# Trend Analysis of Betel Nut-associated Oral Cancer and Health Burden in China

Yan Jia HU[1], Jie CHEN[2], Wai Sheng ZHONG[2], Tian You LING[3] , Xin Chun JIAN[4], Ruo Huang LU[5] , Zhan Gui TANG[1], Lin TAO[6]

**Objective:** *To forecast the future trend of betel nut-associated oral cancer and the resulting burden on health based on historical oral cancer patient data in Hunan province, China.*
**Methods:** *Oral cancer patient data in five hospitals in Changsha (the capital city of Hunan province) were collected for the past 12 years. Three methods were used to analyse the data; Microsoft Excel Forecast Sheet, Excel Trendline, and the Logistic growth model. A combination of these three methods was used to forecast the future trend of betel nut-associated oral cancer and the resulting burden on health.*
**Results:** *Betel nut-associated oral cancer cases have been increasing rapidly in the past 12 years in Changsha. As of 2016, betel nuts had caused 8,222 cases of oral cancer in Changsha and close to 25,000 cases in Hunan, resulting in about ¥5 billion in accumulated financial loss. The combined trend analysis predicts that by 2030, betel nuts will cause more than 100,000 cases of oral cancer in Changsha and more than 300,000 cases in Hunan, and more than ¥64 billion in accumulated financial loss in medical expenses.*
**Conclusion:** *The trend analysis of oral cancer patient data predicts that the growing betel nut industry in Hunan province will cause a humanitarian catastrophe with massive loss of human life and national resources. To prevent this catastrophe, China should ban betel nuts and provide early oral cancer screening for betel nut consumers as soon as possible.*
**Key words:** *betel nut, Excel, forecast, health burden, logistic growth, oral cancer*
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1 Department of Oral Maxillofacial Surgery, Xiangya College and Hospital of Stomatology, Xiangya School of Medicine, Central South University, Changsha, Hunan Province, P.R. China.
2 First Department of Head and Neck Surgery, Hunan Provincial Tumour Hospital, Xiangya School of Medicine, Central South University, Changsha, Hunan Province, P.R. China.
3 Department of Stomatology, Xiangya Second Hospital, Xiangya School of Medicine, Central South University, Changsha, Hunan Province, P.R. China
4 Department of Stomatology, Xiangya First Hospital, Xiangya School of Medicine, Central South University, Changsha, Hunan Province, P.R. China
5 Department of Stomatology, Xiangya Third Hospital, Xiangya School of Medicine, Central South University, Changsha, Hunan Province, P.R. China
6 Department of Oral Biology, College of Dentistry, University of Illinois at Chicago, Chicago, IL 60612, USA.

**Corresponding author:** Dr Lin TAO, Department of Oral Biology, MC 690, University of Illinois at Chicago, 801 South Paulina Street, Chicago, IL 60612, USA. Tel: 312-355-4077; Fax: 312-996-6044. Email: Ltao@uic.edu

Betel nut chewing has been a dietary habit in the city of Xiangtan, Hunan province for hundreds of years, with a small number of consumers before the 1980s[1]. These Hunan-style betel nuts are grown in the tropical Hainan province. After harvest, the fruit is dried and further processed in the Hunan province. Unlike betel nuts consumed elsewhere that use the fresh husk or dried seed of the areca fruit, the Hunan-style betel nut uses the dried areca husk. Due to a short shelf life, fresh betel nuts are only available in the tropical areas of their origin, but the Hunan-style betel nuts are dried, specially preserved and vacuum-packed with a long shelf life[1].

Along with recent progress in food manufacture industrialisation, Hunan-style betel nuts have spread to all cities in Hunan and to nearly all areas of China. Today, these products are available in major food markets, tobacco shops, on newsstands, street stalls, and on commercial websites throughout China.

The International Agency for Research on Cancer has recognised the betel nut as a class I carcinogen, and the main carcinogenic component is arecolin[2]. With an increasing number of consumers in China, oral diseases associated with betel nut chewing are also on the rise. In 1985, two cases of oral submucous fibrosis (OSF), a pre-cancerous condition unique to betel nut consumption, were first reported in the City of Xiangtan[3]. Since then, more betel nut chewing-associated pre-cancer and cancer cases have been reported in Hunan[4-9]. Betel nut consumers include nearly all age groups, even students in elementary school[10]. The presence of patients with betel nut-specific OSF clearly indicates that the recent increase in the number of incidences of oral cancer in Hunan is associated with the consumption of Hunan-style betel nuts[3-9], despite denials by their manufacturers.

The development of cancer after repeated exposure to a carcinogen often requires a latent period[11]. The betel nut industry in Hunan enjoyed profit growth without major health issues in the last two decades of the 20th century. Not until the beginning of this century, did the significant carcinogenic effects of betel nuts appear[3-10]. In Hunan, thousands of betel nut-associated patients with oral cancer have died or suffered facial disfigurement. The sharp rise in oral cancer patients in Hunan puts a great health burden on the local government, which not only pays medical bills, but also bears the loss of productivity due to sick leave, disability, and deaths of oral cancer-affected employees. Fuelled by high profit, the betel nut industry continues to boost production and has conducted a nationwide marketing campaign. Therefore, it is important to study current and forecast future betel nut-associated oral cancer incidences and their associated health burden. The results will help the government to develop intervention policies and health professionals to prepare for a future increase in the number of oral cancer patients.

Based on historical data, the future trend of a cancer can be predicted with appropriate mathematical methods[12,13]. Simple computer programs such as Microsoft Excel[14] are available to forecast future trends by automatic curve fitting and modelling. Short-term forecasts can be readily achieved with good accuracy, but the same cannot be achieved for long-term forecasts because these simple forecast methods do not set an upper limit to the predicted value. In the 18th century, Malthus[15] first forecasted population growth using an exponential model. However, it worked only for a short term. For long-term growth of a population, the growth rate would gradually slow down and stop when a limit was reached. Therefore, the logistic (or S-curve) model that has an upper limit has been used to forecast nearly all aspects of growth, such as that of bacteria, human population, pharmaceutical market demand and incidences of cancer[16-19].

In the present study, we combined three methods, the Microsoft Excel Forecast Sheet, Microsoft Excel Trendline, and the Logistic growth model, to analyse the trend of Hunan-style betel nut-associated oral cancer incidences and its associated burden on health.

## Materials and methods

### *Data collection on oral cancer cases*

Annual data on oral cancer patient cases were obtained from five hospitals affiliated to the Central South University, Xiangya School of Medicine, located in Changsha, the capital city of the Hunan province. These include the Xiangya First, Second and Third hospitals, the Hunan Provincial Tumour Hospital, and the Xiangya College of Stomatology Hospital. Because patients often visit other hospitals to get a second opinion after the initial cancer diagnosis, only patients hospitalised and who have received treatment for oral cancer, such as surgery and/or chemotherapy, were recorded. The information on age and gender of oral cancer patients was also collected from the Hunan Provincial Tumour Hospital.

### *Trend analysis with Microsoft Excel*

The Microsoft Excel program provides forecast functions based on historical data[14]. The procedures include data entry, filling missing data, selecting forecast methods and performing the forecast.

The yearly oral cancer case data from five hospitals were entered into the Excel spreadsheet. The oral cancer case data from five different hospitals started in different years, as early as 2005 from the Hunan Provincial Tumour Hospital. To match the oral cancer case data to 2005, the Xiangya First Hospital missed data from 2005 to 2010, the Xiangya Second Hospital missed data in 2005, and the Xiangya Third Hospital missed data from 2005 to 2011. These missing data were filled with computer-estimated numbers generated by the Excel trend line backward forecast function based on patient data of other years from these hospitals.

The Microsoft Excel computer program provides two methods of forecasting: Forecast sheet and Trendline. Both methods were used for the current study.

The Forecast sheet method creates forecast data automatically using an established suite of methods for time series prediction – exponential smoothing[14]. To

perform the Forecast sheet analysis, the specific series of data was selected in the spreadsheet. After going to "Data", the Forecast sheet function was selected from the Forecast category. In the pop-up window, the line chart was selected, and then the forecast end date, before clicking "Create." A forecast chart was created based on the Excel built-in exponential smoothing algorithm. The mathematical equation was added to the chart by clicking on its forecast data line. When a new pop-up window appeared, the "Add Trendline" icon was selected, before selecting "Power." Under "Forecast", we clicked on "Display Equation on Chart" and "Display R-squared Value on Chart." The data forecast was illustrated with a line chart including the upper and lower 95% confidence intervals. Computer calculated forecast values for future years were also filled in on the Excel spreadsheet.

The Trendline method offers six Trendline options to forecast future trend automatically by curve fitting based on historical data[14]. To perform the Trendline analysis, we selected the specific series of data and went to "Insert". In the Charts category, we selected the Line Chart. In this chart, we right-clicked on the data line before clicking on "Add Trendline" in the pop-up window. In the Format Trendline window and under Forecast, we filled in the number of forecast years in the Forward box, and pressed "Display Equation on Chart" and "Display R-squared Value on Chart." After hitting "Enter" a chart appeared with a linear dotted line representing the default Trendline forecast. In the Format Trendline window, there are six options – Exponential, Linear, Logarithmic, Polynomial, Power and Moving Average. At the same time, we observed the curve fitting between the dotted and solid lines and the R-squared value in the chart. The Trendline option that gives the best curve fitting and an R-squared value closest to 1 should be selected as the right method for Trendline forecasting.

*Trend analysis with the logistic growth model*

Microsoft Excel provides easy methods of data forecast, but these methods do not have an upper limit and thus may lose predictive value when data increase exceeds the limit. Therefore, for long-term forecast of incidences of oral cancer in Hunan, using the Logistic model with its upper limit may be more appropriate. The logistic model has been widely used to forecast population growth and cancer incidence[16-19]. The basic function is:

$$Y = \frac{L}{1 + Ce^{-kt}}$$

Wherein, t is time (year), Y is the dependent variable, where the number refers to annual betel nut-associated oral cancer cases in a specific region of a particular year. L is the upper limit of Y in a specific area. C is constant, and k is the annual growth rate.

Estimate the ceiling

The population of total betel nut consumers in a local area limits the total number of betel nut-associated oral cancer patients. Moreover, chewing betel nut requires functional teeth. Infants and edentulous elderly cannot chew. According to a report[1], about 83% of the population of the city of Xiangtan – almost all people with teeth – chew betel nut. This is currently the highest proportion of a regional population in China to chew betel nut. This may be related to the tradition of Xiangtan. Other areas may not reach this high percentage. For example, people with better knowledge about betel nut, especially those with a college education – about 5% of the total population[20] – may not chew betel nut. About 5% more people may naturally dislike betel nut. Altogether, about 10% of the population with good teeth may never chew betel nut. Therefore, the highest ratio of Hunan-style betel nut consumers in the general population is about 73% (83% - 10%). The upper limit of the total betel nut consumers is 48 million in the Hunan province, 73% of its total population of 66 million.

Based on this estimate, the upper limits of annual betel nut-associated oral cancer incidence in Changsha and Hunan can be estimated. Betel nut-related oral cancer incidence is well-established in Taiwan[21,22]. Approximately 2 million people there chew betel nuts and the betel nut-associated oral cancer in this population has peaked, with an annual incidence constant at about 0.47% new cases per year[23]. By subtracting non-betel nut-associated cases, about 0.25% may be related to betel nut chewing. We can use this ratio – 0.25% of the betel-chewing population per year – to calculate the betel nut-associated oral cancer incidence in Changsha and Hunan. In the Hunan province, the upper limit of betel nut-associated oral cancer annual incidence would be 120,000 per year (48,000,000 × 0.25%). Changsha is the provincial capital of Hunan. Although it has only about 10% of the population of Hunan, many cancer patients outside of the city visit Changsha to receive cancer treatment because it has the best medical resources in the province. It is estimated that about one-third of all cancer patients in Hunan are treated in Changsha. Therefore, the upper limit of betel nut-associated oral cancer annual incidence in Changsha is about 40,000 per year.

Estimate the floor

Although betel nut chewing is the major cause of oral cancer among betel nut consumers, oral cancer can occur spontaneously or be caused by other factors, such as tobacco, alcohol and the human papillomavirus[24]. The number of oral cancer cases unrelated to betel nut chewing should be subtracted from the overall oral cancer cases before analysing betel nut-associated oral cancers.

Historically, betel nut products were limited in Hunan, and the oral cancer incidence was low and largely unrelated to betel nut chewing. Not until the past two decades has the betel nut industry boomed and incidences of oral cancer increased. Apparently, oral cancer cases in the early years were not associated with betel nut, and betel nut chewing-associated oral cancer cases appeared later. It would be difficult to identify the exact ratio between betel nut-associated and unrelated oral cancer cases in the early years. In our research, the earliest oral cancer case data were in 2005 from the Hunan Provincial Tumour Hospital and in 2006 from the Xiangya Second Hospital. To make the forecast analysis in this study more conservative, we assumed that all oral cancer cases occurring in 2005 or earlier were unrelated to betel nut chewing as the floor. Only the increased portion above the oral cancer case numbers in 2005 was considered related to betel nut consumption.

Validation

To validate the established logistic model, the logistic curve plotting computer program[25] from the Rockefeller University (Loglet Lab version 2) was used to draw the logistic growth curve. This Loglet computer program analysis comprises two models: the first is the component logistic model, in which autonomous systems exhibit logistic growth; the second is the logistic substitution model, which models the effects of competitions within a market. The Loglet Lab version 0.8.2 is available on the Rockefeller University website (http://phe.rockefeller.edu/LogletLab/). Based on the data entered into the program, the computer calculates its own upper limit with margins of error and displays other parameters. To show how accurately a logistic S-curve fits the data, in the bottom of a logistic S-curve, residual values are plotted for all data points, which are the differences between observed values and the fitted values for the same time points. A good fit has residuals randomly above and below the X-axis. Conversely, a cluster of consecutive points located all above or all below the X-axis may indicate a poor fit.

## Results

*Trend analysis with Microsoft Excel*

We obtained up to 12 years of records of oral cancer cases (as shown in Table 1) from five hospitals in Changsha. Numbers estimated by the backward forecast function of Microsoft Excel filled missing data. The first year of data collection was 2005. The sum of all oral cancer cases (305) from the five hospitals, regardless of whether they were related to betel nuts, was assumed unrelated to betel nuts to make the forecast

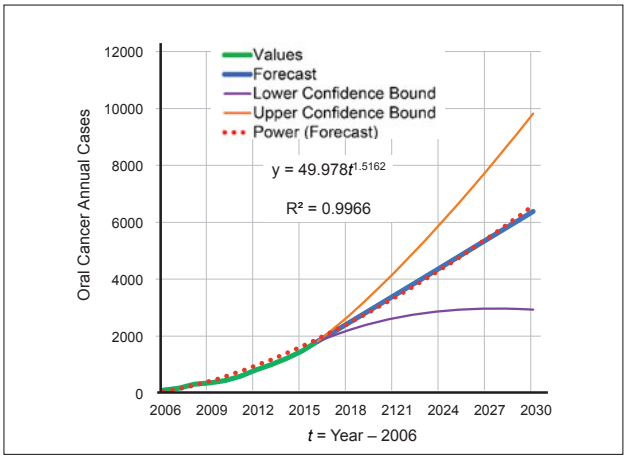


**Fig 1** Trend analysis of betel nut-associated oral cancer annual cases in Changsha by Microsoft Excel Forecast sheet. The upper and lower confidence bounds are 95%.

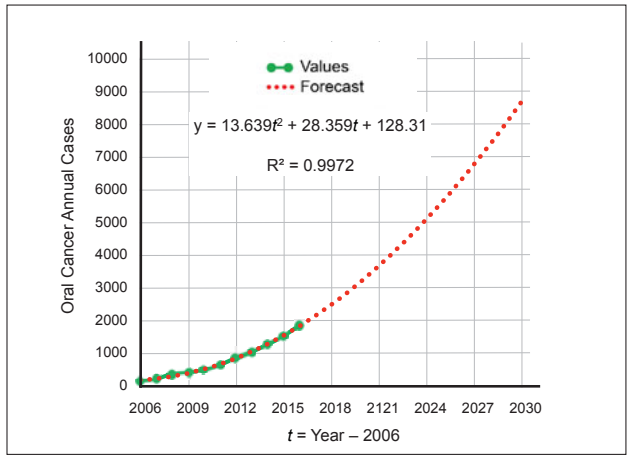


**Fig 2** Trend analysis of betel nut-associated oral cancer annual cases in Changsha by Microsoft Excel Trendline. The Trendline option polynomial with order of 2 is used.

**Table 1** Oral cancer cases in five hospitals affiliated to Xiangya Medical School, Central South University.

| Calendar Year | Data Year | Xiangya 1st Hospital | Xiangya 2nd Hospital | Xiangya 3rd Hospital | Stomatology Hospital[a] | Tumour Hospital[b] | Total | Presumptive betel nut related cases (Total - 305) |
|---|---|---|---|---|---|---|---|---|
| 2005 | | 55[c] | 59 | 34 | | 157 | 305 | 0 |
| 2006 | 0 | 100 | 63 | 35 | | 203 | 401 | 96 |
| 2007 | 1 | 140 | 100 | 36 | | 191 | 467 | 162 |
| 2008 | 2 | 180 | 127 | 37 | | 269 | 613 | 308 |
| 2009 | 3 | 215 | 168 | 38 | | 239 | 660 | 355 |
| 2010 | 4 | 255 | 182 | 39 | | 266 | 742 | 437 |
| 2011 | 5 | 276 | 204 | 40 | | 371 | 891 | 586 |
| 2012 | 6 | 341 | 262 | 45 | | 459 | 1107 | 802 |
| 2013 | 7 | 350 | 354 | 34 | 22 | 531 | 1291 | 986 |
| 2014 | 8 | 376 | 450 | 43 | 25 | 627 | 1521 | 1216 |
| 2015 | 9 | 400 | 562 | 52 | 35 | 727 | 1776 | 1471 |
| 2016 | 10 | 407 | 800 | 41 | 21 | 839 | 2108 | 1803 |
| Total | | 3095 | 3331 | 474 | 103 | 4879 | 11882 | 8222 |

[a] The Xiangya College of Stomatology Hospital was established in 2013.
[b] The average age of oral cancer cases was 51.8 year-old. The male to female ratio was 4:1.
[c] Value in shaded boxes are computer-generated estimate numbers filled for missing data.

more conservative. The number of oral cancer cases from later years had 305 subtracted to represent betel nut-associated oral cancer cases.

Figure 1 shows the forecast using the Microsoft Excel Forecast Sheet method. The betel nut-associated oral cancer case data are plotted for the past 11 years from 2006 to 2016. To facilitate mathematical calculation of these data, the calendar year of 2006 was assigned as year 0. The range of 14 years was selected to forecast betel nut-associated oral cancer incidence in Changsha from 2017 to 2030. Based on the Forecast Sheet method with exponential smoothing, the number of cases of betel nut-associated oral cancer in Changsha would reach 6376 per year in 2030 (Table 2). This method also shows upper and lower margins of error with 95% confidence. It also gives a mathematical equation by curve fitting and an R-squared value of 0.9966.

Figure 2 shows the forecast using the Microsoft Excel Trendline method. The betel nut-associated oral cancer case data were plotted the same way as above and the same range of forecast was selected. Based on the forecast of the Trendline method with the Polynomial option, the number of betel nut-associated oral cancers in Changsha will reach 8665 per year in 2030 (Table 2). It also gives a mathematical equation by curve fitting and an R-squared value of 0.9972.

### *Trend analysis with the Logistic growth model*

Although incidences of betel nut-associated oral cancer have been increasing rapidly in recent years in Changsha, the number cannot exceed an upper limit, which is a percentage of the total number of betel nut consumers. Therefore, the Logistic growth model, which has an upper limit, was used to forecast the trend of the rise in oral cancers in Changsha. It may be more accurate than the two other methods for long-term forecast when the number approaches the upper limit.

Since the data on betel nut-associated oral cancer cases began in 2006, we assigned 2006 as year 0 (Table 1) to calculate the logistic growth model. Because the upper limit for the betel nut-associated oral cancer incidences in Changsha is set at 40,000 per year, the logistic function for the growth of the betel nut-associated oral cancer cases is as follows:

**Table 2** Forecast betel nut-associated oral cancer incidence and associated health burden in Hunan

| Year | Forecast cases of three methods | | | Average case/year | | Accumulated cases since 2006 | | Health burden in Hunan (¥ billion) | |
|---|---|---|---|---|---|---|---|---|---|
| | Forecast Sheet | Trendline | Logistic growth | Changsha City | Hunan Province | Changsha City | Hunan Province | Annual | Accumulated |
| 2016[a] | | | | 1803 | 5409 | 8222 | 24666 | 1.08 | 4.93 |
| 2017 | 2122 | 2091 | 2392 | 2202 | 6606 | 10424 | 31272 | 1.33 | 6.26 |
| 2018 | 2449 | 2433 | 3156 | 2679 | 8037 | 13103 | 39309 | 1.61 | 7.86 |
| 2019 | 2776 | 2802 | 4137 | 3238 | 9714 | 16341 | 49023 | 1.94 | 9.80 |
| 2020 | 3104 | 3199 | 5378 | 3894 | 11682 | 20235 | 60705 | 2.34 | 12.14 |
| 2025 | 4740 | 5591 | 16307 | 8879 | 26637 | 47188 | 141569 | 5.33 | 28.31 |
| 2030 | 6376 | 8665 | 30121 | 25054 | 75162 | 106898 | 320694 | 15.03 | 64.14 |

[a] Data in 2016 are baseline controls for future forecast.

$$Y = \frac{40{,}000}{1 + Ce^{-kt}}$$

First, use the point (0, 96) to solve for $C$.

$$96 = \frac{40{,}000}{1 + Ce^{0}}$$

$$C = 415.67$$

Next, use the point (10, 1803) to solve for $k$.

$$1{,}803 = \frac{40{,}000}{1 + 415.67e^{-10k}}$$

$$k = 0.2977$$

The logistic growth model for annual incidence of betel nut-associated oral cancer in Changsha is:

$$Y = \frac{40000}{1 + 415.67e^{-0.2977t}}$$

Figure 3 shows the logistic growth curve based on this equation. In this curve, $\Delta t = 14.77$ years, the time period required for rapid increase of betel nut-associated oral cancer cases from 10% to 90% of its limit. The rapid oral cancer-growing period will start in 2019 and end in 2034. The mid-point of this period (Tm) is 2026, when the incidence of betel nut-associated oral cancer will increase most rapidly.

To validate the above calculation, the logistic curve plotting computer program from the Rockefeller University (Loglet Lab version 2) was used.

Fig 4 shows the logistic S-shaped curve, based on the betel nut-associated oral cancer case data of the past 11 years from five Changsha hospitals. The solid line represents the trend of forecast, while the grey shaded area represents margins of error, which increases with time. The computer calculation shows that $\Delta t$ is 18.6 years, and the upper limit of the number of betel nut-associated oral cancer cases in Changsha is 32,500 ± 5,000 per year. As with the formula calculation, the computer program also predicted that betel nut-associated oral cancer in Changsha will enter a rapid growth phase in 2019 and end in 2037, reaching the mid-point of the rapid growth period in 2028. In general, the Loglet computer program calculation (Fig 4) matched well the formula calculation (Fig 3), but adjusted its forecast numbers downward and extended the growth period by about 20%, presumably by future competing products in the market.

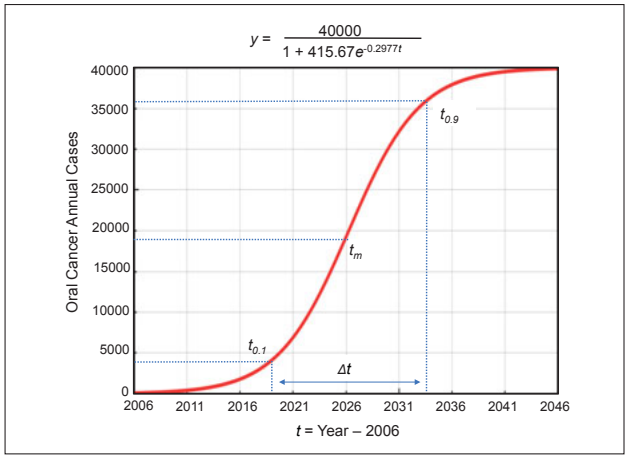


**Fig 3** Trend analysis of betel nut-associated oral cancer annual cases in Changsha by Logistic growth curve. This method predicts that in 2019, the growth of oral cancer cases in Changsha will reach about 4000/year and enter a rapid growth phase, and will reach about 20,000/year in 2026, and about 36,000/year in 2034. By 2041, the growth will approach the upper limit and stay at near 40,000/year.

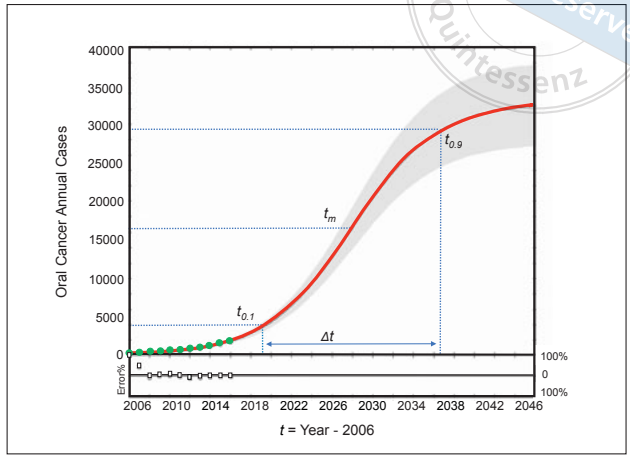


**Fig 4** Trend analysis of betel nut-associated oral cancer annual cases in Changsha by the Loglet Lab computer program (http://phe.rockefeller.edu/LogletLab/). The solid curve represents forecast values. The gray area shows margins of error. In the bottom, residues are shown as small boxes randomly located above and below the X-axis. This confirms that the logistic curve is correctly fitted and can be used for prediction.

*Trend analysis with a combined method*

Among the three forecast methods, the Excel Forecast Sheet method is the most conservative (Fig 1). Although the Logistic model method has an upper limit, it is the most aggressive in the short term (Fig 3). To overcome potential bias of these methods, we combined three forecast methods that did not include the Loglet computer program because competing products against betel nuts are not yet available in the market. Figure 5 shows the curve that represents the average of the three methods. Coincidentally, this curve matches well with the Loglet computer program-calculated curve in Figure 4 up to the year 2046. Therefore, the average of the three forecast methods was used to perform the forecast. Table 2 shows the average numbers for annual betel nut-associated oral cancer cases in future years up until 2030 in Changsha. By multiplying these numbers by three we obtained the estimated number of betel nut-associated oral cancer cases for the entire Human province.

Based on the combined analysis, in Changsha, betel nut-associated oral cancer cases will increase to about 2202 per year in 2017. The cancer case numbers will increase every year progressively to about 3894 per year in 2020, 8879 per year in 2025 and about 25,054 per year by 2030. The number of oral cancer cases for the entire Hunan province will be about three times the number in Changsha. For the accumulated total numbers in Hunan, betel nuts will cause more than 30,000 cases of oral cancer in 2017, 60,000 cases of oral cancer in 2020, 140,000 cases of oral cancer in 2025, and 320,000 cases of oral cancer in 2030.

*Assessing the net health burden caused by betel nuts*

Medical expenses for caring for cancer patients include costs for diagnosis, treatment (surgical, chemo- and/or radiation therapies), drugs, hospitalisation, post-treatment follow-ups, nutritional supplements, and repeated treatment of recurring cancer, and costs for funerals and cemeteries, because about 50% of oral cancer patients die within five years of their treatment[24]. A conservative estimate for the average health burden for each oral cancer patient is ¥200,000.

As shown in Table 2, the accumulated health burden in Hunan as of 2016 has already reached about ¥5 billion. The forecast shows that the accumulated health burden will increase progressively to reach about ¥12 billion in 2020, ¥28 billion in 2025 and ¥64 billion in 2030.

## Discussion

Oral cancer is a serious disease with significant mortality. Major causative factors include the human papillomavirus and tobacco, alcohol, and/or betel nut[24]. Along with the rapid growth of the betel nut industry in recent decades, Hunan province has become a hotspot for oral

cancer[7-9]. Data in Table 1 shows that betel nut-associated oral cancer cases in five hospitals in Changsha have been rapidly increasing, with 8,222 accumulated cases in the past 12 years. In the entire Hunan province, the total accumulated number of betel nut-associated oral cancer cases is estimated to be about three times this number – closer to 25,000 – because hospitals in other cities in Hunan also treat large numbers of oral cancer patients. Due to poor prognosis of oral cancer, about 50% patients die within five years of treatment[26]. Even if the treatment is successful, survivors often suffer from severe facial disfigurement for the rest of their lives.

Demographic data showed that most betel nut-associated oral cancer patients were middle-aged men. These men are often major income providers for families and the backbone of workplaces. High medical expense and loss of ability to work put a great financial burden on their families and on society. Ultimately, the government will have to bear most of the burden due to insurance payments and injury or possible death compensation payouts to sick employees and their families.

It is public knowledge that betel nuts cause oral cancer[2]. Undaunted, the betel nut industry has been continuously booming in Hunan[27,28], fuelled by high profit and the lack of laws or regulations to restrict it. Local governments allow the betel nut industry to grow, probably because they believe it promotes economic prosperity. This may be true only for a short period because oral cancer only appears after some years of exposure to betel nuts[11]. Now that oral cancer cases have risen in Hunan, it has become clear that the booming betel nut industry is to blame. Despite repeated denials by the manufacturers, the relationship between the Hunan-style betel nut and oral cancer is indisputable, because the pre-cancerous condition OSF, which is unique to betel nut consumption, has become widespread in Hunan[3-9].

Over the past 12 years, oral cancer cases in Changsha have been fast increasing, suggesting that significantly more oral cancer patients will appear in the future. The rapid increase in oral cancer cases parallels well with the rapid growth of the betel nut industry in recent years[27]. In fact, today's high oral cancer rate is actually a reflection of the betel nut sales of about 10 years ago because it takes many years of betel nut consumption for oral cancer to appear[11]. In just 10 years, the betel nut industry in Hunan has more than tripled its production scale and expanded its marketing beyond the Hunan province[28], spreading the cancer-causing products to nearly every part of China. If this does not stop, in the future we will see an increasing number of oral cancer patients not only in Hunan, but also nationwide, generating a tremendous health burden to the entire Chinese population.

Due to the sharp rise in incidences of oral cancer, in only a few years' time the current medical resources in Hunan will not be enough to meet the demand of massive numbers of oral cancer patients. This raises serious concerns. How many more oral cancer patients will visit local hospitals in the future? Does this cancer patient increase have a limit? How much will the health burden of the increased oral cancer patients be to society? Therefore, it is important to forecast, as precisely as possible, the trend of betel nut-associated oral cancer incidences in future years. The forecast results will be useful for the medical community to prepare for hospital expansion to meet the future demands of increased patient load and for the government to set up polices to regulate the betel nut industry.

As with the weather forecast, health forecasting is scientifically feasible, but the field is relatively new[29]. So far, only a few studies on cancer forecast have been published[12,13,19]. Forecasting methods are mainly mathematical or computer-based. Among three different forecast methods used in this study, two were from Microsoft Excel. Excel was chosen because the program was available, simple to use, easily understandable, and has multiple options. By curve fitting of existing data, the program automatically generates mathematical equations and R-squared values, which validate the reliability of curve fitting. With two different forecast methods in Excel, their results can complement each other. The charts in Figures 1 and 2 show excellent curve fitting to the data points, with R-squared values very close to 1. A major drawback of these methods is the lack of an upper limit. Their forecast values can increase indefinitely without ceiling, but in reality, the number of total betel nut consumers limits the number of people suffering betel nut-associated cancer, indicating the presence of an upper limit. Therefore, a third method, the Logistic growth model with its upper limit, was used. A problem with the Logistic growth model is that the forecasted growth is very rapid, especially in the rapid growth phase. Interestingly, the rapid growth of the Logistic model calculated by the equation was reduced for about 20% by the Loglet computer program[25]. Because the Loglet program also includes the logistic substitution model, which models the effects of competitions, it is suggested that competing betel nut products would appear in the future to reduce betel nut-associated oral cancer, but such reduction may be limited. Methods restricting betel nut production would be more effective in stopping the increase of oral cancer.

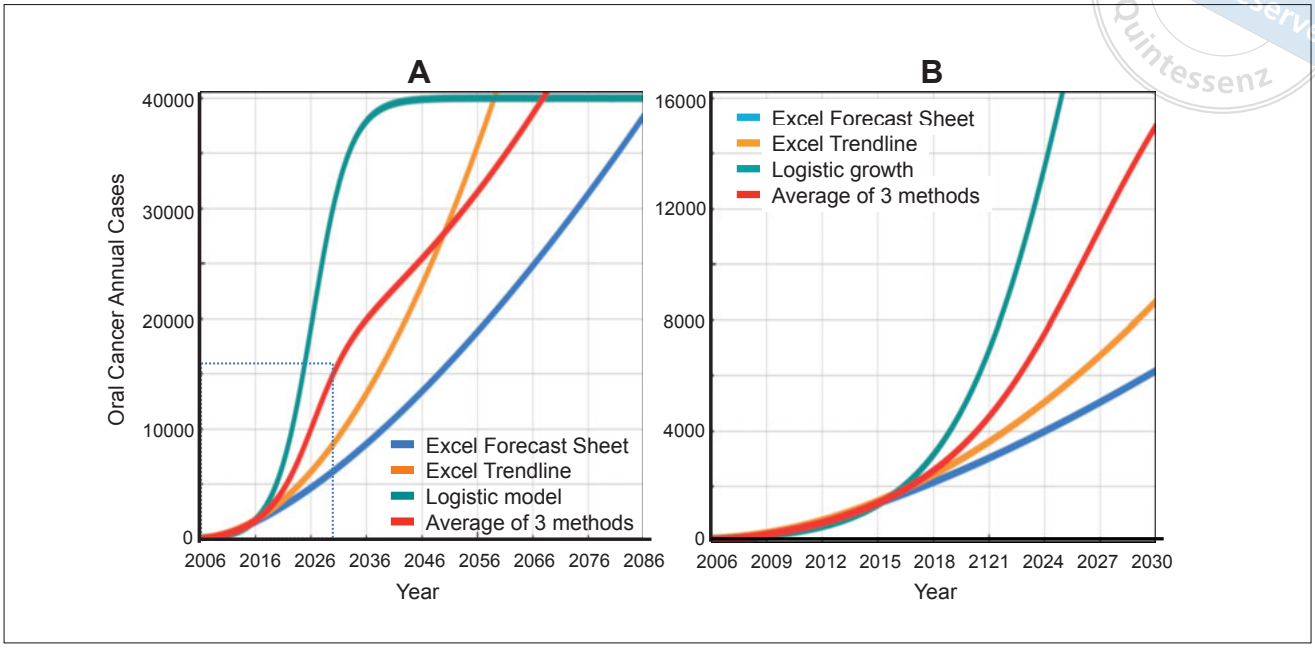


**Fig 5** Trend analysis of betel nut-associated oral cancer annual cases in Changsha by four methods: A, 70-year trend; B, 14-year trend.

To overcome potential bias of individual forecast methods and to avoid enlarged margins of error for longer time (Fig 4), we combined the three methods to forecast a short period of 14 years, from 2017 to 2030. Interestingly, the combined forecast data (Fig 5) matched well with the Loglet computer-generated data (Fig 4), confirming its predictability. Based on the combined forecast, by the year 2030 Hunan will have about 75,000 betel nut-associated oral cancer cases, and a financial health burden of about ¥15 billion each year, about a 14-fold increase from the 2017 case numbers. The accumulated total number of oral cancer cases will exceed 320,000 and the total health burden on society will reach ¥64 billion.

This forecast, which is limited to the Hunan province, could be a severe underestimation nationwide, because the Hunan-style betel nut has spread beyond Hunan to nearly all parts of China. By 2030, betel nut-associated oral cancer cases could easily exceed 1 million nationwide and triple the amount of the predicted health burden for Hunan. This indicates that the huge health burden created by the betel nut industry would soon outweigh its initial economic contribution to society. It is important to inform the government of the facts: that in future years, the betel nut industry will cause a humanitarian catastrophe with massive loss of human life and resources in Hunan and ultimately in the whole of China.

This upcoming catastrophe would be too large to be managed just by the medical community because the betel nut industry in Hunan has been growing rapidly out of proportion thanks to the support of local governments[27,28]. To protect the health of Chinese people and the country's valuable national resources, the central government must intervene.

Firstly, China should ban betel nuts at national level. A government ban would be most effective and should be feasible because there are precedents. Domestically, the city government of Xiamen has banned betel nuts for more than 20 years[30], and internationally, the United Arab Emirates has also banned them[31]. If this cannot be achieved immediately the next best thing is to promote public education about the health risk of betel nuts and ban all commercial advertising. Secondly, increasing taxes on betel nut sales can generate revenue to offset the burden on health. Finally, promoting competing products could also help reduce betel nut consumption.

In summary, betel nut-associated oral cancer cases have been increasing over the past 12 years in Hunan. The trend analysis predicts that the growing betel nut industry will cause a humanitarian catastrophe in Hunan, and ultimately in China, with massive loss of human life and national resources. To prevent this catastrophe, China should ban betel nut and provide early oral cancer screening to its consumers as soon as possible.

## Conflicts of interest

The authors reported no conflicts of interest related to this study.

## Author contribution

Drs Yan Jia HU, Jie CHEN, Wai Sheng ZHONG, Tian You LING, Xin Chun JIAN, Ruo Huang LU, and Zhan Gui TANG participated in data collection; Drs Yan Jia HU and Lin TAO designed the study; Dr Lin TAO analysed data, prepared and revised the manuscript.

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