Healthy lifestyle and the risk of pancreatic cancer in the EPIC study

Sabine Naudin[1], Vivian Viallon[1], Dana Hashim[2] , Heinz Freisling[1], Mazda Jenab[3], Elisabete Weiderpass[4,5,6,7], Flavie Perrier[1], Fiona McKenzie[8], H. Bas Bueno-de-Mesquita[9,10,11], Anja Olsen[12], Anne Tjønneland[12,13], Christina C. Dahm[14], Kim Overvad[14,15], Francesca Romana Mancini[16,17], Vinciane Rebours[18,19], Marie-Christine Boutron-Ruault[16,17], Verena Katzke[20], Rudolf Kaaks[20], Manuela Bergmann[21], Heiner Boeing[21], Eleni Peppa[22], Anna Karakatsani[22,23], Antonia Trichopoulou[22,24], Valeria Maria Pala[25], Giovana Masala[26], Salvatore Panico[27], Rosario Tumino[28], Carlotta Sacerdote[29], Anne M. May[30], Carla H. van Gils[30], Charlotta Rylander[31], Kristin Benjaminsen Borch[31], María Dolores Chirlaque López[32,33], Maria-Jose Sánchez[33,34], Eva Ardanaz[33,35,36], J. Ramón Quirós[37], Pilar Amiano Exezarreta[33,38], Malin Sund[39], Isabel Drake[40], Sara Regnér[40], Ruth C. Travis[41], Nick Wareham[42], Dagfinn Aune[11,43,44], Elio Riboli[11], Marc J. Gunter[3], Eric J. Duell[45], Paul Brennan[46], Pietro Ferrari[1*]

[1] Nutritional Methodology and Biostatistics Group, International Agency for Research on Cancer, Lyon, France; [2] Department of Hematology and Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [3] Nutritional Epidemiology Group, International Agency for Research on Cancer, Lyon, France; [4] Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway; [5] Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway; [6] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [7] Genetic Epidemiology Group, Folkhälsan Research Center and Faculty of Medicine, University of Helsinki, Helsinki, Finland; [8] Environment and Radiation section, International Agency for Research on Cancer, Lyon, France; [9] National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands; [10] Department of Gastroenterology and Hepathology, University Medical Center, Utrecht, The Netherlands; [11] Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, United Kingdom; [12] Danish Cancer Society Research Center, Copenhagen, Denmark; [13] Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen; [14] Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark; [15] Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; [16] CESP, Fac. de médecine - Univ. Paris-Sud, Fac. de médecine - UVSQ, INSERM, Université Paris-Saclay, 94805, Villejuif, France; [17] Gustave

Roussy, F-94805, Villejuif, FranceEPIC France; [18] Pancreatology Department, Beaujon Hospital, DHU Unity, AP-HP, Clichy, and Paris-Diderot University, Paris, France; [19] Inserm UMR1149, DHU Unity, and Paris-Diderot University, Paris, France; [20] Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [21] German Institute of Human Nutrition Potsdam-Rehbrücke; [22] Hellenic Health Foundation, Athens, Greece; [23] Pulmonary Medicine Department, School of Medicine, National and Kapodistrian University of Athens, "ATTIKON" University Hospital, Haidari, Greece; [24] School of Medicine, National and Kapodistrian University of Athens, Greece; [25] Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [26] Cancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network - ISPRO, Florence, ITALY; [27] Department of Clinical and Experimental Medecine, University Federico II, Naples, Italy; [28] Cancer Registry and Histopathology Department, Civic M.P.Arezzo Hospital, Ragusa, Italy; [29] Unit of Cancer Epidemiology, Città della Salute e della Scienza University, Hospital and Center for Cancer Prevention (CPO), Turin, Italy; [30] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [31] Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway; [32] Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria, Universidad de Granada, Granada, Spain; [33] CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain; [34] Escuela Andaluza de Salud Pública. Instituto de Investigación Biosanitaria ibs.GRANADA, Universidad de Granada. Granada, Spain; [35] Navarra Public Health Institute, Pamplona, Spain; [36] IdiSNA, Navarra Institute for Health Research, Pamplona, Spain; [37] Public Health Directorate, Asturias, Spain; [38] Public Health Division of Gipuzkoa, BioDonostia Research Institute, San Sebastian, Spain; [39] Department of Surgical and Preoperative Sciences, Umeå University, Sweden; [40] Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden; [41] Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom; [42] MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom; [43] Department of Nutrition, Bjørknes University College, Oslo, Norway; [44] Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway; [45] Unit of Nutrition and Cancer, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain; [46] Genetic Epidemiology Group, International Agency for Research on Cancer, Lyon, France.

***Corresponding Author**

Pietro Ferrari, PhD

Nutritional Methodology and Biostatistics Group

International Agency for Research on Cancer, WHO

150, cours Albert Thomas

69372 Lyon CEDEX 08, France

Tel. +33 472 738 031

E-mail: ferrarip@iarc.fr

Keywords

Pancreatic cancer; healthy lifestyle index; population attributable fraction; EPIC; prospective study.

Abbreviations

BMI: Body Mass Index

CI: Confidence Interval

EPIC: European Prospective Investigation into Cancer and Nutrition

HR: Hazard Ratio

PC: Pancreatic Cancer

PAF: Population Attributable Fraction

WCRF/AICR: World Cancer Research Fund/American Institute for Cancer Research

WHR: Waist-to-Hip ratio

Abstract (Words=248)

Background. Pancreatic cancer (PC) is a highly fatal cancer with currently limited opportunities for early detection and effective treatment. Modifiable factors may offer pathways for primary prevention. In this study, the association between the healthy lifestyle index (HLI) and PC risk was examined.

Methods. Within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, 1,113 incident PC (57% women) were diagnosed from 400,577 cancer-free participants followed-up for 15 years (median). HLI scores combined smoking, alcohol intake, dietary exposure, physical activity and, in turn, overall and central adiposity using BMI (HLI_{BMI}) and waist-to-hip ratio (WHR, HLI_{WHR}), respectively. High values of HLI indicate adherence to healthy behaviors. Cox proportional hazard models with age as primary time variable were used to estimate PC hazard ratios (HR) and 95% confidence intervals (CI). Sensitivity analyses were performed by excluding, in turn, each factor from the HLI score. Population attributable fractions (PAF) were estimated assuming participants' shift to healthier lifestyles.

Results. The HRs for a one-standard deviation increment of HLI_{BMI} and HLI_{WHR} were 0.84 (95% CI: 0.79, 0.89; p_{trend}=4.3e-09) and 0.77 (0.72, 0.82; p_{trend}=1.7e-15), respectively. Exclusions of smoking from HLI_{WHR} resulted in HRs of 0.88 (0.82, 0.94; p_{trend}=4.9e-04). The overall PAF estimate was 19% (95% CI: 11%, 26%), and 14% (6%, 21%) when smoking was removed from the score.

Conclusion. Adherence to a healthy lifestyle was inversely associated with PC risk, beyond the beneficial role of smoking avoidance. Public health measures targeting compliance with healthy lifestyles may have an impact on PC incidence.

Introduction (Words=4,134)

In the last decades, the rise in pancreatic cancer (PC) incidence has become a major public health concern with mortality rates expected to double by 2030 in American and European populations [1–3]. Commonly diagnosed at late stages, PC is a highly fatal cancer with similar incidence and mortality rates [4]. In the current absence of available screening tools [5], the identification of modifiable risk factors might be important for PC prevention.

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) international expert panel estimated that at least one-third of all cancers could have been prevented through lifestyle management including diet, obesity and physical activity habits [6]. PC incidence rates are nearly four times higher in high-income countries such as the United States and Western European countries than in middle- and low-income countries [4], suggesting that PC occurrence may be associated with lifestyle factors specifically prevalent in the Western world. Individual examination of lifestyle risk factors of PC have led to the identification of smoking, as well as body fatness, adult attained height, type-2 diabetes, and heavy alcohol drinking as positive risk factors, while diet and physical activity have been inconsistently associated with PC risk [7,8]. There is limited evidence regarding the joint association of different lifestyle factors on PC incidence, especially among European populations [9,10].

Previous epidemiological studies have identified clusters of modifiable exposures, assessable through *a priori* scores reflecting compliance with primary prevention guidelines [11], which were evaluated in relation to cardiovascular diseases [12,13], cancer incidence [14,15], and overall and cause-specific mortality [16,17]. A multi-component score termed the Healthy Lifestyle Index (HLI), combining information on smoking, alcohol intake, dietary habits, body mass index (BMI), and physical activity has been previously related to colorectal [18], breast [19], gastric [20], and overall cancers [21] within the European Prospective Investigation into

Cancer and Nutrition (EPIC) study. Within the American Association of Retired Persons (AARP) study a strong inverse association was observed between the HLI and PC risk[9].

In this work, the association between the HLI and PC risk was examined within the EPIC study. Two versions of the score were used, i.e. (i) with BMI to reflect overall adiposity and (ii) with waist-to-hip ratio to reflect central adiposity. The marginal role of single factors in the HLI score was investigated, particularly smoking. Population attributable fractions were also estimated.

Material and Methods

Study population. EPIC is a multicenter prospective study designed to investigate the etiology of cancer in relation to diet and other lifestyle factors [22]. From 1992 to 2000, 521,324 participants aged from 35 to 70 years were recruited across 10 European countries, mostly from the general population, of which 70% were women. Exceptions were the French cohort (school and university employees), the Spanish and Italian centers (blood donors), Utrecht and Florence centers (breast cancer screening participants), and Oxford (vegetarians and 'health conscious' participants). In France, Utrecht and Naples women only were recruited. Study participants provided informed consent before completing questionnaires at baseline. Participants from Norway were excluded from this study, as information on physical activity was not compatible with the other centers [23].

Cancer cases were identified during follow-up based on population cancer registries in Denmark, Italy, Netherlands, Spain, Sweden, and the United Kingdom, and on a combination of methods, including health insurance records, contacts with cancer and pathology registries, and active follow-up of EPIC participants and their next of kin in France, Germany, and Greece.

159 Mortality data were collected from, either the cancer or mortality registries at the regional or
160 national level.

161 The most recent vital status and cancer diagnosis update were used. Vital status was known for
162 98.4% of all EPIC subjects, while 1.6% of participants emigrated, withdrew or were lost to
163 follow-up. The current follow-up period ended as follows: December 2009 in Varese and
164 Murcia, December 2010 in Florence, Ragusa, Turin, Asturias, Bilthoven and Utrecht,
165 December 2011 in Granada, Navarra, San Sebastian and Cambridge, December 2012 in
166 Oxford, Umeå, and Denmark, and December 2013 in Malmö. The end of follow-up was
167 considered as the last known contact with participants in France (June 2008), Heidelberg and
168 Potsdam (December 2009), and Naples (December 2010) and Greece (December 2012). Cases
169 of PC were primary incident tumor of the pancreas, coded according to the International
170 Classification of Diseases (10^{th} edition), which included all invasive pancreatic cancers
171 (C25.0–C25.3, C25.7–C25.9). Endocrine and neuroendocrine tumors of the pancreas (C25.4)
172 were censored at date of diagnosis (n=54). Microscopically confirmed PC represented 83% of
173 the cases (n=928) based on histology of the primary tumor or metastases, cytology or autopsy
174 reports.

175 Exposure assessment. Habitual diet, including alcohol intake, over the year preceding
176 recruitment was assessed at baseline by validated center-specific dietary questionnaires
177 [22,24]. Data on anthropometry (self-reported in France and the UK Oxford center) [25,26]
178 physical activity, smoking habits, and prevalent chronic conditions were collected at
179 recruitment through lifestyle questionnaires [22].

180 A diet score was built from the combination of six dietary factors reflecting diet quality [21],
181 i.e. cereal fibers, red and processed meat, the ratio of polyunsaturated to saturated fatty acids,
182 margarine (to express industrially produced trans-fats) [27,28], glycemic load, and fruits and
183 vegetables. For each dietary factor, residuals were computed in models with total energy intake

184 [29], and grouped into country-specific deciles. Individual scores were summed up and
185 categorized into quintiles.

186 The HLI was generated from the combination of five lifestyle factors, namely: diet score,
187 physical activity, smoking status, alcohol consumption and anthropometry. For each factor,
188 scores ranging from 0 to 4 were assigned to increasingly healthier categories, as described in
189 **Figure 1**. The HLI was obtained as the sum of scores of each lifestyle factor *[19]*. As previous
190 evidence on PC etiology identified waist-to-hip ratio, an indicator of central adiposity, as a PC
191 risk factor *[30,31]*, a HLI based on WHR (HLI_{WHR}) was implemented replacing BMI with sex-
192 specific WHR quintiles.

193 Statistical analysis. From a study population of 521,324 participants, subjects without lifestyle
194 or dietary information (n= 6,902), with ratio of estimated energy intake over energy
195 requirement in the top or bottom 1% (n=10,241),*[32]* with self-reported prevalent cancer
196 (n=24,221), with missing follow-up information (n=3,800), with missing smoking status
197 (n=15,684) or physical activity (n=65,054) were excluded. For analyses with HLI_{WHR}, subjects
198 with missing WHR were also excluded (n=45,105). Country-specific age standardized PC
199 incidence rates (ASR, per 100,000 person-years, PY) were computed using 5-year categories
200 in the range 50 to 70 years and the standard European population.

201 The association between the HLI and PC incidence was evaluated using multivariable Cox
202 proportional hazard models, with age as the primary time variable, and Breslow's method to
203 handle ties *[33]*. The time at study entry was age at recruitment, while the exit time was age at
204 cancer diagnosis, death, loss, or end of follow-up, whichever came first. All models were
205 stratified by study center *[32]*, sex and age at recruitment in 1-year categories.

206 The HLI_{BMI} and HLI_{WHR} were, in turn, modeled as continuous variables to compute HR
207 estimates for a one-standard deviation (1-SD), corresponding to about three-point increase in
208 the score. Analyses were also carried out in categories (0-4, 5-9, 10-14, 15-20), using the group

5-9 as reference. Models were systematically adjusted for potential risk factors of PC and covariates influencing HLI and PC risk *[21,34–36]*, namely education level (no degree/primary school, secondary/technical or professional school, university degree or more, unknown (4%)), self-reported baseline diabetes status (no, yes, unknown (8%)), energy intake from non-alcohol sources (continuous), and height (continuous). Additional adjustment for BMI (continuous) was used in models for HLI_{WHR}. HRs were unchanged after women-specific inclusion of menopausal status, ever use of replacement hormonal replacement therapy and number of full-term pregnancies, thus adjustment for these variables was not pursued. Overall tests for statistical significance of HRs were determined by comparing Wald-test statistics to a χ^2 distribution with degree of freedom (dof) equal to the number of categories minus one for evaluation in categories (p_{Wald}) and dof equal to one as continuous (p_{trend}). The proportionality of hazards (PH) assumption was evaluated through the Schoenfeld's residuals *[37]*.

Sensitivity analyses were carried out by excluding, in turn, each factor from the HLI scores to identify factors mostly driving the HLI association with PC risk. The excluded component was used as a confounder in the model.

Assuming a causal relationship between HLI_{WHR} and PC risk, population attributable fractions (PAF) were estimated as the reduction in PC incidence that would occur if study participants shifted to the adjacent healthier category of HLI_{WHR}, as [38]

$$PAF = \frac{\sum_{i=1}^{k} RR_i \, c_i - \sum_{i=1}^{k} RR_i \, c_i^*}{\sum_{i=1}^{k} RR_i \, c_i},$$

with i=1,…,4 indexing the HLI_{WHR} categories, HR_i and c_i expressing the hazards ratio and the observed proportion of participants in category i, respectively, and c_i^* the counterfactual proportion of participants, as detailed in **Supplementary Table 1**. PAF was also computed assuming a counterfactual scenario whereby men adopted women's lifestyle habits. Given the low PC prevalence and under the proportional hazards assumption, HRs were correct

233 approximations of risk ratios (RR_i). Confidence intervals were obtained using bootstrap
234 sampling [39].

235 The relationship between the HLI and PC risk was estimated by, in turn, sex, European regions
236 (North: Denmark, Sweden; Central: The United Kingdom, The Netherlands, Germany; South:
237 France, Greece, Italy, and Spain), and smoking status (never, former, current). Interactions
238 were evaluated by comparing the difference in log-likelihood of models with and without
239 interaction terms between HLI_{WHR} and, either sex, European region or smoking, to a χ^2
240 distribution, with dof equal to the total number of interaction terms minus one. Although the
241 PH assumption was satisfied, possible selections could operate among study participants within
242 15 year of follow-up, and HR estimates can change with age. The pattern of HR for a 1-SD
243 increase of HLI_{WHR} by age was examined using a flexible parametric survival model on the
244 cumulative hazard scale. Restricted cubic splines with 5 internal knots were used to model the
245 baseline hazard using attained age as the time scale and a time-varying coefficient on HLI_{WHR}
246 [40].

247 To address potential reverse causality, analyses were carried out excluding the first 2 and 5
248 years of follow-up. In analyses excluding smoking from the HLI, HR estimates after adjustment
249 by smoking status (never, former, current), smoking intensity (number of cigarette/day,
250 continuous) and duration of smoking (years, continuous) were examined. Two-sided p-values
251 were used with a 5% nominal statistical significance. Analyses were performed using Stata 14
252 [41].

253

254 **Results**

255 From a total of 400,577 participants (70% women) followed-up for 15 years (median) and a
256 total of 5,544,627 person-years, 1,113 incident PC cases were diagnosed. Exclusion of subjects

without information on their WHR led to 1,075 PC cases from a total of 355,472 participants as reported in **Table 1**. The overall PC ASR was equal to 6.0 per 100,000 person-years, with relatively large and low ASR estimates observed in Germany (9.4 per 100,000 PY) and France (2.1 per 100,000 person-years), respectively. The individual components of the HLI, together with other confounding variables, are described in **Table 2**. The HLI was inversely related to education, while the prevalence of diabetes at recruitment was stable across HLI categories. The hypothesis of PH assumption was not rejected with p-value equal to 0.24.

A 1-SD higher HLI was inversely associated with PC risk, with HR equal to 0.84 (95%CI: 0.79, 0.89, p_{trend}=4.3e-09) for HLI_{BMI} and 0.77 (0.72, 0.82, p_{trend}=1.7e-15) for HLI_{WHR}, as shown in **Table 3**. These patterns were confirmed for PC HR estimates for analyses in categories, consistently for HLI_{BMI} and HLI_{WHR}.

Results of sensitivity analyses are displayed in **Figure 2**. After exclusion of smoking status, the HR for a 1-SD increase of HLI_{BMI} was 0.94 (95%CI: 0.88, 1.01; p_{trend}=0.11), and after exclusions of, in turn, alcohol and BMI, HRs were 0.85 (0.80, 0.91; p_{trend}=6.3e-07) and 0.79 (0.74, 0.85; p_{trend}=7.6e-12), respectively. After exclusion of, in turn, smoking, alcohol, waist-to-hip ratio from the HLI_{WHR} score, HRs were equal to 0.88 (0.82, 0.94; p_{trend}=4.9e-04), 0.79 (0.74, 0.84; p_{trend}=7.0e-13) and 0.79 (0.74, 0.85; p_{trend}=3.2e-11), respectively.

PAF estimates for a shift of participants to the adjacent healthier category of HLI_{WHR} was equal to 19% (95%CI: 11%, 26%) (**Table 4**). Excluding, in turn, smoking, alcohol and WHR from the HLI_{WHR} showed PAF estimates of 14% (6%, 21%), 19% (10%, 25%), and 16% (9%, 22%), respectively. PAF were 8% (-3%, 18%) for non-smokers at baseline (never and former) and 20% (7%, 35%) for current smokers. PAF estimates were 29% (16%, 37%) in men, and 13% (2%, 24%) in women. Counterfactual scenario whereby men adopted women's lifestyle habits showed a PAF of 13% (9%, 26%).

The association between the HLI_{WHR} and PC risk were similar by sex, European region, and smoking status with $p_{heterogeneity}$ equal to 0.35, 0.15 and 0.62, respectively (**Figure 3**). Although the PH assumption was satisfied, PC HR estimates for HLI_{WHR} showed weaker associations at older ages (**Figure 4**). Exclusion of the first 2 and 5 years of follow-up did not materially alter HRs. After exclusion of smoking from the HLI and adjustment by smoking status, intensity and duration, HRs were unchanged (not shown).

Discussion

In this large European prospective study, healthy lifestyle habits expressed as a HLI score were strongly inversely related to the risk of PC. Adherence to healthy behaviors corresponding to a three-point increase in the score was associated with a 16% (95%CI: 11%, 21%) lower PC risk for a score that included BMI, and 23% (18%, 28%) lower PC risk for a score based on WHR. These results support the adoption of healthy lifestyles in PC prevention.

Scores reflecting dietary and lifestyle habits have become increasingly popular in cancer epidemiology research [21,42,43]. In EPIC, scores expressing adherence to either the Mediterranean diet or the WCRF/AICR recommendations have mainly focused on diet, physical activity and anthropometry, and had previously shown null associations with PC risk in both men and women [44,45]. Within the NIH-AARP study, a score based on the American Cancer Society recommendations including physical activity, diet, BMI, alcohol, but not smoking, was associated with a 20% (95%CI: 3%, 35%) lower PC risk in men, comparing the top vs. bottom category, while no association was observed in women [46]. Within the same cohort, an inverse association was observed between HLI and PC, when smoking was added to the score [9].

In the current study, a comprehensive evaluation of the association between HLI and PC risk was undertaken using sensitivity analyses. As smoking is an established strong risk factor of

PC [47], it has been suggested that the association between lifestyle habits and PC might be primarily driven by smoking [45]. In our analysis, HLI was inversely associated with PC risk even after excluding smoking from the score, with a 12% risk reduction associated with a three-point (1-SD) increase in the HLI_{WHR} (95%CI: 6%, 18%; p_{trend}=4.9e-04). Additionally, in never and former smokers, the PC HR for a three-point increase in the HLI was equal to 0.87 (0.79, 0.95; p_{trend}=2.0e-03, data not shown), suggesting the advantage of adopting healthy habits for PC prevention, beyond the benefit of smoking avoidance.

Body fatness is also an established risk factor for PC [8,48]. A recent pooled analysis concluded that central adiposity during adulthood assessed through waist circumference, or waist-to-hip ratio may also predict PC risk independently from BMI [49]. In our study, HLI based on WHR showed a marginally stronger relationship with PC risk than HLI based on BMI. The subcutaneous truncal adipose tissue has been positively associated with the development of insulin resistance and diabetes [31,50,51], two recognized risk factors for PC [52], and may explain the role of central adiposity, rather than overall adiposity, in PC etiology. Moreover, smoking and alcohol consumption have been previously associated with increasing visceral fat deposition [53,54], which may suggest common pathways between smoking, alcohol consumption and central adiposity in pancreas carcinogenesis.

In our study, the association between HLI and PC was marginally stronger at younger ages compared to older ages. This pattern could be due to a depletion overtime of participants susceptible to PC [55], a phenomenon resulting in an over representation of non-susceptible participants with adverse lifestyle profiles at older ages, thus leading to weaker relationships. Alternatively, HR patterns could be ascribed to study participants' changes towards healthier lifestyle habits related to ageing, or ultimately due to a true causal association indicating that PC benefits could be more substantial if favorable lifestyle habits were adopted at younger ages [56].

This study is to date the first evaluation of the association between a combination of healthy lifestyle factors and PC incidence in European populations, thus corroborating previous evidence from a US study [9]. The strengths of the present study rely on its prospective multi-country design reflecting heterogeneous lifestyle habits. Its large sample size and long follow-up time allowed ascertainment of over a thousand incident PC cases, increasing the statistical power in comparison with the previous EPIC evaluation [44]. Furthermore, associations were unchanged after exclusion of the first years of follow-up. However, this study also has limitations. First, measurement errors likely affected dietary and lifestyle assessments, possibly introducing bias in estimated associations. Furthermore, as EPIC participants represent a healthy proportion of the general population, risk estimates in our study were likely attenuated. In addition, the evidence for a role of life course socio-economic status on cancer-related risk factors was suggested [57], and the use of education in our study as a proxy for socio-economic status might have introduced residual confounding. Last, our study did not consider potential changes in dietary and lifestyle exposures after recruitment, which could be relevant to estimate the association between lifestyle factors and PC risk, as well as to explain HR patterns over age.

Assuming that HLI was causally related to PC risk, and that combinations of different lifestyle factors leading to the same value of the HLI had the same effect on PC risk, PAF estimates indicated that 14% (95%CI: 6%, 21%) of PC could have been avoided by controlling central adiposity, alcohol consumption, diet and physical activity, and up to 19% (11%, 26%) if smoking control was also implemented, indicating the benefit of adopting healthy lifestyle beyond smoking control. In the AARP study, the PAF was 27% assuming that participants adopted the healthiest lifestyle pattern [9], while in a recent Australian PC study considering only smoking and BMI, the PAF was 30% [58].

Conclusion

In conclusion, our findings provide evidence that adherence to a combination of healthy lifestyle habits was strongly inversely associated with PC risk in European adults. Inverse associations were observed even after dismissing, in turn, smoking, alcohol drinking, and adiposity. Adherence to healthy lifestyle habits, especially from younger ages, could be an effective primary prevention strategy to control the incidence of PC, a fatal cancer with no screening tools currently available for early detection.

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Conflict of interest

None to declare.

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Data sharing statement

Information to submit an application to have access to EPIC data and/or biospecimens can be found at http://epic.iarc.fr/access/index.ph.

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Figures Captions

Fig 1 Scoring system implemented to combine the 5 lifestyle factors into the Heathy Lifestyle Index based on the waist-to-hip ratio (HLI_{WHR})

[1] For the HLI_{BMI}, sex-specific waist-to-hip ratio quintiles was replaced by categories of BMI at baseline using cut-offs as (4) 22–23.9 $kg.m^{-2}$, (3) 24–25.9$kg.m^{-2}$, (2) <22 $kg.m^{-2}$, (1) 26–29.9$kg.m^{-2}$, and (0) >30 $kg.m^{-2}$.

Fig 2 Hazard ratio estimates for the associations between a 1-SD increment of HLI[1] and PC risk after recalculation of the HLI_{BMI} and the HLI_{WHR} excluding, in turn, each lifestyle factor

[1] One Standard deviation corresponded to about 3 units of either HLI_{BMI} or HLI_{WHR};

[2] Models evaluating associations between the HLI_{BMI} and PC risk were adjusted for education level, diabetes status, non-alcohol energy intakes, height, and the index components currently excluded from the calculation of the HLI, and stratified by study center, age and sex;

[3] Models evaluating associations between the HLI_{WHR} and PC risk were adjusted for education level, diabetes status, non-alcohol energy intakes, height, BMI and the index components currently excluded from the calculation of the HLI, and stratified by study center, age and sex.

Fig 3 Heterogeneity in the relationship between HLI_{WHR} and PC by sex, European region, and smoking status, expressed for a 1-SD increase of HLI_{WHR}[1]

[1] One Standard deviation corresponded to about 3 units of either HLI_{BMI} or HLI_{WHR};

[2] Northern Europe included Denmark and Sweden, Central Europe included United Kingdom, The Netherlands and Germany, and Southern Europe included France, Greece, Italy and Spain;

[3] Models were computed using the HLI_{WHR} excluding smoking;

[4] Models included interaction terms between HLI_{WHR} and, in turn, sex, European region, and smoking status at recruitment. Differences in HRs were assessed comparing the log-likelihood of models with and without interaction terms to a χ^2 distribution with degrees of freedom equal to the number of categories minus one.

Fig 4 Hazard ratio function (and 95%CI)[1] for the association between HLI_{WHR} and PC risk over years of age, for 1-SD increase of HLI_{WHR}

[1] Obtained from a flexible parametric survival model using restricted cubic splines with 5 internal knots and a time-varying coefficient on HLI_{WHR}. Model was adjusted for educational level, BMI, height, non-alcohol energy intake, diabetes status, sex, country, age at recruitment.