

## 1 **Healthy lifestyle and the risk of pancreatic cancer in the EPIC study**

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76 **Keywords**

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

79

80 **Abbreviations**

81 BMI: Body Mass Index

82 CI: Confidence Interval

83 EPIC: European Prospective Investigation into Cancer and Nutrition

84 HR: Hazard Ratio

85 PC: Pancreatic Cancer

86 PAF: Population Attributable Fraction

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

88 WHR: Waist-to-Hip ratio

89 **Abstract** (Words=248)

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

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

103 **Results.** The HRs for a one-standard deviation increment of HLI<sub>BMI</sub> and HLI<sub>WHR</sub> were 0.84  
104 (95% CI: 0.79, 0.89;  $p_{\text{trend}}=4.3e-09$ ) and 0.77 (0.72, 0.82;  $p_{\text{trend}}=1.7e-15$ ), respectively.  
105 Exclusions of smoking from HLI<sub>WHR</sub> resulted in HRs of 0.88 (0.82, 0.94;  $p_{\text{trend}}=4.9e-04$ ). The  
106 overall PAF estimate was 19% (95% CI: 11%, 26%), and 14% (6%, 21%) when smoking was  
107 removed from the score.

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

111 **Introduction** (Words=4,134)

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

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

129 Previous epidemiological studies have identified clusters of modifiable exposures, assessable  
130 through *a priori* scores reflecting compliance with primary prevention guidelines [11], which  
131 were evaluated in relation to cardiovascular diseases [12,13], cancer incidence [14,15], and  
132 overall and cause-specific mortality [16,17]. A multi-component score termed the Healthy  
133 Lifestyle Index (HLI), combining information on smoking, alcohol intake, dietary habits, body  
134 mass index (BMI), and physical activity has been previously related to colorectal [18], breast  
135 [19], gastric [20], and overall cancers [21] within the European Prospective Investigation into

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

138 In this work, the association between the HLI and PC risk was examined within the EPIC study.

139 Two versions of the score were used, i.e. (i) with BMI to reflect overall adiposity and (ii) with

140 waist-to-hip ratio to reflect central adiposity. The marginal role of single factors in the HLI

141 score was investigated, particularly smoking. Population attributable fractions were also

142 estimated.

143

## 144 **Material and Methods**

145 Study population. EPIC is a multicenter prospective study designed to investigate the etiology

146 of cancer in relation to diet and other lifestyle factors [22]. From 1992 to 2000, 521,324

147 participants aged from 35 to 70 years were recruited across 10 European countries, mostly from

148 the general population, of which 70% were women. Exceptions were the French cohort (school

149 and university employees), the Spanish and Italian centers (blood donors), Utrecht and

150 Florence centers (breast cancer screening participants), and Oxford (vegetarians and ‘health

151 conscious’ participants). In France, Utrecht and Naples women only were recruited. Study

152 participants provided informed consent before completing questionnaires at baseline.

153 Participants from Norway were excluded from this study, as information on physical activity

154 was not compatible with the other centers [23].

155 Cancer cases were identified during follow-up based on population cancer registries in

156 Denmark, Italy, Netherlands, Spain, Sweden, and the United Kingdom, and on a combination

157 of methods, including health insurance records, contacts with cancer and pathology registries,

158 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<sup>th</sup> 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<sub>WHR</sub>) 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<sub>WHR</sub>, 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<sub>BMI</sub> and HLI<sub>WHR</sub> 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



209 5-9 as reference. Models were systematically adjusted for potential risk factors of PC and  
 210 covariates influencing HLI and PC risk [21,34–36], namely education level (no degree/primary  
 211 school, secondary/technical or professional school, university degree or more, unknown (4%)),  
 212 self-reported baseline diabetes status (no, yes, unknown (8%)), energy intake from non-alcohol  
 213 sources (continuous), and height (continuous). Additional adjustment for BMI (continuous)  
 214 was used in models for HLI<sub>WHR</sub>. HRs were unchanged after women-specific inclusion of  
 215 menopausal status, ever use of replacement hormonal replacement therapy and number of full-  
 216 term pregnancies, thus adjustment for these variables was not pursued. Overall tests for  
 217 statistical significance of HRs were determined by comparing Wald-test statistics to a  $\chi^2$   
 218 distribution with degree of freedom (dof) equal to the number of categories minus one for  
 219 evaluation in categories ( $p_{\text{Wald}}$ ) and dof equal to one as continuous ( $p_{\text{trend}}$ ). The proportionality  
 220 of hazards (PH) assumption was evaluated through the Schoenfeld’s residuals [37].

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

224 Assuming a causal relationship between HLI<sub>WHR</sub> and PC risk, population attributable fractions  
 225 (PAF) were estimated as the reduction in PC incidence that would occur if study participants  
 226 shifted to the adjacent healthier category of HLI<sub>WHR</sub>, as [38]

$$227 \quad PAF = \frac{\sum_{i=1}^k RR_i c_i - \sum_{i=1}^k RR_i c_i^*}{\sum_{i=1}^k RR_i c_i},$$

228 with  $i=1, \dots, 4$  indexing the HLI<sub>WHR</sub> categories,  $RR_i$  and  $c_i$  expressing the hazards ratio and the  
 229 observed proportion of participants in category  $i$ , respectively, and  $c_i^*$  the counterfactual  
 230 proportion of participants, as detailed in **Supplementary Table 1**. PAF was also computed  
 231 assuming a counterfactual scenario whereby men adopted women’s lifestyle habits. Given the  
 232 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  $\chi^2$   
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

257 without information on their WHR led to 1,075 PC cases from a total of 355,472 participants  
258 as reported in **Table 1**. The overall PC ASR was equal to 6.0 per 100,000 person-years, with  
259 relatively large and low ASR estimates observed in Germany (9.4 per 100,000 PY) and France  
260 (2.1 per 100,000 person-years), respectively. The individual components of the HLI, together  
261 with other confounding variables, are described in **Table 2**. The HLI was inversely related to  
262 education, while the prevalence of diabetes at recruitment was stable across HLI categories.  
263 The hypothesis of PH assumption was not rejected with p-value equal to 0.24.

264 A 1-SD higher HLI was inversely associated with PC risk, with HR equal to 0.84 (95%CI:  
265 0.79, 0.89,  $p_{\text{trend}}=4.3\text{e-}09$ ) for  $\text{HLI}_{\text{BMI}}$  and 0.77 (0.72, 0.82,  $p_{\text{trend}}=1.7\text{e-}15$ ) for  $\text{HLI}_{\text{WHR}}$ , as  
266 shown in **Table 3**. These patterns were confirmed for PC HR estimates for analyses in  
267 categories, consistently for  $\text{HLI}_{\text{BMI}}$  and  $\text{HLI}_{\text{WHR}}$ .

268 Results of sensitivity analyses are displayed in **Figure 2**. After exclusion of smoking status,  
269 the HR for a 1-SD increase of  $\text{HLI}_{\text{BMI}}$  was 0.94 (95%CI: 0.88, 1.01;  $p_{\text{trend}}=0.11$ ), and after  
270 exclusions of, in turn, alcohol and BMI, HRs were 0.85 (0.80, 0.91;  $p_{\text{trend}}=6.3\text{e-}07$ ) and 0.79  
271 (0.74, 0.85;  $p_{\text{trend}}=7.6\text{e-}12$ ), respectively. After exclusion of, in turn, smoking, alcohol, waist-  
272 to-hip ratio from the  $\text{HLI}_{\text{WHR}}$  score, HRs were equal to 0.88 (0.82, 0.94;  $p_{\text{trend}}=4.9\text{e-}04$ ), 0.79  
273 (0.74, 0.84;  $p_{\text{trend}}=7.0\text{e-}13$ ) and 0.79 (0.74, 0.85;  $p_{\text{trend}}=3.2\text{e-}11$ ), respectively.

274 PAF estimates for a shift of participants to the adjacent healthier category of  $\text{HLI}_{\text{WHR}}$  was equal  
275 to 19% (95%CI: 11%, 26%) (**Table 4**). Excluding, in turn, smoking, alcohol and WHR from  
276 the  $\text{HLI}_{\text{WHR}}$  showed PAF estimates of 14% (6%, 21%), 19% (10%, 25%), and 16% (9%, 22%),  
277 respectively. PAF were 8% (-3%, 18%) for non-smokers at baseline (never and former) and  
278 20% (7%, 35%) for current smokers. PAF estimates were 29% (16%, 37%) in men, and 13%  
279 (2%, 24%) in women. Counterfactual scenario whereby men adopted women's lifestyle habits  
280 showed a PAF of 13% (9%, 26%).

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

287

## 288 **Discussion**

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

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

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

306 PC [47], it has been suggested that the association between lifestyle habits and PC might be  
307 primarily driven by smoking [45]. In our analysis, HLI was inversely associated with PC risk  
308 even after excluding smoking from the score, with a 12% risk reduction associated with a three-  
309 point (1-SD) increase in the HLI<sub>WHR</sub> (95%CI: 6%, 18%;  $p_{\text{trend}}=4.9\text{e-}04$ ). Additionally, in never  
310 and former smokers, the PC HR for a three-point increase in the HLI was equal to 0.87 (0.79,  
311 0.95;  $p_{\text{trend}}=2.0\text{e-}03$ , data not shown), suggesting the advantage of adopting healthy habits for  
312 PC prevention, beyond the benefit of smoking avoidance.

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

323 In our study, the association between HLI and PC was marginally stronger at younger ages  
324 compared to older ages. This pattern could be due to a depletion overtime of participants  
325 susceptible to PC [55], a phenomenon resulting in an over representation of non-susceptible  
326 participants with adverse lifestyle profiles at older ages, thus leading to weaker relationships.  
327 Alternatively, HR patterns could be ascribed to study participants' changes towards healthier  
328 lifestyle habits related to ageing, or ultimately due to a true causal association indicating that  
329 PC benefits could be more substantial if favorable lifestyle habits were adopted at younger ages  
330 [56].

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

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

355

356 **Conclusion**

357 In conclusion, our findings provide evidence that adherence to a combination of healthy  
358 lifestyle habits was strongly inversely associated with PC risk in European adults. Inverse  
359 associations were observed even after dismissing, in turn, smoking, alcohol drinking, and  
360 adiposity. Adherence to healthy lifestyle habits, especially from younger ages, could be an  
361 effective primary prevention strategy to control the incidence of PC, a fatal cancer with no  
362 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>.

## References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res.* 2014;74:2913–21.
2. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2014. *Ann Oncol Off J Eur Soc Med Oncol ESMO.* 2014;25:1650–6.
3. Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. *Acta Oncol Stockh Swed.* 2016;55:1158–60.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394–424.
5. Lindquist CM, Miller FH, Hammond NA, Nikolaidis P. Pancreatic cancer screening. *Abdom Radiol N Y.* 2018;43:264–72.
6. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Personal habits and indoor combustions. Volume 100 E. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum World Health Organ Int Agency Res Cancer. 2012;100:1–538.
7. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int J Epidemiol.* 2015;44:186–98.
8. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and pancreatic cancer. [www.dietandcancerreport.org](http://www.dietandcancerreport.org); 2018.

9. Jiao L, Mitrou PN, Reedy J, Graubard BI, Hollenbeck AR, Schatzkin A, et al. A combined healthy lifestyle score and risk of pancreatic cancer in a large cohort study. *Arch Intern Med.* 2009;169:764–70.
10. Lucas AL, Bravi F, Boffetta P, Polesel J, Serraino D, La Vecchia C, et al. Adherence to World Cancer Research Fund/American Institute for Cancer Research recommendations and pancreatic cancer risk. *Cancer Epidemiol.* 2016;40:15–21.
11. Schuit AJ, van Loon AJM, Tijhuis M, Ocké M. Clustering of lifestyle risk factors in a general adult population. *Prev Med.* 2002;35:219–24.
12. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary Prevention of Coronary Heart Disease in Women through Diet and Lifestyle. *N Engl J Med.* 2000;343:16–22.
13. Kurth T, Moore SC, Gaziano JM, Kase CS, Stampfer MJ, Berger K, et al. Healthy Lifestyle and the Risk of Stroke in Women. *Arch Intern Med.* 2006;166:1403–9.
14. Catsburg C, Miller AB, Rohan TE. Adherence to cancer prevention guidelines and risk of breast cancer. *Int J Cancer.* 2014;135:2444–52.
15. Arthur R, Kirsh VA, Kreiger N, Rohan T. A healthy lifestyle index and its association with risk of breast, endometrial, and ovarian cancer among Canadian women. *Cancer Causes Control.* 2018;29:485–93.
16. Inoue-Choi M, Robien K, Lazovich D. Adherence to the WCRF/AICR guidelines for cancer prevention is associated with lower mortality among older female cancer survivors. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol.* 2013;22:792–802.

17. McCullough ML, Patel AV, Kushi LH, Patel R, Willett WC, Doyle C, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol*. 2011;20:1089–97.
18. Aleksandrova K, Pischon T, Jenab M, Bueno-de-Mesquita HB, Fedirko V, Norat T, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC Med*. 2014;12:168.
19. McKenzie F, Ferrari P, Freisling H, Chajès V, Rinaldi S, de Batlle J, et al. Healthy lifestyle and risk of breast cancer among postmenopausal women in the European Prospective Investigation into Cancer and Nutrition cohort study. *Int J Cancer*. 2015;136:2640–8.
20. Buckland G, Travier N, Huerta J m., Bueno-de-Mesquita HB, Siersema P d., Skeie G, et al. Healthy lifestyle index and risk of gastric adenocarcinoma in the EPIC cohort study. *Int J Cancer*. 2015;137:598–606.
21. McKenzie F, Biessy C, Ferrari P, Freisling H, Rinaldi S, Chajès V, et al. Healthy Lifestyle and Risk of Cancer in the European Prospective Investigation Into Cancer and Nutrition Cohort Study. *Medicine (Baltimore)*. 2016;95:e2850.
22. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr*. 2002;5:1113–24.
23. Ekelund U, Ward HA, Norat T, Luan J, May AM, Weiderpass E, et al. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC)123456. *Am J Clin Nutr*. 2015;101:613–21.

24. Kaaks R, Slimani N, Riboli E. Pilot phase studies on the accuracy of dietary intake measurements in the EPIC project: overall evaluation of results. *European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol.* 1997;26 Suppl 1:S26-36.
25. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. *Public Health Nutr.* 2002;5:561–5.
26. Spencer EA, Roddam AW, Key TJ. Accuracy of self-reported waist and hip measurements in 4492 EPIC-Oxford participants. *Public Health Nutr.* 2004;7:723–7.
27. Chajès V, Biessy C, Byrnes G, Deharveng G, Saadatian-Elahi M, Jenab M, et al. Ecological-level associations between highly processed food intakes and plasma phospholipid elaidic acid concentrations: results from a cross-sectional study within the European prospective investigation into cancer and nutrition (EPIC). *Nutr Cancer.* 2011;63:1235–50.
28. Saadatian-Elahi M, Slimani N, Chajès V, Jenab M, Goudable J, Biessy C, et al. Plasma phospholipid fatty acid profiles and their association with food intakes: results from a cross-sectional study within the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2009;89:331–46.
29. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr.* 1997;65:1220S-1228S; discussion 1229S-1231S.
30. Berrington de González A, Spencer EA, Bueno-de-Mesquita HB, Roddam A, Stolzenberg-Solomon R, Halkjaer J, et al. Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol.* 2006;15:879–85.

31. Janssen I, Heymsfield SB, Allison DB, Kotler DP, Ross R. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. *Am J Clin Nutr.* 2002;75:683–8.
32. Ferrari P, Day NE, Boshuizen HC, Roddam A, Hoffmann K, Thiébaud A, et al. The evaluation of the diet/disease relation in the EPIC study: considerations for the calibration and the disease models. *Int J Epidemiol.* 2008;37:368–78.
33. Thiébaud ACM, Bénichou J. Choice of time-scale in Cox’s model analysis of epidemiologic cohort data: a simulation study. *Stat Med.* 2004;23:3803–20.
34. Ferrari P, Jenab M, Norat T, Moskal A, Slimani N, Olsen A, et al. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer.* 2007;121:2065–72.
35. Ferrari P, Licaj I, Muller DC, Kragh Andersen P, Johansson M, Boeing H, et al. Lifetime alcohol use and overall and cause-specific mortality in the European Prospective Investigation into Cancer and nutrition (EPIC) study. *BMJ Open.* 2014;4:e005245.
36. Naudin S, Li K, Jaouen T, Assi N, Kyrø C, Tjønneland A, et al. Lifetime and baseline alcohol intakes and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition study. *Int J Cancer.* 2018;143:801–12.
37. Schoenfeld D. Partial Residuals for The Proportional Hazards Regression Model. *Biometrika.* 1982;69:239–41.
38. Barendregt JJ, Veerman JL. Categorical versus continuous risk factors and the calculation of potential impact fractions. *J Epidemiol Community Health.* 2010;64:209–12.

39. Efron B, Tibshirani R. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. *Stat Sci.* 1986;1:54–75.
40. Lambert PC, Royston P. Further Development of Flexible Parametric Models for Survival Analysis. *Stata J.* 2009;Volume 9 Number 2.:21.
41. StataCorp. 2015. *Stata Statistical Software: Release 14.* College Station, TX: StataCorp LP.
42. Krebs-Smith SM, Pannucci TE, Subar AF, Kirkpatrick SI, Lerman JL, Tooze JA, et al. Update of the Healthy Eating Index: HEI-2015. *J Acad Nutr Diet.* 2018;118:1591–602.
43. Reedy J, Wirfält E, Flood A, Mitrou PN, Krebs-Smith SM, Kipnis V, et al. Comparing 3 Dietary Pattern Methods—Cluster Analysis, Factor Analysis, and Index Analysis—With Colorectal Cancer Risk The NIH–AARP Diet and Health Study. *Am J Epidemiol.* 2010;171:479–87.
44. Romaguera D, Vergnaud A-C, Peeters PH, van Gils CH, Chan DSM, Ferrari P, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. *Am J Clin Nutr.* 2012;96:150–63.
45. Molina-Montes E, Sánchez M-J, Buckland G, Bueno-de-Mesquita HB, Weiderpass E, Amiano P, et al. Mediterranean diet and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition cohort. *Br J Cancer.* 2017;116:811–20.
46. Kabat GC, Matthews CE, Kamensky V, Hollenbeck AR, Rohan TE. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: a prospective cohort study. *Am J Clin Nutr.* 2015;101:558–69.

47. Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, et al. Cigarette Smoking and Pancreatic Cancer: A Pooled Analysis From the Pancreatic Cancer Cohort Consortium. *Am J Epidemiol*. 2009;170:403–13.
48. Rawla P, Thandra KC, Sunkara T. Pancreatic cancer and obesity: epidemiology, mechanism, and preventive strategies. *Clin J Gastroenterol*. 2019;12:285–91.
49. Genkinger JM, Kitahara CM, Bernstein L, Berrington de Gonzalez A, Brotzman M, Elena JW, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. *Ann Oncol*. 2015;26:2257–66.
50. Patel P, Abate N. Body Fat Distribution and Insulin Resistance. *Nutrients*. 2013;5:2019–27.
51. Taylor R. Insulin Resistance and Type 2 Diabetes. *Diabetes*. 2012;61:778–9.
52. Song S, Wang B, Zhang X, Hao L, Hu X, Li Z, et al. Long-Term Diabetes Mellitus Is Associated with an Increased Risk of Pancreatic Cancer: A Meta-Analysis. *PloS One*. 2015;10:e0134321.
53. Chioloro A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat distribution, and insulin resistance. *Am J Clin Nutr*. 2008;87:801–9.
54. Molenaar EA, Massaro JM, Jacques PF, Pou KM, Ellison RC, Hoffmann U, et al. Association of lifestyle factors with abdominal subcutaneous and visceral adiposity: the Framingham Heart Study., Association of Lifestyle Factors With Abdominal Subcutaneous and Visceral Adiposity: The Framingham Heart Study. *Diabetes Care* *Diabetes Care*. 2009;32, 32:505, 505–10.
55. Hernán MA. The Hazards of Hazard Ratios. *Epidemiol Camb Mass*. 2010;21:13–5.



56. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and Cancer Risk. *Am J Prev Med.* 2014;46:S7-15.
57. Akinyemiju T, Ogunsina K, Okwali M, Sakhuja S, Braithwaite D. Lifecourse Socioeconomic Status and Cancer-Related Risk Factors: Analysis of the WHO study on Global Ageing and Adult Health (SAGE). *Int J Cancer.* 2017;140:777–87.
58. Wilson LF, Antonsson A, Green AC, Jordan SJ, Kendall BJ, Nagle CM, et al. How many cancer cases and deaths are potentially preventable? Estimates for Australia in 2013. *Int J Cancer.* 2018;142:691–701.

## 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 ( $HLI_{WHR}$ )

<sup>1</sup> 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<sup>1</sup> and PC risk after recalculation of the HLI<sub>BMI</sub> and the HLI<sub>WHR</sub> excluding, in turn, each lifestyle factor

<sup>1</sup> One Standard deviation corresponded to about 3 units of either HLI<sub>BMI</sub> or HLI<sub>WHR</sub>;

<sup>2</sup> Models evaluating associations between the HLI<sub>BMI</sub> 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;

<sup>3</sup> Models evaluating associations between the HLI<sub>WHR</sub> 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<sub>WHR</sub> and PC by sex, European region, and smoking status, expressed for a 1-SD increase of HLI<sub>WHR</sub><sup>1</sup>

<sup>1</sup> One Standard deviation corresponded to about 3 units of either HLI<sub>BMI</sub> or HLI<sub>WHR</sub>;

<sup>2</sup> Northern Europe included Denmark and Sweden, Central Europe included United Kingdom, The Netherlands and Germany, and Southern Europe included France, Greece, Italy and Spain;

<sup>3</sup> Models were computed using the HLI<sub>WHR</sub> excluding smoking;

<sup>4</sup> Models included interaction terms between HLI<sub>WHR</sub> 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  $\chi^2$  distribution with degrees of freedom equal to the number of categories minus one.

**Fig 4** Hazard ratio function (and 95%CI)<sup>1</sup> for the association between HLI<sub>WHR</sub> and PC risk over years of age, for 1-SD increase of HLI<sub>WHR</sub>

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