Worldwide burden of gastric cancer in 2012 that could have been prevented by increasing fruit and vegetable intake and predictions for 2025

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(Submitted 10 July 2015 – Final revision received 6 November 2015 – Accepted 7 December 2015)

Abstract
The regional and temporal variation in patterns of fruit and vegetable intake contributes to differences in the impact on gastric cancer burden across regions and over the years. We aimed to estimate the proportion and absolute number of gastric cancer cases that could have been prevented in 2012 with an increase in fruit and vegetable intake up to the levels defined by the Global Burden of Disease as the theoretical minimum-risk exposure distribution (300 and 400 g/d, respectively), as well as the corresponding figures expected for 2025. Preventable fractions (PF) were computed for 161 countries, using data on fruit and vegetable availability in 1997 and 2010 and published estimates of the magnitude of the association between fruit and vegetable intake and gastric cancer, assuming a time lag of approximately 15 years. Countries classified as very high Human Development Index (HDI) presented median PF in 2012 much lower than low-HDI countries for both fruits (3.0% < 10.2%, P < 0.001) and vegetables (6.0% < 11.9%, P < 0.001). For vegetables only, PF significantly decreased until 2025 in most settings; however, this corresponded to a reduction in the absolute number of preventable gastric cancer cases in less than half of the countries. Increasing fruit and vegetable intake would allow preventing a relatively high proportion of gastric cancer cases, mostly in developing countries. Although declines in PF are predicted in the near future, changes in order to achieve healthier lifestyles may be insufficient to overcome the load of demographic variation to further reduce the gastric cancer burden.

Key words: Fruit: Vegetables: Stomach neoplasms: Preventable fractions: Predictions

Gastric cancer is the fifth most common malignancy and the third leading cause of death by cancer worldwide11. Despite the declining incidence and mortality rates for several decades22, in the most recent years, the relative declines were smaller in several settings, and a levelling off is already expected in a few countries33. Micronutrients with antioxidant capacity contained in fruits and vegetables were included in the initial model of gastric carcinogenesis, owing to their activity as free-radical scavengers inhibiting the mutagenic progress44. The evidence currently available shows a weaker effect than that initially considered, but confirms the role in intermediate stages of the carcinogenic process55,66. In 2000, the Global Burden of Disease (GBD) Project showed that increasing individual fruit and vegetable consumption could reduce the total worldwide burden of disease associated with gastric cancer by 19%77 and by 12% in the European Union for the same year88. Initiatives to increase the consumption of fruits and vegetables have been implemented in several developed countries, targeting different age groups99,1010. However, the overall impact of these interventions has been small and intake remains inadequate in many settings11–13. In developing countries, the prevalence of low fruit and vegetable consumption is even higher mainly due to barriers to access and affordability14. The regional and temporal variations in the patterns of fruit and vegetable intake contribute to differences in the impact of these dietary exposures in the burden of gastric cancer, across regions and over the years. Therefore, we aimed to estimate, for a large number of countries from all continents, the proportion and absolute number of gastric cancer cases that could have been prevented in 2012 with an increase in the intake of fruits and vegetables up to the levels defined by the GBD as the theoretical minimum-risk exposure distribution (300 and 400 g/d, respectively)15, as well as the corresponding figures expected for 2025.

Methods
Preventable fractions (PF) – that is, estimates of the proportion of gastric cancer cases that could have been prevented if the
levels defined by the GBD as the theoretical minimum-risk exposure distribution for fruits (300 g/d) and vegetables (400 g/d) intake were met – were computed for different countries. For this purpose, we used country-specific data on fruit and vegetable availability and gastric cancer incidence, as well as published estimates of the magnitude of the association between fruit and vegetable consumption and gastric cancer. A time lag of approximately 15 years was assumed, based on the stronger effects of fruit and vegetable intake on gastric cancer observed in cohort studies with longer follow-up periods, compatible with a lag of 10–20 years.

PF estimates were computed for each country with available data on both fruit and vegetable availability in 1997 and 2010 and gastric cancer incidence in 2012 and 2025.

**Association between fruit and vegetable intake and gastric cancer**

We conducted a systematic review of meta-analyses to obtain estimates of the magnitude of association between fruit and vegetable consumption and gastric cancer. A total of fifty-three references were retrieved through a PubMed search, from inception to May 2015, and backward citation tracking. Nine meta-analyses were identified, and data extraction was accomplished following a protocol defined a priori. A detailed description of the published meta-analyses is provided in online Supplementary Table S1 and the results are presented in Fig. 1.

Three meta-analyses presented the results per 100 g/d increment in fruit and vegetable intake, and we selected the most recently published reporting decreasing risks of 0.95 and 0.96 per each increase of 100 g/d in fruit and vegetable intake, respectively. This meta-analysis resulted from an extensive search for papers published up to August 2015 in two of the most important medical databases. The authors followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and report no publication bias. It included all cohort studies summarised in the previous two meta-analyses reporting results of dose–response analyses, and for some of them they considered updated analyses with longer follow-up periods.

**Fruit and vegetable availability**

Fruit and vegetable availability in kg/year per capita was retrieved from the FAO of the UN Food Balance Sheets for 1997 and 2010. Data were available for 177 and 179 countries, respectively. Fruit availability included the following subgroups of food items: oranges, mandarins; lemons, limes and products; grapefruit and products; citrus, other; bananas; plantains; apples and products; pineapples and products; dates; grapes and products (excluding wine); and fruits, other. Vegetable availability included the following subgroups of food items: tomatoes and products; onions; and vegetables, other.

**Preventable fraction**

We estimated the proportional reduction in gastric cancer incidence that would arise if exposure to fruits and vegetables corresponded to a counterfactual distribution scenario, defined as the exposure distribution that would result if the whole population followed the at least 300 and at least 400 g/d of fruit and vegetable intakes, respectively. We used the method proposed by Miettinen, which defines PF as follows:

$$\text{PF} = P(1-\text{RR}),$$

where $P$ is the prevalence of exposure to fruits or vegetables and RR is the relative risk of the association between fruit or vegetable intake and gastric cancer. However, from our systematic review, we obtained an estimate of decrease in gastric cancer risk of 0.95 and 0.96 per each increase of 100 g/d in fruit and vegetable intake, respectively, equivalent to logarithmic coefficients of $0.0005$ and $0.0004$, respectively. Considering the difference between the minimum levels defined by the GBD as the theoretical minimum-risk exposure distribution for fruit (300 g/d) and vegetable (400 g/d) intake and fruit and vegetable availability in each country, the previous formula can be transformed into the following:

$$\text{PF} = 1 - e^{(\text{coefficient} \times \text{difference})}.$$
Fig. 1. Meta-analyses on the association between fruit and vegetable intake and gastric cancer. Meta-analyses were identified through a PubMed search, from inception to May 2015, using the following expressions: (gastric OR stomach) AND cancer AND (fruit OR vegetable OR antioxidant) AND ('systematic review' OR meta-analysis OR 'combined analysis' OR 'pooled analysis'). Full-text papers published in English, Portuguese, Spanish, French, Italian and Polish were evaluated. Screening of reference lists and data extraction were accomplished independently by two researchers (B. P., C. C.), following a protocol defined a priori, and discrepancies were discussed until consensus or resolved involving a third researcher (N. L.). Only meta-analyses presenting data for total fruit and/or total vegetable intake were included.
Fig. 2. Estimates of gastric cancer-preventable fractions (quartiles of the distributions in 2025 were used as cut-offs) as a result of increasing fruit and vegetable intake up to the levels defined by the Global Burden of Disease as the theoretical minimum-risk exposure distribution (300 and 400 g/d, respectively) in 161 countries (countries with no estimates of preventable fractions are presented in white), in 2012 and in 2025. The first five symbols refer to fruit whereas the other five refer to vegetables. □, No data, ■, 0.00–0.09, ▪, 1.0–5.1, □, 5.2–8.3, ▪, 8.4–13.2, □, no data, ■, 0.0–3.7, ▪, 3.8–8.0, □, 8.1–11.0, ▪, 11.1–14.1.
from 7-1 to 6-0 % in medium-HDI countries, \( P = 0.068 \); and from 10-2 to 8-5 % in low-HDI countries, \( P = 0.094 \). Only for vegetable intake did the proportion of preventable cases significantly decrease until 2025 in high-, medium- and low-HDI countries (from 7-0 to 4-4 %, \( P = 0.005 \); from 10-4 to 9-2 %, \( P < 0.001 \); and from 11-9 to 11-5 %, \( P = 0.07 \), respectively), whereas it remained similar in very high-HDI countries (from 6-0 to 5-2 %, \( P = 0.701 \)).

In the 161 countries analysed, the absolute number of gastric cancer cases that could be prevented with an increase in fruit intake up to the levels defined by the GBD decreased by approximately 4900 between 2012 and 2025, whereas an increase of approximately 6400 in the absolute number of gastric cancer cases that could be prevented with an increase in vegetable intake up to the levels defined by the GBD was observed during the same period. The most pronounced changes were a decrease of approximately 10-400 preventable cases in China due to a rise in fruit intake, and increases of approximately 2500 preventable cases due to reductions in the consumption of fruits and vegetables in Japan for the same period. The most pronounced changes were a decrease of approximately 10-400 preventable cases in China due to a rise in fruit intake, and increases of approximately 2500 preventable cases due to reductions in the consumption of fruits and vegetables in Japan for the same period. The smallest changes were observed in African and European countries (online Supplementary Tables S2 and S3).

For less than half of the countries, where a decline in PF occurred from 2012 to 2025, this corresponded to a reduction in the absolute number of preventable gastric cancer cases in 2025 compared with 2012, most of them from low-and medium-HDI settings (Fig. 4).

**Discussion**

The proportion of gastric cancer cases that could have been prevented with increases in the intakes of fruits and vegetables up to the levels defined by the GBD as the theoretical minimum-risk exposure distribution (300 and 400 g/d, respectively) differs substantially across countries with different levels of development, as expected when taking into account regional differences in the intakes of fruits and vegetables.

The burden of gastric cancer attributable to low fruit and vegetable intake has been shown to differ with socio-economic status at the country level, being higher in less-developed countries compared with those more developed \({}^{20}\), which is confirmed by our study. Our results are also in accordance with previous analyses showing low proportions of gastric cancer cases attributable to inadequate intake of fruits and vegetables in selected European countries \({}^{27,28}\), and much higher estimates in China, with large differences between fruit and vegetable intakes in this country \({}^{29}\). However, in a report from the UK \({}^{30}\), 36 % of the gastric cancer cases diagnosed in 2010...
were attributed to low consumption of fruits and vegetables. This estimate is higher than the one reported in this study (4.0% for fruits and 6.5% for vegetables), but their use of much lower RR estimates (0.23 vs. 0.95 per 100 g/d increment in intake of fruits and 0.32 vs. 0.96 per 100 g/d increment in intake of vegetables) and lower mean levels of consumption (95 vs. 218 g/d for fruits and 135 vs. 231 g/d for vegetables) contributed to these differences. Nevertheless, they assumed a latent period based on the duration of follow-up in the two studies contributing to the pooled RR value used in their study, which is shorter than the one we presumed (10 vs. 15 years), further precluding a direct comparison between estimates.

Significant decreases in the proportion of preventable cases from 2012 to 2025 were only observed for vegetable intake in high-, medium- and low-HDI countries, whereas PF for vegetable intake are over half of the estimated values for fruit intake in very high-HDI countries, regardless of the time period. This is in accordance with the complex conceptual framework of the determinants of consuming fruits and vegetables across countries in different stages of economic development, where not only individual but also external factors mediate this relationship. Availability and accessibility are two of the major latter factors. In several low-income countries, especially in rural farming areas, fruits and vegetables are still accessible to the population; nevertheless, because of their high perishability, the cost of buying them may be high and the consumption of some fruits and vegetables may be constrained when they are not homegrown. Thus, differences in the food system and environment, such as policies that regulate fruit and vegetable production and distribution, may contribute to the differences in levels of fruit and vegetable consumption, and therefore preventable cases across countries.

In the higher socio-demographic population groups, a preference for fruit intake is observed, whereas vegetables tend to be more commonly consumed than fruits in lower socio-demographic groups. On the one hand, fruits seem easier to integrate into routine diet, but as it is affected by seasonality its consumption by poor families is largely variable with agricultural cycles. On the other hand, vegetables are perceived as more difficult to prepare in terms of cooking but may require less effort if grown at home, frequently being a component of the cheapest meals, especially in rural areas. Knowledge, tasting preferences and psychological factors also play a role in defining patterns of consumption. In return, cultural aspects along with family factors and social support have major influences in the ability to overcome the barriers to eat fruits and vegetables. Initiatives to increase the consumption of fruits and vegetables have been implemented in several developed countries, targeting different age groups. However, the overall impact has been small and intake remains inadequate in many countries. In developing countries, the prevalence of low fruit and vegetable consumption is even higher mainly due to barriers to access and affordability and also due to characteristics of the stages of nutritional transition that countries are experiencing. Many low-income countries fit in the Famine pattern and Receding Famine pattern, characterised by a low, varied, cereal-based diet. This may have a great impact in countries at early stages of the epidemiological transition, contributing to the double burden of under-nutrition related to infectious diseases and malnutrition related to chronic conditions.

For economically constrained settings or population groups, fruits and vegetables are an expensive source of energy, and the role of coherent policies that enhance their consumption efficiently is crucial. Along with information and education, strategies that shift the food system – for example, by supporting fruit and vegetable production through similar policy instruments used for grain, meat and dairy production as well as strategies for changing food environment such as marketing and advertising fruits and vegetables and increasing their availability – are seen as important responses to the insufficient global consumption of fruits and vegetables.

Assumptions underlying valid estimation of PF include a causal relationship between exposure and disease and that unbiased and free-from-confounding RR estimates are available. Regarding the evidence of a causal role of fruits and vegetables in gastric carcinogenesis, these have already been postulated as major components of the causal mechanisms leading to gastric cancer. In 1997, the World Cancer Research Fund classified fruits and vegetables as protective against gastric cancer. This evaluation was based on cohort, case-control and ecological studies conducted in various parts of the world showing a consistent association between fruit and vegetable intake and gastric cancer, and also presented data regarding a dose-response relationship and their effect on pre-malignant conditions. However, the 2007 report lowered the classification of evidence from convincing to probable; the evidence from cohort studies obtained since the first report is more equivocal, whereas evidence from case-control studies remained strong and consistent. Most of the studies included in these reviews presented RR estimates adjusted for sex, age, Helicobacter pylori infection status, smoking and other dietary factors. For the present study, the RR estimates for the association between fruit and vegetable intake and gastric cancer were retrieved from a meta-analysis of cohort studies, for which weaker associations were observed (RR estimates of 0.95 for fruit and 0.96 for vegetables) compared with other study designs, such as case-control studies (OR estimates of 0.67 for fruit and 0.70 for vegetables), which may have contributed to conservative estimates of PF. In addition, as the selected RR estimates were obtained from previous meta-analyses, it was not possible to ensure the homogeneity of the strategies adopted to control for confounding in each of the original studies. Although most reports provided RR estimates adjusted for the main potential confounders, residual confounding cannot be ruled out, because not all studies took a potential confounding effect of H. pylori infection into account, and this is another limitation of our study. Furthermore, the meta-analysis by Wang et al. provided region-specific data for the comparison of the 'highest' with the 'lowest' levels of consumption of fruit (RR estimates for Asia, Europe and USA: 0.95, 0.81 and 0.90) and vegetables (RR estimates for Asia, Europe and USA: 1.03, 0.84 and 0.95). Although these estimates cannot be used to compute the PF by taking into account the estimated levels of fruit and vegetable availability in each region, the heterogeneity of the results according to the place where the studies were conducted shows that more valid regional
Comparisons may be achieved when population-specific RR estimates are available.

Some studies have reported that gastric cancers of the intestinal type may be more influenced by fruit and vegetable intake compared with diffuse tumours, in accordance with the hypothesised relatively greater impact of environmental factors in the aetiology of intestinal-type carcinomas, whereas the diffuse type is considered more dependent on the individual genetic profile. However, when finer markers of intestinal differentiation, such as CDX2 protein expression, are used, no statistically significant or consistent associations between environmental exposures and CDX2 protein expression status are observed, suggesting that gastric cancer subtypes are essentially homogeneous regarding the relation with most of the established determinants. Nevertheless, the lack of worldwide gastric cancer incidence estimates according to histological type precludes the quantification of the effect of fruit and vegetable intake in gastric cancer subtypes at an international level. As a critical aspect of our analyses is the selection of the RR estimates, the inconsistent results reported for the association between fruit and vegetable intake and gastric cancer according to tumour location, either suggesting stronger or weaker associations with cardia cancer than for non-cardia tumours, preclude the quantification of PF, specifically for each gastric cancer subtype, even if worldwide gastric cancer incidence estimates according to topographical subsites are now available. This is a limitation of our study, because the inclusion of populations with different proportions of cardia and non-cardia cancers might influence the estimated PF. In addition, we used a single RR estimate for all regions of the world, as in the most recent meta-analysis no region-specific dose-response data were available; such data were available in one of the previous meta-analyses, but it included data from both cohort and case-control studies, and using those estimates may contribute to spuriously high PF estimates for all regions.

Estimates of fruit and vegetable intake do not represent the real per capita consumption but describe the availability of such products (usually derived from production, imports and exports), which under certain assumptions may be used as surrogates for intake. Yet, these are the best estimates for monitoring global trends, as they cover more years and more countries than survey-based prevalence of fruit and vegetable intake. Nevertheless, it can be affected by under-reporting, especially if household production accounts for a high proportion of the total fruits and vegetables available for consumption, as occurs in many developing countries. Furthermore, discrepancies between ecological and individual data on fruit and vegetable consumption have been reported for some developed countries, with a tendency for FAO data to overestimate mean intake derived from national food consumption surveys. Taken together, these may have contributed to an overestimation of PF in developing countries and underestimation in developed countries. Nevertheless, variations in the data retrieved from the FAO Food Balance Sheets between 1997 and 2010 are in accordance with the previously reported trends in fruit and vegetable consumption in several countries. Some countries have experienced a decline in fruit and vegetable intake during the period analysed, such as Japan, South Korea, Spain and the USA, whereas in others the consumption increased during the same period – namely, in China, Denmark, Finland and the UK.

Gastric cancer is currently interpreted as a multifactorial complex disease, and therefore different sets of causal mechanisms leading to its occurrence may co-exist. Under this assumption, the same exposure (e.g. low fruit and vegetable intake) may contribute to the incidence of gastric cancer when occurring together with different sets of other exposures (e.g. H. pylori infection or H. pylori infection and salt consumption or H. pylori infection and smoking). Although the different causal mechanisms potentially leading to gastric cancer are not known, the estimated PF reflect a scenario where fruit and vegetable intake is within the range defined by the GBD, and therefore affecting all of the possible pathways to cancer, regardless of persistence or disappearance of the remaining exposures that take part in those causal mechanisms. This is reflected in the fact that if PF are computed for each of the potential protective factors, they may add up to more than 100%. Therefore, our results provide information on the importance of fruit and vegetable intake with respect to causes of gastric cancer, and show the maximum potential for strategies promoting increases in fruit and vegetable intake to gradually contribute to a lower burden of gastric cancer, in countries that have not yet achieved the minimum levels defined by the GBD. Although the proportion of gastric cancer cases that could have been prevented with higher intake of fruits and vegetables is not expected to vary with the trends in exposure to other risk factors, the latter will influence the overall number of gastric cancer cases, and therefore the absolute number of preventable cases, which are being estimated assuming that the observed trends in gastric cancer incidence will be maintained in the next few years, and accounting for the projected changes in the population distribution.

In conclusion, increasing fruit and vegetable intake up to the levels defined by the GBD would allow preventing a relatively high proportion of gastric cancer cases, mostly in developing countries. Although declines in PF are predicted in the near future, changes in order to achieve healthier lifestyles may be insufficient to overcome the load of demographic variation to further reduce the burden of gastric cancer. In addition, strategies need to be setting-specific because of the differences in PF between fruit and vegetables across geographical regions and levels of HDI.

Acknowledgements

This work was supported by Fondo Europeu de Desenvolvimento Regional (FEDER) funds through the Programa Operacional Factores de Competitividade (POFC) – COMPETE (FCOMP-01-0124-FEDER-021181) and by national funds through the Fundação para a Ciência e a Tecnologia (PTDC/SAU-EPI/122460/2010), and by the Epidemiology Research Unit – Institute of Public Health, University of Porto (UID/DTP/047507/2013). Individual grants attributed to B. P. (SRH/BPD/75918/2013), A. F. (PD/BD/105623/2014) and S. M. (SRH/BPD/102585/2014) were supported by ‘Fundação para a Ciência e a Tecnologia’. B. P. formulated the research questions, B. P. and N. L. designed the study, B. P., C. C., A. F. and S. M. carried out the study, B. P. and C. C. analysed the data and B. P., P. P. and N. L. provided funding.
wrote the article. All the authors read and approved the final version of the manuscript. The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S000711451500522X

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