Adherence to Mediterranean diet and risk of gastric cancer: results of a case–control study in Italy

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The aim of this study is to evaluate the association between adherence to Mediterranean diet (MD) and gastric cancer (GC). A case–control study was carried out at the Fondazione Policlinico ‘A. Gemelli’ (Rome, Italy) from 2003 to 2015. A total of 223 incident cases and 223 controls were interviewed. Dietary intake was assessed through a validated food frequency questionnaire that collected information on more than 25 food items. The association between adherence to MD and risk of GC was quantified by calculating Odds Ratios (OR) and 95% confidence intervals (CI). The analysis reports that a higher adherence to MD is associated with a reduced risk of GC (OR: 0.70; 95% CI: 0.61–0.81). A high consumption of vegetables (OR: 0.34; 95% CI: 0.14–0.85), legumes (OR: 0.13; 95% CI: 0.06–0.29), and fish (OR: 0.33; 95% CI: 0.15–0.68), as well as low consumption of meat (OR: 0.29; 95% CI: 0.10–0.85) and alcohol (OR: 0.46; 95% CI: 0.24–0.90) are consistently related to a lower risk of GC. Our study indicates a protective role of the MD eating pattern and MD individual components against GC. Our results showed a beneficial role of high vegetable, legume, and fish consumption, along with low intake of alcohol and meat in the development of GC. European Journal of Cancer Prevention 00:000–000 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Gastric cancer (GC) represents the fifth most common malignancy in the world and it accounted for ~950,000 new cases in the year 2012 [International Agency for Research on Cancer, World Health organization, 2014; World Health Organization (WHO), 2012]. More than 70% of cases occur in developing countries, with rates about twice as high in men as in women. A decline in GC figures over the past century has been noted and the reasons are associated with a more varied diet and better food conservation, as well as control of Helicobacter pylori infection (Guggenheim and Shah, 2013; Boffetta et al., 2014; Torre et al., 2015).

The Mediterranean diet (MD) represents a traditional dietary pattern found in countries bordering the Mediterranean sea, which have been historically associated with lower cancer incidence rates compared with Northern countries, such as the UK or USA (Verberne et al., 2010; Schwingshackl and Hoffmann, 2015a). Although some regional variation is present, the majority of general descriptions and pyramids of the MD are similar among publications, encompassing same key components (Willett et al., 1995; Bach et al., 2006; Bach-Faig et al., 2011; Davis et al., 2015). Emphasis is placed on high intake of fruit, vegetables, cereals, legumes, nuts and seeds, fish or seafood, cold pressed olive oil, moderate consumption of alcohol, dairy products, and a relatively low consumption of red or processed meat and sweets (Trichopoulou and Lagiou, 1997; Davis et al., 2015).

The protective role of the MD on health and its influence on reduced risk of numerous chronic diseases have been confirmed by various studies (La Vecchia and Bosetti, 2006; Roman et al., 2008; Mente et al., 2009; Schwingshackl and Hoffmann, 2015a). The literature on the topic is fast-growing and the evidence points out that adherence to MD is associated with a reduced risk of several cancer types and cancer mortality (Schwingshackl and Hoffmann, 2014). Among plausible biological mechanisms for cancer prevention, the most important aspects of MD are linked to the favorable effects of omega 6 and omega 3 essential fatty acids, high amounts of fiber, antioxidants, and polyphenols found in fruit, vegetables, olive oil, and wine (Zhang et al., 1997; Giacosa et al., 2013).
Few studies have assessed the effects of the MD on GC, taking into consideration whole nutrition patterns (variation in overall food intake) rather than single components of the diet (Buckland et al., 2010; Li et al., 2013; Praud et al., 2014). A meta-analysis carried out on observational studies, evaluating the effects of adherence to MD on overall cancer mortality and incidence of different types of cancer, showed that high adherence to MD was associated with a significant 27% reduction in the risk of GC overall. However, the estimate, based on two cohort studies with contrasting results, and one case–control study, provides interesting insights, but no definite conclusions (Schwingshackl and Hoffmann, 2015b).

To further investigate this issue, we carried out a hospital-based case–control study with the aim of evaluating the association between adherence to MD and GC, as well as the effect of the individual food components on GC risk.

Methods
Participants and study design
Study cases were GC patients admitted to Fondazione Policlinico ‘A. Gemelli’ (Rome, Italy) from 2003 to 2015. Details on the codes of diagnosis used to select patients have been described previously (Boccia et al., 2007). The controls were age matched (within 5 years) with the cases and selected among cancer-free patients with a broad range of diagnoses, admitted to the same hospital during the same time period. Cases and controls were interviewed by medical doctors or trained interviewers using a structured questionnaire, including data on demographics, medical history, family history of cancer with a special focus on GC, alcohol and tobacco consumption, and other relevant lifestyle factors. Written informed consent was obtained from all study participants according to the rules of the Ethical Committee of the University (Università Cattolica del Sacro Cuore, Rome, Italy).

Dietary intake and Mediterranean diet score
A validated food frequency questionnaire was used to obtain information on diet. GC patients were asked to focus on 1 year before the interview when answering the questions. The total energy intake was calculated by 27 food and beverage items, complemented with the Italian food composition database and with other published data [Salvini et al., 1996; Salvini, 1997; Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione (INRAN), 2010].

The level of adherence to the traditional MD pattern was assessed using the MEDI-LITE score developed by Sofi et al. (2017, 2013). In brief, the MEDI-LITE score is based on nine components of the MD, some of them being potentially beneficial and others being potentially detrimental: fruit, vegetables, legumes, cereals, fish, meat and meat products, dairy products, alcohol, and olive oil. However, as our questionnaire did not contain dietary intake for cereals, dairy products, and olive oil, the MEDI-LITE score used in our study was based on six out of nine components of the MD. For each component, an individual is assigned a value of 0, 1, or 2 on the basis of their level of consumption. We assigned 2 points to the highest category, 1 point for the middle category, and 0 point for the lowest category of consumption of fruit, vegetables, legumes, and fish. However, for meat and meat products, we assigned 2 points for the lowest, 1 point for the middle, and 0 point for the highest category of intake. Furthermore, categories related to the alcohol unit were used for alcohol consumption (1 alcohol unit = 12 g of alcohol) by allocating 2 points to the middle category (1–2 alcohol units/day), 1 point to the lowest category (<1 alcohol unit/day), and 0 point to the highest category of consumption (>2 alcohol units/day).

The MEDI-LITE score was generated by summing the points assigned to each individual component and ranges from 0 (minimal adherence) to 12 (maximal adherence).

Statistical analysis
We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) of GC according to the overall MEDI-LITE score, the six dietary components included in the MEDI-LITE score, and the MEDI-LITE score in strata of selected demographic, behavioral, and clinical covariates. A multiple imputation procedure was used for missing data on diet (Donders et al., 2006). We used a logistic regression model adjusted by sex, tobacco smoking (never, exsmoker, and current smoker), and total energy intake (Breslow and Day, 1980). The definition of smoking status was as follows: the participants who were smoking at the time of the study or who had smoked 1 year before diagnosis for cases and 1 year before the interview for controls were defined as current smokers; the participants who had quit smoking more than 1 year before diagnosis for cases and 1 year before the interview for controls were defined as exsmokers; and the participants who had never smoked were defined as nonsmokers.

Statistical analyses were carried out using Stata software (Stata Statistical Software Release 13; StataCorp LP, College Station, Texas, USA).

Results
We included 223 cases and 223 controls in our study. Demographic, behavioral, and clinical characteristics are reported in Table 1. There was a higher prevalence of men among cases and controls (52.5 and 59.2%, respectively). As a result of the matching, cases and controls were identically balanced with respect to age distribution. The majority of the cases were diagnosed with noncardia GC (87.5%) and with advanced tumor stage (grade level 3–4; 70.63%) (data not shown).
The MEDI-LITE score, which ranges from 0 (minimal adherence) to 12 (maximal adherence), was categorized into three groups: 0, 1–2, and 3–7 points.

Table 2 reports the distribution of age and selected risk factors variables by categories of the MEDI-LITE score among 223 gastric cancer cases and 223 controls.

Table 3 reports the ORs of GC risk according to the MEDI-LITE score and the six items included in the score. Adherence to MD was associated with a reduced risk of GC (OR: 0.70; 95% CI: 0.61–0.81) for each unit of increase in the MEDI-LITE score. A high consumption of vegetables (OR: 0.34; 95% CI: 0.14–0.85), legumes (OR: 0.13; 95% CI: 0.06–0.29), and fish (OR: 0.33; 95% CI: 0.15–0.68) was associated significantly with a reduced risk of GC. Low consumption of meat (OR: 0.29; 95% CI: 0.10–0.85) and alcohol (OR: 0.46; 95% CI: 0.24–0.90) was associated with a decreased risk of GC.

When we restricted the analysis to individuals with complete information (no missing data, n=146), the continuous OR for a unit increment of the MEDI-LITE score was 0.60 (0.47–0.75).

Table 4 reports the ORs of GC risk according to the MEDI-LITE score in the strata of selected demographic, behavioral, and clinical covariates. The risk estimates were consistent across strata of sex, age (<70, ≥70), tobacco smoking (never/former, current), alcohol drinking (never, current), anatomical site (cardia, noncardia), and histological type (diffuse, intestinal).

**Discussion**

Our case–control study evaluated the association between adherence to MD and GC, taking into consideration whole nutrition pattern as well as single components of the diet. The analysis showed that adherence to the MD eating pattern was significantly associated with a decreased risk of GC. The risk reduction associated with a one-unit increment in the MD was 30%. In terms of individual components of MD, our analysis showed that high consumption of vegetables, legumes, and fish, as well as low consumption of alcohol and meat, plays a protective role in the development of GC.

Although a role of MD in overall cancer prevention has been a topic of numerous investigations (Schwingshackl and Hoffmann, 2015a, 2014), only few studies have assessed this relation in accordance to GC. The EPIC study reported that a one-unit increase in the MD score was associated with a decreased risk of GC of 5% (Buckland et al., 2010). Furthermore, data from two case–control studies carried out in Italy indicate an
Table 3 Odds ratios and 95% confidence intervals for gastric cancer according to six dietary components included in the MEDI-LITE score

<table>
<thead>
<tr>
<th>Dietary components</th>
<th>Participants [n (%)]</th>
<th>OR (95% CI)a</th>
<th>OR (95% CI)bc</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDI-LITE score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(as continuous)</td>
<td></td>
<td>0.79 (0.71–0.88)</td>
<td>0.70 (0.61–0.81)</td>
</tr>
<tr>
<td>MEDI-LITE score (tertiles)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>156 (37.2)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>177 (39.7)</td>
<td>0.63 (0.41–0.96)</td>
<td>0.53 (0.33–0.83)</td>
</tr>
<tr>
<td>3</td>
<td>103 (23.1)</td>
<td>0.41 (0.25–0.68)</td>
<td>0.27 (0.14–0.49)</td>
</tr>
<tr>
<td>Fruit score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>71 (15.9)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>320 (71.7)</td>
<td>1.58 (0.94–2.66)</td>
<td>1.54 (0.90–2.62)</td>
</tr>
<tr>
<td>2</td>
<td>55 (12.3)</td>
<td>1.40 (0.69–2.84)</td>
<td>1.24 (0.59–2.64)</td>
</tr>
<tr>
<td>Vegetables score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>127 (28.5)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>293 (65.7)</td>
<td>0.72 (0.47–1.09)</td>
<td>0.72 (0.47–1.10)</td>
</tr>
<tr>
<td>2</td>
<td>26 (5.8)</td>
<td>0.40 (0.17–0.98)</td>
<td>0.34 (0.14–0.86)</td>
</tr>
<tr>
<td>Legumes score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>193 (43.3)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>142 (31.8)</td>
<td>0.40 (0.25–0.62)</td>
<td>0.23 (0.13–0.39)</td>
</tr>
<tr>
<td>2</td>
<td>111 (24.9)</td>
<td>0.45 (0.28–0.72)</td>
<td>0.13 (0.06–0.29)</td>
</tr>
<tr>
<td>Fish score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>253 (56.7)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>150 (33.6)</td>
<td>0.55 (0.36–0.82)</td>
<td>0.44 (0.28–0.69)</td>
</tr>
<tr>
<td>2</td>
<td>43 (9.6)</td>
<td>0.45 (0.23–0.87)</td>
<td>0.33 (0.15–0.68)</td>
</tr>
<tr>
<td>Meat score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20 (4.5)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>30 (6.7)</td>
<td>1.00 (0.29–3.44)</td>
<td>0.85 (0.24–2.99)</td>
</tr>
<tr>
<td>2</td>
<td>396 (88.8)</td>
<td>0.39 (0.15–1.03)</td>
<td>0.29 (0.10–0.85)</td>
</tr>
<tr>
<td>Alcohol score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>58 (12.6)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>234 (52.5)</td>
<td>0.58 (0.32–1.06)</td>
<td>0.46 (0.24–0.90)</td>
</tr>
<tr>
<td>2</td>
<td>156 (35.0)</td>
<td>0.65 (0.35–1.20)</td>
<td>0.62 (0.33–1.17)</td>
</tr>
<tr>
<td>MEDI-LITE score (no imputation)</td>
<td></td>
<td>0.66 (0.54–0.81)</td>
<td>0.60 (0.47–0.75)</td>
</tr>
</tbody>
</table>

For fruit, vegetables, legumes, and fish, 2 points to the highest category of consumption, 1 point for the middle category, and 0 point were assigned for the lowest category. Conversely, for meat, 2 points for the lowest category, 1 point for the middle category, and 0 point were assigned for the highest consumption of meat. For alcohol (1 alcohol unit = 12 g of alcohol), 2 points to the middle category (1–2 alcohol units/day), 1 point to the lowest category (<1 alcohol unit/day), and 0 point were assigned to the highest category of consumption (>2 alcohol units/day).

*aEstimated from logistic regression.

*bEstimated from adjusted logistic regression.

Table 4 Odds ratios and 95% confidence intervals for gastric cancer according to the MEDI-LITE score in strata of selected demographic, behavioral, and clinical covariates

<table>
<thead>
<tr>
<th>Sex</th>
<th>OR (95% CI)a</th>
<th>P for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.70 (0.59–0.82)</td>
<td>0.859</td>
</tr>
<tr>
<td>Female</td>
<td>0.72 (0.56–0.94)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>0.75 (0.63–0.90)</td>
<td>0.119</td>
</tr>
<tr>
<td>≥70</td>
<td>0.59 (0.47–0.75)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0.70 (0.56–0.86)</td>
<td>0.587</td>
</tr>
<tr>
<td>Current</td>
<td>0.62 (0.43–0.89)</td>
<td></td>
</tr>
<tr>
<td>Alcohol drinking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0.56 (0.39–0.79)</td>
<td>0.173</td>
</tr>
<tr>
<td>Current</td>
<td>0.73 (0.62–0.86)</td>
<td></td>
</tr>
<tr>
<td>Anatomical siteb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardia</td>
<td>0.73 (0.55–0.96)</td>
<td>0.865</td>
</tr>
<tr>
<td>Noncardia</td>
<td>0.75 (0.64–0.87)</td>
<td></td>
</tr>
<tr>
<td>Histological typeb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>0.80 (0.66–0.96)</td>
<td>0.686</td>
</tr>
<tr>
<td>Intestinal</td>
<td>0.76 (0.64–0.90)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

*aEstimates from logistic regression adjusted for sex, tobacco smoking, and total energy intake.

*bMissing data >20%.

association related to citrus fruits was observed in four out of these 14 studies (Bae et al., 2008). The protective role of total and citrus fruits on GC risk, mainly explained by high levels of vitamin C, was confirmed in the recent meta-analysis on prospective cohort studies evaluating dietary factors and GC risk (Fang et al., 2015). Unfortunately, the data from the questionnaire used in the present study were insufficient to reliably separate citrus from total fruit category, which may explain the lack of a significant association.

Studies assessing the relation between vegetable intake and GC risk produced some inconsistent results (Jansen et al., 1999; Wang et al., 2014). A seven-country cohort study, with 25 years of follow-up, suggested no association between vegetable intake and GC risk (Jansen et al., 1999). The EPIC cohort data indicated a weak inverse association between the risk of intestinal GC and leafy vegetables, onion, and garlic intake (González et al., 2006a, 2006b), but this association was no longer present when a reanalysis on a larger sample with a longer follow-up was carried out (González et al., 2012). Furthermore, consumption of white vegetables, but not total vegetables, was proved to be protective against GC in one recent meta-analysis (Fang et al., 2015).

In 2007, the World Cancer Research Fund, in conjunction with the American Institute for Cancer Research, published a report related to food, nutrition, and cancer prevention. Public health goals included increasing intake of pulses or legumes, which could help meet the recommended intake of 25 g of nonstarch polysaccharides per day. In reference to GC, the panel concluded that there is limited, but suggestive, evidence on protective effects of legumes (World Cancer Research

In terms of the single components of the MD, previous findings from the literature related to GC risk are somewhat inconsistent. The EPIC cohort data showed an inverse association between the total fruit intake and diffuse GC, and between intake of citrus fruits and cardia GC (González et al., 2012). In addition, the study of Bae et al. (2008) pooled the results from 14 observational studies and concluded that high citrus fruit intake has a protective effect on GC. However, the significant

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Fund, American Institute for Cancer Research, 2007). It should also be noted that the majority of the cohort studies included in the evaluation were carried out in western countries, where consumption of pulses tends to be rather low, leading to limited power to detect an association between pulses and GC. Thus, our significant findings may be related to the assumption that Italy has traditionally been related to MD, an eating pattern that implies a high intake of legumes. Furthermore, a biological background of their positive effect has been connected to high fiber content, as well as substantial levels of selenium and zinc, elements that showed numerous antitumor properties in animal models (Mudryj et al., 2014; Gong et al., 2016). Dietary zinc intake was significantly associated with reduced GC risk in Asian, but not in American and European populations (Li et al., 2014).

With reference to the effect of alcohol, there is considerable evidence deriving from the literature that links high consumption of alcohol, especially liquor and beer, with an increased GC risk and decreased survival (Palli et al., 2000; Ferronha et al., 2012; Tramacere et al., 2012; Fang et al., 2015). However, moderate alcohol consumption in MD and its relation to GC is still discussed controversially (Baan et al., 2007; Lucenteforte et al., 2008; Tramacere et al., 2012).

When the effects of meat consumption were considered, total red meat intake was linked to higher gastric non-cardia cancer risk in the EPIC cohort (González et al., 2006a, 2006b). Processed meats were found to increase GC risk, because of the excess salt they contain and because of high levels of nitrates or other preservatives that can potentially lead to the development of carcinogenic N-nitroso compounds during metabolism (Palli et al., 2001; González et al., 2006a, 2006b; World Cancer Research Fund, American Institute for Cancer Research, 2007).

Similar to previous facts, salted and processed fish products are also considered to alter the risk for GC development (Tsugane, 2005). Despite the fact that there are numerous biological benefits of long-chain fatty acids found in fish related to suppression of mutations, inhibition of cell growth, and sequent cancer risk reduction, findings from the literature on fresh fish consumption and GC risk are not so conclusive (Wu et al., 2011; Lee and Derakhshan, 2013; Yu et al., 2014; Fang et al., 2015). Yu et al. (2014) pooled the data from 27 independent cohorts, including 24,115 incident cases of gastrointestinal cancers, and the results of their study indicated that a 20 g increase in fish consumption per day is associated with a 2% reduced risk of gastrointestinal cancers. However, this protective effect was not proven in the subgroup analyses of GC patients. Another meta-analysis of 17 observational studies, evaluating only fresh fish intake, reported a combined risk ratio for GC of 0.87 (95% CI: 0.71–1.07), thus concluding that additional studies are needed to provide more definitive conclusions (Wu et al., 2011).

Some limitations of the study should be considered in interpreting our results. First, as in all case–control studies, information bias might be an issue. To reduce this impact, the questionnaires were administered by trained medical professionals and under similar conditions. Although GC patients were asked to focus on lifestyle habits 1 year before the interview, we cannot rule out the possibility that cases might have modified their diet during the early prediagnostic period of the disease. In addition, a rather long period of recruitment of our study might have influenced the findings. A further study constraint was the lack of information on intake of all the components of the MEDI-LITE score, as well as particular categories of individual components of MD, such as meat, fish, fruit, and vegetables. Nevertheless, we presented our results across the strata of available components to complement our findings. Moreover, we did not have information on H. pylori infection among the control population; thus, we could not adjust for this confounder in our analyses.

Besides the acknowledged limitations, this research represents one of the first case–control studies assessing the relationship between MD eating pattern and GC risk. The number of participants included in our study allowed us to capture the favorable effects of the MD on GC. Moreover, the reproducibility of this research adds to the existing evidence and encourages further investigation.

Our results implicate a possible protective role of MD against GC. Adherence to MD, as well as high intake of vegetables, legumes, and fish, and low consumption of alcohol and meat, was significantly associated with a reduction in the risk of GC.

Acknowledgements
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Conflicts of interest
There are no conflicts of interest.

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