Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis

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Background: Neuroendocrine neoplasms (NENs) are rare cancers mainly of lung and digestive tract. Little is known on risk factors. The aim of this work is to define the risk factors for NEN development by extensive review and meta-analysis of published data.

Methods: The search was conducted on Medline, Scopus, and Web of Science following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The Newcastle–Ottawa scale was used for study quality. Meta-analyses were conducted by primary site. Odds ratio (OR), hazard ratio, risk ratio, standardized incidence ratio, and associated 95% confidence intervals (CIs) were abstracted. Data were combined and analyses carried out for risk factors considered by at least two studies. Random-effects model was adopted for study variation.

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Results: Of 1535 extracted articles, 24 were enrolled. Meta-analyses were possible for pancreas, small intestine, and rectum. Risk for NEN associated with: (i) family history of cancer at all investigated sites (lung, stomach, pancreas, small intestine, appendix, and colon; OR 2.12 [95% CI 1.40–3.22,  $I^2 = 0.0\%$, $P = 0.681$] at meta-analysis in pancreas); (ii) body mass index (BMI) or diabetes (stomach, pancreas, and small intestine; OR of 2.76 [95% CI 1.65–4.64,  $I^2 = 58.5\%$, $P = 0.009$] for diabetes at meta-analysis in pancreas); (iii) cigarette smoking (lung, stomach, pancreas, and small intestine; OR of 1.34 [95% CI 1.10–1.63,  $I^2 = 0.0\%$, $P = 0.780$] and of 1.59 [95% CI 1.07–2.37,  $I^2 = 32.9\%$, $P = 0.225$] for smokers versus never-smokers at meta-analysis for pancreas and small intestine); (iv) alcohol consumption (pancreas and rectum; OR of 2.44 [95% CI 1.07–5.59,  $I^2 = 65.8\%$, $P = 0.054$] and of 1.53 [95% CI 0.99–2.35,  $I^2 = 0.0\%$, $P = 0.630$] for heavy drinkers versus never-drinkers at meta-analysis for pancreas and rectum).

Conclusions: Family history of cancer is the most relevant risk factor for NEN development at all investigated sites, followed by BMI and diabetes. Cigarette smoking and alcohol consumption are potential risk factors for selected anatomical sites.

Key words: neuroendocrine neoplasms, lung, digestive tract, risk factors

introduction

Neuroendocrine neoplasms (NENs) are rare tumors, accounting for 1% of all new cancers diagnosed in the USA [1, 2]. NENs include a spectrum of malignancies with neuroendocrine cell phenotypes and arising throughout the body. Overall, it is estimated that 52%–58% of all NENs originate in the gastrointestinal tract and 21%–32% originate in the bronchopulmonary system [1, 3, 4]. The most common primary sites of NEN are rectum, lung, and bronchus, and small intestine followed by stomach, pancreas, and colon; the distribution by primary tumor site, however, appears to differ by ethnicity [5].

Increasing incidence rates of NENs were reported for the early 1970s in the USA by Modlin and Sandor [6], followed shortly by similar findings from Switzerland [7] and Sweden [8]. Based on most recent studies from North America, Western Europe, Asia, and Australia, the worldwide incidence of NEN has continued to increase suggesting an incidence range of 1.5–5.25/100,000, possibly reflecting a better detection capacity and increased awareness [1, 3–5, 9, 10].

Although several epidemiological studies have described the incidence of NEN by age, gender, and ethnicity and the survival, a limited number of studies on risk factors for NEN have been reported in the literature. Most of them had a case–control design and have been conducted in the USA [11–16] and Europe [17–23]. Several risk factors for NENs have been postulated. These include family history of any cancer (including NEN), smoking habits, alcohol consumption, high body mass index (BMI), meat or fat intake, few chronic diseases and conditions (e.g. diabetes) or medical treatments, and occupational exposures. Results, however, are conflicting among studies, and to date, we could find only one review on risk factors for pancreas NEN in the literature [24]. This prompted us to perform a systematic review and meta-analysis on the risk factors for NEN by primary tumor site and overall.

methods

search strategy

We conducted a systematic review to identify all studies on the risk factors for NEN published on Medline, Scopus, and Web of Science. We carried out the search in June 2014 using the following search terms: ‘carcinoid tumor’, ‘neuroendocrine tumor’, ‘risk factors’, ‘epidemiology’, and ‘etiolog’. The reference lists of the included articles were also reviewed to ensure all relevant studies were identified. The recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were followed [25].

eligibility criteria

We included observational epidemiological studies investigating potential risk factors for NEN. Effect measures, such as a risk ratio (RR), odds ratio (OR), hazard ratios (HR), standardized incidence ratio (SIR), and associated 95% confidence intervals (CI), had to be available in the publication. Studies involving patients with a particular illness or condition were excluded (e.g. autoimmune disease and inflammatory bowel disease). When studies had overlapping data, the most comprehensive was included. Only English language studies were included.

data extraction

Two investigators (GC and EL) independently selected articles that potentially met the inclusion criteria on the basis of their titles and abstracts. Full articles were also retrieved for a more detailed assessment and eligibility for inclusion into the review. From every included article, one investigator (GC) extracted data related to author details, year of publication, study location, study period, study design, sample size, participant characteristics, enrollment criteria, procedures for data collection, analytic methods (including adjustment for confounders), and any information about risk factors investigated. OR, HR, RR, SIR, and associated 95% CI, based on unadjusted or, whenever available, adjusted estimates, were also abstracted for each risk factor. A second investigator (EL) confirmed the accuracy of extracted data.

The Newcastle–Ottawa scale was used to assess information on study quality; this scale varies from zero to a maximum possible score of nine and incorporates information on participant selection, outcome, and exposure ascertainment, and the potential for confounding [26].

statistical analysis

The meta-analyses were conducted by primary tumor site. Data were combined and the analyses were carried out when the risk factor was considered in at least two studies. It was possible to conduct a meta-analysis on selected risk factors, only for three tumor sites: pancreas, small intestine, and rectum. Exposure
definitions and categories of exposures, extracted from the full text of each eligible paper for meta-analysis, are reported in supplementary Table S1, available at Annals of Oncology online. We used random-effects model to account for variation between studies as this can provide more conservative results than a fixed-effects model [27]. We quantified the proportion of the total variation due to that heterogeneity by using the $I^2$ statistic [28]. Meta-analyses were conducted with Stata software (StataCorp. 2013; Stata Statistical Software: Release 13, College Station, TX: StataCorp LP).

**results**

Figure 1 shows the study selection process and the results from the literature search. The search strategy identified 1535 articles across Medline, Scopus, and Web of Science. After the initial screening of titles and abstracts and exclusion of duplicates, 28 articles remained for further investigation. Of these, we excluded seven: four articles that did not report a quantitative estimate, and three articles because of the impossibility to distinguish NEN from other tumors. We also identified three additional articles by manually searching the references lists from the extracted papers.

After detailed assessments, 24 articles met the inclusion criteria and were included in this review.

Tables 1 and 2 summarize the characteristics of the studies included.

Case–control studies were published between 1994 and 2014, and involved a total of 4144 cases and 108 303 controls. Overall, the cohort studies included 24 456 cases of NENs.

Eight studies were cohort studies [8, 29–35], 15 case–control [11–23, 36], 1 nested case–control [37], and 1 cross-sectional [38]. Nine studies were conducted in the USA [11–16, 29, 30, 32], 13 in Europe [8, 17–23, 31, 33–35, 37], and 2 studies in Asia [36, 38].

First are considered the three sites (pancreas, small intestine, and rectum) for which more data are available, followed by other sites according to the International Classification of Disease (ICD).

**pancreas**

For a graphical description of various risk factors for NENs in the pancreas, see Figure 2.

**family history of cancer.** Four case–control studies investigated the association between family history and pancreatic NEN [12, 15, 20, 36]. All studies reported a significant association between a positive family history of cancer and the development of pancreatic NEN.

A case–control study from Texas (USA) reported that the ORs of pancreatic NENs were 2.00 (95% CI 1.20–3.30) for every positive family history of cancer, 1.80 (95% CI 1.10–3.10) for first-degree relatives, 1.70 (95% CI 0.90–2.90) for parents, 0.90 (95% CI 0.40–1.90) for siblings, and 1.50 (95% CI 0.40–6.70) for offspring [12]. Moreover, first-degree family history of esophageal cancer was associated with the development of pancreatic NEN (OR 5.60, 95% CI 1.10–29.60). Positive family histories of other specific cancers among first-degree relatives were not significantly related to pancreatic NEN development.

A case–control study of prospectively enrolled patients with pancreatic NEN from Arizona (USA) reported that cases were more likely than controls to have a family member with pancreatic NEN ($P = 0.02$), gallbladder cancer ($P = 0.02$), gastric cancer ($P = 0.01$), sarcoma ($P = 0.02$), and ovarian cancer ($P = 0.04$) [15]. No other consistent associations between pancreatic NEN and cancers at other organ sites were found.

An Italian study observed a twofold increased risk (OR 2.20, 95% CI 1.50–3.20) of developing pancreatic NEN in individuals with a first-degree family history of any cancer; however, the risk of pancreatic NEN was not increased for subjects with a positive history of cancer in second-degree relatives [20].

A Chinese study also found that a first-degree family history of any cancer other than pancreatic NEN (OR 2.36, 95% CI 1.05–5.29) as well as a family history of pancreatic NEN (OR 16.75, 95% CI 2.13–132.06) were significant risk factors for pancreatic NEN [36].
Meta-analysis on the risk of pancreatic NEN among individuals with a positive family history indicates an OR of 2.12–2.52 (95% CI 1.40–3.22, $I^2 = 0.0\%$, $P = 0.681$) and 2.19-fold (95% CI 1.65–2.92, $I^2 = 0.0\%$, $P = 0.696$) increased risk, respectively, depending on whether the affected relative was a first- or second-degree relative or a first-degree relative. The combined estimate for individuals with a first- or second-degree history of any cancer was based on two studies [12, 36]; three studies [12, 20, 36] were used to estimate the odds ratio for individuals with a history of any cancer in first-degree family members.

### Tobacco smoking

Four case–control studies investigated tobacco smoking and pancreatic NEN [11, 15, 20, 36]. The meta-analysis provided a summary effect estimate of 1.34 (95% CI 1.10–1.63, $I^2 = 0.0\%$, $P = 0.780$) for smokers compared with never-smokers. Heavy smoking had a pooled estimate of 1.35 (95% CI 0.96–1.89, $I^2 = 0.0\%$, $P = 0.638$).

### Alcohol consumption

Four case–control studies investigated the association between alcohol drinking and pancreatic NEN [11, 15, 20, 36]. Meta-analysis gave an adjusted summary effect estimate of 1.09 (95% CI 0.67–1.77, $I^2 = 81.0\%$, $P < 0.01$) for...
<table>
<thead>
<tr>
<th>First author (year of publication)</th>
<th>Source (*)</th>
<th>Mean age (*)</th>
<th>Female % (*)</th>
<th>Adjustment factors</th>
<th>Measures of associations</th>
<th>Investigated exposure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (1994)</td>
<td>Cancer registry/hospital</td>
<td>64.9/54.2</td>
<td>59.0/44.0</td>
<td>Age, gender, tobacco smoking, and alcohol consumption</td>
<td>OR</td>
<td>Cholecystectomy, peptic ulcer, tobacco smoking, and alcohol consumption</td>
</tr>
<tr>
<td>Hemminki (2001)</td>
<td>Nationwide cancer registries</td>
<td>NEN diagnosis 60.0</td>
<td>53.8</td>
<td>Age, gender, tumor type, cohort, period of diagnosis year, area of residence, socioeconomic status, and family history of cancer</td>
<td>RR</td>
<td>Family history of cancer, residence, socioeconomic status, and parity</td>
</tr>
<tr>
<td>Hemminki (2001)</td>
<td>Nationwide cancer registries</td>
<td></td>
<td>56.1</td>
<td>Age, gender, and tumor type</td>
<td>SIR</td>
<td>Family history of cancer</td>
</tr>
<tr>
<td>Kaerlev (2002) (A)</td>
<td>Hospital, cancer registries/population</td>
<td>60.0/55.0</td>
<td>39.3/30.1</td>
<td>Age, gender, and country</td>
<td>OR</td>
<td>Tobacco smoking, gallstone, ovariectomy, cholecystitis, hepatitis or jaundice, cirrhosis of the liver, drugs, and treatments</td>
</tr>
<tr>
<td>Kaerlev (2002) (B)</td>
<td>Hospital, cancer registries/population</td>
<td>60.0/55.1</td>
<td>39.3/30.1</td>
<td>Age, gender, and country</td>
<td>OR</td>
<td>Occupations and industries</td>
</tr>
<tr>
<td>Berkovic (2006)</td>
<td>Hospital/hospital</td>
<td>47.0/47.0</td>
<td>52.3/52.3</td>
<td>Age and gender</td>
<td>Chi-square test</td>
<td>TNF-α polymorphism -1.031, -857, -308, -238</td>
</tr>
<tr>
<td>Cross (2008)</td>
<td>Population (NIH-AARP Diet and Health Study)</td>
<td>62.1</td>
<td>40.3</td>
<td>Gender, person-years, education, marital status, family history of cancer, ethnicity, BMI, tobacco smoking, physical activity, intake of total energy, alcohol consumption, fruits, and vegetables</td>
<td>HR</td>
<td>Total fat, saturated fat, red meat, processed meat, monounsaturated fat, and polyunsaturated fat</td>
</tr>
<tr>
<td>Hassan (2008) (A)</td>
<td>Hospital/hospital</td>
<td>54.3/60.0</td>
<td>54.2/38.7</td>
<td>Age, gender, ethnicity, and other not specified variables</td>
<td>OR</td>
<td>Family history of cancer</td>
</tr>
<tr>
<td>Hassan (2008) (B)</td>
<td>Hospital/hospital</td>
<td>54.3/60.0</td>
<td>54.2/38.7</td>
<td>Age, gender, ethnicity, family history of cancer, diabetes, BMI, tobacco smoking, and alcohol consumption</td>
<td>OR</td>
<td>Family history of cancer, tobacco smoking, BMI, diabetes, and alcohol consumption</td>
</tr>
<tr>
<td>Burnik and Yalcin (2009)</td>
<td>Hospital/population</td>
<td>53.6/Not reported</td>
<td>48/74</td>
<td>None</td>
<td>Chi-square test</td>
<td>NFKB1 -94 insertion/deletion ATTG promoter polymorphism</td>
</tr>
<tr>
<td>Capurso (2009)</td>
<td>Hospital/hospital</td>
<td>53.2/52.7</td>
<td>49/52.0</td>
<td>Not specified</td>
<td>OR</td>
<td>Family history of cancer, alcohol consumption, diabetes, history of chronic pancreatitis, tobacco smoking, and BMI</td>
</tr>
<tr>
<td>Hiripi (2009)</td>
<td>National cancer registry</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Age, gender, cancer calendar year</td>
<td>RR</td>
<td>Family history of cancer</td>
</tr>
<tr>
<td>Ter-Minassian (2011)</td>
<td>Hospital/population</td>
<td>52/56 (55/53)</td>
<td>53/64/43.3 (47/7/63.7)</td>
<td>Age, gender, tobacco smoking—discovery set (age, gender—replication set)</td>
<td>OR</td>
<td>Family history of cancer</td>
</tr>
<tr>
<td>Amin (2012)</td>
<td>Cancer registries (SEER Program)</td>
<td>64.7</td>
<td>47.3</td>
<td>Age, gender, and ethnicity</td>
<td>MP-SIR</td>
<td>1536 single-nucleotide polymorphisms in 355 candidate genes</td>
</tr>
<tr>
<td>Berkovic (2012)</td>
<td>Hospital/hospital</td>
<td>55.1/50.3</td>
<td>60.0/48.3</td>
<td>None</td>
<td>OR</td>
<td>Personal history of cancer</td>
</tr>
<tr>
<td>Kamp (2012)</td>
<td>National cancer registry</td>
<td>NEN diagnosis 62.3</td>
<td>47.1</td>
<td>Age and gender</td>
<td>SIR</td>
<td>II15 polymorphism -511, +3954</td>
</tr>
<tr>
<td>Liu (2012)</td>
<td>National cancer registry</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Age, gender, education, diabetes, obesity, tobacco smoking, and alcohol consumption (parity, age at first birth when appropriate)</td>
<td>OR</td>
<td>Personal history of cancer</td>
</tr>
<tr>
<td>Cross (2013)</td>
<td>Population (NIH-AARP Diet and Health Study)</td>
<td>62.1</td>
<td>43.5/67.7</td>
<td>Age, gender, and follow-up time</td>
<td>HR</td>
<td>Parity, number of children, and age at first birth</td>
</tr>
<tr>
<td>Kharazmi (2013)</td>
<td>Nationwide cancer registries</td>
<td>58.3</td>
<td>41.0</td>
<td>Age, gender, period, cancer site, morphology, and country</td>
<td>SIR</td>
<td>BMI, menopausal hormone therapy use, family history of cancer, tobacco smoking, alcohol consumption, diabetes, education, ethnicity, physical activity, personal history of colorectal polyps, and multivitamin use</td>
</tr>
<tr>
<td>Zhan (2013)</td>
<td>Hospital/hospital</td>
<td>43.8/45.9</td>
<td>58.7/51.5</td>
<td>Residence, education, ethnicity, tobacco smoking, alcohol consumption, and family history of cancer</td>
<td>OR</td>
<td>Family history of cancer, tobacco smoking, residence, alcohol consumption, BMI, and education</td>
</tr>
</tbody>
</table>
Family history of cancer, alcohol consumption, diabetes, BMI, and tobacco smoking were significant risk factors. Alcohol consumption, HDL-C level OR, family history of cancer, tobacco smoking, BMI, physical activity, education, family history of physical activity, education, fatty liver, metabolic syndrome, abdominal obesity, blood pressure, and HOMA-IR fasting blood glucose, triglycerides, and HOMA-IR were also associated with pancreatic NEN risk. A study by Karakaxas (2014) showed no significant association between the -94 I/D between cases and controls was reported. A case-control study from Italy, a hospital-based study conducted in Turkey examined the association between the NFKB1 SNP and susceptibility to pancreatic NEN patients and controls was observed in the -1031 TC and CC genotype distribution, suggesting its possible role in pancreatic NEN development.

Three case-control studies investigated the association between diabetes and pancreatic NEN [11, 15, 20]. All case-control studies reported a strong significant association; the effect estimates were 2.80 (95% CI 1.50–5.20) [11], 4.80 (95% CI 2.30–9.90) [20], and 1.91 (95% CI 1.26–2.91) [15]. Meta-analysis provided a summary effect estimate of 2.76 (95% CI 1.65–4.64, I² = 58.5%, P = 0.090). When subjects with recent onset diabetes were considered, the effect estimate was higher (OR 12.80, 95% CI 2.47–66.42, I² = 55.3%, P = 0.135).

Estimates by the type of diabetes treatment were reported in one of the three studies; the estimated adjusted OR was greater among patients with diabetes receiving insulin than in those without diabetes (OR 4.80, 95% CI 1.20–18.90) [11].

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Estimates by the type of diabetes treatment were reported in one of the three studies; the estimated adjusted OR was greater among patients with diabetes receiving insulin than in those without diabetes (OR 4.80, 95% CI 1.20–18.90) [11].

genetics. A case-control studies investigated the potential association between -238, -308, -857 and -1031 TNF-α promoter polymorphism and pancreatic NEN [21]. A significant difference among pancreatic NEN patients and controls was observed in the -1031 TC and CC genotype distribution, suggesting its possible role in pancreatic NEN development.

A case-control study examined the association between the IL1β gene single-nucleotide polymorphisms (SNPs) with pancreatic NEN in a Croatian population [17]. Results of this study suggest IL1β involvement in pancreatic NEN development; an association between the IL1β–511 SNP and susceptibility to pancreatic NEN was found, especially functional pancreatic NEN.

A case-control study conducted in Turkey examined the prevalence of nuclear factor-kappaB (NF-kB)—94 insertion/deletion ATTG promoter polymorphism. No significant difference of deletion/deletion or insertion/insertion genotypes of NFKB1 -94 I/D between cases and controls was reported [23].

other risk factors. In a large case-control study from Italy, a previous history of chronic pancreatitis was associated with an increased pancreatic NEN risk [20]. Living in rural areas has also been suggested as a risk factor in a Chinese case-control study [36].

small intestine
For a graphical description of various risk factors for NEN in the small intestine, see Figure 3.

family history of cancer. Four studies investigated family history and small intestinal NEN [12, 30, 31, 35]. A cohort study from six US states (California, Florida, Louisiana, New Jersey,
North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) found a borderline significant elevated risk for malignant carcinoid tumors in the small intestine among individuals with a positive family history of any cancer (HR 1.42, 95% CI 0.99–2.03), and family history of colorectal cancer specifically (HR 1.61, 95% CI 0.97–2.65) [30].

A population-based study on medically diagnosed cases of small intestinal cancer and registered family relationship from Sweden and Finland found that small intestinal NENs were associated with an increased risk of concordant histology subtype among any first-degree relative (SIR 13.10, 95% CI 8.40–19.50): for siblings the SIR was 28.40 (95% CI 14.70–49.60) and for parent/child pairs the SIR was 9.90 (95% CI 5.40–16.60) [31]. A significant association was also reported between small intestinal NEN and small intestine cancer (SIR 7.90, 95% CI 5.20–11.50), kidney cancer (SIR 1.50, 95% CI 1.00–2.10), and polycythemia vera (SIR 2.90, 95% CI 1.10–5.90) among any first-degree relative, and in particular with parent/child pairs for polycythemia vera (SIR 3.50, 95% CI 1.40–7.10).

A study conducted in Sweden reported that the risk of small intestinal NEN was significantly higher among individuals with a parental history of carcinoid tumors (RR 11.80, 95% CI 6.45–

### Figure 2

Study-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for neuroendocrine neoplasms of the pancreas, by various potential risk factors. The square size indicates the weight of each study and of pooled data.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassan et al.</td>
<td>2008</td>
<td>160</td>
<td>924</td>
<td>2.00 (1.20, 3.30)</td>
<td>69.57</td>
</tr>
<tr>
<td>Zhan et al.</td>
<td>2013</td>
<td>196</td>
<td>233</td>
<td>2.42 (1.14, 5.16)</td>
<td>30.43</td>
</tr>
<tr>
<td>Subtotal (p = 0.0%, P = 0.681)</td>
<td></td>
<td></td>
<td></td>
<td>2.12 (1.40, 3.22)</td>
<td>100.00</td>
</tr>
<tr>
<td>Hassan et al.</td>
<td>2008</td>
<td>160</td>
<td>924</td>
<td>1.80 (1.10, 3.10)</td>
<td>27.87</td>
</tr>
<tr>
<td>Capurso et al.</td>
<td>2009</td>
<td>162</td>
<td>648</td>
<td>2.30 (1.60, 3.30)</td>
<td>61.91</td>
</tr>
<tr>
<td>Zhan et al.</td>
<td>2013</td>
<td>196</td>
<td>233</td>
<td>2.53 (1.03, 6.21)</td>
<td>10.22</td>
</tr>
<tr>
<td>Subtotal (p = 0.0%, P = 0.696)</td>
<td></td>
<td></td>
<td></td>
<td>2.19 (1.65, 2.92)</td>
<td>100.00</td>
</tr>
<tr>
<td>Hassan et al.</td>
<td>2008</td>
<td>160</td>
<td>924</td>
<td>1.20 (0.70, 1.90)</td>
<td>18.30</td>
</tr>
<tr>
<td>Capurso et al.</td>
<td>2009</td>
<td>162</td>
<td>648</td>
<td>1.40 (0.90, 2.00)</td>
<td>30.38</td>
</tr>
<tr>
<td>Zhan et al.</td>
<td>2013</td>
<td>196</td>
<td>233</td>
<td>1.60 (1.01, 2.54)</td>
<td>18.10</td>
</tr>
<tr>
<td>Subtotal (p = 0.0%, P = 0.780)</td>
<td></td>
<td></td>
<td></td>
<td>1.34 (1.10, 1.63)</td>
<td>100.00</td>
</tr>
<tr>
<td>Hassan et al.</td>
<td>2008</td>
<td>160</td>
<td>924</td>
<td>1.10 (0.60, 1.90)</td>
<td>37.94</td>
</tr>
<tr>
<td>Capurso et al.</td>
<td>2009</td>
<td>162</td>
<td>648</td>
<td>1.50 (1.00, 2.40)</td>
<td>51.30</td>
</tr>
<tr>
<td>Zhan et al.</td>
<td>2013</td>
<td>196</td>
<td>233</td>
<td>1.67 (0.61, 4.66)</td>
<td>10.76</td>
</tr>
<tr>
<td>Subtotal (p = 0.0%, P = 0.638)</td>
<td></td>
<td></td>
<td></td>
<td>1.35 (0.96, 1.89)</td>
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<tr>
<td>Hassan et al.</td>
<td>2008</td>
<td>160</td>
<td>924</td>
<td>1.20 (0.70, 1.90)</td>
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<tr>
<td>Capurso et al.</td>
<td>2009</td>
<td>162</td>
<td>648</td>
<td>1.50 (1.00, 2.20)</td>
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<tr>
<td>Zhan et al.</td>
<td>2013</td>
<td>196</td>
<td>233</td>
<td>1.45 (0.86, 2.37)</td>
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<td>Halfdanarson et al.</td>
<td>2014</td>
<td>273</td>
<td>602</td>
<td>0.560 (0.82)</td>
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<tr>
<td>Subtotal (p = 0.0%, P = 0.001)</td>
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<td>1.09 (0.67, 1.77)</td>
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<tr>
<td>Hassan et al.</td>
<td>2008</td>
<td>160</td>
<td>924</td>
<td>1.00 (0.30, 3.10)</td>
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<td>Capurso et al.</td>
<td>2009</td>
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<td>648</td>
<td>4.80 (2.40, 9.50)</td>
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<tr>
<td>Zhan et al.</td>
<td>2013</td>
<td>196</td>
<td>233</td>
<td>2.29 (1.07, 4.91)</td>
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<td>Subtotal (p = 65.8%, P = 0.054)</td>
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<td>2.44 (1.07, 5.59)</td>
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<td>Hassan et al.</td>
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<td>924</td>
<td>0.30 (0.10, 0.40)</td>
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<td>2013</td>
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<td>233</td>
<td>5.31 (3.51, 8.04)</td>
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<td>Halfdanarson et al.</td>
<td>2014</td>
<td>273</td>
<td>602</td>
<td>1.65 (1.11, 2.45)</td>
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<td>Subtotal (p = 98.5%, P = 0.000)</td>
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<td>1.37 (0.25, 7.69)</td>
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<td>Hassan et al.</td>
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<td>160</td>
<td>924</td>
<td>2.80 (1.50, 5.20)</td>
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<td>Capurso et al.</td>
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<td>162</td>
<td>648</td>
<td>4.80 (2.30, 9.90)</td>
<td>27.02</td>
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<tr>
<td>Halfdanarson et al.</td>
<td>2014</td>
<td>273</td>
<td>602</td>
<td>1.91 (1.26, 2.91)</td>
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<td>Subtotal (p = 58.5%, P = 0.090)</td>
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<td>2.76 (1.65, 4.64)</td>
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<td>Hassan et al.</td>
<td>2008</td>
<td>160</td>
<td>924</td>
<td>6.90 (2.70, 17.70)</td>
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</tr>
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<td>Capurso et al.</td>
<td>2009</td>
<td>162</td>
<td>648</td>
<td>40.10 (4.80, 328.90)</td>
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<td>Subtotal (p = 55.3%, P = 0.136)</td>
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<td>12.80 (2.47, 66.42)</td>
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NOTE: Weights are from random effects analysis

Pancreas

Figure 2. Study-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for neuroendocrine neoplasms of the pancreas, by various potential risk factors. The square size indicates the weight of each study and of pooled data.
21.40) and in those with a sibling history of carcinoid tumors (RR 9.29, 95% CI 3.47–24.90) [35]. The risk of small intestinal NEN was also increased among the offspring of patients with cancers of the endometrium (RR 2.21, 95% CI 1.18–4.14), kidney (RR 1.92, 95% CI 1.05–3.49), squamous cell skin (RR 1.79, 95% CI 1.01–3.18), nervous system (RR 2.14, 95% CI 1.01–4.02), brain (RR 2.37, 95% CI 1.27–4.45), and non-Hodgkin’s lymphoma (RR 2.06, 95% CI 1.10–3.86). The risk of small intestinal NEN was elevated among those whose siblings were affected by oral cancer (RR 3.99, 95% CI 1.28–12.50).

A case–control study from Texas (USA) reported that the ORs of small intestinal NEN were 1.70 (95% CI 1.20–2.40) for every positive family history of cancer (first-degree or second-degree relative) and 1.60 (95% CI 1.10–2.40) for first-degree relatives: 1.50 (95% CI 1.10–2.30) for parents, 1.01 (95% CI 0.60–1.70) for siblings, and 0.70 (95% CI 0.20–2.60) for offspring [12]. Only first-degree family history of colorectal (OR 1.70, 95% CI 1.00–2.90) and prostate cancer (OR 2.30, 95% CI 1.30–3.90) were associated with the development of small intestinal NEN.

tobacco smoking. Three case–control studies [11, 16, 18] and one cohort study [30] investigated tobacco smoking and small intestinal NEN development. Both case–control studies conducted in the USA [11, 16] reported no significant association; the effect estimates for ever- versus never-smokers were 1.30 (95% CI 0.90–1.80) [11] and 4.20 (95% CI 0.80–22.40) [16]. The population-based European multicenter case–control study reported that ever being a smoker was associated with small intestinal NEN (OR 1.90, 95% CI 1.10–3.20) [18]. The cohort study from the USA reported no dose–effect relationship for both smoking intensity and duration [30].

Meta-analysis of case–control data gave an adjusted summary effect estimate of 1.59 (95% CI 1.07–2.37, \( I^2 = 32.9\%), P = 0.225) for smokers compared with never-smokers. Heavy smoking had a pooled estimate of 1.38 (95% CI 0.55–3.74, \( I^2 = 79.1\%), P < 0.05).

alcohol consumption. Two case–control studies [11, 16] and one cohort study [30] investigated alcohol consumption and small
intestinal NEN development. No studies reported statistically significant increased risk among alcohol users. Meta-analysis of case–control data gave an adjusted summary effect estimate of 1.38 (95% CI 0.51–3.74, $I^2 = 51.9\%$, $P = 0.149$) for drinkers compared with never-drinkers.

**body mass index.** One case–control [11] and one cohort study [30] from the USA investigated BMI and small intestinal NEN with contrasting results. The case–control study reported an inverse association of overweight and obesity with small intestinal NENs: adjusted ORs for overweight and obese were 0.40 (95% CI 0.30–0.60) and 0.40 (95% CI 0.20–0.50), respectively [11]. The cohort study reported an increased risk for the highest body fatness group when compared with the lowest one (HR 1.95, 95% CI 1.06–3.58) [30].

**diabetes.** One case–control [11] and one cohort study [30] from the USA investigated diabetes and small intestinal NEN. Both studies reported no significant association. The case–control study reported an effect estimate of 1.20 (95% CI 0.70–2.10) for patients with diabetes when compared with subjects who did not have diabetes. Concerning duration, with a history of diabetes >1 year had an adjusted OR of 0.90 (95% CI 0.50–1.70) for small intestinal NEN, whereas those with diabetes for ≤1 year had an adjusted OR of 2.20 (95% CI 0.90–5.40) [11] pointing to possible diagnostic bias. The cohort study reported an HR of 0.88 (95% CI 0.50–1.57) for patients with diabetes mellitus when compared with those who did not have diabetes [30].

**cholecystectomy.** Two case–control studies investigated cholecystectomy and small intestinal NEN development [13, 16]. Both studies were conducted in the USA and reported a significant association. The population-based study using SEER data found an OR of 1.78 (95% CI 1.41, 2.25) [13]; similarly, a much smaller study observed that cases were more likely than controls had cholecystectomy ($P < 0.01$) [16].

**gallstones.** Two population-based case–control studies investigated gallstones and small intestinal NEN development [13, 18]. Both studies reported a significant association. In the European multicenter study, subjects with a history of gallstone or gallstone surgery had a 1.9-fold increased OR of small intestinal NEN (95% CI 1.00–3.60). No association was seen when time since diagnosis of gallstones was at least 2 years before the diagnosis of cancer [18]. The population-based study, using SEER data, found an OR of 1.27 (95% CI 1.01–1.60) [13]. Meta-analysis was possible on both studies, giving a summary effect estimate of 1.39 (95% CI 1.00–1.92, $I^2 = 25.9\%$, $P = 0.245$).

**previous cancer.** A US population-based study, including 8331 individuals diagnosed with a small intestinal NEN between 1973 and 2007, investigated the risk of developing small intestinal NEN after other primary malignancies [32]. The results of this study suggest an increased risk of small intestinal NEN after cancers of the small bowel (RR 11.86, 95% CI 6.13–20.72), esophagus (RR 4.05, 95% CI 1.10–10.36), colon (RR 1.39, 95% CI 1.05–1.81), kidney (RR 1.93, 95% CI 1.12–3.09), prostate (RR 1.38, 95% CI 1.17–1.62), and leukemia (RR 2.15, 95% CI 1.18–3.61).

A study conducted in the Netherlands on occurrence of second primary malignancies in patients with NENs of the digestive tract and pancreas reported that the number of patients with a cancer history was lower than expected, although not significant ($n = 25$ versus 34.5; SIR 0.72, 95% CI 0.47–1.07) [34].

**other medical conditions.** A large prospective study conducted in the USA reported a relationship between menopausal hormone therapy use and small intestinal NEN [30]. The HR was 2.29 (95% CI 1.00–5.24) for women who previously took menopausal hormones and 1.94 (95% CI 1.07–3.50) for women who were currently taking menopausal hormones, compared with women who had never used menopausal hormones. No significant associations were observed for either multivitamin use or personal history of polyps.

A European population-based case–control study found ovariectomy associated with small intestinal NEN (OR 6.00, 95% CI 2.60–14.10) [18]. No association was seen for a history of cholecystitis, hepatitis, cirrhosis, ulcerative disease, or Crohn’s disease, as well as medical treatments with radioactive substances or corticosteroid.

In a small US study, cases were more likely than controls to report peptic ulcer disease ($P < 0.01$) [16].

**occupation.** A European population-based case–control study reported that the small intestinal NEN occurrence was increased (twofold or more) for women working in food and beverage wholesaling (OR 8.20, 95% CI 1.90–34.90) and for men working in motor vehicle body manufacturing (OR 5.20, 95% CI 1.20–22.40), footwear production (OR 3.90, 95% CI 0.90–16.10), and metal structure (OR 3.30, 95% CI 1.00–10.40) [19]. Some of these findings, however, were due to multiple comparisons.

**meat and fat intake.** Only one US study examined meat and fat intake in relation to small intestinal NEN [29]. A positive association between saturated fat intake and small intestinal NEN in both the categorical (HR 3.18, 95% CI 1.62–6.25, $P$-trend <0.001, highest versus lowest tertile) and continuous data analysis (HR 3.72, 95% CI 1.79–7.74 for each 10-g increase in intake per 1000 kcal) was reported, whereas no relationship was found with monounsaturated and polyunsaturated fat intakes. No significant associations were also observed for red or processed meat intake.

**rectum**

For a graphical description of various risk factors for NEN in the rectum, see Figure 4.

**family history of cancer.** Three studies investigated the association between family history and rectal NEN [12, 35, 38]. A cross-sectional study carried out on 62 171 Koreans who underwent screening colonoscopy found no association between first-degree relatives with colorectal cancer and rectal NEN development (OR 1.70, 95% CI 0.79–3.67) [38]. The results of a Swedish study showed that the risk of rectal NEN for individuals with a parental history of carcinoid tumor was 2.43 (95% CI 0.34–17.40) [35].
A case–control study from the USA reported a not statistically significant relationship between rectal NEN development and family history: the estimated ORs of rectal carcinoid were 2.10 (95% CI 0.90–4.80) for ever positive family history (defined as the first-degree or second-degree relative having a recorded cancer diagnosis) and 1.70 (95% CI 0.70–4.40) for first-degree relatives [12].

Tobacco smoking. One case–control [11] and one cross-sectional study [38] investigated tobacco smoking and rectal NEN. Both studies reported no significant association; the effect estimates for ever- versus never-smokers were 1.50 (95% CI 0.70–3.30) [11] and 1.11 (95% CI 0.69–1.78) [38]. In the US study, when compared with non-smokers, smokers had no significant trend in the risk of rectal NEN development by the number of smoked cigarettes/day: for subjects with ≤20 pack years of smoking, the OR was 1.10 (95% CI 0.40–2.80) compared with non-smokers; for subjects with >20 pack years of smoking, the odds ratio was 1.30 (95% CI 0.50–3.70).

Meta-analysis provided an adjusted summary effect estimate of 1.20 (95% CI 0.80–1.80, \( I^2 = 0.0\%), P = 0.521\) for smokers compared with never-smokers.

Alcohol consumption. One case–control [11] and one cross-sectional study [38] investigated the association between alcohol consumption and rectal NEN development. A study from the USA reported no significant association [11]. In contrast, the Korean study reported that alcohol drinking (≥20 g of alcohol/ day) was an independent risk factor for rectal NEN (OR 1.56, 95% CI 1.01–2.42) [38]. Meta-analysis of case–control data gave an adjusted summary effect estimate of 1.53 (95% CI 0.99–2.35, \( I^2 = 0.0\%), P = 0.630\) for heavy alcohol drinkers compared with never-drinkers.

Body mass index. One case–control [11] and one cross-sectional study [38] investigated BMI and rectal NEN. Both studies reported no significant association. The meta-analysis gave an adjusted summary effect estimate of 1.53 (95% CI 0.99–2.35, \( I^2 = 0.0\%), P = 0.630\) for obese individuals compared with individuals of normal weight.

Other risk factors. One cross-sectional study form Korea [38] found that low high-density lipoprotein-cholesterol levels were an independent risk factor for rectal NENs (OR 1.85, 95% CI 1.10–3.11), while fatty liver, metabolic syndrome,
abdominal obesity, blood pressure, fasting blood glucose, triglycerides, and insulin resistance assessed with the homeostasis model assessment of insulin resistance were not associated with rectal NEN.

A US case–control study investigated the role of diabetes on the risk of rectal NEN and no consistent association was reported [11].

stomach
family history of cancer. Two studies investigated the association between family history and gastric NEN [12, 35]. A case–control study from the USA reported that the ORs of gastric NEN were 2.30 (95% CI 1.10–5.20) for every positive family history of cancer (defined as first-degree or second-degree relative having a recorded cancer diagnosis) and 2.50 (95% CI 1.10–6.30) for first-degree relatives [12]. Positive family histories of other specific cancers among first-degree relatives were not significantly related to gastric NEN development.

The results of the population-based study from Sweden showed that the risk of gastric NEN was: (i) not significantly elevated among the offspring of patients affected by invasive cancer (excluding carcinoid tumors); (ii) not significantly elevated among the offspring of patients affected by carcinoid tumors; (iii) elevated among those whose siblings were affected by cancer of the ovary (RR 6.06, 95% CI 1.49–24.60) and cancer of the urinary organs (RR 5.24, 95% CI 1.29–21.40) [35].

other risk factors. A case–control study from the USA reported that history of diabetes was a significant risk factor for gastric NEN (OR 4.90, 95% CI 2.00–12.30), whereas cigarette smoking, alcohol consumption, and BMI were not significantly associated with risk for gastric NEN [11].

appendix
A study conducted in Sweden reported that the risk of appendiceal NEN was not significantly higher among individuals with a parental history of carcinoid tumors (RR 2.36, 95% CI 0.98–5.69) and in those with a sibling history of carcinoid tumors (RR 2.82, 95% CI 0.70–11.29) [35]. The risk of appendiceal NEN was also increased among the offspring of patients with cancers of the urinary organs (RR 2.14, 95% CI 1.51–3.03), breast (RR 1.43, 95% CI 1.10–1.85), and endocrine glands (RR 1.95, 95% CI 1.10–3.45). The risk of appendiceal NEN was elevated among those whose siblings were affected by cancers of the nervous system (RR 2.27, 95% CI 1.18–4.37) and endocrine glands (RR: 2.95, 95% CI 1.23–7.12).

colon
A Swedish study investigated the association between family history and colon NEN [35]. In that study, the risk of colon NEN was significantly higher among individuals with a parental history of carcinoid tumors (RR 2.78, 95% CI 1.32–5.84) [35]. No increased risk of colon NEN was found among individuals with a sibling history of carcinoid tumors (RR 2.29, 95% CI 0.57–9.17).

lung
family history of cancer. Two studies investigated the association between family history and lung NEN [12, 35]. A case–control study from the USA, involving 740 patients with histologically confirmed NEN and 924 controls, reported a strong association between positive family history of cancer and lung NEN development [12]. The estimated ORs for lung NEN were 2.40 (95% CI 1.40–4.00) for ever positive family history of cancer, 2.60 (95% CI 1.50–4.50) for first-degree relatives, 2.30 (95% CI 1.30–4.30) for parents, 2.10 (95% CI 1.10–4.10) for siblings, and 5.30 (95% CI 1.50–18.50) for offspring. Moreover, first-degree family history of lung cancer was associated with the development of lung NEN (OR 2.30, 95% CI 1.20–4.50). Positive family histories of other specific cancers among first-degree relatives were not significantly related to lung NEN development.

The results of a Swedish study reported that the risk of lung NEN was not significantly higher among individuals with a parental history of carcinoid tumors (OR 2.60, 95% CI 0.64–10.64) [35].

other risk factors. A US case–control study reported that cigarette smoking was a significant risk factor for lung NEN (OR 1.50, 95% CI 1.00–2.40), whereas alcohol consumption, history of diabetes, and BMI were not significantly associated with the risk of lung NEN [11].

NEN overall at a glance
For a graphical description of various risk factors for NEN, overall see supplementary Figure S1, available at Annals of Oncology online.

tobacco smoking. Seven studies reported comparable estimates for the impact of smoking on NEN development from various sites of origin including the lung [11], stomach [11], pancreas [11, 15, 20, 36], small intestine [11, 16, 18], and rectum [11, 38]. The effect estimates for ever- versus never-smokers were always >1.00, two significantly, for pancreatic and small intestinal NEN, respectively. As for the frequency and duration of tobacco smoked, seven of the eight estimates are >1.00, one significantly for small intestine, with only one <1.00.

alcohol consumption. Five studies reported estimates for the impact of alcohol consumption on NEN development from various sites of origin including the lung [11], stomach [11], pancreas [11, 15, 20, 36], small intestine [11, 16], and rectum [11]. With respect to the effect estimates for drinkers compared with never-drinkers, seven individual estimates are >1.00, only one statistically significant for pancreas, and one <1.00 (and one is equal to 1.00). For frequency and the duration of alcohol consumption, there is a considerable heterogeneity, with estimates varying from a decrease of 0.40 (95% CI 0.15–1.10) for small intestine to a significant increase of 4.80 (95% CI 2.43–9.50) for pancreas. In particular, four individual estimates are >1.00, 3 significantly, and three <1.00 (and one is equal to 1.00).

obesity. Four studies reported comparable estimates for the impact of obesity on NEN development from various sites of origin including the lung [11], stomach [11], pancreas [11, 15, 36], small intestine [11], and rectum [11, 38]. Two of the eight estimates are >1.00, both significantly, and six <1.00, two significantly.
diabetes. Three studies reported comparable estimates for the impact of diabetes on NEN development from various sites of origin including lung [11], pancreas [11, 15, 20], small intestine [11], stomach [11], and rectum [11]. The effect estimates were always >1.00, with four of the six estimates significantly, for pancreatic and gastric NEN, respectively.

discussion

Acquiring evidence on risk factors in rare cancer is per se a major challenge, given the difficulties expected in recruiting significant and clean figures to analyze. This is particularly true for NENs, a cancer area significantly suffering of the lack of reference standards and research funding [39]. Indeed, information on neuroendocrine cancer has been generated in a sporadic and non-uniform fashion, overall resulting in dispersed data of difficult approach for the medical and the scientific community. One possible way to overcome such problems is to generate evidence by building meta-analysis of published data. This is considered an effective strategy to consolidate evidence in cancer. The aim of this investigation was to fill the gap between information available and clinicians, in light of the almost complete absence of meta-analysis information in this field.

The present investigation indicates that (i) data, although scattered and not homogenous, are indeed available for risk factor and NEN development and (ii) some risk factors (family history of malignancy, tobacco smoking, alcohol consumption, and abnormal metabolic states including diabetes and obesity) are recurrently found at various anatomical sites, indicating their relevance on NEN. Most studies indicate that family history of cancer appears as a recurrent risk factor at all investigated sites, though with variable statistical significance. With the exception of specific familial syndromes (MEN1-4, Von Hippel-Lindau, and neurofibromatosis) and some familial clustering where patients are usually younger, NENs are reported in elderly patients and usually from the sixth decade of life [34, 40]. Ageing is per se a risk factor for cancer development. Indeed, NEN incidence rate analysis from large dataset indicates an incremental trend and usually in older patients [41]. In addition, the risk for second cancer development is increased in patients with NENs, in turn carrying the burden of poorer survival [34, 42–46].

Tobacco smoking and alcohol drinking are well-known risk factors for several common cancer (adenocarcinoma or squamous cell carcinoma) development in the upper digestive tract and pancreas. Our meta-analysis consistently showed that such risk factors may be important for neuroendocrine cancer development too, though with relevant site-specific differences. For pancreas, both tobacco smoking and alcohol drinking were positively associated, whereas for the small intestine smoking only and in the rectum alcohol only still retained significance. No studies examined the effect of these exposures on appendicular and colon NEN. Overall, our data suggest a higher risk trend in the upper digestive tract and pancreas, anatomical sites more closely and directly exposed to such factors. Diabetes and obesity were consistently found as relevant risk factors for neuroendocrine cancer development in pancreas, as previously described [24], while impaired gall bladder function (gall stones and cholecystectomy) was relevant for the small intestine only. Both such findings would suggest the existence of site-specific neuroendocrine cancer risk factors, either directly related to some specific regulatory function of the organ (diabetes and fat control for the pancreas) or to a direct/indirect effect of bile fluid and biliary salts (for small intestine). Bile acid, obesity-induced metabolic syndrome, and diabetes have been recently linked as cooperating risk factors for digestive cancer via gut microbiota [47, 48].

The overall impression from our data is that common cancers and NENs may share risk factors. This is particularly evident for pancreas. Pancreatic cancer risk is about two times higher in current smokers compared with never-smokers [49] as well as in diabetics compared with non-diabetics [50–52]. Alcohol consumption is also classified by the International Association for Research on Cancer (IARC) as a possible cause of pancreatic cancer [49]. However as for body fatness, a factor also classified by the IARC as a cause of pancreatic cancer [49], we found statistically significant results with effect estimates pointing to opposite directions. This may be partly explained by the fact that BMI, as measure of body fat, has serious flaws with consequent potentially important bias in estimating the obesity-related effects [53].

In this review of NEN risk factors in 24 studies, we included data from >1 million participants from 13 countries for a total of 28 600 cases. The meta-analyses on the risk factors for pancreas, small intestine, and rectum were based on several studies from various populations. In some circumstances, the combined sample size was large, and robust detailed analysis was carried out. There were, however, several limitations in these meta-analyses. First, although a substantial number of studies were included in this review; for each risk factor considered there were usually less than five studies included, limiting the statistical power to detect heterogeneity across studies and the potential effect modification by study characteristics. Second, heterogeneity may have been introduced because of the different ranges used to define categories of the exposure investigated (e.g. heavy drinking). Third, adjustments for potential confounding factors were not consistent across studies (supplementary Table S1, available at Annals of Oncology online). As an example, if most studies provided data adjusted for age and gender, few were adjusted for factors such as diet, nutrition, and physical activity, the most important modifiable determinants of cancer risk [54]. Fourth, formal tests of publication bias were not carried out because of the limited number of identified studies in each meta-analysis. Finally, despite the current review was not restricted to studies with particular methodological strengths, it was limited by an overall lack of available data on this subject and most importantly referring to genetic susceptibility.

In conclusion, family history of cancer appears to be the most relevant risk factor for NEN development at all investigated sites, followed by BMI and diabetes. Cigarette smoking and alcohol consumption appear also to be relevant risk factors, especially for some anatomical sites including pancreas (both alcohol and cigarette smoking), lung, and small intestine (smoking only). The risk factors for NEN development partly overlap those for regular cancer at various anatomical sites.

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funding

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disclosure

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references

Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis

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Background: Lung cancer is the most common cause of cancer death. Fruits and vegetables containing carotenoids and other antioxidants have been hypothesized to decrease lung cancer risk. As part of the World Cancer Research Fund International Continuous Update Project, we conducted a systematic review and meta-analysis of prospective studies.

Methods: We searched PubMed and several databases up to December 2014 for prospective studies. We conducted meta-analyses comparing the highest and lowest intakes and dose–response meta-analyses to estimate summary relative risks (RRs) and 95% confidence intervals (CIs), and examine possible non-linear associations. We combined results from the Pooling Project with the studies we identified to increase the statistical power of our analysis.

Results: When comparing the highest with the lowest intakes, the summary RR estimates were 0.86 [95% CI 0.78–0.94; n (studies) = 18] for fruits and vegetables, 0.92 [95% CI 0.87–0.97; n = 25] for vegetables and 0.82 [95% CI 0.76–0.89; n = 29] for fruits. The association with fruit and vegetable intake was marginally significant in current smokers and inverse but not significant in former or never smokers. Significant inverse dose–response associations were observed for each 100 g/day increase: for fruits and vegetables [RR: 0.96; 95% CI 0.94–0.98, I² = 64%, n = 14, N (cases) = 9609], vegetables (RR: 0.94; 95% CI 0.89–0.98, I² = 48%, n = 20, N = 12 563) and fruits (RR: 0.92; 95% CI 0.89–0.95, I² = 57%, n = 23, N = 14 506). Our results were consistent among the different types of fruits and vegetables. The strength of the association differed across locations. There was evidence of a non-linear relationship (P < 0.01) between fruit and vegetable intake and lung cancer risk showing that no further benefit is obtained when increasing consumption above ~400 g per day.

Conclusions: Eliminating tobacco smoking is the best strategy to prevent lung cancer. Although residual confounding by smoking cannot be ruled out, the current evidence from prospective studies is consistent with a protective role of fruit and vegetables in lung cancer aetiology.

Key words: fruits, vegetables, lung cancer, smoking, meta-analysis, review

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