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Family history of cancer in first degree relatives and risk of cancer of unknown primary

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Abstract

Objective: Cancer of Unknown Primary (CUP) refers to the presence of metastatic lesions, with no identifiable primary site during the patient's lifetime. Poor survival and lack of available treatment highlight the need to identify potential CUP risk factors. We investigated whether a family history of cancer is associated with increased CUP risk.

Methods: We performed a case cohort analysis using data from the Netherlands Cohort Study, which included a total of 963 CUP cases and 4,288 subcohort members. A Cox Proportional Hazards Regression was used to compare CUP risk in participants who reported to have a family member with cancer to those who did not, whilst adjusting for confounders.

Results: In general, we observed no increased CUP risk in those who reported a family history of cancer. CUP risk appeared slightly increased in those who reported cancer in a sibling (HR: 1.16, 95% CI: 0.97–1.38), especially in those with a sister with cancer compared with those without (HR: 1.23, 95% CI: 0.99–1.53), although these findings are not statistically significant.

Conclusion: Having a family history of cancer is not an independent risk factor of CUP.

KEYWORDS
Cancer of Unknown Primary (CUP), family history of cancer, prospective cohort study

1 | INTRODUCTION

Cancer of Unknown Primary (CUP) refers to the presence of metastatic lesions in a patient without an identifiable primary site (National Institute for Health and Care Excellence, 2010). Globally, CUP incidence has been decreasing. This decrease may be partly explained by improved imaging techniques and molecular investigation(s) used to identify primary tumour sites (E. Rassy & Pavlidis, 2019). It is difficult to determine the true international incidence and prevalence of CUP; centres define CUP differently, and definitions have varied over time within centres. Nevertheless, in the Netherlands, CUP accounted for approximately 1,300 patients in 2018 (Comprehensive Cancer Centre the Netherlands, 2020).

Despite advances in diagnostics leading to identification of primary sites in patients that would previously have been classified as CUP patients, the limited improvement in treatment means CUP remains difficult to treat. Therefore, the prognosis for most CUP patients is notoriously poor, with a median survival of around

2 months (Schroten-Loef et al., 2018). The limited opportunity for curative and life-prolonging treatment highlights the need for a preventative approach to managing CUP (E. Rassy et al., 2020). Such approaches require identification of risk factors as well as identification of people most at risk, which is challenging given that CUP aetiology studies are relatively understudied.

Demographic factors appear to be important for CUP risk, since increased CUP risks are seen both in women and with increasing age (Luke et al., 2008). Studies in younger patients demonstrate higher rates of CUP incidence in metropolitan areas with lower socioeconomic status. A higher prevalence of potential risk factors and reduced access to healthcare, and/or overdiagnosis of CUP as a result of poorer access to diagnostic facilities that specifically identify primary tumours could explain these findings (Pavlidis et al., 2020). Additionally, modifiable lifestyle-related risk factors have been highlighted as influential. For instance, CUP is associated with cigarette smoking (K. Hemminki, Chen, et al., 2015; Hermans et al., 2021; Kaaks et al., 2014; Vajdic et al., 2019). Similarly, alcohol consumption is also associated with CUP risk in a dose–response relationship (Hermans et al., 2021). A weaker association was found for waist circumference which was no longer statistically significant after adjusting for confounders (Kaaks et al., 2014).

Some evidence shows that CUP is associated with a multitude of pre-existing health conditions. In an Australian population, CUP patients were found to be more likely to suffer with diabetes and a pre-existing cancer diagnosis (Vajdic et al., 2019). This was also seen in a Swedish population where CUP was associated with diabetes and various autoimmune disorders (K. Hemminki, Försti, et al., 2016; K. Hemminki, Sundquist, et al., 2015).

The lack of studies that investigate the associations between CUP and modifiable and demographic characteristics makes it difficult to draw firm conclusions on which factors increase CUP risk. This is also the case for the possible familial aspects of CUP. The possible role of genetic susceptibility and shared environmental factors contributing to increase CUP risk is hinted at by the extensive evidence for clustering of cancer within families across anatomical sites (K. Hemminki et al., 2011; K. Hemminki et al., 2012; Zeegers et al., 2008).

This propensity for familial clustering also appears to be a trait of CUP, as familial clustering was demonstrated in a study using the Swedish Family Cancer Database, which found CUP patients were more likely to have a sibling with CUP. Moreover, patients who had a diagnosis of lung, liver, kidney, pancreatic, ovarian or colorectal cancer were also more likely to have a family member diagnosed with CUP. The same authors redemonstrated these associations using an updated version of the database (K. Hemminki et al., 2011; K. Hemminki, Sundquist, et al., 2016). This finding is supported by evidence from a nested case control study in a Utah population which similarly found an increased CUP risk, as well as increased risk of lung and pancreatic cancer, myeloma and non-Hodgkin lymphoma in family members of CUP patients compared with relatives of population controls without CUP (Samadder et al., 2016). K. Hemminki et al. (2012) examined the association between the anatomical site of cancer in a family member and the risk of metastasis of CUP at that same site. The strongest significant associations were seen for lung, pancreatic and ovarian cancer, suggesting that the location of the hidden primary in CUP patients may coincide with the anatomical site of cancer in their family members (K. Hemminki et al., 2012).

These findings imply that CUP may have a familial component, yet the number of studies is small, and the studies are limited in terms of variety of populations and the study designs applied. Therefore, in the present study, we examined the association between cancer in family members (both overall and in specific relatives) and CUP risk as well as the association between cancer in family members at specific anatomical sites and CUP risk. In order to do so, we formulated the following research questions: (1) what is the association between a family history of any cancer in first degree relatives and CUP risk? And (2) what is the association between a family history of cancer in first degree relatives at specific anatomical sites and CUP risk?

2 | METHODS

2.1 | Design and study population

The NLCS is a prospective cohort study which started in 1986. Its primary aim was to investigate associations between diet and cancer. The design and methods used in the NLCS are described in detail elsewhere (P.A. van den Brandt, Goldbohm, et al., 1990). A total of 120,852 participants aged 55–69 were sampled from 204 Dutch municipalities. Key demographic variables were extracted from municipal population registries. Participants were asked to complete a baseline questionnaire which entailed detailed information regarding diet and other cancer-related risk factors. The case-cohort design was applied for increased efficiency of data processing and analyses. Therefore, a subcohort of 5,000 participants was used to estimate both the person-years at risk accumulated and the characteristics of the full cohort. The subcohort comprises a randomly selected group of participants at baseline, in whom CUP cases can occur (Barlow et al., 1999). Participants with a prevalent diagnosis of cancer at recruitment were excluded, unless that diagnosis was skin cancer.

2.2 | Outcome measure

For this study, CUP cases are patients with either a histologically and/or cytologically confirmed epithelial malignancy with no identifiable primary site during the patient's lifetime (ICD-O-3: M-8000–M8570). With the focus on epithelial malignancies, CUP cases who had a histology of sarcomas, lymphomas, mesotheliomas and melanomas were not considered.

2.3 | Follow-up

CUP cases were identified from the total cohort of the NLCS during a follow up period of 20.3 years using record linkage to the Netherlands

Cancer Registry (NCR) and the Dutch Pathology Registry (PALGA; P.A. van den Brandt, Schouten, et al., 1990). A total of 963 CUP cases and 4,288 subcohort members were available for analyses after excluding participants with missing data for variables used in the multivariable model.

2.4 | Questionnaire data

Data were obtained through a self-administered questionnaire that included detailed questions on dietary information and other cancer risk factors such as smoking, alcohol consumption, history of cancer and comorbidities. With respect to family history of cancer, participants were asked whether they had a brother, sister or parent who had cancer. Participants who responded yes were then asked to document the relative affected, the type of cancer, the age at diagnosis and the relative's current age or age of death if applicable. Participants were asked to give information about the number of siblings they had and, if applicable, their year and cause of death. The questionnaire also included questions on smoking behaviour, which was measured based on smoking status (never, former or current smokers), smoking duration (number of years) and smoking frequency (cigarettes per day). The questionnaire also addressed alcohol consumption, most notably the number of alcoholic drinks that had been consumed in the previous week (in glasses), which represented average alcohol consumption in 10 g/day increments. BMI (kg/m^2) was calculated using self-reported height (cm) and weight (kg) at baseline. Participants were asked to state their highest level of education achieved, to represent socioeconomic status. Diabetes status was asked to indicate whether the participant had self-reported a doctor's diagnosis of diabetes in the questionnaire. For non-occupational physical activity (gardening, cycling and walking, and sports/physical exercise), participants could report their activity value, which was summed into a total non-occupational physical activity value.

2.5 | Statistical analysis

Characteristics of CUP cases and subcohort members were compared based on the variables of interest. Frequencies and percentages were used for categorical variables, with means and standard deviations for continuous variables. Cox Proportional Hazards Regression was used for case-cohort analyses. Cases were derived from the full cohort, and the person-time-at-risk for the cohort was calculated using the subcohort. CUP risk was modelled against a family history of cancer to produce hazard ratios (HRs) and 95% confidence intervals (CIs). CUP risk was assessed in participants with any first degree relative with cancer, specifically in siblings or parents as well as discordant anatomical sites. To perform such analyses, three variables were created. The first binary variable compared participants with at least one family member (either a sibling or parent) with cancer to participants with no reported family members with cancer. A binary variable was created to represent specific first-degree relatives including brothers, sisters, fathers and mothers individually. A separate variable was created both for brothers and sisters to account for the difference in biological sex, a factor which has been demonstrated to influence CUP risk. Similarly, a binary variable was used to compare participants with at least one parent affected with cancer against participants with no parents affected. The CUP risk in participants who reported a family history of cancer at specific sites was also analysed. This analysis was done for breast, ovarian, endometrial, bowel, stomach, lung, kidney, prostate, bladder, pancreas, head and neck, leukaemia and lymphoma, as it has been shown that family members of patients with such cancers are at an increased CUP risk. Here, binary variables were used to indicate presence or absence of this cancer in the family history.

Age, sex, smoking and alcohol consumption were considered as predefined confounders and were used in all statistical models, as these factors have been demonstrated to be associated with CUP (K. Hemminki, Chen, et al., 2015; Hermans et al., 2021; Kaaks et al., 2014; Vajdic et al., 2019). Potential confounders (BMI, socio-economic status, physical activity and diabetes status) were evaluated using the backward elimination procedure. A variable was considered a confounder if it introduced a greater than 10% change in the HRs once it was removed. Accordingly, none of the potential confounders were included in the final model. Once the variables and interaction terms had been established, CUP was modelled against family history of cancer overall, in siblings and in parents separately. Lastly, CUP was modelled against family history of cancer in discordant anatomical sites of the family members. Scaled Schoenfeld residuals were used to test for the proportional hazards assumption (Lin & Wei, 1989). Log minus log plots were visually inspected for confirmation. If the assumption was deemed to be violated, this was managed by including a time varying covariate (TVC) for the variable at which the violation occurred. Consequently, we added a TVC for age in the age-sex adjusted analysis and for cigarette smoking status and cigarette smoking duration in multivariable analyses. Standard errors were calculated using the robust Huber-White sandwich estimator to account for additional variance introduced by sampling from the full cohort. The Wald test was used to test for multiplicative interaction between age and family history of cancer, sex and family history of cancer and smoking and family history of cancer. All analyses were conducted using the sixteenth edition of Stata. *P* values below 0.05 indicate statistical significance.

A sensitivity analysis was performed by restricting the analysis to the histologically verified cases of CUP only, as these participants were more likely to have undergone extensive diagnostic investigations before a diagnosis was made. Also, these participants were more likely to meet to more stringent CUP case definitions, such as those given by NICE (National Institute for Health and Care Excellence, 2010). CUP cases that had been confirmed cytologically but not histologically were excluded from this part of the analysis.

3 | RESULTS

A total of 963 CUP cases and 4,288 subcohort members were available in our multivariable models. The majority of CUP cases were male

(62.6%), which differs substantially from the distribution seen in the subcohort (49.2%; see Table 1). On average, cases were a year older than subcohort members (62 years old and 61 years old, respectively). A greater proportion of cases were current cigarette smokers (37.8%) compared with the subcohort (27.6%). A greater frequency and duration of cigarette smoking were seen among smokers in cases compared with smokers in the subcohort. Average alcohol consumption (in grammes) was also higher in cases compared with the subcohort, with 14 and 10 g consumed per day, respectively. A slightly higher proportion of cases reported a family history of cancer in at least one first degree relative (47.7%) compared with the subcohort (45.4%).

Participants who had at least one family member with a history of cancer were not at an increased CUP risk (multivariable adjusted HR: 1.10, 95% CI: 0.95–1.27) compared with participants without (see Table 2). An age-stratified analysis was conducted to obtain age category specific hazard ratios. CUP risk was slightly increased in those

TABLE 1 General characteristics of Cancer of Unknown Primary cases and subcohort members in the Netherlands Cohort Study

	Subcohort members ($n = 4,288$)		Cancer of unknown primary cases ($n = 963$)	
Exposure variables and potential confounders	***n***	**(%)**	***n***	**(%)**
Age at baseline (years)				
55–59	1,164	38.8	288	29.9
60–64	1,461	34.1	372	38.6
65–69	1,163	27.1	303	31.5
Sex				
Male	2,110	49.2	603	62.6
Female	2,178	50.8	360	37.4
Family history of cancer				
Yes	1,945	45.4	459	47.7
Cigarette smoking status				
Never smokers	1,584	36.9	265	27.5
Ex-smokers	1,521	35.5	334	34.7
Current smokers	1,183	27.6	364	37.8
Frequency of cigarette smoking (N/day), mean (SD)[a]	15.7 (10.1)		17.8 (10.4)	
Duration of cigarette smoking (years), mean (SD)[a]	31.9 (12.1)		35.6 (11.6)	
Ethanol intake (grams/day)[b]				
Abstainers	1,024	23.9	186	19.3
<5	1,228	28.6	247	25.7
5- < 15	979	22.8	217	22.5
15 ≤ 30	672	15.7	153	15.9
≥30	385	9.0	160	16.6
BMI (kg/m^2) at baseline, mean (SD)	25.0 (3.1)		25.0 (3.0)	
Non-occupational physical activity (min/day)				
≤30	908	21.5	204	21.5
>30–60	1,318	31.2	291	30.6
>60–90	879	20.8	170	17.9
>90	1,122	26.5	285	30.0
Level of education (years of education)				
Primary	1,257	29.5	271	28.5
Lower vocational	937	22.0	204	21.4
Secondary and medium vocational	1,483	34.8	341	35.8
University and higher vocational	590	13.8	136	14.3
Diabetes				
Yes	153	3.6	39	4.1

[a]In users only.
[b]In consumers only.

aged 60–64 years old (multivariable adjusted HR: 1.27, 95% CI: 1.01–1.61) with a family history of cancer in any relative compared with participants of the same age with no family history of cancer. In terms of siblings and parents, a slightly increased CUP risk was observed in participants with at least one sibling with a history of cancer (multivariable adjusted HR: 1.16, 95% CI: 0.97–1.38) compared with those without, though this was not statistically significant. Multivariable adjusted estimates for parents did not reveal a significant association (HR: 1.02, 95% CI: 0.88–1.19). When mutually adjusting for both siblings and parents, these estimates did not change notably, compared with sibling and parent only analyses. We further adjusted for the number of brothers and sisters the participants had, but this did not alter estimates either. With respect to specific first-degree relatives, a slightly increased CUP risk was observed in participants with a family history of cancer in a sister (multivariable adjusted HR: 1.23, 95% CI: 0.99–1.53), though this was not statistically significant. No association was found in those with a brother with a family history of cancer. Similarly, CUP risk was not increased in those with a family history of cancer in a father compared with those without nor was the risk increased in those with a family history of cancer in a mother.

TABLE 2 Hazard ratios and 95% confidence intervals for Cancer of Unknown Primary risk in participants with family history of cancer in specific relatives in the Netherlands Cohort Study

	Subcohort members	Cancer of unknown primary cases				
		Cases	Age and sex adjusted[a]		Multivariable adjusted[b]	
First degree relative	Person time at risk (years)	*n*	HR	95% CI	HR	95% CI
Age at baseline (all ages)						
No	39,347	504	1	Reference	1	Reference
Yes	32,995	459	1.09	(0.94–1.26)	1.10	(0.95–1.27)
Age at baseline (ages 55–59)						
No	16,773	149	1	Reference	1	Reference
Yes	13,552	139	1.17	(0.91–1.50)	1.18	(0.91–1.52)
Age at baseline (ages 60–64)						
No	13,468	184	1	Reference	1	Reference
Yes	10,919	188	1.27	(1.00–1.60)	1.27	(1.01–1.61)
Age at baseline (ages 65–69)						
No	9,106	171	1	Reference	1	Reference
Yes	8,524	132	0.85	(0.66–1.11)	0.87	(0.67–1.13)
Siblings						
No	58,179	744	1	Reference	1	Reference
Yes	14,163	219	1.17	(0.99–1.40)	1.16	(0.97–1.38)
Parents						
No	48,397	648	1	Reference	1	Reference
Yes	23,945	315	1.00	(0.86–1.17)	1.02	(0.88–1.19)
Sisters						
No	64,138	828	1	Reference	1	Reference
Yes	8,204	135	1.24	(1.00–1.54)	1.23	(0.99–1.53)
Brothers						
No	65,049	852	1	Reference	1	Reference
Yes	7,293	111	1.10	(0.88–1.38)	1.07	(0.85–1.35)
Mothers						
No	60,069	797	1	Reference	1	Reference
Yes	12,273	166	1.01	(0.83–1.22)	1.04	(0.86–1.26)
Fathers						
No	58,135	774	1	Reference	1	Reference
Yes	14,207	189	1.03	(0.86–1.23)	1.04	(0.87–1.25)

[a]Analyses were adjusted for age at baseline (years) and sex, and age as a time-varying covariate.
[b]Multivariable analyses were adjusted for age at baseline (years), sex, alcohol consumption (g ethanol/day), current cigarette smoking, cigarette smoking frequency (N/day; continuous; centred), cigarette smoking duration (years; continuous; centred), and cigarette smoking status (never/ever), cigarette smoking duration (continuous; centred) as time-varying covariates.

TABLE 3 Hazard ratios and 95% confidence intervals for Cancer of Unknown Primary risk in participants with family history of cancer in specific relatives and specific sites in those relatives in the Netherlands Cohort Study

	Subcohort members	Cancer of unknown primary cases				
		Cases	Age and sex adjusted[a]		Multivariable adjusted[b]	
Cancer site in family member	Person time at risk (years)	*n*	HR	95% CI	HR	95% CI
Breast						
No	66,211	871	1	Reference	1	Reference
Yes	6,131	92	1.13	(0.88–1.44)	1.15	(0.90–1.48)
Ovarian						
No	72,258	960	1	Reference	1	Reference
Yes	84	3	2.50	(0.57–10.86)	2.01	(0.36–11.38)
Uterine						
No	70,497	938	1	Reference	1	Reference
Yes	1,845	25	1.00	(0.64–1.58)	1.05	(0.67–1.67)
Bowel						
No	68,233	899	1	Reference	1	Reference
Yes	4,109	64	1.15	(0.86–1.54)	1.18	(0.88–1.59)
Stomach						
No	67,559	889	1	Reference	1	Reference
Yes	4,783	74	1.11	(0.84–1.46)	1.14	(0.87–1.51)
Lung						
No	65,336	880	1	Reference	1	Reference
Yes	7,006	83	0.90	(0.70–1.16)	0.89	(0.69–1.15)
Kidney						
No	71,517	960	1	Reference	1	Reference
Yes	825	3	0.29	(0.09–0.95)	0.27	(0.08–0.90)
Prostate						
No	70,687	938	1	Reference	1	Reference
Yes	1,655	25	1.13	(0.72–1.78)	1.20	(0.76–1.89)
Bladder						
No	71,555	951	1	Reference	1	Reference
Yes	787	12	1.14	(0.60–2.17)	1.17	(0.61–2.26)
Pancreas						
No	71,639	951	1	Reference	1	Reference
Yes	703	12	1.45	(0.76–2.75)	1.38	(0.72–2.66)
Head and neck						
No	71,025	948	1	Reference	1	Reference
Yes	1,317	15	0.83	(0.47–1.47)	0.81	(0.45–1.44)
Leukaemia						
No	70,260	937	1	Reference	1	Reference
Yes	2,082	26	0.98	(0.64–1.52)	0.99	(0.64–1.55)
Lymphoma						
No	71,706	958	1	Reference	1	Reference
Yes	636	5	0.59	(0.23–1.52)	0.59	(0.23–1.55)

[a]Analyses were adjusted for age at baseline (years) and sex, and age as a time-varying covariate.
[b]Multivariable analyses were adjusted for age at baseline (years), sex, alcohol consumption (g ethanol/day), current cigarette smoking, cigarette smoking frequency (N/day; continuous; centred), cigarette smoking duration (years; continuous; centred), and cigarette smoking status (never/ever), cigarette smoking duration (continuous; centred) as time-varying covariates.

CUP was not associated with family history of cancer of breast, ovarian, endometrial, bowel, stomach, lung, prostate, bladder, pancreas, head and neck, lymphoma and/or leukaemia (see Table 3). However, CUP risk appeared to be reduced in those who reported a family history of kidney cancer (multivariable adjusted HR: 0.27, 95% CI: 0.08–0.90), though only three CUP cases reported a family history of kidney cancer.

A total of 687 CUP cases and 4,288 subcohort members were available when the analysis was restricted to histologically verified cases alone. The results of this analysis did not differ markedly from the unrestricted analyses with the exception of the association seen for kidney cancer (data not shown). For kidney cancer, CUP risk remained to be reduced, but it was no longer statistically significant. No multiplicative interaction was detected between age and family history of cancer, between sex and family history of cancer, nor between smoking status and family history of cancer.

4 | DISCUSSION

In this prospective cohort study, having a family history of cancer is not an independent risk factor of CUP. The only consistent association observed was a moderately increased CUP risk in participants who reported a sibling with cancer compared with those who did not. An increased CUP risk was also found in sisters with cancer. However, the association seen for both siblings and sisters was not statistically significant.

Previous studies have investigated CUP risk in relatives of the proband whilst this study has investigated risk in the proband. A cohort study using the Swedish Family-Cancer Database examined CUP risk in family members of patients with various cancers. It demonstrated that people with kidney, lung and colorectal cancers had higher CUP risks in relatives (K. Hemminki et al., 2011). This association was stronger for siblings than for parents. This evidence was supported by similar results when the study was repeated using an updated version of the database by the same authors (K. Hemminki et al., 2011; K. Hemminki, Sundquist, et al., 2016). Similarly, a nested case control study of an American population (Utah) found an elevated CUP risk in family members of lung, pancreatic, myeloma and non-Hodgkin lymphoma patients compared with relatives of population controls without CUP (Samadder et al., 2016). These three studies were, however, unable to adjust for confounders. To provide further evidence and examination of the family history-CUP association, we investigated whether this association is present in the opposite direction to previous investigations (K. Hemminki et al., 2011; K. Hemminki, Sundquist, et al., 2016; Kaaks et al., 2014; Samadder et al., 2016), by assessing whether CUP risk is increased by the presence of cancer in family members. Extrapolating from the associations seen in these previous studies, we expected CUP risk to be elevated in those with a family history of cancer compared with those without, particularly at the specific cancer sites mentioned above. We observed slightly increased CUP risk in those who reported a sibling with any cancer, but not in parents. This association appears to be accounted for by the increased CUP risk that we observed in participants who reported to have sisters with a diagnosis of cancer compared with participants who did not. In general, the association appears to be comparable with evidence from the Swedish cohort study, in which an increased CUP risk was observed in siblings of patients with cancer at many different anatomical sites. Associations between siblings partly point towards lifestyle-related factors, such as smoking behaviour and alcohol consumption, which may be more similar between siblings, rather than between parents and children.

The findings of the NLCS are inconsistent with the considerable associations observed between CUP risk and discordant cancer sites in previous studies (K. Hemminki et al., 2011; K. Hemminki, Sundquist, et al., 2016; Samadder et al., 2016). We found that only kidney cancer appeared to be associated with lower CUP risk; however, only three CUP cases were available for analysis, so it is likely to be a chance finding. Previous associations observed between CUP and family history may possibly be explained by the general tendency for cancers of varying and discordant sites to cluster within families, rather than the family history itself directly increasing CUP risk. The most consistent association we observed was a marginally increased CUP risk in those with a sister with any cancer compared with those without sisters with cancer. The risk was moderately increased in age-sex adjusted models and multivariable adjusted models, and it remained statistically significant when restricting to histologically confirmed CUP cases. This finding may suggest that CUP is associated with cancers that occur in females, such as breast, uterine and ovarian cancer. However, we observed no associations between CUP and these cancers, so it is unlikely that the association seen in sisters is explained by female specific cancers. Instead, it is more likely that the association can be explained by sex specific excesses at other cancer sites such as lung cancer.

The strengths of this study lie in its prospective design, large cohort size and high number of CUP cases available for analyses (compared with previous studies). Moreover, the data obtained from the NCR ensured that CUP cases were uniformly recorded and coded by trained registry clerks. Our study offers one particular advantage over previous studies, in that we were able to adjust for multiple confounders when estimating CUP risk. Addressing these confounders is essential as these lifestyle-related factors (such as smoking and alcohol consumption) may modulate CUP risk, which could explain the marked associations in the Swedish studies. However, it should be noted that their methods to establish a participant's family history of cancer status may be more valid than those used in our study, as they were able to use the same registry to identify CUP cases and cancer in the family (K. Hemminki et al., 2011; K. Hemminki, Sundquist, et al., 2016). Furthermore, the use of a one-time measurement of presence of family history of cancer at baseline may lead to non-differential misclassification of the participant's exposure status; participants may not report a family history of cancer at baseline, yet they may have family members diagnosed with cancer during the course of

the follow-up. This misclassification may be augmented by the use of a questionnaire, relying on recall and close family ties, especially without verification of documented diagnoses in family members as in this study. This problem is likely to be increased if participants were asked to recall more specific details regarding the cancer site; it is easier for participants to recall whether their family members had cancer or not, rather than recall whether it was ovarian cancer or metastatic cancer (Schrijvers et al., 1994).

It has previously been highlighted that some familial cancers have a tendency for a younger age of diagnosis, and it is possible that any familial mechanism in CUP may present a similar pattern (K. Hemminki et al., 2011). This finding may explain the slightly higher estimates we observed between a family history of cancer and age. With our dataset being composed of those between the ages of 55–69, whilst CUP can occur at younger ages, it is possible that CUP cases where family history played a more prominent role might not have been available in our study population. Therefore, it remains highly plausible that this unavailability markedly reduced associations between family history and CUP in the NLCS.

To the best of our knowledge, this study is the first to have examined whether the presence of cancer in a person's family history affects their CUP risk. We thus provide new evidence to help uncover the role of familial aspects in CUP development. Within this cohort, having a family history of cancer is not an independent risk factor of CUP. In light of our findings, we suggest caution be employed when attempting to draw conclusions as to whether a family history of cancer increases CUP risk.

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CONFLICT OF INTEREST

There are no conflicting interests in this study.

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DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are not publicly available because the informed consent does not allow for that. However, anonymous data that are minimally required to replicate the outcomes of the study will be made available upon reasonable request and approval by the institutional review boards.

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