Personal history of non-melanoma skin cancer diagnosis and death from melanoma in women

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Novelty and Impact: This study investigates the effect of a personal history of non-melanoma skin cancer (NMSC) on risk of melanoma diagnosis and death. We demonstrate the importance of vigilance in melanoma detection after the diagnosis of non-melanoma skin cancer and its potential role in decreasing deaths from melanoma.

Abbreviations used: Non-melanoma Skin Cancer (NMSC), Odds Ratio (OR), Hazard Ratio (HR), Confidence Interval (CI), Ultraviolet (UV), Nurses' Health Study (NHS), American Joint Committee on Cancer (AJCC), Squamous Cell Carcinoma (SCC)

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ABSTRACT

Melanoma incidence is increasing. We evaluated risk of melanoma death after diagnosis of non-melanoma skin cancer (NMSC).

We followed 77,288 female American nurses from the Nurses' Health Study from 1986 to 2012. We used Cox proportional hazards models to determine the hazard ratio (HR) of lethal and non-lethal melanoma diagnosis and melanoma death, according to personal NMSC history. Among melanoma cases, we examined the HR of melanoma death and the odds ratio (OR) of melanoma with a Breslow thickness ≥ 0.8mm or Clark's level of IV and V according to history of NMSC.

We documented 930 melanoma cases without NMSC history and 615 melanoma cases with NMSC history over 1.8 million person-years. The multivariate-adjusted HR (95% confidence interval) of melanoma death associated with personal history of NMSC was 2.89 (1.85-4.50). Women with history of NMSC were more likely to develop non-lethal melanoma than lethal melanoma (HR (95% CI): 2.31 (2.05–2.60) vs. 1.74 (1.05-2.87)). Among melanoma cases, women with history of NMSC had a non-significant decreased risk of melanoma deaths (0.87 (0.55-1.37)), Breslow thickness ≥0.8mm (0.85 (0.59-1.21)) and Clark's levels IV and V (0.81(0.52-1.24)).

Women with NMSC history were less likely to be diagnosed with a lethal melanoma than a non-lethal melanoma, but overall rate of melanoma diagnosis was increased in both subtypes, leading to the increased risk of subsequent melanoma death. Our findings suggest the continued need for dermatologic screening for patients after NMSC diagnosis, given increased melanoma risk. Early detection among NMSC patients may decrease deaths from subsequent melanoma.

INTRODUCTION

The incidence of cutaneous melanoma (melanoma) has been increasing steadily in recent decades. The American Cancer Society estimates that in 2017 approximately 87,000 new cases of melanoma will be diagnosed, and that over 9,000 people will die from the disease.[1] Although early melanoma can be treated cost-effectively, the cost for the care of a melanoma patient can skyrocket with advanced disease.[2] The costs in the 6-month terminal period have been estimated to account for 90% of the healthcare cost of any given melanoma patient, and the care required by a melanoma patient with advanced disease has been estimated to cost as much as that needed for a colorectal cancer patient.[2] With the increasing burden of disease, prevention and early detection are critical in curbing the devastating effects of melanoma on the health of the public.

Several risk factors have been described for melanoma. There are certain non-modifiable risk factors in the development of melanoma such as high number of nevi, family history of melanoma, light skin complex, and certain genetic mutations.[2] Modifiable risk factors for melanoma include ultraviolet (UV) light exposure and the use of artificial sunlamps.[3,4,5,6] While many markers of UV light exposure have been studied as a means to help risk-stratify patients, they are less useful clinically. For example, a study that assessed 25-OH-vitamin D levels found that higher levels, conceivably a marker of more sun exposure, increased the risk of the development of melanoma and non-melanoma skin cancer (NMSC).[7,8] However, Vitamin D levels are not checked routinely, and it would be costly to do so purely for the purposes of risk-stratifying patients.

Rather, we would pose that personal history of NMSC is a critical part of the patient's medical history that indicates past high levels of UV exposure. As such, a patient's NMSC

history may portend a higher risk of melanoma and subsequent risk of death from melanoma. Indeed, prospective studies showed that NMSC history is associated with a higher risk of certain cancers, including melanoma.[9, 10] However, literature on personal history of NMSC and the risk of death from melanoma is lacking. Additionally, there have been no reports of risk associated with particular histopathologic features such as depth of invasion of each case of melanoma. We sought to use a large prospective cohort to examine the relationship between personal history of NMSC and future risk of not only melanoma, but melanoma death.

METHODS

Study Population

The Nurse's Health Study (NHS) began in 1976 when 121,701 American registered nurses aged 30-55 were enrolled and filled out a questionnaire regarding lifestyle and personal health information. Since then, surveys have been sent out to participants biennially to collect data prospectively. Response rates have been over 90% in follow-up. Our study period includes data collected in surveys from 1986 to 2012. Only Caucasian patients were included in our analysis, given the differing risks of melanoma based on ethnicity.[10] Our study was approved by the Human Research Committee of the Brigham and Women's Hospital (Boston, MA).

Assessment of NMSC

Participants were asked about receiving a diagnosis of "basal cell skin cancer," "squamous cell skin cancer," among other diagnoses every two years since 1986. With participants' permission, their medical records were reviewed to confirm self-reported diagnoses of squamous cell carcinoma. Self-reported basal cell carcinomas were not verified by medical records given prior

studies demonstrating >90% validity.[12] Given the way data are collected, these are treated as "first NMSC."

Assessment of melanoma and death

Participants have self-reported the diagnosis of "cutaneous melanoma" every two years since 1986. After self reporting the diagnosis of melanoma, permission was sought to review medical records, including any pathological reports. Only confirmed invasive cases were included in the current study, and self-reported cases that could not be confirmed were excluded. Information collected in addition to time of first melanoma diagnosis included major histopathologic factors, such as Breslow depth and Clark's level. Death events were reviewed in one of three ways. Deaths were reported by next of kin or by the US Post Office. Additionally, a search was made in the National Death Index for participants who did not respond to surveys. Death certificates and when necessary, medical records were used to determine the date of death. More than 98% of deaths in the NHS were confirmed by one of these methods.[13] Furthermore, cause of death was determined from death certificates by blinded physician reviewers. This was supplemented with family or health-care provider interviews, as well as medical records. The primary cancer was recorded as the cause of death in cases of fatal metastatic disease. Of note, patients who reported both melanoma and NMSC for the first time in one questionnaire cycle were excluded.

Assessment of covariates

Covariate information was collected by self-reported questions in biennial surveys. This included information on age, smoking (never, past, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), body mass index (<25, 25-29.9, ≥30 kg/m^2), and physical activity (in quintiles,

metabolic equivalent hours/wk). Certain factors were not asked biennially but rather at certain time points. These included the following factors: childhood reaction to sun (tan without burn, burn, or painful burn/blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan), times of sunburns (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), and cumulative UV flux (in quintiles). UV flux was calculated for each participant based on her state of residence using a previously described method.[14]

Statistical Analysis

All analyses were carried out using SAS (version 9.4; SAS Institute Inc., Cary, NC). All P values were 2-tailed with the significance level set at $P < 0.05$. The study baseline was 1986, and association of NMSC history with subsequent melanoma diagnosis and melanoma death were examined until 2012.

We calculated person-years of follow-up from baseline to death or end of follow-up, whichever came first. Melanoma deaths were considered the major end point, whereas deaths from other causes were censored. Using a Cox proportional hazards model stratified by age and 2-year intervals, we calculated hazard ratios (HRs) for melanoma death comparing participants with and without a history of NMSC. The analyses were adjusted for the previously mentioned covariates (BMI, smoking, alcohol intake, physical activity, childhood reaction to sun, number of sunburns, family history for melanoma, hair color, ability to tan, UV flux, and physical exam frequency). Missing data for any covariate required creation of an indicator variable. In secondary analysis, we looked at the association between prior history of NSMC and incident cases of both lethal and non-lethal melanoma. In this analysis, follow-up was ended based on date of melanoma

diagnosis, death from any cause, or end of follow-up period, whichever came first. Similarly, we used a Cox proportional hazards model with adjustment for the same covariates.

Among melanoma cases, we further examined whether a history of NMSC portended a worse prognosis by analyzing the rate of death from melanoma. Participants were included from time of diagnosis of melanoma and followed until either end of follow-up time or death from any cause, whichever came first. Our predetermined end point was melanoma death, whereas death from any other cause was censored. As above, we used a Cox proportional hazards model with time in months since diagnosis as the time variable to calculate HRs, adjusting for the same covariates. We also created an additional model adjusting for Breslow thickness and Clark's level. Events (melanoma death) were compared only among participants who were at the same month of follow-up to control for confounding since time of diagnosis. Then, using the logistic regression, we calculated odds ratios (OR) to examine the association between personal history of NMSC and Breslow thickness (defined as <0.8 mm or ≥0.8 mm) and Clark's Level (defined as I, II, and III or IV and V), adjusting for the same aforementioned covariates. A cutoff of 0.8 mm for Breslow thickness was used in accordance with new staging guidelines published by the American Joint Committee on Cancer (AJCC).[15]

RESULTS

A total of 930 of melanoma patients had no personal history of NMSC, while 615 did carry a prior diagnosis of NMSC. Baseline characteristics are shown in Table 1. Compared to those without personal history of NMSC, women with personal history of NMSC were older and more

likely to have family history of melanoma, have red or blonde hair, have tendency to burn instead of tan, and have more sunburns. In addition, women with personal history of NMSC had more frequent physical exams and were less likely to develop Clark's level IV and V melanoma. Median age at diagnosis of first NMSC was 65 years.

When evaluating HR of melanoma death associated with personal history of NMSC, the age-adjusted HR and 95% confidence interval (CI) was 2.99 (1.94 - 4.62). When covariates other than age were included in the model, the multivariate-adjusted HR was 2.89(1.85-4.50) (Table 2).

We examined the risk of developing either a lethal or non-lethal melanoma depending on prior history of NMSC. The mean and median number of months between first NMSC and first melanoma were 112 and 95 respectively. The age-adjusted HR and 95%CI for developing a lethal melanoma for those with a history of NMSC was 1.97 (1.21 – 3.22) when compared to those without NMSC history. Of note, we controlled for age carefully using a two year interval in our Cox model. In multivariate analysis, this HR was 1.74 (1.05 – 2.87). For the risk of non-lethal melanoma, the HRs for age-adjusted and multivariate-adjusted modeling were 2.65 (2.36 – 2.98) and 2.31 (2.05 – 2.60) (Table 3). These data indicated a higher risk of being diagnosed with a non-lethal melanoma than a lethal melanoma among those with personal history of NSMC diagnosis.

Furthermore, in analysis limited to melanoma patients, comparing those with personal history of NMSC to those without any such history, we found a HR of 0.83 (0.54 – 1.29) for melanoma death in the age-adjusted model. Multivariate modeling revealed a HR of 0.85 (0.54 – 1.33), and

in further multivariate modeling with the addition of controlling for Breslow thickness and Clark's level, the HR was 0.87 (0.55 – 1.37) (Table 4).

Finally, among melanoma patients, we examined the OR of having a "thicker" melanoma (Breslow thickness ≥ 0.8 mm) in relation to personal history of NMSC. The age-adjusted HR (95%CI) was 0.85 (0.61 – 1.19), and the multivariate-adjusted model yielded an HR of 0.85 (0.59 – 1.21) (Table 5). We observed similar results for the Clark's level. Women with personal history of NMSC had an age-adjusted HR of 0.85 (0.58-1.26) and multivariate-adjusted HR of 0.81 (0.52-1.24) for developing Clark's level IV and V melanoma (Table 6).

DISCUSSION

Our data indicate that personal history of NMSC predicts not only a higher risk of death from melanoma, but also was associated with an increased risk of both lethal and non-lethal melanomas. Importantly, the magnitude of this positive association was greater for non-lethal melanomas than for lethal melanomas.

Our study demonstrates that one aspect of a patient's medical history, in this case a prior diagnosis of NMSC, is an important factor when considering melanoma screening. We show that a prior diagnosis of NMSC is associated with an increased risk of subsequent melanoma diagnosis. Personal history of NMSC diagnosis indicates higher UV exposure history, the increased risk of subsequent melanoma diagnosis is not surprising. In addition, melanoma and NMSC share similar non-modifiable host factors, including light skin complex, sunburns and family history of skin cancer. These may lead us to believe that personal history of NMSC

diagnosis would be associated with more severe melanoma at time of diagnosis. However, we observed that personal history of NMSC diagnosis predicted an increased risk of non-lethal melanoma greater than that of lethal melanoma.

While a history of NMSC diagnosis increases the risk of melanoma diagnosis across the board, it may also lead to earlier detection, making it less likely that the melanoma diagnosed will be lethal. The increased rate of diagnosis of non-lethal melanomas that we observed likely stems from the increased surveillance of patients with personal history of NMSC diagnosis due to their higher likelihood of regular skin checks with a dermatologist or healthcare professional. This shows a benefit of frequent skin checks, leading to a propensity toward diagnosing non-lethal melanomas. These findings are of important clinical significance, as we demonstrate that although personal history of NMSC diagnosis increases subsequent melanoma risk, the potential benefit of early detection can help mitigate the adverse effects of the modifiable risk factors to which NMSC patients have already exposed themselves. We find this to be a critical message to our patients and the healthcare community. NMSC history portends a higher risk of melanoma diagnosis in women, but that risk can be mitigated with appropriate surveillance.

Our study has several strengths: the prospective study design, high survey response rate, large sample size, detailed covariate information allowing for the ability to control for a variety of host factors, and long follow-up. Additionally, surveys were collected from participants from a variety of locations in the United States, and the pathologic confirmation of both SCCs and melanomas by medical record review is methodologically rigorous. However, our study also has limitations. Our study was limited to white, well-educated female health professionals, making our results less generalizable to the general public. However, the fact that our population

comprised healthcare professionals implies better follow-up for their own health issues in that reporting may be more accurate and participants may be more likely to follow-up appropriate with clinicians. As such, our calculations are more likely to represent true estimates in ideal circumstances, which is helpful when quoting risks for patients. Our study focused on women and some studies have shown that the largest epidemiologic group among whom melanoma diagnosis is currently increasing is young women,[6] lending our data ongoing vital importance.

Our findings suggest the continued need for dermatologic screening for patients after NMSC diagnosis, with attention paid to the increased risk of melanoma. Early detection among NMSC patients may help decrease their deaths from subsequent melanoma.

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Table 1. Age-standardized baseline characteristics of participants with melanoma by personal history of NMSC[1]

	Personal history of NMSC	
	no	**yes**
n	930	615
Age at diagnosis, years, mean (SD)	62.4 (10.8)	69.0 (9.0)
Body mass index, kg/m^2, mean (SD)	26.1(4.8)	25.9(4.7)
Current smoking, %	8.2	7.0
Alcohol intake, g/d, mean (SD)	6.5(10.0)	7.1(11.1)
Physical activity, metabolic equivalents hours/week, mean (SD)	15.3(18.4)	16.9(19.3)
Family history of melanoma, %	9.2	12.1
Red or blonde hair, %	21.0	26.0
Childhood/adolescent tendency to sunburn or blistering response, %	44.2	55.4
Childhood/adolescent tendency to average to deep tanning response, %	62.9	50.3
Number of sunburns, 6 or more, %	57.9	71.1
UV flux, $\times 10^{-4}$ RB units, mean (SD)	124.7(25.5)	126.5(26.9)
Breslow thickness, mm, mean (SD)	1.0(1.2)	0.9(1.0)
Clark's level IV or V, %	28.2	25.5
Body site (%)		
Head and neck	17.4	20.0
Trunk	27.2	28.7
Limbs	55.4	51.3
Physical exam frequency[2] (%)	84.7(23.8)	86.5(19.3)

[1] All values shown are for the time of melanoma diagnosis or the questionnaire cycle closest to the melanoma diagnosis year except where otherwise noted. All variables other than age at diagnosis were age (at diagnosis)-adjusted

[2] Skin exam may not be included in the physical exam.

Table 2. HRs (95% CIs) for the association between personal history of NMSC and risk of melanoma death

	Personal history of NMSC	
	no	**yes**
Deaths/Person-years	53/1571590	38/284214
Age-adjusted HR (95% CI)	1.00	2.99(1.94-4.62)
Multivariate-adjusted HR[1] (95% CI)	1.00	2.89(1.85-4.50)

[1] Multivariate-adjusted analyses were performed adjusting for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hours/wk), body mass index (<25, 25-29.9, ≥30 kg/m^2), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), childhood reaction to sun (tan without burn, burn, or painful burn/blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan), times of sunburns (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), cumulative UV flux (in quintiles) and physical exam frequency. An indicator variable was created for a missing value for each covariate.

Table 3. HRs (95% CIs) for the association between personal history of NMSC and risk of incident lethal melanoma and non-lethal melanoma

	Personal history of NMSC	
	no	**yes**
Lethal melanoma		
Cases/Person-years	67/1563369	24/278654
Age-adjusted HR (95% CI)	1.00	1.97 (1.21-3.22)
Multivariate-adjusted HR[1] (95% CI)	1.00	1.74 (1.05-2.87)
Non-lethal melanoma		
Cases/Person-years	888/156339	501/278654
Age-adjusted HR (95% CI)	1.00	2.65 (2.36-2.98)
Multivariate-adjusted HR[1] (95% CI)	1.00	2.31 (2.05-2.60)

[1] Multivariate-adjusted analyses were performed adjusting for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hours/wk), body mass index (<25, 25-29.9, ≥30 kg/m^2), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), childhood reaction to sun (tan without burn, burn, or painful burn/blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan), number of sunburns (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), cumulative UV flux (in quintiles), and physical exam frequency. An indicator variable was created for a missing value for each covariate.

Table 4. HRs (95% CIs) for the association between personal history of NMSC and risk of melanoma deaths among melanoma cases only[1]

	Personal history of NMSC	
	no	**yes**
Age-adjusted HR (95% CI)	1.00	0.83 (0.54-1.29)
Multivariate-adjusted HR[2] (95% CI)	1.00	0.85 (0.54-1.33)
Multivariate-adjusted HR[3] (95% CI)	1.00	0.87 (0.55-1.37)

[1] Melanoma cases entered the followed-up only after they were diagnosed.

[2] Multivariate-adjusted analyses were performed adjusting for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hours/wk), body mass index (<25, 25-29.9, ≥30 kg/m^2), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), childhood reaction to sun (tan without burn, burn, or painful burn/blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan, for Nurses' Health Study only), number of sunburns (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), cumulative UV flux (in quintiles), and physical exam frequency. An indicator variable was created for a missing value for each covariate.

[3] Additionally adjusting for Breslow thickness and Clark's level.

Table 5. ORs (95% CIs) for the association between personal history of NMSC and the risk of Breslow thickness ≥ 0.8 mm of melanoma

	Personal history of NMSC	
	no	**yes**
Breslow thickness <0.8 mm	289	161
Breslow thickness ≥0.8 mm	170	95
Age-adjusted OR (95% CI)	1.00	0.85 (0.61-1.19)
Multivariate-adjusted OR[2] (95% CI)[2]	1.00	0.85 (0.59-1.21)

1 Analysis only among melanoma cases.

2 Multivariate-adjusted analyses were performed adjusting for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hours/wk), body mass index (<25, 25-29.9, ≥30 kg/m2), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), childhood reaction to sun (tan without burn, burn, or painful burn/blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan, for Nurses' Health Study only), number of sunburns (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), cumulative UV flux (in quintiles), and physical exam frequency. An indicator variable was created for a missing value for each covariate.

Table 6. ORs (95% CIs) for the association between personal history of NMSC and the risk of Clark's level IV and V melanoma

	Personal history of NMSC	
	no	**yes**
Clark's level I, II and III	321	151
Clark's level IV and V	112	63
Age-adjusted OR (95% CI)	1.00	0.85(0.58-1.26)
Multivariate-adjusted OR[2] (95% CI)[2]	1.00	0.81(0.52-1.24)

1 Analysis only among melanoma cases.

2 Multivariate-adjusted analyses were performed adjusting for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hours/wk), body mass index (<25, 25-29.9, ≥30 kg/m2), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), childhood reaction to sun (tan without burn, burn, or painful burn/blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan, for Nurses' Health Study only), number of sunburns (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), cumulative UV flux (in quintiles), and physical exam frequency. An indicator variable was created for a missing value for each covariate.