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The impact of longitudinal surveillance on tumor thickness for melanoma-prone families with and without pathogenic germline variants of *CDKN2A* and *CDK4*

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Abstract

Background: Skin cancer screening is routinely performed for members of melanoma-prone families, but longitudinal studies evaluating the efficacy of surveillance in this high-risk population are lacking.

Methods: We evaluated thickness for first primary melanomas diagnosed in melanoma-prone families (2 individuals with melanoma) enrolled in [NCT00040352](#) (National Cancer Institute [NCI] familial melanoma study) from 1976 through 2014; enrolled patients received routine skin cancer screening and education about skin self-exams. We used linear and ordinal logistic regression models adjusted for gender and age with a generalized estimating equations approach to report changes in thickness and tumor (T) stage over time, comparing outcomes for NCI cases diagnosed before (“pre-study”) vs. after study participation (“prospective”) and for NCI cases vs. non-familial cases (Surveillance, Epidemiology, and End Results [SEER] 9 registries).

Results: Tumor thickness was evaluated for 293 NCI (pre-study=246; prospective=47) patients. Compared to NCI pre-study cases, NCI prospective melanomas were thinner (0.6mm vs. 1.1mm; $P<0.001$) and more likely to be T1 stage (39/47 [83%] vs. 98/246 [40%]; $P<0.001$). Similar findings ($P<0.05$) were observed for familial cases with and without germline *CDKN2A* and *CDK4* mutations. Peters-Belson modeling suggested that calendar period effects of decreasing thickness in the general population (SEER 9) did not fully explain thickness trends in NCI families.

Conclusion: Participation in a longitudinal surveillance program providing skin cancer screening and education about skin self-exams was associated with thinner melanomas for members of melanoma-prone families.

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Impact: The study findings support the clinical benefit of screening (physician and self) for this high-risk population.

Keywords

melanoma; melanoma thickness; screening; melanoma-prone families; melanoma susceptibility syndromes; *CDKN2A*; *CDK4*

Introduction

In 2016, the United States Preventive Services Task Force (USPSTF) concluded that evidence was “insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults.”(1) This recommendation did not apply to groups with an elevated risk for melanoma, including individuals with a family history of melanoma or familial atypical multiple mole melanoma (FAMMM) syndrome.(2) FAMMM syndrome is defined by the presence of multiple atypical nevi (n>50) and a personal or family history of melanoma.(3) A subset of patients with FAMMM syndrome will harbor pathogenic germline variants of *CDKN2A*, which is associated with an increased risk for melanoma and pancreatic cancer.(2) Among individuals with FAMMM syndrome, the likelihood of a pathogenic germline *CDKN2A* variant is highest (20–40%) for individuals from families with ≥ 3 members with melanoma.(4,5) A smaller subset of patients with FAMMM syndrome (<1%) will harbor pathogenic germline variants of *CDK4*.(6)

In contrast to USPSTF recommendations, current guidelines from the American Academy of Dermatology and American Cancer Society recommend interval skin cancer screening for high-risk groups including individuals with pathogenic germline variants of melanoma susceptibility genes.(2,7) Several studies have previously investigated the efficacy of skin cancer screening for groups with an elevated risk for melanoma. In two prospective studies, screening with dermoscopy was associated with the diagnosis of thin melanomas (mean Breslow thickness < 0.8mm; T1a stage) for individuals with a personal or family history of melanoma or FAMMM syndrome.(8,9) Furthermore, melanomas diagnosed in 2,080 individuals belonging to 280 melanoma-prone families participating in a Swedish screening program from 1987 to 2001 showed favorable histopathologic characteristics with a median tumor thickness of 0.5mm and the absence of ulceration (24 of 26 tumors, 92%) in the majority of tumors.(10)

These prior studies had several important limitations. First, they did not include a control group to assess whether the intervention of screening directly contributed to the detection of thin melanomas.(8,9) Second, none of the prior studies systematically evaluated the efficacy of screening according to the absence or presence of pathogenic *CDKN2A* and *CDK4* germline variants, and screening of mutation carriers may be particularly important with one prior study finding an increased risk of death for *CDKN2A* mutation carriers compared to *CDKN2A* wild type individuals in melanoma-prone families.(11) Lastly, melanoma thickness in the United States general population has also been decreasing for several decades(12,13), and these prior studies did not assess the effect of decreasing thickness in

the general population on tumor thickness for melanomas detected during surveillance. To address these limitations, the current study evaluates trends in thickness for invasive melanomas diagnosed in United States melanoma-prone families by mutation status over four decades and compares them with trends in the general population.

Methods

NCI Study Population

The National Cancer Institute (NCI) familial melanoma study was initiated in April 1976. Results of this longitudinal study have included the identification of clinical (dysplastic nevi(14,15)) and genetic (germline mutations in *CDKN2A*(16) and *CDK4*(17)) risk factors for the development of melanoma in families. Currently, 1,319 individuals from 56 families have, or are, actively participating, of whom 293 have developed invasive melanoma. From April 1, 1976 through December 31, 1989, a family was eligible for the NCI study if it had two individuals (first-degree relatives) with melanoma (2 probands per family). With the dramatic increase of melanoma incidence over the calendar period of the study, the eligibility criteria changed to three or more individuals with melanoma (3 probands per family) starting on January 1, 1990. The date of last complete systematic ascertainment and confirmation of melanomas was December 31, 2014, allowing at least 5 years of follow-up for the included families.

In previous publications of NCI melanoma-prone families, we have referred to three groups of melanoma patients: “index”, the probands defining eligibility of the family (n=135); “retrospective”, family members other than probands who developed their first melanoma before or at the time of joining the study (n=111); and “prospective”, family members who developed their first melanoma after joining the study (n=47). For these analyses, we combined the index cases with the retrospective group as a larger “pre-study” group, since each group’s initial melanomas occurred prior to participating in the study and prior to receiving educational materials about melanoma prevention and early detection. Tumor thickness for the index (mean, 1.2mm) and retrospective (mean, 1.0mm) groups was also similar (P=0.10), further supporting their consolidation into a single group. Thus, we had 246 individuals in the pre-study group and 47 in the prospective group. In the pre-study group, 90 individuals developed their initial melanoma before the study started on April 1, 1976; 79 developed their first melanoma between April 1, 1976 through December 31, 1989, and 77 between January 1, 1990 through December 31, 2014. Among the prospective group, 11 individuals developed their first melanoma between April 1, 1976 through December 31, 1989 and 36 between January 1, 1990 through December 31, 2014.

When possible, we collected representative slides of pigmented lesions for systematic histologic review by one of three study pathologists: Wallace H. Clark, Jr.; David E. Elder, or Michael R. Sargen. Data were collected on standardized forms. All willing participants underwent full body skin exams and photography of pigmented lesions of interest, primarily dysplastic nevi. Participants were counselled about monthly skin self-exams using the photographs from the clinic visit(s); sun protective measures; and regular skin exams by their local physicians. We requested that participants notify us when they had pigmented lesions removed so that our study pathologists could review the lesions. Over the study

period, 600 melanomas were verified by expert review of histology slides or by pathology report.

Participants received intermittent updates of new information about melanoma from the study and were invited back to the National Institutes of Health for exams when they had lesions of concern to them or their physicians; when they could not find a care provider who was comfortable with pigmented lesion exams; after puberty for dysplastic nevi classification if not definitely diagnosed earlier; or when we conducted systematic update examinations, if they were willing.

Written informed consent was obtained from all participants or their legal guardians prior to participating in this NCI institutional review board-approved protocol (NCI 02–0211; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00040352) identifier [NCT00040352](https://clinicaltrials.gov/ct2/show/study/NCT00040352)).

Outcome Measures

We evaluated Breslow thickness and pathologic tumor (T) stage by year of diagnosis for cases from NCI melanoma-prone families (1939 to 2013) and the SEER 9 cancer registries (1973 to 2016); all individuals from NCI families were White, and therefore analyses of SEER data were also restricted to Whites. The primary aim of the analyses was to compare the thickness of initial melanomas occurring in members of high-risk families prior to the family's study participation ("pre-study") to initial melanomas occurring after participation in the study ("prospective"), taking into account calendar period changes in general population (SEER 9 cancer registries) melanoma thickness over the duration of the study. We also compared trends in tumor thickness for NCI families versus the general population. Analyses of NCI melanoma-prone families and SEER data were restricted to first primary melanomas. We used the 2017 American Joint Committee on Cancer (AJCC) 8th edition melanoma staging manual to classify pathologic tumor stage for each case.(18) Detailed information about SEER tumor thickness data is available in Table 2 footnotes.(19–21)

Statistical Analysis

We fit logistic regression with gender as the outcome and case type (SEER/NCI family) as an independent variable to assess differences between the NCI family cases and the SEER general population cases by gender. To assess differences in the distribution age of diagnosis between the NCI family cases and the SEER cases we used linear models with log-transformed age of first melanoma diagnosis as the outcome and case type as an independent variable. Correlations among family members were incorporated in the p-value (variance) computations via a generalized estimating equations (GEE)(22) approach.

Information on thickness was missing on 59 (24%) family members (all pre-study melanomas) and 6,950 (8.7%) SEER cases, and we used multiple imputation with chained regression equations (IVEware)(23) to impute it. We allowed the imputation of thickness to vary by year of diagnosis and between SEER cases and family members. All melanomas diagnosed before 1964 (n=30 pre-study melanomas) were reassigned 1964 as diagnosis year for the imputation, due to very limited numbers.

We analyzed the log-transformed values of Breslow thickness using a GEE(22) approach to accommodate correlations among family members. We fit linear models that contained calendar period (<1981, 1981–1990, 1991–2000, 2001–2010, 2011–2016) and were adjusted for gender and age (in groups <30, 30–49, 50–64 and 65+ years). Calendar period was fitted with dummy coding variables and also as a linear trend to assess changes over time. We fit models separately to the NCI families (and also separately to pre-study and prospective cases) and to the SEER data and jointly after imputation (additionally adjusting for case type [NCI study/SEER]), with an interaction term for “case type (SEER/NCI family study)” with calendar period to assess if there were differences in trends over calendar time between SEER and the NCI family study. We then exponentiated the coefficients to obtain fold changes in thickness as functions of calendar time.

To assess time trends for tumor stage, we fit multinomial distributions with cumulative logistic regression to accommodate covariates, that treated stage as ordered values. These models included calendar year and were adjusted for age and gender and we computed GEE based p-values and confidence intervals. All models were fit with SAS 9.4.

To assess if changes in melanoma thickness over time among members of the NCI family study differed from the general population we used a Peters-Belson approach.(24) For the Peters-Belson analysis, we fit calendar period coded in categories (<1981, 1981–1990 1991–2000, 2001–2010, 2011–2016), without assuming a linear relationship with Breslow thickness to the log-transformed thickness observed in SEER. The model was adjusted for age and gender (results were not noticeably different when we included interaction terms). We then fit the predicted values as the independent variable to the log-transformed thickness values observed in the family members. If the predictions agree with the observed values, then the slope estimate in the regression model for the family members should be one and the intercept should be zero (or, on the fold change scale, the fold change for the intercept should be one and the fold-change corresponding to the slope should be one). Thus, on the original thickness scale, the fold intercept multiplies the observed thickness and the slope relates to a multiplier of the predicted value. For all analyses, multiple imputations were accounted for in the computation of variances and p-values using Rubin’s formula as implemented in PROC MIANALYZE, SAS 9.4.

Results

Among NCI families, 103 (35.2%) of the 293 study subjects with melanoma developed multiple primary (n=2–32) melanomas. The two individuals who developed the highest number of multiple primary melanomas used tanning beds.(25) Of the living pre-study individuals who entered with one melanoma (n=173), 17 (9.8%) developed one to three additional melanomas. Of the living individuals who entered the study with two or more melanomas (n=40), 18 (45.0%) developed one to 26 additional melanomas. Among the pre-study group, 33 (13.4%) of the subjects were deceased from their first melanoma.

Table 1 reports the clinical characteristics of individuals from NCI melanoma-prone families (293 total cases; 246 pre-study cases; 47 prospective cases) and the SEER 9 cancer registries (n=79,530 individuals). Gender composition was similar between the NCI and SEER groups

(54% male, both groups), while age of first melanoma diagnosis was younger for members of NCI melanoma-prone families (mean age of first melanoma diagnosis: 38 vs. 55; $P<0.001$). Germline mutation status was known for 274 (94%) of 293 individuals in the NCI cohort ($n=160$ with *CDKN2A* or *CDK4* mutations; $n=114$ with no identifiable mutation in *CDKN2A* or *CDK4*).

Compared to pre-study cases, prospective melanomas were more likely to be T1 stage (39 of 47 cases [83%] vs. 98 of 246 cases [40%], $P<0.001$) and thinner (mean Breslow thickness, 0.6mm vs. 1.1mm; $P<0.001$) (Table 2). Similar findings ($P<0.05$) were observed for familial cases with and without *CDKN2A* and *CDK4* mutations (Figure 1), and also for sensitivity analyses by gender (Supplemental Table 1).

For pre-study cases, there was a 10% decrease in tumor thickness every 10 years after adjustment for age and gender (per year fold change = 0.99, 95% CI, 0.98–0.998; $P=0.03$; change in 10 years = $0.99^{10} = 0.90$) (Figure 2). Similar findings were also observed for SEER cases (per year fold change in thickness = 0.99; 95% CI, 0.98–0.99; $P=0.006$) (Figure 2). In contrast, there was no statistically significant change in thickness for prospective melanomas during the study period (per year fold change in thickness, 1.00; 95% CI, 0.99–1.02; $P=0.46$) (Figure 2).

The per year odds ratio of being in a lower tumor stage was non-significantly higher among pre-study cases (OR=1.04; 95% CI, 1.00–1.09; $P=0.07$) and similar to the statistically significant higher odds ratio of being in a lower tumor stage observed for SEER 9 cases (OR=1.04; 95% CI, 1.01–1.07; $P=0.01$). Among prospective melanomas, changes in tumor stage during the study period were non-significant, but confidence intervals were considerably wider than for pre-study and SEER cases (OR=0.98; 95% CI, 0.89–1.07; $P=0.68$) (Supplemental Table 2). Lastly, the Peters-Belson analysis using imputed data and models adjusted for gender and age showed that tumor thickness for pre-study and prospective cases was systematically lower than the thickness in SEER as indicated by the intercept terms (fold change 0.33 and 0.41, respectively, Table 3). The slope obtained from this model indicated that other than a shift, there was no difference between the pre-study cases compared to SEER (fold change for slope = 0.96), which also reflects that the curves in Figure 2 for the SEER and pre-study cases are parallel. For the prospective cases, in addition to a lower mean thickness (intercept on fold change = 0.41), the slope (fold change = 0.23) showed that they had much lower observed values than would be predicted from SEER, albeit not significantly (Table 3). Similar findings were observed for Peters-Belson analyses stratified by gender and mutation status (Supplemental Table 3).

Results from analyses restricted to individuals with complete (unimputed) data were similar to those using imputed data and are therefore not shown.

Most individuals who developed melanoma in the NCI study had clinical and/or histologic evidence of dysplastic nevi (Supplemental Figure 1). Eight individuals without dysplastic nevi developed nine melanomas; four of these carried their family's mutation, one of whom developed two melanomas (Supplemental Table 4). Three individuals were from families without identified mutations, and one was from a family with an identified mutation who did

not carry the family mutation. This person, however, had very extensive sun exposure over decades and clinically had extensive solar damage. In addition, nine individuals with dysplastic nevi developed melanoma, but did not have their family's mutation. One individual who was indeterminate for dysplastic nevi because of age at the time of exam developed melanoma, but did not have the family mutation.

Discussion

We report trends in melanoma tumor thickness over four decades for individuals of melanoma-prone families longitudinally followed at the National Cancer Institute, and compare changes in thickness for families to the general population (SEER 9 cancer registries) and between cases diagnosed before (pre-study) versus after (prospective) study participation. Prospective cases were more likely to be T1 stage and thinner than pre-study cases and similar findings were observed for individuals with and without mutations of highly penetrant melanoma susceptibility genes (*CDKN2A*, *CDK4*).

We also fit linear regression models with interaction terms and performed a Peters-Belson analysis adjusted for gender and age, which showed that all NCI family cases had systematically lower thickness than SEER cases during the study period (1976–2014). For patients diagnosed with melanoma after study enrollment, melanomas were thinner even beyond the mean shift, suggesting that screening (physician and self), provided as part of a longitudinal surveillance program, contributes to reductions in melanoma thickness for members of melanoma-prone families independent of calendar period effects. Similar findings were observed for sensitivity analyses by gender and mutation status.

The study findings are consistent with previous studies showing reductions in melanoma tumor thickness associated with screening for the general population.(26,27) The study findings are also consistent with prior analyses demonstrating an association between the diagnosis of thin melanomas (<0.8mm) and screening with dermoscopy for other high-risk groups (individuals with a personal or family history of melanoma, FAMMM syndrome). (8,9,28) It is unknown whether the decreasing thickness of tumors over time among the individuals within NCI families is associated with improved survival. However, the proportion of T1 cases, which are associated with a 5-year survival of 99%, were increased among patients diagnosed after study enrollment suggesting that the trends in thickness may improve melanoma-specific survival in this high-risk population.(18)

As part of this analysis, we also evaluated dysplastic nevi by mutation status in NCI families (Supplemental Figure 1 and Supplemental Table 4). Dysplastic nevi are often increased among individuals with pathogenic germline variants of *CDKN2A* and *CDK4*.(29,30) However, among NCI patients with melanoma from families with a mutation, clinical or histologic evidence of dysplastic nevus was not always predictive of an underlying mutation. These findings are consistent with a previous study of Swedish *CDKN2A* positive melanoma-prone families in which the presence of clinically atypical nevi was not always predictive of mutation status.(31) These data reinforce the importance of examining and following all willing members of melanoma-prone families irrespective of dysplastic nevus status.

The NCI familial melanoma study has followed high-risk melanoma-prone families for up to four decades. The close follow-up over an extended period of time permitted comparisons of pre-study versus prospective cases in the NCI cohort. Nonetheless, several limitations of our study need to be mentioned. First, the number of melanoma cases (N=293) in the NCI study was modest. Despite this limitation, we identified similar results by gender and mutation status (each analysis restricted to Whites only), which supports the overall study findings. We also used imputation of missing thickness data, which was higher in earlier years. However, a complete data analysis (without imputing data) confirmed that melanomas diagnosed after study entry were thinner and more likely to be T1 stage than pre-study cases, which suggests that long-term surveillance that includes screening (physician and self) contributes to reductions in thickness over time.

In conclusion, we demonstrate that providing screening and education about skin self-exams to melanoma-prone families enrolled in a longitudinal study is associated with a reduction in melanoma thickness and tumor stage. These changes were not fully explained by calendar period effects of decreasing thickness in the general population and point to the potential benefit of skin cancer screening for patients with a family history of melanoma and those with pathogenic germline variants of melanoma-susceptibility genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Box plot of melanoma thickness for pre-study versus prospective familial melanoma cases by *CDKN2A/CDK4* mutation status.

The above figure shows the interquartile range and median thickness for pre-study (129 *CDKN2A/CDK4* mutation carriers; 99 individuals with no mutation identified by whole exome sequencing) versus prospective (31 *CDKN2A/CDK4* mutation carriers; 15 individuals with no mutation identified by whole exome sequencing) familial melanoma cases by mutation status. P-values were calculated from generalized linear models that account for relatedness of family members.

Figure 2. Trends in tumor thickness for United States familial melanoma cases and general population.

The above figure shows changes in melanoma thickness over time for familial cases (National Cancer Institute [NCI] pre-study melanomas, NCI prospective melanomas) and the general population. Smoothed curves were produced for each group using the “lpoly” code in STATA 15 (College Station, Texas), which performs unadjusted kernel-weighted local polynomial regression. General population data was obtained from the Surveillance, Epidemiology, and End Results (SEER) 9 cancer registries. The per year fold change in tumor thickness is reported for each group using multivariable models adjusted for gender and age category (0–29, 30–49, 50–64, 65) (all cases in each group were from White patients).

Table 1.

Characteristics of National Cancer Institute melanoma-prone families and the United States general population

	National Cancer Institute melanoma-prone families	Surveillance, Epidemiology, and End Results 9 cancer registries	P-value
Date of family accrual	1976 to 2009	1973 to 2016	
Number of families	56	-	
Number of examined individuals in families ^a	1,319	-	
Number of individuals (Whites only) with melanoma	293 (100%)	79,530 (100%)	
Male	158 (54%)	42,723 (54%)	0.95 ^b
Female	135 (46%)	36,807 (46%)	
Mean age of first melanoma diagnosis (range)	38 (9 to 95)	55 (3 to 103)	<0.001
Total number of melanomas (range: # of melanomas per individual)	598 (1 to 32)	79,530 (1)	
Number of first melanomas diagnosed by metastatic disease	24	-	
Dates of diagnoses of initial melanomas	1939 to 2014	1973 to 2016	

^aIncludes all participating family members^bGlobal p-value adjusted for familial correlations among cases from National Cancer Institute melanoma-prone families

Table 2.

Thickness and pathologic tumor stage of first primary invasive melanomas by study period

	National Cancer Institute melanoma-prone families		Surveillance, Epidemiology, and End Results 9 cancer registries	National Cancer Institute pre-study vs. prospective cases	National Cancer Institute melanoma-prone families vs. Surveillance, Epidemiology, and End Results 9 cancer registries
	Pre-study cases (%)	Prospective cases (%)	Patients with invasive melanoma as their first or only cancer diagnosis (%)	P-value	P-value
Total cases	246 (100)	47 (100)	79,530 (100)		
Pathologic tumor stage for invasive melanomas ^b				<0.001 ^a	<0.001 ^a
T1	98 (40)	39 (83)	41,149 (52)		
T2	65 (26)	5 (11)	18,717 (24)		
T3	17 (6.9)	2 (4.3)	8,113 (10)		
T4	7 (2.8)	1 (2.1)	4,601 (5.8)		
Unknown	59 (24)	0	6,950 (8.7)		
Tumor thickness for invasive melanomas, mm ^c					
Mean	1.1	0.6	1.3	<0.001	0.001
Range	0.1 to >10	0.1 to 6.5	0.1 to >10		

^aComputation accounts for percent missing in each group^bAmerican Joint Committee on Cancer (AJCC) 8th edition melanoma staging

^cA case listing of melanomas in the Surveillance, Epidemiology, and End Results (SEER) 9 cancer registries was generated using the MP-SIR session in SEER*Stat and using International Classification of Diseases for Oncology codes 8721/3 (nodular melanoma), 8742/3 (lentigo maligna melanoma), 8743/3 (superficial spreading melanoma), 8744/3 (acral lentiginous melanoma), and 8745/3 (desmoplastic melanoma). All melanomas were microscopically confirmed and diagnoses were excluded if they were made by “death certificate only” or “autopsy only”. SEER variables “EOD 10 – size (1988–2003)” and “CS site-specific factor 1 (2004+ varying by schema)” were used to download melanoma thickness for cases diagnosed from 1988 through 2016. From 1973 through 1987, melanoma tumor thickness was estimated using tumor thickness ranges and Clark level. SEER variable “EOD 4 – extent (1983–1987)” provided information on tumor thickness ranges (<0.76mm; 0.76 – 1.50mm; 1.51–4.00mm; >4.00mm) from 1983 through 1987. To estimate thickness for cases diagnosed during this period, we assumed a normal distribution of thicknesses for each range, and subsequently applied the median tumor thickness (0.38mm for category “<0.76mm”; 1.13mm for category “0.76–1.50mm”; 2.76mm for category “1.51–4.00mm”) to all cases within a category. For tumors in category “>4.00mm”, we estimated a thickness of 4.0mm for all tumors since an upper limit was not available to define the median. Lastly, SEER variables “Expanded EOD(2) – CP54 (1973–1982)”, which provided information on tumor thickness categories (<2.0mm; 2.0–3.9mm; 4.0–5.9mm; 6.0–7.9mm; 8.0–9.9mm), and “Expanded EOD(5) – CP57 (1973–1982)”, which provided information on Clark level (1=in situ, Clark level 1; 2=papillary dermis, Clark level 2; 3=papillary-reticular dermal interface, Clark level 3), were used to estimate thickness for cases diagnosed from 1973 through 1982. For tumor thickness category “<2.0mm”, we assumed a maximum tumor thickness of 0.6mm, 1.0mm, and 1.99mm for cases with Clark level 2, 3, and >3 respectively. After defining the upper and lower limits for these thickness ranges using Clark level, we used a similar methodology as for the years 1983 through 1987, and applied the following median tumor thickness estimates to cases in each thickness category: 0.3mm for cases <2.0mm and Clark level 2; 0.5mm for cases <2.0mm and Clark level 3; 1.0mm for cases <2.0mm and Clark level >3; 3.0mm for cases 2.0–3.9mm; 5.0mm for cases 4.0–5.9mm; 7.0mm for cases 6.0–7.9mm; 9.0mm for cases 8.0–9.9mm.

Table 3.

Parameters (presented as fold changes) from linear regression models fit to log-Breslow thickness for first primary invasive melanomas diagnosed in National Cancer Institute melanoma-prone families compared to general population (Peters Belson analysis)

	Parameters from linear regression models fit to log-Breslow thickness with log-thickness values predicted from SEER 9 cancer registries as independent variable			
	Intercept (presented as fold change) (95% CI) ^a	P-value	Slope (presented as fold change) (95% CI) ^a	P-value
National Cancer Institute melanoma-prone families				
Before Study Enrollment (Pre-study)	0.33 (0.17, 0.65)	0.002	0.96 (0.41, 2.26)	0.922
After Study Enrollment (Prospective)	0.41 (0.08, 1.99)	0.20	0.23 (0.02, 2.16)	0.198

^aThe table reports the results of the Peters-Belson analysis for fold difference in Breslow thickness in the National Cancer Institute melanoma-prone families compared to the expected thickness computed from the Surveillance, Epidemiology, and End Results (SEER) 9 cancer registries. For this model, calendar period was coded in categories (<1981, 1981–1990, 1991–2000, 2001–2010, 2011–2016), without assuming a linear relationship to the log-transformed Breslow thickness values observed in SEER. The model was also adjusted for age and gender (results were not noticeably different when we included interaction terms). The values predicted from the SEER model were included as the independent variable in a linear model fit to the log-transformed thickness values observed in the family members.