

Nut and peanut butter intake are not directly associated with the risk of endometrial or ovarian cancer

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1 **Nut and peanut butter intake are not directly associated with the risk of endometrial or**
2 **ovarian cancer: results from a Dutch prospective cohort study**

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15 **Abstract**

16 **Background & aims:** Nut intake has been associated with reduced cancer-related mortality and cancer risk.
17 However, very few studies investigated the association between nut consumption and the risk of endometrial and
18 ovarian cancer, with inconclusive results. We prospectively examined the relation between total nut, tree nut,
19 peanut, and peanut butter intake and the risk of endometrial and ovarian cancer in the prospective Netherlands
20 Cohort Study (NLCS).

21 **Methods:** In 1986, 62,573 women aged 55-69 years were included in the NLCS. At baseline, all participants
22 filled in a questionnaire and a subcohort of 2,589 women was randomly selected. After 20.3 years of follow-up,
23 389 endometrial and 347 ovarian cancer cases with complete data were included in the analysis. Hazard ratios
24 (HRs) were calculated in multivariable-adjusted Cox regression analyses, using a case-cohort approach.

25 **Results:** Compared to nonconsumers, the HRs (95% confidence intervals) for women consuming 10+ g total
26 nuts/day were 1.23 (0.82-1.87) for endometrial cancer and 0.84 (0.57-1.24) for ovarian cancer. For tree nut,
27 peanut, and peanut butter intake, also no significant relations with endometrial or ovarian cancer were observed.
28 In the endometrial cancer analyses, significant interactions of total nut intake with body mass index and cigarette
29 smoking status were found.

30 **Conclusions:** The results of this study suggest that intake of total nuts, tree nuts, peanuts, and peanut butter is
31 not related to the risk of endometrial or ovarian cancer. The observed interactions in the endometrial cancer
32 analyses, in particular with cigarette smoking status, require confirmation in other studies.

33

34 **Keywords:** Endometrial cancer, Ovarian cancer, Nuts, Peanut butter, Cohort studies

35

36 **Abbreviations:** AIC, Akaike Information Criterion; aMED, alternate Mediterranean diet; BMI, body mass
37 index; CI, confidence interval; HR, hazard ratio; NLCS, Netherlands Cohort Study; PH, proportional hazards;
38 SD, standard deviation

39 **Introduction**

40 In 2012, uterine corpus cancer, which predominantly comprises endometrial cancer [1], was the fourth most
41 common cancer in women in developed countries; ovarian cancer ranked fifth [2]. The development of
42 endometrial cancer has mainly been linked to an excess of estrogen relative to progesterone [3]. For ovarian
43 cancer, the most common explanation is the incessant ovulation hypothesis, which suggests that reproductive
44 tissue turnover results in an accumulation of genetic damage [3-5]. Although endometrial and ovarian cancers
45 are two distinct entities, these hypothesized mechanisms might apply to both cancer types [3]. Other proposed
46 mechanisms for both cancer types relate, amongst others, to inflammation, gonadotropin stimulation, and mucin-
47 related immunity [3, 5-7].

48 Recently, increased nut consumption has been associated with reduced cancer-related mortality and cancer risk
49 [8-15]. Several animal and human studies stated that phytoestrogens in nuts (isoflavonoids and lignans) might
50 modify sex hormone metabolism and activity, thereby possibly reducing the risk of hormone-dependent cancers
51 [16, 17]. Other proposed mechanisms by which nuts have been suggested to conduct their cancer-
52 chemopreventive effects relate, amongst others, to their antioxidant activity, regulation of immunological and
53 anti-inflammatory responses, and regulation of cell proliferation and differentiation [16, 18-20].

54 Very few studies investigated the association between nut consumption and the risk of endometrial and ovarian
55 cancer, with contradictive results: to our knowledge, only three case-control studies were performed for
56 endometrial cancer [21-23], and one cohort [24] and two case-control studies for ovarian cancer [25, 26].
57 Because these studies are inconclusive and because prospective evidence regarding these relations is very
58 limited, we investigated the role of tree nut, peanut, and peanut butter consumption in the development of
59 endometrial and ovarian cancer in the prospective Netherlands Cohort Study on diet and cancer (NLCS).

60 **Materials and methods**

61 **Study design and cancer follow-up**

62 The NLCS was initiated in September 1986, when 62,573 women aged 55-69 years were enrolled [27]. These
63 women agreed to participate by filling in and returning a baseline questionnaire, which measured dietary habits
64 and other cancer risk factors. Ethical approval of the NLCS was obtained from the institutional review boards of
65 the Maastricht University and the Netherlands Organization for Applied Scientific Research (TNO). The NLCS
66 was conducted in accordance with the Declaration of Helsinki. A case-cohort approach was applied to improve

67 the efficiency of the data processing and analysis. Following this approach, incident cases were derived from the
68 entire cohort, whereas person-years at risk were estimated from a subcohort. This subcohort consisted of 2,589
69 women who were randomly sampled from the total cohort directly after baseline. Subcohort members were
70 followed up biennially for vital status information until December 2006. After 20.3 years of follow-up
71 (September 1986 until December 2006), no subcohort members were lost to follow-up.

72 Follow-up for cancer incidence was performed through annual record linkage with the Netherlands Cancer
73 Registry and the Netherlands Pathology Registry (PALGA) [28]. The completeness of the cancer follow-up was
74 estimated to be higher than 95% [29].

75 After 20.3 years of follow-up, 551 incident endometrial and 498 incident ovarian cancer cases were detected.
76 Prevalent cancer cases (except for skin cancer), non-epithelial or borderline invasive cases, or cases without
77 microscopic confirmation were excluded. Participants were excluded if they had a hysterectomy (excluded from
78 the endometrial cancer analysis) or an oophorectomy (excluded from the ovarian cancer analysis). Moreover,
79 cases and subcohort members with incomplete or inconsistent dietary data, or with missing data on confounders
80 were also excluded. Applying these criteria resulted in 1,452 subcohort members and 389 endometrial cancer
81 cases for the analyses of endometrial cancer, and 1,646 subcohort members and 347 ovarian cancer cases for the
82 analyses of ovarian cancer (Figure 1).

83 **Exposure assessment**

84 Smoking habits, physical activity, anthropometrics, dietary intakes, and other cancer risk factors were evaluated
85 with a mailed, self-administered, 11-page baseline questionnaire. Information about habitual diet in the year
86 preceding baseline was assessed with a validated 150-item semi-quantitative food frequency questionnaire [30].
87 Intake of peanuts, tree nuts, and peanut butter was estimated by asking for intake frequencies and number of
88 standard portion sizes consumed per intake of 'peanuts', 'other, mixed nuts' (tree nuts), and 'peanut butter'.
89 Intake frequencies could range from 'never or less than 1x/month' to '6-7x/week'. A standard portion size was
90 assumed 28 g for tree nuts and peanuts, and 15 g per slice of bread for peanut butter. Daily intakes were
91 calculated by multiplying intake frequencies and portion sizes. Total nut intake was calculated as the sum of
92 daily tree nut and peanut intake.

93 **Statistical analysis**

94 The relation between nut and peanut butter intake and the risk of endometrial and ovarian cancer was analyzed in
95 age- and multivariable-adjusted Cox regression analyses. The proportional hazards (PH) assumption was
96 evaluated with Schoenfeld residuals [31], log-log survival plots, and by including time-varying covariates. No
97 violations of this assumption were observed in the endometrial and ovarian cancer analyses for the exposure
98 variables. In case the PH assumption was violated for confounders, time-covariate interactions for those
99 variables were included. Standard errors were calculated with the robust Huber-White sandwich estimator to
100 account for the additional variance introduced by the sampling from the entire cohort [32].

101 The relation between nut and peanut butter intake and endometrial and ovarian cancer risk was tested on a
102 categorical and continuous scale (per 5 g/day increment). For the categorical analyses, total nut and peanut
103 intake were divided into categories of 0, 0.1-<5, 5-<10, and 10+ g/day, and tree nut and peanut butter intake into
104 0, 0.1-<5, and 5+ g/day, because of the lower number of cases in the higher intake categories. Linear trends were
105 investigated by assigning median nut intake values in the subcohort to the intake categories and fitting these as a
106 continuous variable in the regression models.

107 In the multivariable-adjusted models, estimates were adjusted for the following predefined confounders: age
108 (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day; continuous, centered),
109 and duration (years; continuous, centered)), body mass index (BMI; <18.5, 18.5-<25, 25-<30, ≥ 30 kg/m²),
110 nonoccupational physical activity (≤ 30 , >30-60, >60-90, >90 min/day), educational level (primary or lower
111 vocational (low), secondary or medium vocational (medium), higher vocational or university (high)), age at
112 menarche (years; continuous), age at menopause (years; continuous), parity and age at first child birth
113 (nulliparous, 1-2 children - <25 years, 1-2 children - ≥ 25 years, ≥ 3 children - <25 years, ≥ 3 children - ≥ 25 years),
114 oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake
115 (kcal/day; continuous), and the alternate Mediterranean diet (aMED) score excluding alcohol and nuts [33] (0-2,
116 3-4, 5-7 points). In the endometrial cancer analyses, we additionally adjusted for family history of endometrial
117 cancer (no, yes), and in the ovarian cancer analyses for family history of breast cancer (no, yes). Initially, we
118 also adjusted the ovarian cancer analyses for family history of ovarian cancer. However, because only three
119 participants reported a positive family history, this factor was excluded from the final model, which did not
120 importantly change the estimates. We also checked the following potential confounders: intake of coffee,
121 nutritional supplement use, history of diabetes (for the endometrial cancer analyses only), history of
122 hypertension (for the endometrial cancer analyses only), hysterectomy (for the ovarian cancer analyses only),

123 and height. Because these variables did not change the estimates with minimally 10% when using a backward
124 stepwise selection procedure, they were excluded from the final model.

125 To further investigate the linearity of the exposure-response relation between nut and peanut butter intake and
126 endometrial and ovarian cancer risk, we performed restricted cubic splines analyses with three fixed knots at 0,
127 5, and 10 g intake/day. To examine the assumptions regarding the number and placement of knots, we compared
128 the fit of several models with additional knots or different knot positions using the Akaike Information Criterion
129 (AIC) score [34].

130 Potential residual confounding and interactions were investigated by stratifying the relation between total nut
131 intake and endometrial and ovarian cancer by BMI, nonoccupational physical activity, cigarette smoking status,
132 educational level, and aMED score excluding alcohol and nuts. For ovarian cancer, we also investigated
133 potential interactions by family history of breast cancer (no, yes). We could not stratify by family history of
134 endometrial cancer (in the endometrial cancer analysis) or by family history of ovarian cancer (in the ovarian
135 cancer analysis), because of the limited number of participants with a positive family history. The total nut intake
136 categories of 5-<10 g/day and 10+ g/day were merged to increase statistical power. Participant with a BMI <18.5
137 kg/m² were excluded from the analysis stratified by BMI because of the small number of cases in this category.
138 Interactions were tested by including cross-product terms in the Cox models and performing Wald tests.

139 To check for potential reversed causation, we excluded the first two years of follow-up. Secondly, we divided
140 the total follow-up duration in two-year periods and compared the median baseline nut and peanut butter intake
141 of cases diagnosed during these periods, using a Kruskal-Wallis test. Moreover, we restricted the analysis of
142 peanut butter to participants who had stated having had a constant peanut butter intake in the five years
143 preceding baseline. These data were not available for tree nut or peanut intake. In another sensitivity analyses,
144 we adjusted for consumption of fruits, vegetables, dairy and cheese, and red and processed meat instead of the
145 aMED score excluding alcohol and nuts. Furthermore, associations of tree nut, peanut, and peanut butter intake
146 with endometrial and ovarian cancer were mutually adjusted.

147 Analyses were performed with Stata 15 software (StataCorp. 2017. College Station, TX). P-values were tested
148 two-sided and were considered statistically significant if <0.05.

149 **Results**

150 In the analyses of endometrial cancer, mean (SD) total nut intake was slightly higher in cases (4.4 (8.6) g/day)
151 than in the subcohort (4.2 (7.8) g/day) (Table 1). In the ovarian cancer analyses, mean (SD) total nut intake was
152 4.2 (8.4) g/day among cases and 4.4 (8.6) g/day among subcohort members. Average intakes of tree nuts,
153 peanuts, and peanut butter were almost similar in subcohort members and endometrial and ovarian cancer cases.

154 Regarding other baseline characteristics, both endometrial and ovarian cancer cases were on average less
155 physically active and less often ever cigarette smokers, parous, or oral contraceptive users than subcohort
156 members. Moreover, endometrial and ovarian cancer cases had a later mean age at menopause and scored lower
157 on the aMED score excluding alcohol and nuts (Table 1). Furthermore, compared to subcohort members,
158 endometrial cancer cases were on average heavier, lower educated, reported a positive family history of
159 endometrial cancer more often, had a lower age at menarche, and used hormone replacement therapy more often.
160 Ovarian cancer cases more often reported a positive family history of ovarian cancer than subcohort members,
161 but less often a positive family history of breast cancer, and they used hormone replacement therapy less often.

162 Age- and multivariable-adjusted associations between nut and peanut butter intake and endometrial and ovarian
163 cancer risk are presented in Table 2. In the age-adjusted analyses, no statistically significant relation of total nut
164 intake was found with endometrial or ovarian cancer risk (HR (95% CI) for 10+ g/day vs. nonconsumers = 1.03
165 (0.71-1.49), p-trend = 0.743, and 0.83 (0.57-1.20), p-trend = 0.305, respectively). Tree nut, peanut, and peanut
166 butter consumption were also not significantly related to endometrial or ovarian cancer risk in age-adjusted
167 analyses. After multivariable-adjustment, the nonsignificant positive associations between total nut and peanut
168 intake and endometrial cancer risk became somewhat stronger, whereas the nonsignificant inverse associations
169 between tree nut and peanut butter intake and endometrial cancer risk attenuated or became positive. For ovarian
170 cancer, multivariable-adjustment did not change the results importantly. Total nut intake was not significantly
171 associated with endometrial or ovarian cancer risk after multivariable-adjustment (HR (95% CI) for 10+ g/day
172 vs. nonconsumers = 1.23 (0.82-1.87), p-trend = 0.449, and 0.84 (0.57-1.24), p-trend = 0.452, respectively). Also
173 no significant relations with endometrial or ovarian cancer were observed for tree nut, peanut, and peanut butter
174 intake. In continuous analyses, nut and peanut butter consumption were also not related to the risk of endometrial
175 or ovarian cancer.

176 In restricted cubic spline analyses with three fixed knots at 0, 5, and 10 g nut intake/day, no statistical evidence
177 for nonlinear relations with endometrial or ovarian cancer risk were observed for all four exposure variables
178 (Figure 2). However, the tests for nonlinearity were borderline significant for the relations between peanut butter

179 intake and endometrial cancer risk (p -nonlinearity = 0.062) and between total nut intake and ovarian cancer risk
180 (p -nonlinearity = 0.081). When using additional knots or different knot positions, the model fit, as measured with
181 the AIC score, did not improve importantly (data not shown).

182 Table 3 and Supplementary Table 1 present the associations between total nut intake and endometrial and
183 ovarian cancer risk in strata of potential effect modifiers. In the analyses of endometrial cancer stratified by BMI,
184 no significant association between total nut intake and endometrial cancer risk was observed in participants with
185 a BMI of 18.5-<25 kg/m² (Table 3). A nonsignificant positive trend was observed in participants with a BMI \geq 25
186 kg/m², with a significantly increased risk in the category of 0.1-<5 g total nut intake/day compared to
187 nonconsumers (HR (95% CI) = 1.68 (1.13-2.48)). The test for interaction by BMI was significant (p -interaction
188 = 0.016). For cigarette smoking status, no relation between total nut intake and endometrial cancer risk was
189 found in never smokers, a nonsignificant positive association in former smokers, and a significant positive trend
190 in current smokers (HR (95% CI) for 5+ g/day vs nonconsumers = 3.49 (1.25-9.73), p -trend = 0.021). The p -
191 interaction by smoking status was 0.019. In Figure 3, we further investigated the joint effects of total nut intake
192 and cigarette smoking status on endometrial cancer risk, with never smokers who consumed 0 g total nuts/day as
193 reference category. Increasing nut intake attenuated the inverse association between former cigarette smoking
194 and endometrial cancer risk, and in women who consumed 5+ g total nuts/day, current smoking was even
195 associated with a non-significantly increased endometrial cancer risk. In never smokers, no significant relation
196 between nut intake and endometrial cancer was observed. Nevertheless, only currently smoking nonconsumers
197 had a significantly lower endometrial cancer risk than never smoking nonconsumers (HR (95% CI) = 0.45 (0.25-
198 0.81)). For ovarian cancer, no significant interactions between total nut intake and potential effect modifiers
199 were observed (Supplementary Table 1).

200 No significant differences were found in the median baseline nut and peanut butter intake of endometrial and
201 ovarian cancer cases diagnosed over the follow-up period in Kruskal-Wallis tests ($p \geq 0.206$) (data not shown).
202 Exclusion of the first two years of follow-up resulted in similar results as when the total follow-up period was
203 included (data not shown). Moreover, restricting the analyses of the relation between peanut butter intake and
204 endometrial and ovarian cancer risk to those participants who had stated having had a constant peanut butter
205 intake in the five years before baseline also did not importantly change the results (data not shown).

206 In another sensitivity analysis, adjustment for intake of fruits, vegetables, dairy and cheese, and red and
207 processed meat gave similar estimates as when adjusting for the aMED score excluding nuts and alcohol (data

208 not shown). Moreover, mutually adjusting intake of tree nuts, peanuts, and peanut butter in relation to
209 endometrial and ovarian cancer risk also did not change the results (data not shown).

210 **Discussion**

211 In the current study, total nut intake was not significantly related to the risk of endometrial or ovarian cancer.
212 Similar results were found for tree nut, peanut, and peanut butter intake. For the relation between total nuts and
213 endometrial cancer risk, we observed significant interactions by BMI and cigarette smoking status.

214 Our results for ovarian cancer are in line with the results from the Swedish Women's Lifestyle and Health
215 Cohort Study [24], in which also no statistically significant association between nut consumption and ovarian
216 cancer risk was observed. To our knowledge, this is the only other prospective cohort study investigating the
217 relation between nut intake and ovarian cancer risk. No other prospective evidence is available for endometrial
218 cancer.

219 Besides the abovementioned cohort study, only two case-control studies have been performed on this topic for
220 ovarian cancer [25, 26], and three case-control studies for endometrial cancer [21-23]. Regarding ovarian cancer,
221 a Canadian case-control study did not find a relation between nut product intake frequency and ovarian cancer
222 risk [26], and in an Australian case-control study, intake of omega-6 fatty acids from nuts was significantly
223 associated with a reduced risk of epithelial ovarian cancer [25]. Because the relation of omega-6 fatty acids with
224 ovarian cancer risk varied between the food sources of the omega-6 fatty acids, the authors stated that the
225 estimates probably reflect a relation with nuts rather than with omega-6 fatty acids [25].

226 Regarding endometrial cancer, one case-control study in Greece observed significant positive associations for
227 intake of pulses and nuts combined [23], whereas a later Greek case-control study found a significant inverse
228 association for pulse, nut, and seed consumption together [21]. In a Japanese case-control study, consuming
229 peanuts $\geq 1-2$ times/week was associated with a significantly reduced risk of endometrial endometrioid carcinoma
230 [22]. A borderline significant inverse trend was seen when peanut intake was expressed as intake density (g/1000
231 kcal) [22]. Case-control studies are prone to selection and information biases, which may explain the
232 contradictory results for both endometrial and ovarian cancer. Furthermore, none of the above-mentioned studies
233 investigated the interaction between nut intake and cigarette smoking. Thus, the evidence on the relation between
234 nut intake and endometrial and ovarian cancer is very limited, and further (prospective) research is required to
235 confirm our results.

236 For endometrial cancer, we observed significant interactions of total nut intake with BMI. However, only the
237 category of 0.1-<5 g total nut intake/day was significantly associated with an increased endometrial cancer risk
238 in participants with a BMI higher than 25 kg/m², and no significant exposure-response trends were observed in
239 both BMI strata. Because of the number of significance tests performed, this finding may be due to chance. Nuts
240 are energy-dense foods, and therefore concerns have been raised about weight gain resulting from increased nut
241 intake. In case of hormone-dependent cancers, like endometrial and ovarian cancer, this is especially important
242 because of the hormonal activity of adipose tissue [3, 35, 36]. However, several cross-sectional and prospective
243 studies have indicated that higher nut intake is actually associated with reduced weight gain and a lower risk of
244 becoming overweight or obese [37-40].

245 The interaction between total nut intake and cigarette smoking in relation to endometrial cancer risk was also
246 significant. In contrast to most cancer sites, cigarette smoking has been associated with a lower risk of
247 endometrial cancer, particularly among postmenopausal women [41, 42]. This protective effect is hypothesized
248 to be related to a reduction in the level of circulating unopposed estrogens: smoking has been found to modify
249 the production and metabolism of estrogens, androgens, and progesterone, and to reduce body weight [41-43].
250 Moreover, smoking might have direct cytotoxic effects on the ovaries, which causes oocyte destruction and
251 induces earlier menopause [42, 43]. In our study, increasing total nut intake appeared to counteract the protective
252 effect of smoking (Figure 3), and even a non-significantly increased endometrial cancer risk was found in current
253 smokers who consumed at least 5 g nuts/day. One possible explanation for this observation is that
254 phytoestrogens in nuts might have estrogenic activity if the circulating concentration of unopposed endogenous
255 estrogens is low [17, 44], which possibly counteracts the protective antiestrogenic effects of smoking. Nuts also
256 contain several components with antioxidant, anti-inflammatory, and cell metabolism-modifying properties [16,
257 19], which might also potentially oppose the effects of smoking. However, this is the first study investigating the
258 interaction between nut intake and cigarette smoking in relation to endometrial cancer risk, and this finding
259 needs to be confirmed in other studies first.

260 Our study has some limitations. Only baseline measurements were performed, while dietary intakes may have
261 changed over the 20.3 year follow-up period. Nevertheless, dietary habits appeared to be quite stable for at least
262 five years in a reproducibility study [45]. Potential measurement error might have resulted in misclassification
263 and thus in an attenuation of the results. Moreover, potential residual confounding by measured and unmeasured
264 confounders cannot be excluded. For example, we had no information on risk factors like breastfeeding and tubal

265 ligation. Because these factors are unlikely to be associated with nut intake, they are not expected to confound
266 our results.

267 Strengths of the study are the prospective nature and the long and complete follow-up, which make selection and
268 information bias unlikely. The large number of participants allowed us to extensively correct for potential
269 confounders. Moreover, we were able to distinguish between tree nut, peanut, and peanut butter intake.

270 In conclusion, the results of this prospective cohort study suggest that total nut, tree nut, peanut, and peanut
271 butter intake are not related to the risk of endometrial or ovarian cancer. The observed interactions of nut intake
272 in relation to endometrial cancer risk, in particular with cigarette smoking, need confirmation in other studies.

273

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278 Review & Editing. P.A. van den Brandt: Conceptualization, Funding acquisition, Investigation, Methodology,
279 Project Administration, Supervision, Writing – Review & Editing.

280 **Conflict of Interest:** The authors declare no conflict of interest.

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374 **Table 1.** Baseline characteristics (mean (SD) or %) of subcohort members and endometrial and ovarian cancer
 375 cases in the Netherlands Cohort Study, 1986-2006

	Endometrial cancer		Ovarian cancer	
	Subcohort ^a	Cases	Subcohort ^a	Cases
N	1,452	389	1,646	347
Age (years)	61.4 (4.2)	61.4 (4.3)	61.3 (4.2)	61.5 (4.2)
Never cigarette smoker (%)	58.9	66.8	58.4	64.6
Body Mass Index (kg/m ²)	25.0 (3.5)	26.4 (4.1)	25.0 (3.5)	25.1 (3.6)
Non-occupational physical activity (min/day)	66.3 (51.0)	58.6 (46.3)	66.0 (50.4)	57.8 (37.5)
University or higher vocational education (%)	9.7	8.7	9.7	9.5
Family history of endometrial cancer (%)	2.8	4.4		
Family history of ovarian cancer (%)			0.1	0.6
Family history of breast cancer (%)			8.7	7.8
Age at menarche (years)	13.7 (1.8)	13.4 (1.6)	13.7 (1.8)	13.7 (1.8)
Age at menopause (years)	49.1 (4.3)	50.2 (3.9)	48.9 (4.4)	49.3 (3.9)
Parous (%)	81.2	73.5	81.8	76.1
Age at first birth (in parous, years)	27.1 (4.2)	27.1 (3.9)	27.0 (4.2)	27.6 (4.1)
Number of children (in parous, n)	3.4 (1.9)	3.1 (1.7)	3.4 (1.9)	3.2 (1.7)
Ever used oral contraceptives (%)	24.5	13.9	25.3	19.0
Ever used hormone replacement therapy (%)	11.8	16.5	13.4	12.4
Daily energy intake (kcal)	1,687 (390)	1,658 (398)	1,688 (392)	1,695 (389)
Total nut intake (g/day)	4.2 (7.8)	4.4 (8.6)	4.4 (8.6)	4.2 (8.4)
Tree nut intake (g/day)	1.0 (2.7)	1.0 (3.0)	1.1 (4.1)	1.0 (2.9)
Peanut intake (g/day)	3.3 (6.8)	3.4 (6.9)	3.3 (6.9)	3.2 (6.6)
Peanut butter intake (g/day)	1.2 (3.6)	1.1 (3.2)	1.2 (3.5)	1.2 (3.7)
aMED score (excl. alcohol and nuts) of 5-7 pts (%)	26.5	23.1	26.6	23.9

376 ^a The subcohort sizes of the endometrial and ovarian cancer analyses differ because of differences in the in- and
 377 exclusion criteria (Figure 1).

Table 2. Age- and multivariable-adjusted HRs (and 95% CIs) for endometrial and ovarian cancer according to nut consumption; NLCS, 1986-2006

	Endometrial cancer					Ovarian cancer				
	Median intake ^a	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR ^b (95% CI)	Median intake ^a	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR ^b (95% CI)
<i>Total nuts (g/day)</i>										
0	0.0	9,912	143	1.00 (reference)	1.00 (reference)	0.0	11,388	158	1.00 (reference)	1.00 (reference)
0.1-<5	2.1	9,500	160	1.18 (0.91-1.53)	1.26 (0.94-1.67)	2.1	10,817	117	0.80 (0.61-1.04)	0.79 (0.59-1.05)
5-<10	7.8	2,876	37	0.91 (0.60-1.38)	1.21 (0.76-1.92)	7.8	3,115	28	0.68 (0.43-1.06)	0.71 (0.45-1.14)
10+	15.5	3,338	49	1.03 (0.71-1.49)	1.23 (0.82-1.87)	15.7	3,919	44	0.83 (0.57-1.20)	0.84 (0.57-1.24)
<i>P</i> _{trend}				0.743	0.449				0.305	0.425
Continuous, per 5 g/day increment				1.01 (0.93-1.08)	1.06 (0.97-1.14)				0.98 (0.91-1.06)	0.99 (0.91-1.07)
<i>Tree nuts (g/day)</i>										
0	0.0	17,973	277	1.00 (reference)	1.00 (reference)	0.0	20,505	248	1.00 (reference)	1.00 (reference)
0.1-<5	1.6	6,204	93	0.98 (0.75-1.27)	1.03 (0.76-1.39)	1.6	7,008	85	1.02 (0.78-1.33)	1.04 (0.77-1.41)
5+	8.9	1,450	19	0.85 (0.51-1.43)	1.08 (0.62-1.90)	8.9	1,727	14	0.69 (0.38-1.23)	0.71 (0.39-1.32)
<i>P</i> _{trend}				0.543	0.767				0.226	0.317

Continuous, per 5 g/day increment				0.99 (0.78-1.25)	1.06 (0.83-1.36)				0.94 (0.80-1.12)	0.96 (0.82-1.13)
<i>Peanuts (g/day)</i>										
0	0.0	11,772	175	1.00 (reference)	1.00 (reference)	0.0	13,535	182	1.00 (reference)	1.00 (reference)
0.1-<5	2.1	9,548	151	1.08 (0.84-1.39)	1.20 (0.91-1.57)	2.0	10,791	111	0.78 (0.60-1.02)	0.81 (0.61-1.06)
5-<10	8.5	2,063	31	1.03 (0.66-1.61)	1.19 (0.73-1.96)	8.5	2,249	21	0.73 (0.44-1.19)	0.75 (0.45-1.26)
10+	14.4	2,242	32	0.97 (0.63-1.49)	1.16 (0.73-1.85)	17.1	2,666	33	0.94 (0.63-1.43)	0.96 (0.62-1.47)
<i>P_{trend}</i>				0.896	0.499				0.699	0.792
Continuous, per 5 g/day increment				1.01 (0.93-1.09)	1.06 (0.98-1.16)				0.99 (0.90-1.08)	1.00 (0.91-1.10)
<i>Peanut butter (g/day)</i>										
0	0.0	18,388	298	1.00 (reference)	1.00 (reference)	0.0	21,173	257	1.00 (reference)	1.00 (reference)
0.1-<5	1.2	4,654	58	0.77 (0.57-1.06)	0.83 (0.59-1.17)	1.2	5,275	55	0.87 (0.63-1.20)	0.88 (0.63-1.21)
5+	5.3	2,584	33	0.79 (0.53-1.18)	0.84 (0.54-1.30)	5.3	2,792	35	1.05 (0.71-1.56)	1.02 (0.67-1.54)
<i>P_{trend}</i>				0.186	0.359				0.896	0.989
Continuous, per 5 g/day increment				0.92 (0.77-1.11)	0.96 (0.79-1.17)				1.02 (0.85-1.22)	1.00 (0.83-1.21)

379 ^a Median intake in the female subcohort.

380 ^b Adjusted for age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day; continuous, centered), and duration (years; continuous, centered)),
381 BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m²), nonoccupational physical activity (≤30, >30-60, >60-90, >90 min/day), educational level (low, medium, high), family history of
382 endometrial cancer (no, yes; in the endometrial cancer analysis only), family history of breast cancer (no, yes; in the ovarian cancer analysis only), age at menarche (years;
383 continuous), age at menopause (years; continuous), parity and age at first child birth (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3 children - <25 years,
384 ≥3 children - ≥25 years), oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake (kcal/day; continuous), alternate
385 Mediterranean diet score excluding alcohol and nuts (0-2, 3-4, 5-7 points).

386 **Table 3.** Multivariable-adjusted associations between total nut intake and endometrial cancer risk in strata of
 387 potential effect modifiers; NLCS, 1986-2006

	Total nut consumption (g/day)			P_{trend}	$P_{\text{interaction}}$
	0 g/day	0.1-<5 g/day	5+ g/day		
Endometrial cancer					
<i>Overall</i>					
Cases/person-time at risk (years)	143/9,912	160/9,500	86/6,214		
HR (95% CI) ^a	1.00 (reference)	1.26 (0.94-1.67)	1.22 (0.86-1.74)	0.410	
<i>Body mass index^b</i>					
18.5-<25 kg/m ²					
Cases/person-time at risk (years)	65/4,959	51/5,085	48/4,121		
HR (95% CI) ^a	1.00 (reference)	0.76 (0.49-1.18)	1.07 (0.65-1.77)	0.512	0.016
25+ kg/m ²					
Cases/person-time at risk (years)	76/4,768	108/4,343	38/2,033		
HR (95% CI) ^a	1.00 (reference)	1.68 (1.13-2.48)	1.24 (0.73-2.09)	0.775	
<i>Nonoccupational physical activity</i>					
≤30 min/day					
Cases/person-time at risk (years)	46/2,650	44/1,752	23/1,073		
HR (95% CI) ^a	1.00 (reference)	1.44 (0.83-2.50)	1.24 (0.56-2.73)	0.689	0.650
>30-≤60 min/day					
Cases/person-time at risk (years)	36/3,029	56/3,121	33/2,109		
HR (95% CI) ^a	1.00 (reference)	1.74 (1.01-3.00)	1.61 (0.83-3.12)	0.341	
>60-≤90 min/day					
Cases/person-time at risk (years)	31/2,153	32/2,392	13/1,447		
HR (95% CI) ^a	1.00 (reference)	0.93 (0.45-1.91)	0.84 (0.36-1.94)	0.682	
>90 min/day					
Cases/person-time at risk (years)	30/2,080	28/2,235	17/1,585		
HR (95% CI) ^a	1.00 (reference)	0.97 (0.40-2.33)	0.96 (0.36-2.54)	0.937	
<i>Cigarette smoking status</i>					
Never					

	Cases/person-time at risk (years)	106/6,166	114/5,791	40/3,320		
	HR (95% CI) ^a	1.00 (reference)	1.21 (0.86-1.71)	0.83 (0.51-1.35)	0.322	0.019
Former						
	Cases/person-time at risk (years)	20/1,507	28/2,148	24/1,758		
	HR (95% CI) ^a	1.00 (reference)	1.23 (0.55-2.78)	1.32 (0.56-3.07)	0.594	
Current						
	Cases/person-time at risk (years)	17/2,239	18/1,562	22/1,137		
	HR (95% CI) ^a	1.00 (reference)	1.97 (0.78-4.94)	3.49 (1.25-9.73)	0.021	
<i>Educational level</i>						
Low						
	Cases/person-time at risk (years)	84/6,013	92/4,941	37/2,673		
	HR (95% CI) ^a	1.00 (reference)	1.50 (1.02-2.21)	1.32 (0.79-2.21)	0.397	0.620
Medium						
	Cases/person-time at risk (years)	49/3,316	54/3,507	39/2,696		
	HR (95% CI) ^a	1.00 (reference)	1.05 (0.62-1.77)	1.11 (0.59-2.09)	0.752	
High						
	Cases/person-time at risk (years)	10/583	14/1,052	10/845		
	HR (95% CI) ^a	1.00 (reference)	0.84 (0.14-5.16)	0.64 (0.10-4.05)	0.576	
<i>Adapted Mediterranean diet score excluding nuts and alcohol</i>						
0-2 points						
	Cases/person-time at risk (years)	35/2,980	50/2,088	17/1,372		
	HR (95% CI) ^a	1.00 (reference)	2.22 (1.15-4.28)	1.27 (0.54-2.99)	0.883	0.169
3-4 points						
	Cases/person-time at risk (years)	79/4,855	74/4,596	44/2,875		
	HR (95% CI) ^a	1.00 (reference)	1.04 (0.69-1.57)	1.23 (0.74-2.05)	0.424	
5-7 points						
	Cases/person-time at risk (years)	29/2,077	36/2,817	25/1,967		
	HR (95% CI) ^a	1.00 (reference)	0.87 (0.43-1.74)	1.05 (0.48-2.28)	0.720	

388 ^a Adjusted for age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day;
389 continuous, centered), and duration (years; continuous, centered)), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m²),
390 nonoccupational physical activity (≤30, >30-60, >60-90, >90 min/day), educational level (low, medium, high),

391 family history of endometrial cancer (no, yes), age at menarche (years; continuous), age at menopause (years;
392 continuous), parity and age at first child birth (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3
393 children - <25 years, ≥3 children - ≥25 years), oral contraceptive use (never, ever), hormone replacement therapy
394 use (never, ever), daily energy intake (kcal/day; continuous), alternate Mediterranean diet score excluding
395 alcohol and nuts (0-2, 3-4, 5-7 points).

396 ^b Participants with a BMI <18.5 kg/m² (n = 22) were excluded from the interaction analysis.

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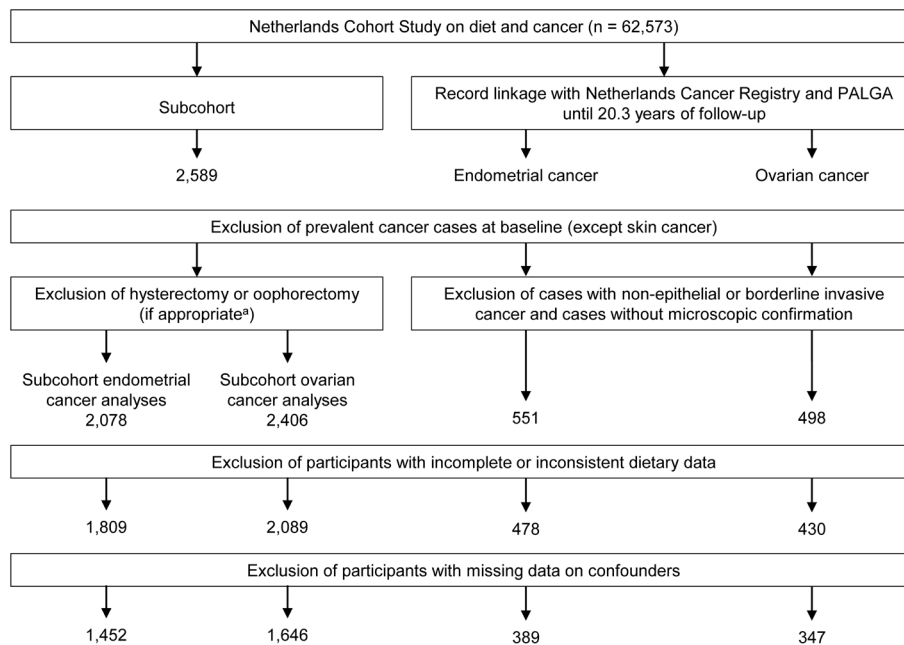
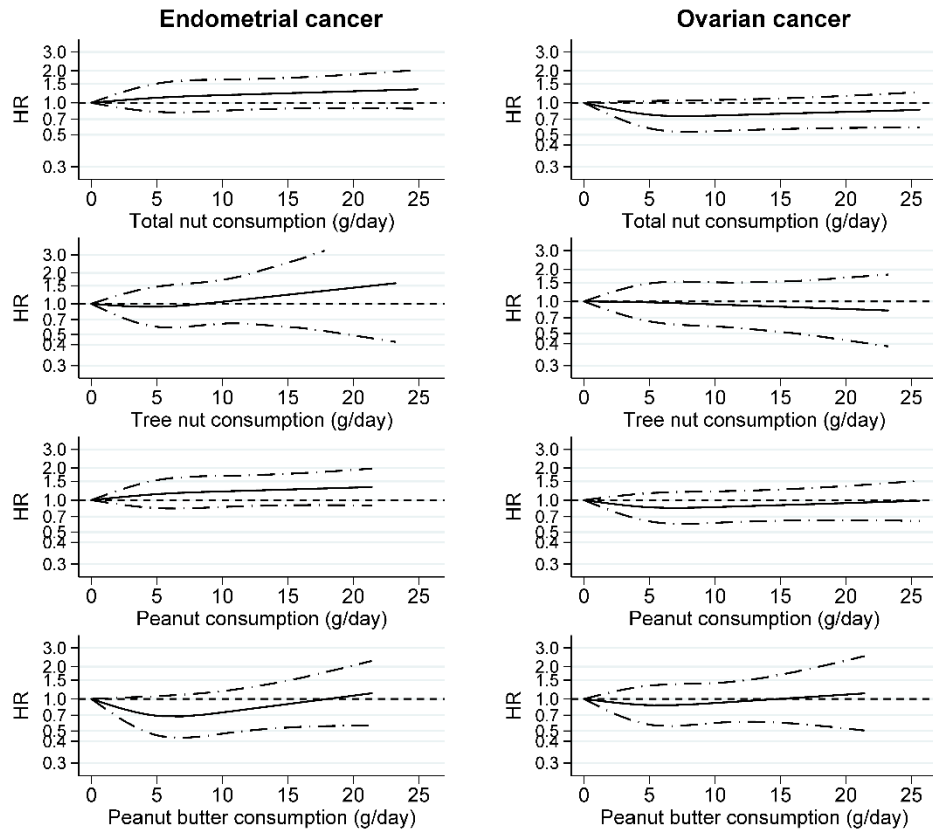


Figure 1. Flow chart of the number of subcohort members and ovarian and endometrial cancer cases; the NLCS, 1986-2006
^a Hysterectomy excluded from the analysis of endometrial cancer, oophorectomy excluded from the analysis of ovarian cancer



412 **Figure 2.** Restricted cubic spline analyses with three fixed knots at 0, 5, and 10 g intake/day, investigating the
 413 relation between nut and peanut butter consumption and the risk of endometrial and ovarian cancer. Solid lines
 414 represent HRs, dashed lines 95% confidence limits. P-values for nonlinearity for total nut, tree nut, peanut, and
 415 peanut butter intake were 0.724, 0.558, 0.640, and 0.062 for endometrial cancer, and 0.081, 0.911, 0.283, and
 416 0.492 for ovarian cancer, respectively. Results were adjusted for age (years; continuous), cigarette smoking
 417 (status (never, former, current), frequency (n/day; continuous, centered), and duration (years; continuous,
 418 centered)), BMI (<18.5, 18.5-<25, 25-<30, ≥ 30 kg/m²), nonoccupational physical activity (≤ 30 , >30-60, >60-90,
 419 >90 min/day), educational level (low, medium, high), family history of endometrial cancer (no, yes; in the
 420 endometrial cancer analyses only), family history of breast cancer (no, yes; in the ovarian cancer analyses only),
 421 age at menarche (years; continuous), age at menopause (years; continuous), parity and age at first child birth
 422 (nulliparous, 1-2 children - <25 years, 1-2 children - ≥ 25 years, ≥ 3 children - <25 years, ≥ 3 children - ≥ 25 years),
 423 oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake
 424 (kcal/day; continuous), alternate Mediterranean diet score excluding alcohol and nuts (0-2, 3-4, 5-7 points)

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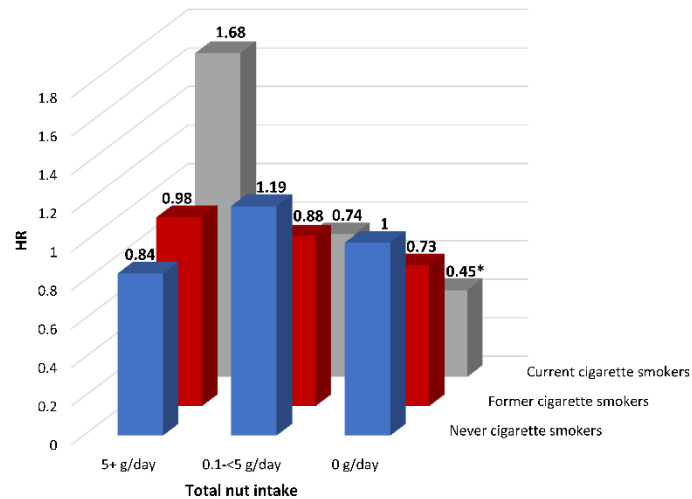


Figure 3. Combined exposure to total nuts and cigarette smoking and the risk of endometrial cancer; the NLCS, 1986-2006. Never cigarette smokers who consumed 0 g nuts/day are the reference category. Results were adjusted for age (years; continuous), cigarette smoking (frequency (n/day; continuous, centered) and duration (years; continuous, centered)), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m²); nonoccupational physical activity (≤30, >30-60, >60-90, >90 min/day), educational level (low, medium, high), family history of endometrial cancer (no, yes), age at menarche (years; continuous), age at menopause (years; continuous), parity and age at first child birth (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3 children - <25 years, ≥3 children - ≥25 years), oral contraceptive use (never, ever), hormone replacement therapy use (never, ever), daily energy intake (kcal/day; continuous), alternate Mediterranean diet score excluding alcohol and nuts (0-2, 3-4, 5-7 points)

* indicates a significant association (p<0.05)

447 **Supplementary Table 1.** Multivariable-adjusted associations between total nut intake and ovarian
 448 cancer risk in strata of potential effect modifiers; NLCS, 1986-2006

	Total nut consumption (g/day)			<i>P</i> _{trend}	<i>P</i> _{interaction}
	0 g/day	0.1-<5 g/day	5+ g/day		
<i>Ovarian cancer</i>					
<i>Overall</i>					
Cases/person-time at risk (years)	158/11,388	117/10,817	72/7,034		
HR (95% CI) ^a	1.00 (reference)	0.79 (0.60-1.05)	0.78 (0.56-1.10)	0.258	
<i>Body mass index^b</i>					
18.5-<25 kg/m ²					
Cases/person-time at risk (years)	78/5,765	65/5,651	38/4,666		
HR (95% CI) ^a	1.00 (reference)	0.96 (0.65-1.42)	0.71 (0.45-1.13)	0.135	0.194
25+ kg/m ²					
Cases/person-time at risk (years)	80/5,389	51/5,095	32/2,309		
HR (95% CI) ^a	1.00 (reference)	0.61 (0.39-0.95)	0.85 (0.50-1.46)	0.869	
<i>Nonoccupational physical activity</i>					
≤30 min/day					
Cases/person-time at risk (years)	44/2,942	24/2,033	17/1,287		
HR (95% CI) ^a	1.00 (reference)	0.73 (0.38-1.38)	0.77 (0.37-1.57)	0.534	0.718
>30-≤60 min/day					
Cases/person-time at risk (years)	56/3,411	46/3,580	21/2,418		
HR (95% CI) ^a	1.00 (reference)	0.77 (0.47-1.26)	0.59 (0.32-1.10)	0.125	
>60-≤90 min/day					
Cases/person-time at risk (years)	34/2,633	27/2,720	22/1,657		
HR (95% CI) ^a	1.00 (reference)	0.69 (0.36-1.32)	0.95 (0.47-1.93)	0.827	
>90 min/day					
Cases/person-time at risk (years)	24/2,403	20/2,485	12/1,672		
HR (95% CI) ^a	1.00 (reference)	0.89 (0.42-1.91)	0.85 (0.35-2.06)	0.743	
<i>Cigarette smoking status</i>					

Never						
	Cases/person-time at risk (years)	103/7,077	82/6,612	39/3,677		
	HR (95% CI) ^a	1.00 (reference)	0.84 (0.59-1.19)	0.73 (0.47-1.13)	0.193	0.399
Former						
	Cases/person-time at risk (years)	27/1,744	19/2,444	17/2,008		
	HR (95% CI) ^a	1.00 (reference)	0.47 (0.22-0.99)	0.48 (0.21-1.08)	0.219	
Current						
	Cases/person-time at risk (years)	28/2,567	16/1,761	16/1,349		
	HR (95% CI) ^a	1.00 (reference)	0.94 (0.44-1.99)	1.53 (0.66-3.51)	0.283	
<i>Educational level</i>						
Low						
	Cases/person-time at risk (years)	87/6,909	60/5,730	41/3,156		
	HR (95% CI) ^a	1.00 (reference)	0.85 (0.58-1.26)	1.08 (0.67-1.73)	0.654	0.304
Medium						
	Cases/person-time at risk (years)	60/3,780	43/3,904	23/2,933		
	HR (95% CI) ^a	1.00 (reference)	0.62 (0.38-0.99)	0.47 (0.26-0.85)	0.031	
High						
	Cases/person-time at risk (years)	11/669	14/1,183	8/946		
	HR (95% CI) ^a	1.00 (reference)	2.38 (0.39-14.46)	0.92 (0.18-4.57)	0.583	
<i>Family history of breast cancer</i>						
No						
	Cases/person-time at risk (years)	147/10,472	107/9,679	66/6,527		
	HR (95% CI) ^a	1.00 (reference)	0.81 (0.60-1.10)	0.79 (0.56-1.12)	0.267	0.699
Yes						
	Cases/person-time at risk (years)	11/916	10/1,138	6/507		
	HR (95% CI) ^a	1.00 (reference)	0.53 (0.13-2.18)	0.83 (0.18-3.75)	0.960	
<i>Adapted Mediterranean diet score excluding nuts and alcohol</i>						
0-2 points						
	Cases/person-time at risk (years)	41/3,362	37/2,430	15/1,506		

	HR (95% CI) ^a	1.00 (reference)	1.36 (0.71-2.61)	0.75 (0.36-1.55)	0.299	0.165
3-4 points						
	Cases/person-time at risk (years)	82/5,625	56/5,199	33/3,306		
	HR (95% CI) ^a	1.00 (reference)	0.72 (0.48-1.08)	0.72 (0.44-1.18)	0.286	
5-7 points						
	Cases/person-time at risk (years)	35/2,401	24/3,188	24/2,223		
	HR (95% CI) ^a	1.00 (reference)	0.55 (0.29-1.04)	0.98 (0.47-2.01)	0.620	

449 ^a Adjusted for age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day;
450 continuous, centered), and duration (years; continuous, centered)), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m²),
451 nonoccupational physical activity (≤30, >30-60, >60-90, >90 min/day), educational level (low, medium, high),
452 family history of breast cancer (no, yes), age at menarche (years; continuous), age at menopause (years;
453 continuous), parity and age at first child birth (nulliparous, 1-2 children - <25 years, 1-2 children - ≥25 years, ≥3
454 children - <25 years, ≥3 children - ≥25 years), oral contraceptive use (never, ever), hormone replacement therapy
455 use (never, ever), daily energy intake (kcal/day; continuous), alternate Mediterranean diet score excluding
456 alcohol and nuts (0-2, 3-4, 5-7 points).

457 ^b Participants with a BMI <18.5 kg/m² (n = 25) were excluded from the interaction analysis.