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ORIGINAL PAPER

Eye color and the risk of skin cancer

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Abstract

Melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common skin cancers. The incidence rates of all three types of skin cancers have increased in the past three decades. Light pigmentary traits have been recognized as one of the host risk factors for skin cancer, but findings on associations between eye colors and risk of skin cancers have been inconsistent.

We performed a prospective analysis to examine the association between eye colors and risk of skin cancers using the Health Professionals Follow-up Study (HPFS). Cox proportional hazard models were applied to estimate relative risks (RRs) and their 95% confidence intervals (CIs). Effect modifications due to hair color and skin reaction to sun were also examined.

The HPFS included 35,662 males. During a median follow-up of 19 years (1988–2012), 445 melanoma, 1123 SCC, and 7198 BCC cases were documented. Compared to those whose eye colors were dark or brown, participants with hazel/green/medium and blue/light colors had a 24% (RR = 1.24, 95% CI: 1.06–1.45) and a 19% (RR = 1.19, 95% CI: 1.01–1.41) higher risk of SCC, respectively. Similarly, a higher risk of BCC was observed in participants with hazel/green/medium eye colors (RR = 1.16, 95% CI: 1.09–1.23) and blue/light eye colors (RR = 1.17, 95% CI: 1.10–1.25). We did not find significant associations between eye color and risk of melanoma. Lighter eye color was associated with increased risks of SCC and BCC among those with dark hair colors (p for interaction ≤ 0.02).

In conclusion, in this large prospective study of men, we found that light eye colors were associated with higher risks of SCC and BCC, but not melanoma. Further studies are needed to confirm this association in other populations.

Keywords Melanoma skin cancer · Nonmelanoma skin cancer · Eye color · Pigmentation

Background

Skin cancer is one of the most common malignancies worldwide, especially in the white population [1]. Melanoma is the most malignant type of skin cancer, causing more than 70% of skin cancer deaths despite an improved survival rate after the introduction of new therapies [2]. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common subtypes of non-melanoma skin cancer and greatly burden health management due to their high incidence and recurrence rates [3]. Incidence rates of melanoma and non-melanoma skin cancer have increased worldwide during the past three decades [4]. Lighter pigmentary traits (lighter hair, lighter skin, and severe skin reaction after sun exposure) have been linked to increased risk for skin cancers [5–8]. However, studies on the association between eye color and risk of skin cancer have been less consistent [5, 8–16]. The lack of concordance in the literature regarding the associations between eye color and skin cancer may partially be due to small sample sizes, or to the drawbacks of case–control study designs such as selection bias. Also, few studies exist on eye color and risks of SCC and BCC.

The genes coding eye color are at least partially different from those for skin and hair color [17, 18]. How the human pigmentation phenotype is determined and how it varies are

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not yet well understood, but it has been suggested that the type and amount of melanin in skin, hair, and eyes are the result of interactions of many genes [19–21]. To date, one of the best-established genes related to hair and skin color is melanocortin-1 receptor (MC1R) gene [22]. Genes such as ASIP, IRF4, SLC24A4, SLC24A5, TPCN2, TYR, and TYRP1 are also involved in human pigmentation [19, 22, 23]. Genetic studies have proposed that the effect of MC1R on pigmentation phenotypes has notable interactions with the OCA2 gene, which is known as an eye color-associated gene [17, 19, 24]. These findings suggest that even within populations with lighter eye colors, such as blue or green/hazel eyes, skin cancer risk may vary due to the potential effect modifications of other factors. Thus, it may be problematic to treat lighter pigmentation traits as one homogeneous risk category when evaluating risk of skin cancers.

Therefore, we aimed to prospectively examine the associations between eye color and incidence of melanoma, BCC and SCC, as well as potential interactions with hair color and skin reaction to the sun. We hypothesized that 1) participants with light eye color have higher risks of skin cancers 2) people with lighter hair color, lighter eye color, and worse skin reaction to the sun have higher risks of skin cancers.

Methods

Study population

The Health Professionals Follow-up Study (HPFS) started in 1986 with the aim of evaluating risk factors, especially nutritional factors, in relation to diseases such as cancer and cardiovascular disease. The HPFS included 51,529 male health professionals aged between 40 and 75 years, who completed a baseline questionnaire regarding medical history and lifestyle. Detailed information on the HPFS cohort has been published elsewhere [25]. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. In this study, we excluded men whose eye color information was missing and who had skin cancers before baseline, leaving a total of 35,662 participants for data analysis.

Exposures assessment

Information on eye color was collected from the 1988 HPFS questionnaire from the following question "which of the following categories most closely describes the color of your eyes (brown/dark, hazel/green/medium, or blue/light)?".

Identification of outcomes

Information on melanoma, SCC and BCC diagnoses was extracted from biannual follow-up questionnaires. Medical and pathological reports for SCC and melanoma were reviewed by physicians to confirm the diagnosis. Invasive melanoma and SCC cases included in this study including tumors on mucosa sites. Self-report records were used for BCC, as previous validations studies have demonstrated that the accuracy of self-reported BCCs reach 90% when confirmed with histopathology records [26]. Deaths were identified via systematic searches of the National Death Index, or reported by the participants' family members, coworkers, or postal authorities.

Covariates

Covariates were determined based on previous literature, which included age (continuous), family history of melanoma, smoking status (never, past with < 10, 10–20, 20–40, > 40, or unknown pack-years, current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, ≥ 20.0 g/day), body mass index (< 18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥ 35 [calculated as weight in kilograms divided by height in meters squared]), ultraviolet B (UVB) radiation exposure at residence, skin reaction to the sun (tan, burn then tan, peel), number of lifetime severe sunburns (0, 1–2, 3–5, or ≥ 6), number of moles on upper extremities (0,1–2, 3–5, or ≥ 6), and natural hair color (red/ blonde, light brown, dark brown or black). UVB exposure was assessed by calculating the average July ambient erythemal UVB radiation at each participant's residence using the area-to-point kriging method [27].

Statistical analysis

Person-year was measured from the completion of the 1988 questionnaire to the date of first skin cancers diagnosis, loss to follow-up, death, or the end of follow-up (January 2012), whichever occurred first.

Cox proportional hazard models were applied to estimate the associations between eye color with risk of melanoma, BCC, and SCC. Relative risks (RRs) and corresponding 95% confidence intervals (CIs) were reported. The statistical models were stratified by age in months and biennial questionnaire cycle. Models were additionally adjusted for covariates including family history of melanoma, smoking status, alcohol intake, body mass index, UVB exposure at residence, number of severe sunburns in lifetime, skin reaction to the sun, number of moles on upper extremities, and natural hair color.

Effect modifications due to hair color and skin reaction to the sun were assessed by including interaction terms between eye color and hair color and between eye color and skin reaction to sun one at a time in the multi-variable adjusted model. Stratified analysis by hair color and by skin reaction to the sun was then performed separately. We also evaluated the interaction between eye color and melanoma Breslow thickness in relation to melanoma death among participants with melanoma, utilizing the widely accepted clinical cutoff of 1 mm [28]. We performed three-way interaction analyses for skin reaction to sun, hair color and eye color in relation to skin cancer. We also evaluated the association between eye color and melanoma and SCC by body location of the tumor based on sun exposure patterns (high vs. low sun exposure sites). In the analyses, the occurrence of tumors on the other sites were censored at the time of diagnosis.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina) using by 2-tailed statistical tests. A P value < 0.05 was considered as statistically significant.

Results

During a median of 19 years of follow up, 445 melanoma, 1123 SCC and 7198 BCC cases were documented. The distribution of baseline characteristics by eye color is shown in Table 1. Participants with blue/light eyes were more likely to have red/blonde hair and to be current smokers, to consume more alcohol, and to have a worse skin reaction to sun.

In an age-adjusted analysis, blue/light eye-colored individuals had higher risk of melanoma in comparison to those with brown/dark eyes (RR = 1.43, 95% CI: 1.13–1.80) (Table 2). However, the association attenuated and was no longer significant after adjusting for other covariates. Compared to those whose eye colors were brown/dark, participants with hazel/green/medium and blue/light eyes had 24% (RR = 1.24, 95% CI: 1.06–1.45) and 19% (RR = 1.19, 95% CI: 1.01–1.41) higher risk of SCC, respectively. Similarly, higher risk of BCC was observed in participants with hazel/green eyes (RR = 1.16, 95% CI: 1.09–1.23) and blue/light eyes (RR = 1.17, 95% CI: 1.10–1.25), respectively.

When we evaluated eye color with hair color using a common reference group of those with dark hair and eye colors, the risks of all three skin cancers were elevated in other hair and eye color combinations, although not all of the RRs were statistically significant (Table 3). Those who had red/blond hair and brown/dark eyes had the highest risk of melanoma (RR = 2.57, 95% CI: 1.32–5.00). For SCC, participants with red/blonde hair and hazel/green/medium eyes had the highest risk of SCC, with a RR of 1.78 (95% CI: 1.34–2.36; p for interaction = 0.003). Similarly, for BCC, participants with red/blonde hair and hazel/green/medium eyes had the highest risk, with a RR of 1.41 (95% CI: 1.25–1.60; p for interaction = 0.02). The interaction between hair color and

Table 1 Baseline Characteristics of Study Participants According to Eye Color in the HPFS, 1988

Characteristics [a]	Eye color		
	Brown/dark	Hazel/green/medium	Blue/light
No. of participants	11,722	11,457	12,483
Age, mean (SD), years [b]	56.6 (9.8)	56.3 (9.7)	56.8 (9.8)
Family history of melanoma, %	2.9	3.9	3.6
Current smoker, %	8.5	8.8	9.3
Alcohol intake, mean (SD), g/d	11.1 (15.4)	12.0 (16.2)	12.7 (16.9)
BMI, mean (SD), kg/m^2	25.6 (3.2)	25.5 (3.1)	25.5 (3.2)
Ultraviolet radiation exposure at residence, mean (SD), mW m^{-2}	189.6 (27.3)	192.6 (27.9)	192.4 (27.4)
Hair color			
Dark brown/black, %	49.1	17.5	8.1
Light brown, %	30.7	35.8	28.3
Red/blonde, %	20.1	46.6	63.5
Burn or blistering skin reaction to the sun, %	27.7	37.0	40.1
History of ≥ 6 severe or blistering sunburns, %	58.5	72.5	79.2
≥ 6 Moles on the upper extremities (> 3 mm), %	5.0	5.2	6.0

HPFS: Health Professionals Follow-up Study; *BMI*: body mass index (calculated as weight in kilograms divided by height in meters squared)

[a]HPFS only includes male participants. Data are standardized to the age distribution of the study population

[b]Values are not age adjusted

Table 2 Relative Risks (95% CIs) of Skin Cancers by Eye Color in the HPFS

Skin Cancer/Eye color	No. of cases	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI) [a]
Melanoma			
Brown/dark	125	1.00	1.00
Hazel/green/medium	140	1.22 (0.95–1.55)	0.96 (0.75–1.24)
Blue/light	180	1.43 (1.13–1.80)	0.99 (0.77–1.29)
SCC			
Brown/dark	302	1.00	1.00
Hazel/green/medium	389	1.40 (1.20–1.63)	1.24 (1.06–1.45)
Blue/light	432	1.45 (1.25–1.68)	1.19 (1.01–1.41)
BCC			
Brown/dark	2053	1.00	1.00
Hazel/green/medium	2399	1.25 (1.18–1.33)	1.16 (1.09–1.23)
Blue/light	2746	1.33 (1.26–1.41)	1.17 (1.10–1.25)

HPFS: Health Professionals Follow-up Study; *Cis:* confidence intervals; *BCC:* basal cell carcinoma; *SCC:* squamous cell carcinoma

[a]HPFS only includes male participants. Multivariate models were adjusted for age (continuous), family history of melanoma, smoking status (never; past with < 10, 10–20, 20–40, > 40, or unknown pack-years; current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, ≥ 20.0 g/day), body mass index (< 18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥ 35 kg/m^2), UVB exposure at residence (quintiles), number of lifetime severe sunburns (0, 1–2, 3–5, or ≥ 6), skin reaction to sun (tan, burn then tan, burn then peel), number of moles on the upper extremities (0,1–2, 3–5, or ≥ 6), natural hair color (red/blonde, light brown, dark brown/black)

Table 3 Relative Risks (95% CIs) of Skin Cancers by Eye Color and Hair Color in the HPFS

Hair color							
	Dark brown/black		Light brown		Red/blonde		P for interaction
Eye color	No. of cases	Multivariable-adjusted RR (95% CI)[a]	No. of cases	Multivariable-adjusted RR (95% CI)[a]	No. of cases	Multivariable-adjusted RR (95% CI)[a]	
Melanoma							0.48
Brown/dark	81	1.00	33	1.62 (1.07–2.45)	11	2.57 (1.32–5.00)	
Hazel/green/medium	70	1.28 (0.92–1.77)	52	1.17 (0.82–1.67)	18	1.31 (0.77–2.21)	
Blue/light	40	1.03 (0.70–1.51)	81	1.42 (1.03–1.95)	59	1.67 (1.17–2.38)	
SCC							0.003
Brown/dark	224	1.00	60	1.12 (0.83–1.49)	18	1.58 (0.96–2.58)	
Hazel/green/medium	174	1.19 (0.97–1.46)	148	1.35 (1.09–1.68)	67	1.78 (1.34–2.36)	
Blue/light	135	1.38 (1.11–1.72)	190	1.33 (1.09–1.63)	107	1.21 (0.95–1.53)	
BCC							0.02
Brown/dark	1561	1.00	408	1.14 (1.02–1.28)	84	1.17 (0.93–1.46)	
Hazel/green/medium	1152	1.17 (1.08–1.26)	912	1.25 (1.15–1.36)	335	1.41 (1.25–1.60)	
Blue/light	781	1.21 (1.11–1.32)	1243	1.31 (1.21–1.41)	722	1.30 (1.19–1.43)	

HPFS: Health Professionals Follow-up Study; *Cis:* confidence intervals; *BCC:* basal cell carcinoma; *SCC:* squamous cell carcinoma

[a]HPFS only includes male participants. Multivariate models were adjusted for age (continuous), family history of melanoma, smoking status (never; past with < 10, 10–20, 20–40, > 40, or unknown pack-years; current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, ≥ 20.0 g/day), body mass index (< 18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥ 35 kg/m^2), UVB exposure at residence (quintiles), number of lifetime severe sunburns (0, 1–2, 3–5, or ≥ 6), skin reaction to sun (tan, burn then tan, burn then peel), and number of moles on the upper extremities (0,1–2, 3–5, or ≥ 6)

Table 4 Relative Risks (95% CIs) of Skin Cancers by Eye Color and Skin Reaction to Sun in the HPFS

Skin reaction to sun							
	Tan		Burn Then Tan		Peel		P for interaction
Eye color	No. of cases	Multivariable-adjusted RR (95% CI)[a]	No. of cases	Multivariable-adjusted RR (95% CI)[a]	No. of cases	Multivariable-adjusted RR (95% CI)[a]	
Melanoma							0.22
Brown/dark	37	1.00	49	1.22 (0.79–1.88)	24	1.36 (0.80–2.32)	
Hazel/green/medium	12	0.51 (0.26–0.97)	69	1.52 (1.01–2.29)	47	1.72 (1.09–2.70)	
Blue/light	19	0.95 (0.54, 1.66)	69	1.36 (0.90, 2.05)	77	2.02 (1.33, 3.05)	
SCC							0.38
Brown/dark	86	1.00	131	1.56 (1.18–2.05)	68	2.02 (1.46–2.81)	
Hazel/green/medium	78	1.44 (1.05–1.96)	169	1.91 (1.46–2.49)	124	2.39 (1.80–3.19)	
Blue/light	57	1.32 (0.94, 1.85)	186	1.83 (1.41–2.38)	160	2.38 (1.81–3.13)	
BCC							0.03
Brown/dark	650	1.00	855	1.32 (1.19–1.46)	361	1.45 (1.27–1.65)	
Hazel/green/medium	485	1.17 (1.04–1.32)	1079	1.58 (1.43–1.74)	602	1.58 (1.41–1.77)	
Blue/light	434	1.31 (1.16–1.48)	1194	1.57 (1.42–1.73)	856	1.68 (1.51–1.87)	

HPFS: Health Professionals Follow-up Study; *Cis*: confidence intervals; *BCC:* basal cell carcinoma; *SCC:* squamous cell carcinoma

[a]HPFS only includes male participants. Multivariate models were adjusted for age (continuous), family history of melanoma, smoking status (never; past with < 10, 10–20, 20–40, > 40, or unknown pack-years; current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, ≥ 20.0 g/day), body mass index (< 18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥ 35 kg/m^2), UVB exposure at residence (quintiles), number of lifetime severe sunburns (0, 1–2, 3–5, or ≥ 6), number of moles on the upper extremities (0,1–2, 3–5, or ≥ 6), and natural hair color (red/blonde, light brown, dark brown/black)

eye color was significant for BCC and SCC risks but not for melanoma risk.

Table 4 shows the association between eye color and skin reaction to sun and skin cancer risk. In comparison to those with brown/dark eyes and whose skin tans after sun exposure, the risks of all three skin cancers were generally elevated in other eye color and skin reaction combinations, although not all of the RRs were statistically significant. Participants with blue/light eye color and whose skin peels after sun exposure had the highest risk of melanoma, SCC and BCC. Lighter eye colors were generally associated with an increased risk of skin cancer, regardless of skin reaction to sun. The interaction between eye color and skin reaction to sun was significant only for the risk of BCC and not for SCC or melanoma.

In melanoma cases where the Breslow thickness was ≥ 1.0 mm (Table S1), individuals with hazel/green/medium eyes (RR = 1.39, 95% CI 0.78–2.50) and those with blue/light eyes (RR = 1.65, 95% CI: 0.95–2.88) had non-significantly higher melanoma mortalities than those with brown/dark eyes, and the test for trend was not significant (p-trend = 0.08). The trend was also not observed for Breslow thickness < 1 mm (p-trend = 0.43).

We also evaluated the combination of eye color, hair color, and skin reaction to sun in relation to skin cancer (Table S2). In comparison with those with brown/dark eye and hair color with skin that tans in response to sun exposure, the risks of all three skin cancers were generally elevated in other eye and hair color and skin reaction combinations, although not all of the RRs were statistically significant. For melanoma, participants with brown/dark eye color and red/blonde hair color who painfully burn then peel had the highest risk (RR = 3.25; 95% CI:1.27–8.35) (Table S2). For SCC, participants with brown/dark eye color and red/blonde hair color who burn then tan had the highest risk (RR = 2.74, 95% CI: 1.09–6.91). For BCC, those with brown/dark eye color and light brown hair color who painfully burn then peel had the highest risk (RR = 1.81, 95% CI: 1.47–2.24).

When stratified by body site (head/neck/extremities vs. trunk) of tumors based on sun-exposure patterns, the associations between eye color and risks of melanoma and SCC were similar across the body sites (Table S3).

Discussion

Light pigmentation has been recognized as one of the risk factors for skin cancers. To date, there have been few large cohort studies examining eye color and risks of melanoma, SCC and BCC. In this study, we found light eye colors were independently associated with elevated risks of BCC and SCC, but not melanoma. When taking hair color into consideration, participants with both light eye and hair colors had

higher risks of SCC and BCC. Light eye colors were also associated with higher skin cancer risk among those with worse skin reaction to sun.

To date, studies of the association between eye color and risk of SCC are limited [8]. Our findings support previous studies of BCC that people with lighter eye colors had elevated risks of BCC including a previous evaluation in HPFS based on a follow-up up to 1994 [8, 11–14].

We did not detect a significant association between eye color independently and risk of melanoma, which is consistent with some previous studies [9, 15]. However, in a meta-analysis including 37 case–control studies on eye colors and risk of melanoma, people with fair eye colors had significantly higher risks of melanoma than those with dark eyes, with a pooled RR of 1.62 (95% CI: 1.44–1.81) (5). The risks were similar for green (RR: 1.76, 95% CI: 1.06–2.45), hazel (RR: 1.52, 95% CI: 1.26–1.83), and blue (RR: 1.47, 95% CI: 1.28–1.69) eye colors [5]. Also, in a recent case–control study including 616 melanoma cases, blue/grey eye-colored participants had a 40% higher risk of melanoma in comparison to those with brown/dark eyes [16]. In our age-adjusted analysis, blue/light eyes were associated with a 40% higher risk of melanoma in comparison to brown/dark eyes, which was similar to the results from the meta-analysis and the recent case–control study. But the point estimate was attenuated and no longer significant after adjustment for multiple skin cancer risk factors. Our results suggest that the positive association between eye color and risk of melanoma found in previous studies might be at least partly confounded by some skin cancer risk factors.

Individuals with blue/light eye colors and a ≥ 1 mm Breslow score had an increased risk for melanoma mortality, although the association was not significant. Breslow score has been recognized as an important indicator of melanoma prognosis [29]. A previous study evaluating the association between cutaneous nevi and risk of melanoma death found that men with higher mole counts were at higher risks of developing thicker melanomas (Breslow thickness > 1 mm) [28]. Thus, further studies are needed to determine whether Breslow thickness interacts with phenotypes such as light pigmentation in association with melanoma mortality.

For SCC and BCC, lighter eye colors were largely associated with higher risks, in combination with lighter hair color. Studies have found genetic underpinnings for hair and eye color pigmentation, including gene such as MATP are important in the formation of human pigmentation [19, 30–32]. OCA2 (also known as the P gene) is associated with oculocutaneous albinism type 2 and has been recognized as an important gene in eye color formation [33]. However, cumulative evidence has suggested that the OCA2 gene and its variations are also associated with the formation of skin and hair pigmentation [34, 35], which suggests that while hair color is a stronger indicator for skin cancer risk, eye color may serve as an additional indicator, especially for people with light hair colors [13]).

Skin reaction to sun is a non-differentiating independent risk factor for melanoma, SCC and BCC [7]. Lighter eye colors in combination with worse skin reaction to sun were consistently associated with elevated risks of melanoma, SCC and BCC, although p-value for interaction was only significant for BCC. The findings on BCC were consistent with previous evaluation in the HPFS [11].

Our study had several strengths. First was its prospective design while almost all of the prior studies evaluating eye color and. Although eye color is an exposure which may not be susceptible to recall bias, case–control studies may suffer from selection bias. Second, we had a large cohort study with long follow-up time which generated large number of skin cancer cases. Third, we had extensive information on large number of skin cancer risk factors and were able to adjust for them. Fourth, diagnoses of melanoma and SCC were initially self-reported but were confirmed by medical and pathology reports reviewed by physicians. We have only included confirmed melanoma and SCC cases to reduce misclassification of outcomes.

Our study also had several limitations. Self-reported information such as eye color and childhood skin reactions to sun may be subject to misclassifications, although some characteristics which does not change such as eye color may be relatively accurately reported. Diagnosis of BCC was based on self-report only and may be subject to misclassification. However, if such misclassifications exist, it should be non-differential, which would have attenuated the true associations, and drove our results towards the null. Also, it was suggested that the validity of self-report of BCC was high in the HPFS, as it consists of a medically knowledgeable population [11]. In addition, our data are from male health professionals with high health awareness, and thus may not represent the general population. However, the biological association between eye color and skin cancer may not differ by health awareness.

Conclusion

This study found that people with lighter eye colors had higher risks of SCC and BCC but not melanoma. In addition, lighter eye colors were associated with an increased risk of skin cancer, especially among those with worse skin reactions to sun and among those with lighter hair colors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10552-021-01508-z.

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Data availability (data transparency): Information including the procedures to obtain and access data from the Health Professionals Follow-up Study is described at https://sites.sph.harvard.edu/hpfs/for-collaborators/.

Code availability (software application or custom code): SAS software was used for all the data analyses in this study. The SAS code used in the current study is not publicly available due to the aforementioned data restrictions but will be available from the corresponding author upon request.

Declarations

Conflict of Interest The authors declare no potential conflicts of interest.

Ethical approval The present study used secondary data from the Health Professionals Follow-up Study in which no participant identifying information was included.

Consent for publication All authors of the current study consent for publication.

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