married and unmarried), aspirin prescription for cardiovascular diseases (CVD [no, yes, or missing]), personal history of diabetes (no or yes) and family history of cancer (no, yes, or missing). We tested the proportional-hazard assumption using Schoenfeld residuals and found no evidence of departure from the assumption in models (all $P > 0.05$). Because we previously found a modifying effect by residential status on the associations between poor oral health with cancer risk,[18] we further performed analyses among rural and urban residents separately.

We examined the multiplicative interaction between oral health and healthy lifestyle index by incorporating the two variables and their cross-product term in the same model using the Wald test. We performed additive interaction analysis between oral health status and healthy lifestyle index using two indexes: the relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP). The 95% CIs of the RERI and AP were estimated using the delta method, which would contain 0 if there was no additive interaction. Linear trends were tested by treating the healthy lifestyle index as a continuous variable. To estimate the proportion of total cancer that would have been

Table 1
Baseline characteristics of participants in China Kadoorie Biobank and incident cancer cases during follow-up.

Characteristic	Rural residents	Urban residents	Total participants
Participant, N	285,377	224,769	510,146
Average follow-up, mean (SD), years	9.00 (1.86)	8.81 (1.67)	8.92 (1.78)
Age, mean±SD, years	50.87±10.50	52.31±10.85	51.50±10.68
Male sex, N (%)	118,370 (41.48)	90,865 (40.43)	209,235 (41.01)
Baseline BMI, mean±SD, kg/m^2	23.17±3.28	24.28±3.40	23.66±3.38
University or college degree, N (%)	3098 (1.09)	26,664 (11.86)	29,762 (5.83)
Annual household income > 20,000 N (%), CNY	89,444 (31.34)	128,530 (57.18)	217,974 (42.72)
Aspirin current use, N (%)	2952 (1.03)	2392 (1.06)	5344 (1.05)
Prevalent diabetes, N (%) [a]	11,774 (4.13)	18,233 (8.11)	30,007 (5.88)
Cancer family history, N (%) [b]	42,612 (14.93)	43,056 (19.16)	85,668 (16.79)
Poor oral health, N (%)	56,125 (19.67)	19,769 (8.80)	75,894 (14.88)
Healthy lifestyle factors, N (%)			
No smoking	187,577 (65.73)	157,279 (69.97)	344,856 (67.60)
No drinking	234,739 (82.26)	178,762 (79.53)	413,501 (81.06)
Health body shape	210,976 (73.93)	147,604 (65.67)	358,580 (70.29)
Healthy diet	8132 (2.85)	30,405 (13.53)	38,537 (7.55)
Being physically active	158,567 (55.56)	94,543 (42.06)	253,110 (49.62)
Primary site of caner, N			
All cancers	12,411	11,394	23,805
Lung	2509	2498	5007
Breast	739	1345	2084
Stomach	1538	1426	2964
Esophageal	1739	380	2119
Liver	1486	1079	2565
Colorectal	1145	1533	2678
Cervix uteri	661	326	987
Pancreas	347	359	706
Head & neck	301	313	614
Leukemia	289	262	551
Lymphoma	412	262	722

[a] Prevalent diabetes was defined as self-reported diabetes or screen-detected diabetes at baseline.
[b] A positive family history of cancer was defined as any first-degree relative having a recorded cancer diagnosis.
Abbreviations: BMI, body mass index; CNY, Chinese yuan; N, number; SD, standard deviation.

prevented if all participants adhered to all these healthy lifestyle behaviors, we calculated the multivariable adjusted population-attributable risk percent (PAR%) and 95% CIs using a previously proposed method.[26] The specific formula used to calculate PAR can be found in the Supplementary Methods section. We conducted two sensitivity analyses by: 1) excluding participants who were diagnosed with cancer within the first 2 years after baseline to avoid potential effects of reverse causality; 2) using the subdistribution method[27] to assess the competing risk of death due to other causes.

All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc. Cary, New York, USA) and R software (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria). Statistically significance was set at two-sided $P < 0.05$. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

3. Results

At baseline, 285,377 rural and 224,769 urban residents aged 30–79 were included. Compared with urban residents, rural residents were more likely to be younger and less educated, had less household income, lower prevalence of diabetes, and lower proportion of cancer family history, but had a higher proportion of poor oral health and unhealthy diet (Table 1). About 15% of participants reported having poor oral health at baseline, with 20% in rural and 9% in urban areas. During a median follow-up of 9.1 years (range, 0.1–11.5), we documented 23,805 incident cancer cases, 52% of whom resided in rural areas and 48% in urban areas.

We observed a significant multiplicative interaction between oral health and lifestyle factors on cancer risk. Compared with participants with good oral health and favorable lifestyle (with 4–5 favorable lifestyle factors), those with poor oral health and unfavorable lifestyle (0–1 factor) had a 1.5-fold higher risk of cancer (adjusted HR, 1.52 [95% CI, 1.39–1.66]; P for trend < 0.001, Fig. 1). A stronger association was observed in rural residents (adjusted HR, 1.55 [95% CI, 1.39–1.74]; P for trend < 0.001) than in urban residents (adjusted HR, 1.44 [95% CI, 1.24–1.67]; P for trend < 0.001). Compared with participants with good oral health, participants with poor oral health had higher cancer incidence rates in all lifestyle subgroups, except for the favorable lifestyle behavior group. For example, the largest differences in cancer incidences were observed in rural residents with intermediate lifestyle behavior (good vs poor oral health: 7.26 vs 4.48 per 1000 person-years) and those with unfavorable lifestyle behaviors (10.03 vs 6.54 per 1000 person-years, Fig. 2). The results were not substantially changed when excluding cancer cases within the first two years of follow-up or considering the competing risk by deaths from other causes (Supplementary Table 2). We observed a significant multiplicative interaction for healthy lifestyle index with oral health status in rural residents (P for interaction = 0.004), but not in urban residents (P for interaction = 0.973). In addition, an additive interaction between poor oral health and unfavorable lifestyle factors on overall cancer risk was observed. Specifically, the RERI was 0.27 (95% CI, 0.07–0.47), accounting for 16% of the risk in rural residents with both a poor oral health and an unfavorable lifestyle (Supplementary Table 9). When treating “rarely brushing teeth” and “always had gum bleeding” as separate variables, we only found a significant multiplicative interaction between “rarely brushed teeth” and lifestyle factors on cancer risk (P for interaction = 0.028, Supplementary Tables 7–8).

For site-specific cancers, the joint associations of poor oral health and unfavorable lifestyle behaviors showed a regional difference (Supplementary Tables 3–5). In rural areas (Supplementary Table 4), participants with poor oral health and unfavorable lifestyle had higher cancer risks of esophageal (adjusted HR, 4.83 [95% CI, 3.68–6.33]), liver (adjusted HR, 1.69 [95% CI, 1.24–2.30]), lung (adjusted HR, 1.45 [95 %CI, 1.13–1.86]) and stomach (adjusted HR, 1.53 [95% CI, 1.16–2.02]), compared with those with good oral health and favorable lifestyle. A sig-

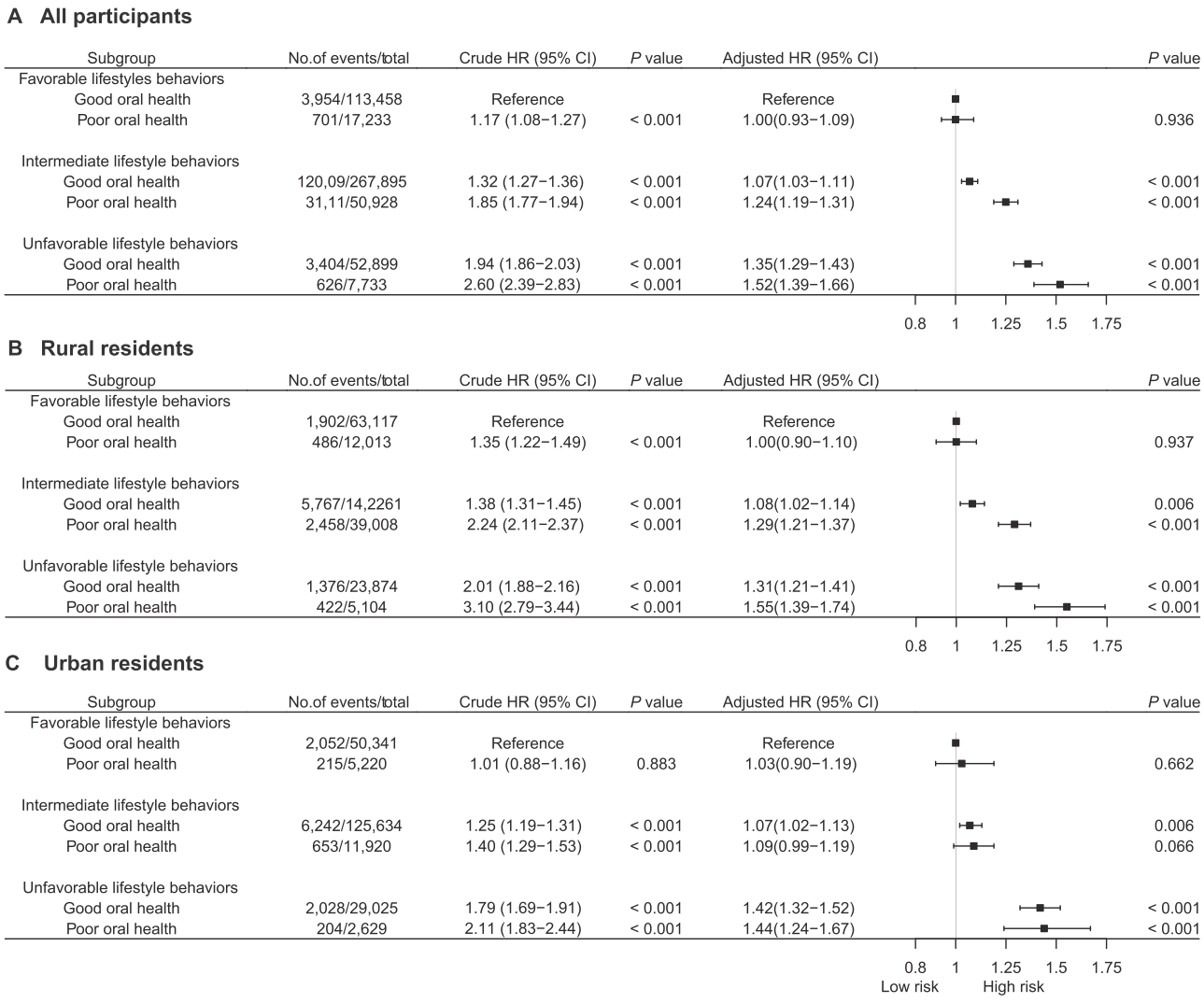

Fig. 1. Risk of total cancer by joint effect of oral health and lifestyle behaviors. Forest plots showed HRs and 95% CIs (horizontal line). Covariates in the adjusted model included age, sex, region, education level, annual household income, marital status, aspirin prescription for cardiovascular diseases, personal history of diabetes and family history of cancer. (A) All participants. (B) Rural residents. (C) Urban residents. HR, hazard ratio; CI, Confidence interval.

nificant interaction was observed for stomach cancer (*P* for interaction = 0.032). In urban areas (Supplementary Table 5), participants with poor oral health and unfavorable lifestyle had higher cancer risks of breast (adjusted HR, 2.48 [95% CI, 1.02–6.01]), lung (adjusted HR, 2.22 [95% CI, 1.72–2.87]) and liver (adjusted HR, 1.69 [95% CI, 1.10–2.59]), compared with those with good oral health and favorable lifestyle. However, no statistically significant interaction was observed (all *P* for interaction > 0.05).

For participants adopting intermediate lifestyle behaviors, the PAR% of total cancer was 9.7% (95% CI, 7.5–12.3%; Fig. 3 and Supplementary Table 6), and the PAR% increased to 12.7% (9.7–15.6%) when adding poor oral health. For participants adopting unfavorable lifestyle behaviors, the PAR% of total cancers increased from 18.9% (16.5–21.3%) to 20.0% (16.8–23.2%). In particular, for rural residents adopting an intermediate lifestyle behavior, the PAR% increased from 11.7% (8.4–15.0%) to 16.3% (12.1–20.5%) when adding poor oral health as an additional risk factor. For site-specific cancers, 44.8% (33.2–55.1%) esophageal cancer cases, 21.2% (11.0–30.9%) stomach cancer cases and 27.5% (16.3–37.9%) liver cancer cases might be attributable to the combination of unfavorable lifestyle behaviors and poor oral health (Supplementary Table 6). Notably, for rural residents, additionally considering poor oral health substantially increased PAR% for cancers from the stomach, esophageal and liver. In contrast, further inclusion of poor oral health caused little increase in PAR% for urban residents (Supplementary Table 6).

4. Discussion

In this large, nationwide, prospective cohort study, we found that participants with poor oral health and unfavorable lifestyle behaviors had the highest risk of developing cancer in both rural and urban areas. A significant interaction of oral health status with healthy lifestyle index on cancer risk was observed in rural residents, but not in urban residents. When considering poor oral health as an additional risk factor, the PAR% of total cancer increased by 3.0% and 1.1%, respectively, for participants with intermediate lifestyle and unfavorable lifestyle. Our findings emphasize the importance of integrating good oral health into healthy lifestyle behaviors. They also help identify and prioritize future research needs in oral health research to advance global health equity.

Consistent with results from other large cohort studies,[20,28-30] our findings indicate a significant association between conventional lifestyle factors and risk of incident cancer. The estimated PAR% for incident cancer is comparable to those reported from other Chinese studies,[31,32] but lower than most western studies.[33,34] Possible explanations for this

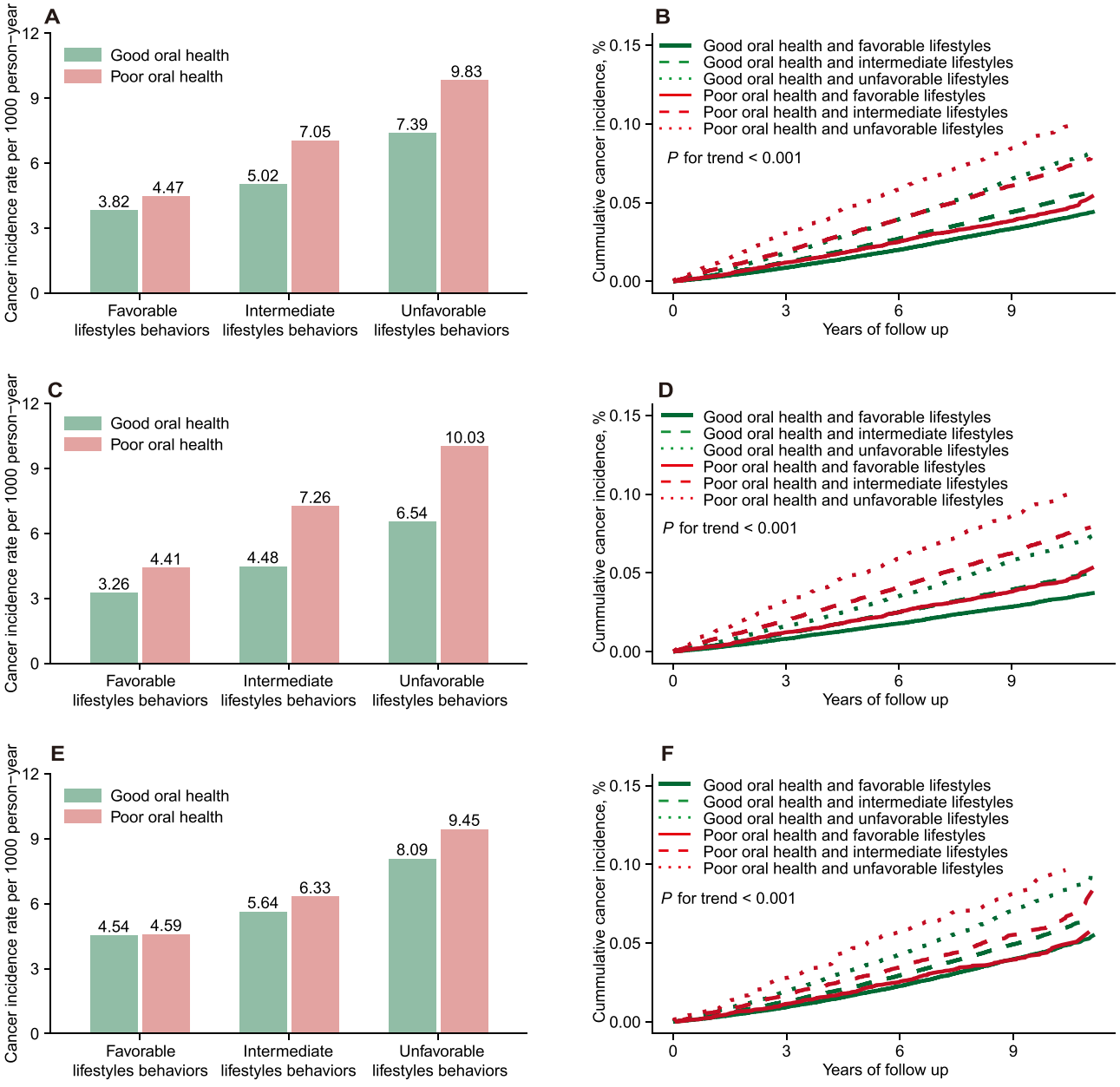

Fig. 2. Cumulative cancer incidence according to lifestyle behaviors and oral health status. Cancer incidence rates per 1000 person-years according to the risk groups of lifestyle behaviors and oral health status among all participants (A), rural residents (C) and urban residents (E). Hazard plot for cancer risk according to the risk groups of lifestyles behaviors and oral health status for all participants (B), rural residents (D) and urban residents (F).

difference could be that we did not take into account other related factors that could be associated with the results, such as specific dietary pattern or waist-to-hip ratio. Moreover, to estimate cancer attributable risk more accurately, undetermined cancer risk factors for the Chinese population should be thoroughly investigated. Nevertheless, we found the incremental value of poor oral health to cancer risk in both rural and urban residents. In particular, because a large proportion (27.4%) of rural residents with intermediate lifestyle behaviors reported had poor oral health, the largest difference of PAR% (16.3% vs 11.7%) was observed in this group. Therefore, we creatively propose that good oral health could be included as a part of healthy lifestyle factors for cancer primary prevention, besides non-smoking, non-drinking, appropriate physical activity, healthy diet, and healthy body shape.

Although poor oral hygiene and oral diseases have been linked to systemic diseases and cancer,[35,36] the association between a combination of oral health and lifestyle factors on cancer risk has not been reported to date. Our study showed for the first time that there was a significant interaction between oral health status and healthy lifestyle index on cancer risk. In rural Chinese residents, the PAR% increased by about 4.6% when assuming poor oral health as an additional risk factor. In particular, about 50% of esophageal cancer risk could be attributed to poor oral health and unhealthy lifestyles. The prevalence of poor oral health was disproportionately higher among rural residents compared to urban residents.[10] This can be partly explained by the great heterogeneity of many major risk factors for chronic disease and variation in dental care expenditure between rural and urban residents.[10] Therefore, oral disease prevention and lifestyle modification could be a simple but effective way to cancer prevention, especially in rural areas. Our findings suggest that rural residents may be able to alter or reduce their cancer risk by keeping good oral health, especially for those with intermediate or unhealthy lifestyles.

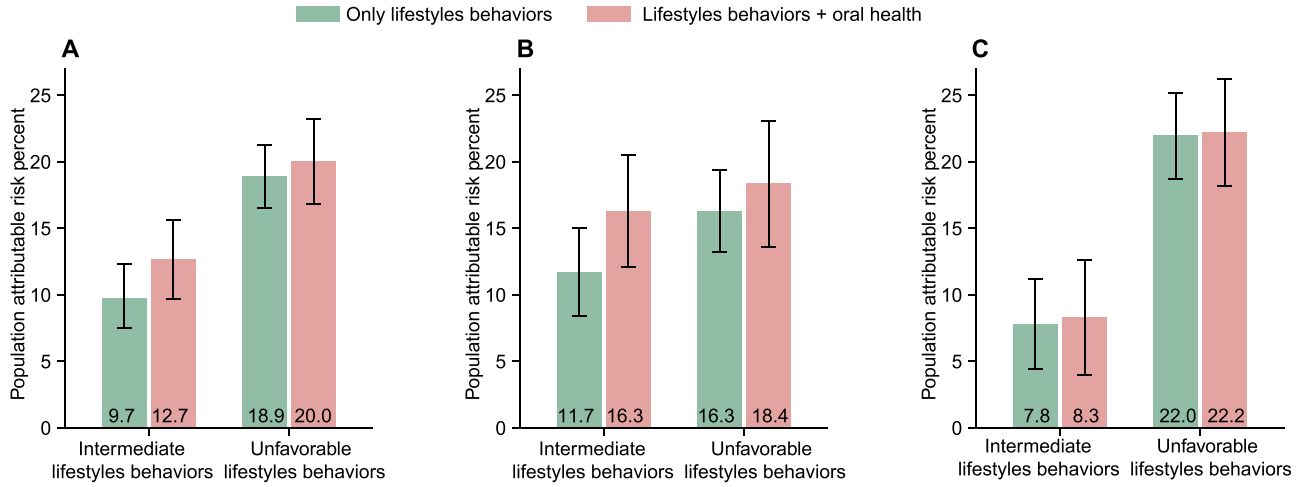

Fig. 3. Population attributable risk percent (PAR%) and 95 % confidence interval (CI) for total cancer by combination of lifestyle behaviors and oral health status. Multivariable model was adjusted for age, sex, region, education level, annual household income, and marital status, personal history of diabetes and family history of cancer. Lifestyle behaviors were also included simultaneously in the same model. (A) All participants. (B) Rural residents. (C) Urban residents.

Oral health conditions may share many of the same underlying risk factors as non-communicable diseases, such as sugar consumption, tobacco use and harmful alcohol consumption.[37] Smoking is a leading risk factor and contributes a large proportion to the total cancer burden in China.[38] There is a higher prevalence of smoking and tobacco dependence in rural residents than in urban residents.[39,40] In individuals with poor oral health, gingival pathogens or food debris may interact with tobacco toxins and further increase cancer risk.[41,42] Other modifiable lifestyle factors, such as alcohol intake, obesity and diet may also interact with periodontal disease or oral microbiota and need further investigations.[43,44] Nevertheless, our findings could have important public health implications globally that promotion of these modifiable lifestyle behaviors would be beneficial to consider in cancer prevention strategies.

Major strengths of this study include the large sample size, multicenter nature, prospective design and comprehensive examination of the combined association between oral health and five common lifestyle factors. Our study included both rural and urban residents, highlighting the heterogeneity of subpopulation. Several limitations also should be noted. First, oral health assessment and some lifestyle factors were self-reported and a non-differential classification error could exist. Second, lifestyle factors, as well as oral health status, were assessed only at baseline, and lifestyle changes could not be analyzed. Third, the estimated PAR% was based on CKB cohort during the study period and should be cautious to generalize to other populations. Finally, due to the nature of the study design, residual confounding is still possible. Therefore, the causal effect of these lifestyle factors in cancer development cannot be fully determined.

5. Conclusions

In summary, this prospective study indicates that the combination of good oral health and healthy lifestyle behaviors is associated with lower cancer risk. Since oral health is essential to general health, we promote the integration of oral health habits into general lifestyle factors for cancer primary prevention. Our findings align with the WHO global strategy that essential oral health care should be included in universal health coverage and accessed to all countries, especially those in low-income and middle-income settings.[45,46]

Declaration of competing interest

The authors declare that they have no competing interests.

Ethics approval and patient consent

The CKB study was approved by the ethics committees of the University of Oxford (approval number: 025–04, 3.2.2005) and the China National Center for Disease Control and Prevention (approval number: 005/2004, 9.7.2004). All participants provided written informed consent.

Data availability

This research was conducted using the CKB Resource under Application Number DAR-2020-00233. We thank the CKB project for providing data. Data underlying this article can be accessed at https://www.ckbiobank.org/CKBDataAccess/.

Acknowledgements

The authors thank the Chinese Center for Disease Control and Prevention, the Chinese Ministry of Health, the National Health and Family Planning Commission of China, and 10 provincial/regional health administrative departments. The most important acknowledgement is to the participants in the study and the members of the survey teams in each of the 10 regional centers, as well as to the project development and management teams based at Beijing, Oxford and the 10 regional centers. The authors also thank the staff of the CKB study for their important contributions. This work was supported by the National Key Research and Development Program of China (grant numbers: 2021YFC2500400, 2021YFC2500402) and the Tianjin Key Medical Discipline (Specialty) Construction Project (grant number: TJYXZDXK-009A). Funding for the development of and maintenance of the CKB resource has been received from the Chinese Ministry of Science and Technology, the Chinese National Natural Science Foundation, the British Heart Foundation, the Cancer Research UK, the Kadoorie Charitable Foundation in Hong Kong of China, the Medical Research Council UK, and the Wellcome Trust.

Author contributions

H.D., X.Z. and K.C. conceived the study. C.S. and H.D. accessed and verified the data reported in the manuscript, and performed statistical analyses. C.S., X.Z. and H.D. conducted the literature review and drafted the manuscript. B.L. and H.L. provided methodological support. H.L. and K.C. gave critical comments. All authors reviewed and revised the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2023.10.004.

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