

Cutaneous nevi and internal cancer risk: results from two large prospective cohorts of US women

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List of Abbreviations: NHS, Nurses' Health Study; NHS2, Nurses' Health Study 2; BMI, body mass index; UV, ultraviolet; HR, hazard ratio; CI, confidence interval; GH, growth hormone; IGF, insulin-like growth factor; PMH, postmenopausal hormone; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; T2D, type 2 diabetes.

Novelty and Impact: In two large prospective cohorts of US women, compared to those with no nevi on extremity, there is an increase in overall internal cancer risk among individuals with ≥ 1 nevi in a dose-dependent trend. To the best of our knowledge, this is the first study reporting higher nevus count is associated with an increased risk of internal cancer; further investigations are needed to evaluate nevus count as a phenotypic marker of cancer risk.

Conflict of interest: The authors declare no conflict of interest.

Abstract

Elevated cutaneous nevus number has been linked to longer telomeres. Recently, a large systematic Mendelian randomization study identified a significant positive association between telomere length and risk of cancer. Here, we hypothesized that higher nevus count, as a phenotypic marker of longer telomere, may be associated with increased risk of internal cancer, and prospectively examined the association between nevus count and total as well as site-specific cancer risk among participants in the Nurses' Health Study (NHS, 1986-2012) and the Nurses' Health Study 2 (NHS2, 1989-2013) using Cox proportional hazards models. During 3,900,264 person-years of follow-up, we documented a total of 23,004 internal cancer cases (15,484 in the NHS and 7,520 in the NHS2). Compared to participants who had no nevi, the multivariate hazard ratios of total cancer (excluding skin cancer) were 1.06 (95% confidence interval [CI], 1.03-1.09) for women with 1-5 nevi, 1.08 (95% CI, 1.03-1.15) for those who had 6-14 nevi, and 1.19 (95% CI, 1.05-1.35) for those with 15 or more nevi (p trend < 0.0001). Moreover, because nevus count has been associated with risk of breast cancer previously, we conducted a secondary analysis by excluding breast cancer from the outcomes of interest. The results were very similar to those of our primary analysis. For individual cancer, most of the associations with nevus count were positive but not statistically significant. In conclusion, we identified the number of cutaneous nevi as a phenotypic marker associated with internal cancer risk, which may be explained by telomere biology.

Introduction

Nevi, also referred to as moles, are benign clonal proliferations of melanocytes¹. Sun exposure may be involved in nevus formation, but variation in nevus count between individuals is primarily determined by genetic factors, as shown by family and twin studies²⁻⁴.

Elevated nevus number has been associated with longer telomeres^{5,6}. And telomere length has been implicated in cancer development⁷. Despite inconsistent results from observational studies⁸⁻¹², a recent systematic Mendelian randomization study reported a positive association between telomere length and risk of cancer¹³. Their findings are generally consistent with those from previous prospective observational studies, most of which found weak positive association or null association between telomere length and total as well as site-specific cancer risk^{5, 11, 14-26}. Moreover, the results are similar to those reported by several other Mendelian randomization studies on the association of telomere length with risk of lung cancer, melanoma, glioma, and chronic lymphocytic leukemia²⁷⁻³⁰.

Having a large number of nevi on sun-exposed body sites is a well-known risk factor for malignant melanoma^{31, 32}. However, limited evidence is available for the association between number of nevi and risk of internal cancer. In the current study, we hypothesized that higher nevus count, as a phenotypic marker of longer telomere, may be associated with increased internal cancer risk, and prospectively investigated this association in two large cohorts of US women.

Methods

Study Population, Inclusion, and Exclusion

Our study population consisted of participants from two ongoing cohort studies: the Nurses' Health Study (NHS) and the Nurses' Health Study 2 (NHS2). The NHS is a prospective cohort study

established in 1976 with 121,700 female U.S registered nurses who were then 30-55 years old. All of them completed and returned a mailed self-administered questionnaire about their medical histories and lifestyle at baseline. The NHS2 was established in 1989, when 116,671 female registered nurses aged 25–42 and residing in the United States at the time of enrollment responded to an initial questionnaire on their medical histories and baseline health-related exposures. In both cohorts, information regarding medical history, lifestyle, and disease diagnoses was updated every 2 years with a follow-up rate of 90%.

In the present analyses, the baselines in the NHS and NHS2 were 1986 and 1989, respectively, when participants reported self-counted number of cutaneous nevi. We excluded participants diagnosed with cancer before baseline. Participants who did not report number of cutaneous nevi were excluded, as were those reporting non-white ancestry. In total, 72,726 women from the NHS and 103,766 from the NHS2 were included. The study was approved by the Institutional Review Board of Brigham and Women’s hospital and the Harvard T.H. Chan School of Public Health, and those of participating registries as required.

Measurements of nevus count and other covariates

In the NHS, in 1986, participants were asked to provide information on melanocytic nevus count (larger than 3 mm in diameter) from shoulder to wrist on left arm by choosing from the following categories: none, 1-2, 3-5, 6-9, 10-14, 15-20, and 21+. In the baseline questionnaire in 1989, the NHS2 participants reported numbers of cutaneous nevi, without specification of size, on lower legs (knees to ankles, both legs) using the same categories.

Data on body mass index (BMI), smoking status, physical activity, menopausal status, use of

postmenopausal hormones, and disease history (including heart disease, stroke, type 2 diabetes, squamous cell carcinoma, and basal cell carcinoma) was first collected at baseline and then updated biennially in subsequent questionnaires for both cohorts. Information on alcohol consumption was first asked in 1986 and 1991 in the NHS and NHS2, respectively, and then updated every four years. In 1990s, participants were asked about their location of residence (US states) at birth, age 15, and age 30. The 50 US states were categorized into low, medium, and high ultraviolet (UV) index groups³³ and incorporated into the multivariable-adjusted models.

Ascertainment of cancer cases

Participants in the NHS and NHS2 reported diagnosis of cancers every two years. With their permission, medical records were then obtained and reviewed by physicians to confirm their self-reported diagnosis. Eligible cases consisted of women with incident cancers (excluding melanoma and non-melanoma skin cancers) diagnosed any time after baseline up to the 2012 follow-up cycle in the NHS and 2013 follow-up cycle in the NHS2. Only pathologically confirmed invasive cases were included. In total, 23,004 internal cancer cases were documented (15,484 in the NHS and 7,520 in the NHS2).

Statistical analysis

We used age-adjusted and multivariable-adjusted Cox proportional hazards models stratified by follow-up cycles and age to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of the association between nevus count and internal cancer risk. Person-time was calculated for each participant from the date of baseline questionnaire return to the date of the first report of cancer

diagnosis, death, or the end of follow-up, whichever came first. We grouped women into four categories based on their self-reported nevus count (none, 1-5, 6-14, and 15+) and created a continuous variable (0, 3, 10, and 15) to represent the four exposure categories for the linear trend test. In the multivariate analysis, we simultaneously controlled for age, smoking status, alcohol intake, BMI, physical activity, UV index, menopausal status/postmenopausal hormone use, and history of heart disease, stroke, type 2 diabetes, squamous cell carcinoma, and basal cell carcinoma. We used the most updated information for time-varying variables prior to each follow-up interval to take into account potential changes over follow-up. Missing data during any follow-up interval were coded as a missing indicator category for categorical variables and with carried-forward values for continuous variables. Multiplicative interactions between nevus count and other covariates were tested using the likelihood ratio test comparing a “main effect only” model vs. a model with product term. All covariates in the multivariable-adjusted models were considered individually and sequentially tested for interaction. We tested the heterogeneity of the results between the two cohorts using the Q statistic and conducted a fixed-effect inverse variance-weighted meta-analysis if there was no significant difference^{34, 35}. All statistical analyses were performed using SAS software (version 9.4 for UNIX; SAS Institute, Cary, North Carolina). We considered two-sided P values less than 0.05 to be statistically significant.

Data Availability

Further information including the procedures to obtain and access data from the Nurses’ Health Studies is described at <https://www.nurseshealthstudy.org/researchers> (contact email: nhsaccess@channing.harvard.edu).

Results

The baseline age-standardized characteristics of participants by categories of nevus count are listed in *Table 1*. Compared to participants who reported having no nevi on their arms/legs, women in higher nevus count categories were less likely to be current smokers, and more likely to have personal history of basal cell carcinoma (in both cohorts), squamous cell carcinoma and type 2 diabetes (in NHS). Other characteristics were similar among groups having different numbers of cutaneous nevi.

During 3,900,264 person-years of follow-up, we documented a total of 23,004 internal cancer cases (15,484 in the NHS and 7,520 in the NHS2). In both cohorts, higher numbers of cutaneous nevi were associated with increased risk of cancer, though the multivariate HRs are slightly higher in the NHS compared to those in the NHS2 for women with 6-14 and 15+ nevi (*Table 2*). Because we did not detect significant heterogeneity between the results of the NHS and NHS2 (p for heterogeneity in trend test = 0.14 for multivariable-adjusted model), we combined the estimates using fixed-effect inverse variance-weighted meta-analysis. Compared to participants who had no nevi, the multivariate HRs were 1.06 (95% CI, 1.03-1.09) for women with 1-5 nevi, 1.08 (95% CI, 1.03-1.15) for those who had 6-14 nevi, and 1.19 (95% CI, 1.05-1.35) for those with 15 or more nevi (P for trend < 0.0001). Additionally, we did not find significant interactions between the number of nevi and other covariates in the multivariable-adjusted model after adjusting for multiple comparisons (p-values for interaction > 0.05 for all covariates).

Nevus count has been associated with risk of breast cancer previously³⁶. Thus, we conducted a secondary analysis by excluding breast cancer from the outcomes of interest. The results

(*Supplementary Table 1*) were very similar to those of our primary analysis using all internal cancer sites. Moreover, we assessed the associations between nevus count and risk of developing site-specific cancers (*Supplementary Table 2*). We combined the results of trend tests for total and site-specific cancer of the two cohorts, and presented the HRs and 95% CIs associated with per 5 count increase in nevus number in *Figure 1*. For individual cancer sites, results of bladder cancer, lymphoma, and breast cancer reached borderline significance, associations with nevus count for the remaining cancer sites were positive but not statistically significant.

Discussion

In this analysis of two large prospective cohort studies, the number of cutaneous nevi was positively associated with incidence of total internal cancer with a significant dose-response relationship. After adjusting for potential confounding factors, there was a 19% higher risk of overall cancer among participants with ≥ 15 nevi on their limbs as compared to those without any nevi. Importantly, the association remained significant in the secondary analysis, indicating that the observed significant association was not solely driven by previously reported association between nevus count and breast cancer. The association with nevus count was nonsignificant for most of the individual cancer sites, which may be due to a lack of power. These findings suggest that nevus count may be etiologically linked to cancer development.

One potential mechanism for this association is telomere length which has been linked to both nevus count and risk of cancer. Telomeres are long hexameric (TTAGGG) $_n$ repeats at the ends of linear eukaryotic chromosomes that are shortened by each round of DNA replication³⁷. They serve to track the number of divisions a cell has undergone and reflect the future replication potential of a

cell⁷. Efforts have been made to study relationships between telomere length and cancer risk. However, the direction and magnitude of the associations found are inconsistent across observational studies, e.g., retrospective studies tend to report increased cancer risk among individuals with shorter telomeres^{9, 10, 38}, whereas more prospective studies find weak or null associations of telomere length with overall and site-specific cancer^{5, 8-10, 16, 22, 23, 26, 39-42}. Such inconsistency may reflect reverse causation bias in the retrospective design or variation in controlling confounding effects due to shared environmental factors. To rule out the influences of these methodological issues, Haycock *et al.* recently conducted a systematic Mendelian randomization study with more than 1,200,000 participants and found that increased telomere length is associated with increased risk of cancers¹³. This positive association is supported by known biology. Telomere length may regulate senescence process. When telomeres shorten to a critical length, the cells may enter senescence, an important tumor-suppressive mechanism⁷. Cells with longer telomeres have higher proliferative potential, leading to acquiring more somatic mutations⁴³. Previous studies found that telomeres appear to be longer among people with more and larger nevi^{5, 6}. Consistent with those findings, we report increased cancer risk among women with more cutaneous nevi.

Alternatively, nevus count and cancer may be connected through growth factors, as they both positively related to adult height. Data suggested that melanocytic nevi grow more rapidly during growth hormone (GH) therapy⁴⁴. Growth hormone exerts many of its functions through insulin-like growth factor (IGF)-1, which has numerous roles, including accelerating cell proliferation and inhibiting apoptosis^{45, 46}. The GH-IGF-1 axis has been demonstrated to play a role in the development of most common cancers among Western populations⁴⁷.

Our study has several strengths. First, this is a prospective cohort study with large sample size,

long follow-up, and updated assessment of cancer diagnosis every two years. Second, we were able to control for a number of potential confounders based on detailed cohort follow-up information, and this allowed us to determine that the association between nevus count and cancer risk was independent of the confounders being considered. Third, besides primary analysis, we also tested the association of nevus count with risk of total internal cancer (excluding breast cancer) and individual cancer to better illustrate the observed positive association.

We also acknowledge several limitations. One is that nevus count in our cohorts was self-reported. However, previous studies have evaluated the validity of self-reported information on nevus counts, and the majority found substantial agreement between nevus self-counts and dermatologist counts^{48, 49}. In one study, the Spearman's correlation coefficient was 0.91 between the two measurements⁵⁰. In our cohorts, the ordinal variable of nevus count is a highly significant predictor of melanoma risk⁵¹. Genome-wide association studies of nevi number using our genetic datasets revealed biologically plausible susceptibility loci for nevus count and melanoma risk, and the same loci were replicated by other independent studies⁵²⁻⁵⁴. In addition, we do not have information on type or size of nevi, thus could not evaluate whether the association of interest is modified by these histopathological factors. The second limitation was that we collected information on nevus count on the left arm in the NHS, while on both legs in the NHS2. Despite such difference, conclusion regarding association between nevus count and cancer risk was consistent based on cohort-specific results. And examining the limbs was suggested previously to be a practical and suitable tool for predicting whole body nevus count⁵⁵⁻⁵⁷. Thirdly, average number of nevi varies among different age groups. Studies found nevus count typically reaches its maximum between ages 30 and 50, with a slight decrease after age 50⁵⁸. Considering participants of the NHS (age range

40-65 when nevus count was asked) on average are older than those of the NHS2 (age range 25-42 when nevus count was asked), natural regression of nevus may influence results in the NHS.

Furthermore, our cohorts consist primarily of white, educated US women, and thus results may not be generalizable. However, such homogeneity in a study population would minimize confounding by socioeconomic status and differential access to healthcare and assure a high quality of returned data.

In conclusion, we identified the number of cutaneous nevi as a novel phenotypic marker associated with internal cancer risk. Telomere length and growth factors may contribute to this association. Further studies are needed to better assess the relationships between nevus count and individual cancer sites and to reveal the underlying mechanisms.

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Table 1. Age-adjusted baseline characteristics according to categories of nevus count in the NHS and NHS2

	NHS (number of nevi on left arm from shoulder to wrist)				NHS2 (number of nevi on both lower legs from knees to ankles)			
	None (n=46,136)	1-5 (n=23,304)	6-14 (n=2,643)	>=15 (n=643)	None (n=51,756)	1-5 (n=30,216)	6-14 (n=12,295)	>=15 (n=9,499)
Age (year) ^a , mean (SD)	52.7 (7.2)	52.0 (7.1)	51.9 (7.1)	52.0 (7.1)	34.3 (4.7)	34.4 (4.6)	34.3 (4.7)	34.3 (4.6)
Body mass index (kg/m ²), mean (SD)	25.1 (4.7)	25.6 (5.0)	26.5 (5.5)	26.9 (5.7)	24.3 (5.2)	24.1 (5.1)	23.8 (4.8)	23.5 (4.5)
Height (inch), mean (SD)	64.4 (3.1)	64.5 (3.2)	64.7 (3.0)	64.9 (2.5)	64.9 (2.6)	64.9 (2.6)	65.0 (2.6)	65.2 (2.6)
Current smoking, %	22.3	20.6	20.2	19.4	14.1	13.8	11.8	10.1
Alcohol intake (g/d), mean (SD)	6.3 (11.0)	6.0 (10.4)	5.7 (9.8)	5.0 (8.5)	3.0 (5.8)	3.0 (5.5)	3.0 (5.7)	3.1 (6.2)
Physical activity (metabolic-equivalents hours/wk), mean (SD)	14.1 (20.8)	13.9 (20.7)	13.5 (19.3)	14.8 (24.6)	25.3 (37.3)	24.5 (35.6)	24.4 (36.0)	24.8 (36.2)
Menopausal status/PMH ^b status								
- Premenopausal, %	43.2	43.3	44.4	44.9	97.2	96.8	97.1	97.1
- PMH never use, %	26.2	25.5	25.1	21.9	0.2	0.2	0.2	0.1
- PMH current use, %	14.0	14.5	14.7	16.0	0.2	0.2	0.2	0.2
- PMH past use, %	12.4	12.9	11.9	14.3	1.8	2.1	2.1	2.0
UV index at birth, age 15, and age 30 >=7, %	5.5	5.9	4.5	5.5	9.7	11.5	10.7	10.7
Personal history of BCC ^b	4.4	5.6	7.3	8.0	0.3	0.4	0.4	0.5
Personal history of SCC ^b	0.3	0.3	0.4	0.5	0.0	0.0	0.0	0.0
Personal history of T2D ^b	3.9	4.5	6.2	5.7	0.2	0.2	0.2	0.1

NOTE: Values are means (SD) or percentages and are standardized to the age distribution of the study populations. Values of multi-level categorical variables may not sum to 100% due to rounding or missingness.

a Value is not age-adjusted;

b Abbreviation: PMH – postmenopausal hormone use; BCC – basal cell carcinoma; SCC – squamous cell carcinoma; T2D – type 2 diabetes.

Table 2. HRs and 95% CIs for the association between nevus count and total internal cancer risk

	Levels of nevus count				P for trend
	None	1-5	6-14	15 and up	
NHS					
Person-years	996,663	503,996	56,378	13,273	.
No. of cases	9,672	5,053	596	163	.
Age-adjusted HR	1	1.06 (1.03, 1.10)	1.12 (1.03, 1.22)	1.33 (1.14, 1.56)	<.0001
Multivariate HR ^a	1	1.05 (1.02, 1.09)	1.10 (1.01, 1.19)	1.30 (1.11, 1.52)	<.0001
NHS2					
Person-years	1,164,586	677,135	275,691	212,542	
No. of cases	3,578	2,269	923	750	
Age-adjusted HR	1	1.09 (1.03, 1.15)	1.09 (1.01, 1.17)	1.16 (1.07, 1.25)	0.0001
Multivariate HR ^a	1	1.08 (1.03, 1.14)	1.07 (1.00, 1.16)	1.14 (1.05, 1.23)	0.0011
Meta-analysis ^b					
Person-years	2,161,249	1,181,131	332,069	225,815	
No. of cases	13,250	7,322	1,519	913	
Age-adjusted HR	1	1.07 (1.04, 1.10)	1.10 (1.04, 1.17)	1.22 (1.07, 1.39)	<.0001
Multivariate HR	1	1.06 (1.03, 1.09)	1.08 (1.03, 1.15)	1.19 (1.05, 1.35)	<.0001

a Multivariate models adjusted for age, smoking status (never, past, current 1-14, 15-24, or 25+ cigarettes/day), alcohol intake (no, <5.0, 5.0-9.9, 10.0-19.9, or 20.0+ g/day), body mass index (<25.0, 25.0-29.9, 30.0-34.9, or 35.0+ kg/m²), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9 or 27.0+ metabolic equivalent hours/wk), history of heart disease (yes or no), history of stroke (yes or no), history of type 2 diabetes (yes or no), history of squamous cell carcinoma (yes or no), history of basal cell carcinoma (yes or no), menopausal status/postmenopausal hormones use (premenopausal, PMH never, PMH past, or PMH current), and states lived at birth, age 15, and age 30 (UV index ≤5, =6, or ≥7);

b No significant difference were found between results of the NHS and the NHS2, p-value for heterogeneity is greater than 0.05.

Figure Legend

Figure 1. Multivariable-adjusted HRs and 95% CIs of per 5 count increase in nevus count for incident cancer at 15 specific sites, total internal cancer, and total internal cancer excluding breast cancer

Supplementary Table 1. HRs and 95% CIs for the association between nevus count and total internal cancer (excluding breast cancer) risk

	Levels of nevus count				P for trend
	None	1-5	6-14	15 and up	
NHS					
Person-years	937,758	472,459	52,622	12,220	
No. of cases	6,020	3,114	351	97	
Age-adjusted HR	1	1.06 (1.02, 1.11)	1.09 (0.98, 1.21)	1.31 (1.07, 1.60)	0.0004
Multivariate HR ^a	1	1.06 (1.02, 1.11)	1.07 (0.96, 1.19)	1.28 (1.05, 1.57)	0.0018
NHS2					
Person-years	1,136,405	658,967	268,641	206,560	
No. of cases	2,049	1,310	543	438	
Age-adjusted HR	1	1.10 (1.03, 1.18)	1.12 (1.01, 1.23)	1.18 (1.07, 1.31)	0.0005
Multivariate HR ^a	1	1.10 (1.02, 1.18)	1.11 (1.01, 1.22)	1.18 (1.06, 1.31)	0.0006
Meta-analysis ^b					
Person-years	2,074,163	1,131,426	321,263	218,780	
No. of cases	8,069	4,424	894	535	
Age-adjusted HR	1	1.07 (1.04, 1.12)	1.10 (1.03, 1.19)	1.21 (1.10, 1.33)	<.0001
Multivariate HR	1	1.07 (1.03, 1.11)	1.09 (1.02, 1.17)	1.20 (1.09, 1.32)	<.0001

a Multivariate models adjusted for age, smoking status (never, past, current 1-14,15-24, or 25+ cigarettes/day), alcohol intake (no, <5.0, 5.0-9.9, 10.0-19.9, or 20.0+ g/day), body mass index (<25.0, 25.0-29.9, 30.0-34.9, or 35.0+ kg/m²), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9 or 27.0+ metabolic equivalent hours/wk), history of heart disease (yes or no), history of stroke (yes or no), history of type 2 diabetes (yes or no), history of squamous cell carcinoma (yes or no), history of basal cell carcinoma (yes or no), menopausal status/postmenopausal hormones use (premenopausal, PMH never, PMH past, or PMH current), and states lived at birth, age 15, and age 30 (UV index ≤5, =6, or ≥7);

b No significant difference were found between results of the NHS and the NHS2, p-value for heterogeneity is greater than 0.05.

Supplementary Table 2. Risks of subsequent primary cancers at different sites ^a according to levels of nevus count in the NHS and NHS2

		NHS					NHS2				
		Levels of nevus count				P for trend	Levels of nevus count				P for trend
		None	1-5	6-14	15 and up		None	1-4	5-14	15 and up	
Breast cancer ¹	Person-years	1014997	517422	58789	13772	.	1171323	682624	278852	216265	.
	No. of cases	3652	1939	245	66	.	1529	959	380	312	.
	Age-adjusted HR	1	1.06 (1.00, 1.12)	1.17 (1.03, 1.33)	1.38 (1.08, 1.76)	0.0003	1	1.07 (0.99, 1.16)	1.04 (0.93, 1.17)	1.12 (0.99, 1.26)	0.09
	Multivariate HR ^b	1	1.03 (0.97, 1.09)	1.11 (0.97, 1.27)	1.35 (1.05, 1.72)	0.0089	1	1.05 (0.97, 1.14)	0.99 (0.88, 1.11)	1.03 (0.91, 1.17)	0.84
Lung cancer	Person-years	1017783	518912	58969	13816	.	1172668	683432	279169	216538	.
	No. of cases	1184	531	68	15	.	117	53	25	18	.
	Age-adjusted HR	1	0.92 (0.83, 1.02)	1.07 (0.84, 1.37)	1.01 (0.61, 1.69)	0.77	1	0.78 (0.56, 1.07)	0.91 (0.59, 1.41)	0.84 (0.51, 1.38)	0.49
	Multivariate HR	1	0.96 (0.86, 1.06)	1.15 (0.90, 1.47)	1.10 (0.66, 1.84)	0.60	1	0.77 (0.55, 1.06)	0.94 (0.61, 1.46)	0.93 (0.56, 1.54)	0.77
Colorectal cancer	Person-years	1017666	518818	58981	13822	.	1172607	683389	279153	216518	.
	No. of cases	933	504	48	14	.	159	103	44	32	.
	Age-adjusted HR	1	1.12 (1.01, 1.25)	0.95 (0.71, 1.27)	1.17 (0.69, 1.98)	0.34	1	1.13 (0.88, 1.44)	1.13 (0.81, 1.58)	1.09 (0.74, 1.59)	0.52
	Multivariate HR	1	1.12 (1.00, 1.25)	0.93 (0.70, 1.25)	1.14 (0.67, 1.94)	0.42	1	1.12 (0.87, 1.43)	1.13 (0.80, 1.58)	1.07 (0.73, 1.57)	0.56
Endometrial cancer ²	Person-years	1017803	518886	58976	13823	.	1172531	683349	279150	216513	.
	No. of cases	737	395	41	12	.	228	153	44	38	.
	Age-adjusted HR	1	1.07 (0.94, 1.21)	0.98 (0.71, 1.34)	1.26 (0.71, 2.23)	0.46	1	1.14 (0.93, 1.40)	0.81 (0.59, 1.12)	0.90 (0.64, 1.27)	0.24
	Multivariate HR	1	1.02 (0.90, 1.15)	0.86 (0.63, 1.18)	1.07 (0.60, 1.91)	0.70	1	1.14 (0.93, 1.41)	0.84 (0.61, 1.16)	0.95 (0.67, 1.35)	0.41
Ovarian cancer ²	Person-years	1018149	519062	59000	13824	.	1172608	683380	279162	216523	.

	No. of cases	421	222	23	9	.	144	94	34	27	.
	Age-adjusted HR	1	1.07 (0.91, 1.26)	0.96 (0.62, 1.46)	1.58 (0.81, 3.06)	0.37	1	1.11 (0.85, 1.44)	0.99 (0.68, 1.44)	1.03 (0.68, 1.55)	0.98
	Multivariate HR	1	1.07 (0.91, 1.26)	0.95 (0.62, 1.45)	1.53 (0.78, 2.97)	0.43	1	1.11 (0.85, 1.44)	0.99 (0.68, 1.43)	1.00 (0.66, 1.51)	0.93
Bladder cancer	Person-years	1018287	519113	59003	13830	.	1172721	683464	279187	216544	.
	No. of cases	229	132	14	2	.	18	13	7	8	.
	Age-adjusted HR	1	1.15 (0.92, 1.42)	1.09 (0.64, 1.88)	0.63 (0.16, 2.54)	0.68	1	1.25 (0.61, 2.56)	1.61 (0.67, 3.86)	2.44 (1.06, 5.65)	0.03
	Multivariate HR	1	1.16 (0.93, 1.44)	1.13 (0.66, 1.95)	0.69 (0.17, 2.80)	0.54	1	1.33 (0.64, 2.74)	1.78 (0.73, 4.32)	2.82 (1.21, 6.60)	0.01
Pancreas cancer	Person-years	1018374	519196	59007	13828	.	1172722	683462	279187	216547	.
	No. of cases	259	124	19	7	.	28	15	6	5	.
	Age-adjusted HR	1	0.98 (0.79, 1.22)	1.37 (0.86, 2.19)	2.27 (1.07, 4.83)	0.06	1	0.93 (0.49, 1.74)	0.91 (0.37, 2.19)	0.98 (0.38, 2.54)	0.89
	Multivariate HR	1	0.99 (0.79, 1.22)	1.35 (0.84, 2.16)	2.20 (1.03, 4.70)	0.07	1	0.93 (0.49, 1.75)	0.96 (0.39, 2.33)	1.05 (0.40, 2.75)	0.97
Kidney cancer	Person-years	1018348	519163	59009	13826	.	1172680	683434	279180	216531	.
	No. of cases	172	104	11	3	.	63	38	13	14	.
	Age-adjusted HR	1	1.23 (0.96, 1.57)	1.12 (0.61, 2.07)	1.34 (0.43, 4.20)	0.24	1	1.02 (0.68, 1.53)	0.85 (0.47, 1.54)	1.20 (0.67, 2.15)	0.83
	Multivariate HR	1	1.19 (0.93, 1.52)	1.03 (0.56, 1.90)	1.18 (0.37, 3.73)	0.46	1	1.00 (0.66, 1.49)	0.85 (0.46, 1.54)	1.24 (0.69, 2.23)	0.77
Melanoma³	Person-years	1018151	518946	58937	13820	.	1172520	683308	279078	216427	.
	No. of cases	394	327	78	14	.	204	165	110	132	.
	Age-adjusted HR	1	1.64 (1.41, 1.90)	3.47 (2.72, 4.44)	2.74 (1.60, 4.68)	<.0001	1	1.38 (1.13, 1.70)	2.28 (1.80, 2.87)	3.48 (2.80, 4.34)	<.0001
	Multivariate HR	1	1.53 (1.32, 1.78)	3.02 (2.35, 3.87)	2.50 (1.46, 4.28)	<.0001	1	1.35 (1.10, 1.66)	2.18 (1.72, 2.75)	3.10 (2.48, 3.87)	<.0001
Stomach cancer	Person-years	1018449	519227	59010	13831	.	1172736	683472	279189	216550	.
	No. of cases	72	33	7	2	.	7	3	2	2	.

	Age-adjusted HR	1	0.97 (0.64, 1.46)	1.87 (0.86, 4.08)	2.39 (0.58, 9.82)	0.11	1	0.71 (0.18, 2.74)	1.15 (0.24, 5.55)	1.53 (0.32, 7.41)	0.57
	Multivariate HR	1	0.92 (0.61, 1.40)	1.76 (0.80, 3.86)	1.92 (0.45, 8.11)	0.21	1	0.73 (0.18, 2.91)	1.36 (0.27, 6.80)	1.58 (0.31, 8.00)	0.50
Brain cancer	Person-years	1018439	519222	59011	13830	.	1172713	683460	279182	216546	.
	No. of cases	108	49	8	2	.	37	21	14	9	.
	Age-adjusted HR	1	0.94 (0.67, 1.31)	1.34 (0.65, 2.75)	1.42 (0.35, 5.80)	0.54	1	0.97 (0.57, 1.65)	1.54 (0.83, 2.86)	1.32 (0.64, 2.75)	0.18
	Multivariate HR	1	0.92 (0.65, 1.29)	1.28 (0.62, 2.64)	1.27 (0.31, 5.20)	0.68	1	0.96 (0.56, 1.65)	1.51 (0.81, 2.80)	1.25 (0.60, 2.60)	0.25
Non-Hodgkin lymphoma	Person-years	1017995	518961	58990	13828	.	1172618	683400	279156	216520	.
	No. of cases	594	332	32	8	.	134	80	38	36	.
	Age-adjusted HR	1	1.13 (0.99, 1.29)	0.99 (0.69, 1.42)	1.07 (0.53, 2.15)	0.41	1	1.01 (0.77, 1.33)	1.20 (0.84, 1.73)	1.44 (1.00, 2.08)	0.04
	Multivariate HR	1	1.12 (0.98, 1.28)	0.98 (0.69, 1.41)	1.04 (0.52, 2.09)	0.49	1	1.00 (0.76, 1.33)	1.18 (0.82, 1.70)	1.41 (0.97, 2.04)	0.06
Leukemia	Person-years	1018429	519217	59011	13832	.	1172711	683457	279186	216547	.
	No. of cases	108	72	8	2	.	33	21	7	8	.
	Age-adjusted HR	1	1.39 (1.03, 1.87)	1.38 (0.67, 2.83)	1.34 (0.33, 5.43)	0.10	1	1.07 (0.62, 1.85)	0.90 (0.40, 2.04)	1.35 (0.62, 2.92)	0.65
	Multivariate HR	1	1.37 (1.02, 1.86)	1.30 (0.63, 2.68)	1.20 (0.29, 4.92)	0.16	1	1.04 (0.60, 1.80)	0.85 (0.38, 1.94)	1.38 (0.63, 3.02)	0.66
Multiple Myeloma	Person-years	1018393	519213	59009	13832	.	1172726	683469	279184	216548	.
	No. of cases	131	51	8	0	.	17	7	6	7	.
	Age-adjusted HR	1	0.82 (0.59, 1.14)	1.16 (0.57, 2.38)	NA ^c	0.38	1	0.67 (0.28, 1.64)	1.52 (0.59, 3.87)	2.35 (0.97, 5.69)	0.04
	Multivariate HR	1	0.81 (0.58, 1.12)	1.13 (0.55, 2.33)	NA ^c	0.34	1	0.64 (0.26, 1.58)	1.50 (0.58, 3.85)	2.17 (0.88, 5.38)	0.06
Oral cancer	Person-years	1018428	519217	59013	13831	.	1172729	683460	279183	216546	.
	No. of cases	70	33	2	1	.	19	13	7	7	.
	Age-adjusted HR	1	0.92	0.48	1.11	0.42	1	1.16	1.40	2.13	0.09

			(0.61, 1.40)	(0.12, 1.98)	(0.15, 8.04)			(0.57, 2.35)	(0.58, 3.37)	(0.89, 5.08)	
	Multivariate HR	1	0.93 (0.61, 1.41)	0.51 (0.12, 2.08)	1.27 (0.17, 9.28)	0.49	1	1.11 (0.55, 2.28)	1.44 (0.60, 3.50)	2.23 (0.93, 5.34)	0.07
Other cancers	Person-years	1017856	518878	58968	13821	.	1171719	682784	278910	216325	.
	No. of cases	1002	532	62	20	.	1045	696	296	227	.
	Age-adjusted HR	1	1.07 (0.96, 1.19)	1.10 (0.85, 1.43)	1.54 (0.99, 2.41)	0.05	1	1.15 (1.04, 1.26)	1.19 (1.05, 1.36)	1.19 (1.03, 1.37)	0.003
	Multivariate HR	1	1.07 (0.97, 1.19)	1.10 (0.85, 1.42)	1.52 (0.97, 2.37)	0.05	1	1.14 (1.04, 1.26)	1.18 (1.03, 1.34)	1.16 (1.01, 1.34)	0.01

a Cancer sites that have more than 100 diagnosed cases in either cohort were included in the single site analyses. Cancer sites with smaller numbers of cases were grouped as other cancers;

b Multivariate models adjusted for age, smoking status (never, past, current 1-14, 15-24, or 25+ cigarettes/day), alcohol intake (no, <5.0, 5.0-9.9, 10.0-19.9, or 20.0+ g/day), body mass index (<25.0, 25.0-29.9, 30.0-34.9, or 35.0+ kg/m²), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9 or 27.0+ metabolic equivalent hours/wk), history of heart disease (yes or no), history of stroke (yes or no), history of type 2 diabetes (yes or no), history of squamous cell carcinoma (yes or no), history of basal cell carcinoma (yes or no), menopausal status/postmenopausal hormones use (premenopausal, PMH never, PMH past, or PMH current), and states lived at birth, age 15, and age 30 (UV index <=5, =6, or >=7);

c Estimates are not available because the number of cases is zero in those exposure categories;

1 For breast cancer, we additionally included in the multivariate model duration of hormone replacement therapy use (pre-menopause, dubious menopause, post menopause age < 48 and never user, post menopause age < 48 and past user, post menopause age < 48 and current user < 5 y, post menopause age < 48 and current user >= 5 y, 48 < post menopause age < 52 and never user, 48 < post menopause age < 52 and past user, 48 < post menopause age < 52 and current user < 5 y, 48 < post menopause age < 52 and current user >= 5 y, post menopause age >= 52 and never user, post menopause age >= 52 and past user, post menopause age >= 52 and current user < 5 y, post menopause age >= 52 and current user >=5 y), duration of menopause (continuous variable), family history of breast cancer (yes or no), history of benign breast disease (yes or no), height (< 160.02 cm, 160.02–162.56 cm, 162.56–167.64 cm, >= 167.64 cm), weight change from age at 18 (loss > 4 kg, stable, gain 4–10 kg, gain 10–20 kg, gain 20–40 kg, gain > 40 kg), parity and age at first birth (nulliparous, parity 1–2 and age at first birth < 25, parity 1–2 and 25 < age at first birth < 30, parity 1–2 and age at first birth > 30, parity 3–4 and age at first birth < 25, parity 3–4 and 25 < age at first birth < 30, parity 3–4 and age at first birth > 30, parity >=5 and age at first birth < 25, parity >=5 and 25 < age at first birth < 30), and age at menarche (<=12 y, 13 y, >=14 y);

2 For ovarian cancer and endometrial cancer, the multivariate model additionally included duration of hormone replacement therapy use, parity and age at first birth, and age at menarche, categorized as previously;

3 For melanoma, the multivariate model additionally included childhood reaction to sun (some redness or none, burn, painful burn or blisters), number of severe sunburns (none, 1–2, 3–5, 6–9, >=10), hair color (black, dark brown, light brown, blonde, red), family history of melanoma (yes or no), average time spent in sun light in summer at different age intervals (0-2hr, 2-6hr, 6-10hr, >10hr), and cumulative UV flux (quintiles).

