Published OnlineFirst August 15, 2013; DOI: 10.1158/1055-9965.EPI-13-0422

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Melanoma Genetic Counseling and Test Reporting Improve Screening Adherence Among Unaffected Carriers 2 Years Later

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Abstract

Background: A major goal of predictive genetic testing for melanoma is to promote early detection to reduce mortality. This study evaluated the long-term impact of melanoma genetic test reporting and counseling on screening adherence.

Methods: This study assessed adherence to recommendations for annual total body skin examinations (TBSE) and monthly skin self-examinations (SSE) among 37 members of Utah *CDKN2A/p16* kindreds (10 unaffected carriers, 11 affected carriers, and 16 unaffected noncarriers; response rate = 64.9% of eligible participants).

Results: Two years following test reporting, adherence to annual TBSE among unaffected carriers increased from 40% to 70%. However, unaffected noncarriers' adherence decreased from 56% to 13%. Affected carriers reported TBSEs at both assessments (91% and 82%, respectively). Monthly SSE frequency remained highly variable in all patient groups: at 2 years, 29.7% reported monthly SSEs, 27.0% reported more frequent self-examinations, and 43.2% reported underscreening. However, SSE quality improved significantly: participants checked more body sites at 2 years than at baseline, especially feet, shoulders, legs, and genitals. Perceived logistic barriers to TBSEs (e.g., expensive, inconvenient) and SSEs (hard to remember, time-consuming) predicted lower adherence.

Conclusions: Unaffected carriers reported increased TBSE adherence and thoroughness of SSEs 2 years following melanoma genetic test reporting, suggesting clinical benefit in this modest sample. Unaffected noncarriers reported comparable gains in SSE thoroughness, but decreased TBSEs.

Impact: Melanoma genetic counseling and test reporting may improve adherence among unaffected carrier members of *p16* families. Further interventions to reduce logistic barriers and to promote continued screening adherence among unaffected noncarrier family members may be needed. *Cancer Epidemiol Biomarkers Prev; 22(10); 1687–97. ©2013 AACR.*

Introduction

Using next generation sequencing and molecular diagnostics, scientists are now able to establish increased risk for multiple diseases and professionals such as genetic counselors can then communicate these risks to patients. Currently, a gap exists between our understanding of molecular technologies and translating this information into public health improvements (1). Enacting these improvements may entail using genetic information to motivate prevention and early detection behaviors and reduce barriers to behavior change. The US National Human Genome Research Institute/NIH (Bethesda, MD) has identified a challenge of determining how genetic risk information can "influence health strategies and behaviours" (2). For this reason, we conducted a study of genetic test reporting for increased melanoma risk to determine whether reporting genetic information results in behavioral change and to identify beliefs associated with nonadherence that can be targeted with additional intervention.

A pathogenic *CDKN2A/p16* (or simply, *p16*) mutation inherited in a familial context confers a 76% lifetime risk of developing melanoma to U.S. residents (3). If melanoma is detected in early stages (stage IA or IB), the 5-year survival rate is 92% to 97%; however, if not detected until stage IV, the 5-year survival rate drops to 15% to 20% (4, 5). To detect melanoma in its earlier, more treatable stages, it is recommended that members of high-risk families engage in monthly skin self-examinations (SSE) and visit a physician at least annually for a total body skin examination (TBSE; ref. 6).

Melanoma genetic testing may promote more frequent and improved screening behavior among *p16*

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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doi: 10.1158/1055-9965.EPI-13-0422

Published OnlineFirst August 15, 2013; DOI: 10.1158/1055-9965.EPI-13-0422

mutation-carrying families, but most evidence to date concerns short-term outcomes in relatively small samples of mostly affected participants. One month following test reporting, Utah *p16* families showed overall improvement in SSE adherence, number of body sites examined during SSEs and intentions to obtain annual TBSEs (7). Similarly, Glanz and colleagues (8) found that participants randomly assigned to receive individualized *CDKN2A/p16* and *MC1R* genotyping results reported conducting SSEs more recently at a 4-month follow-up than control participants who received a skin cancer prevention brochure via mail. An Australian study found that 86% of carriers reported obtaining at least one professional TBSE in the year following receipt of genetic test results (up from 60% at baseline), compared with only 50% of those who declined counseling and testing (9). Trends toward increased frequency of SSE among carriers were also reported, but there were too few noncarriers ($n = 4$) to analyze. Taken together, these findings suggest some reliable short-term improvements; however, because many of the studies included all or mostly affected participants (8, 10), the impact of melanoma genetic testing on both unaffected carriers and unaffected noncarriers remains unexamined.

Thus, to more fully evaluate the impact of melanoma genetic testing on screening adherence in different patient groups and to determine the longevity of behavior change following test reporting, we evaluated changes from baseline in adherence to annual TBSEs and in the frequency and thoroughness of SSEs 2 years following test reporting and counseling. We stratified the findings by both *p16* status and melanoma history to examine patterns of change among unaffected carrier, affected carrier, and unaffected noncarrier family members. Finally, we examined perceived barriers to TBSE and SSE using both qualitative and quantitative measures. Rather than examining specific components of barriers, most work has instead examined either demographic variables or psychological predictors such as perceived skin cancer/melanoma risk or self-efficacy for conducting skin exams as predictors of SSEs (11–13).

Materials and Methods

Study population and procedures

Companion test reporting and follow-up studies were approved by the Institutional Review Board at the University of Utah (IRB#s 7916 and 13816; Salt Lake City, UT). Participants recruited for this study were adult members of two large melanoma pedigrees who had contributed DNA samples for research genetic testing through their participation in previous studies, starting with an IRB-approved study in the late 1980s that used the Utah Population Database to identify pedigrees with a hereditary pattern of melanoma (14, 15). No specific enrollment criteria for that study have been published, but the pedigrees used in this study are available (14). In the early 2000s, every living participant in the gene identification studies was invited to participate in a phenotyping study (16). This study included comprehensive phenotyping and mutation testing for *p16*, but no participants were aware of their *p16* status or the presence of the *p16* mutation in their family. As part of the phenotyping study, participants were informed of their familial risk and provided with recommendations for annual TBSE, monthly SSE, and consistent ultraviolet radiation (UVR) protection during an individual education session.

For the purposes of the present study, each of the DNA samples was subjected to genetic testing through a Clinical Laboratory Improvement Amendments-certified laboratory. Every participant in the phenotyping study who was a member of a *p16*-positive kindred ($n = 77$[1]) was recontacted and invited to participate in the present study (see 7 and 17 for additional details). The genetic counseling was provided with the test reporting free of charge and participants received modest nonmonetary incentives for completing follow-up questionnaires.

Recruitment and retention are summarized in Fig. 1. From May through November 2005, 61 (82.4%) participants completed a written baseline questionnaire immediately before undergoing a predisclosure genetic counseling session (see Predisclosure melanoma genetics education and subsequent test-reporting session below). All 61 participants elected to receive results and tailored postdisclosure counseling and 59 completed an immediate postcounseling assessment of melanoma genetics knowledge and intentions to engage in screening and photoprotection (7, 18). Two participants did not complete the postcounseling assessment. One elderly participant with a chronic illness was fatigued and asked to discontinue study participation. The other participant left to pick up his children and planned to return the questionnaire by mail, but it was never received.

Invitation to and enrollment in follow-up study of long-term outcomes

Following the postcounseling assessment, 57 of these participants from two *p16* kindreds were then invited

[1]Not included in the following analyses or the summary of recruitment and retention (Fig. 1) are 3 additional participants with a history of melanoma who tested negative for the *p16* mutation. These participants completed both baseline and follow-up assessments, but were excluded from analysis because there were too few participants to permit statistical analyses from which meaningful inferences or comparisons with other patient groups could be made. However, this group merits additional study, as their experiences with genetic counseling and test reporting are likely to be different from those of other high-risk family members, as genetic testing does not yet provide an explanation for their melanoma diagnosis. While adherence to TBSE was variable in this group (of the 3 affected noncarriers, 2 reported receiving TBSEs at both baseline and 2 years, whereas the third did not receive a TBSE at either assessment), all affected noncarriers reported highly frequent SSEs at one or both assessments.

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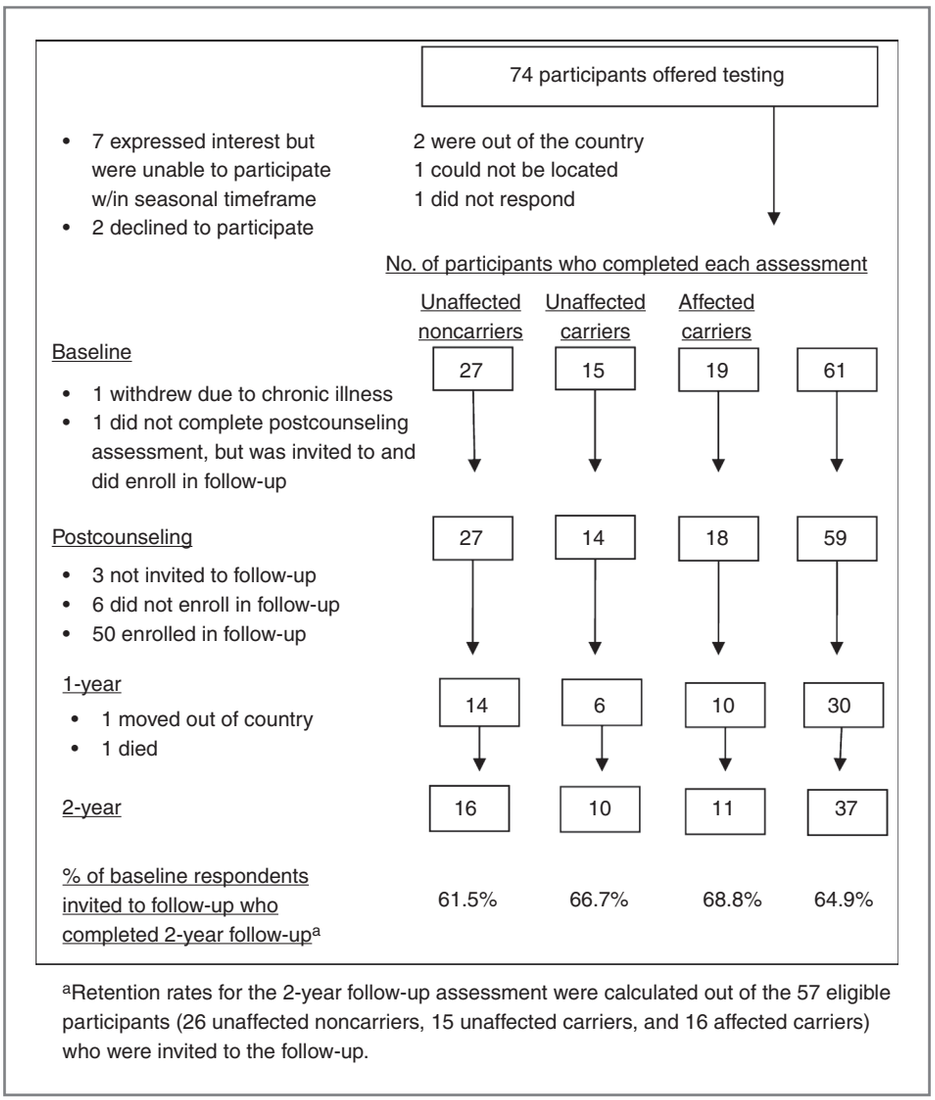

Figure 1. Recruitment, retention, and attrition of unaffected noncarriers, unaffected carriers, and affected carriers at each assessment, along with reasons for participant nonresponse to initial invitation to participate in follow-up study.

to enroll in the companion follow-up study of long-term psychological and behavioral responses to *p16* test reporting. In addition to the participant who withdrew from the study, 3 participants were not invited. One began study participation after the seasonal cutoff date (an eligibility criterion intended to provide seasonal adjustment for measures of photoprotection completed by all participants). The other 2 were not invited because 1 patient was adopted and the other was from a small kindred. Given the focus on family communication and other familial issues in other parts of the questionnaire, it was decided that the experience of these participants with genetic counseling and test reporting would be substantially different from the experiences of other participants. As shown in Fig. 1, of the 57 eligible participants, 50 (87.7%) enrolled and 30 (52.6%) completed written questionnaires at 1 year. Following an intensive effort to recontact participants, 37 (64.9%) completed the follow-up assessment at 2 years.

The final sample for analysis consisted of 37 participants (unaffected carriers, $n = 10$; affected carriers, $n = 11$; unaffected noncarriers, $n = 16$) who completed both the baseline and 2-year follow-up assessments. There was no evidence of differential attrition among the 3 patient groups, nor were there differences between participants who did or did not complete the 2-year assessment on any demographic variable (age, sex, education, income, or insurance status), baseline SSE or TBSE adherence, or perceived barriers to screening.

Predisclosure melanoma genetics education and subsequent test-reporting session

Because genetic test results were obtained through prior research (and subsequently confirmed through clinical testing), predisclosure melanoma genetics education and

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test-reporting sessions were conducted in a single session after the completion of the baseline questionnaire. Immediately before being offered the option to receive genetic test results, participants received melanoma genetics education (ref. 7; Supplementary Materials). Risk associated with *p16* mutations was presented as a 35- to 70-fold increase from general population risk and 50% by age 50 and 76% by age 80. After informed consent, participants were then offered the opportunity to receive their genetic test result, which all the 61 participants elected to do. Those testing negative for the familial mutation were informed that they still might have up to a 1.7-fold residual risk due to other familial risks such as melanoma-prone phenotype and UVR exposure. After result disclosure, photoprotection and screening recommendations (annual TBSE, monthly SSE) were provided. All participants received a letter approximately 1 month later that reiterated their test results and these management recommendations.

Measures

Standard demographic information. Participants completed standard questions concerning age, ethnicity, gender, marital status, education, income, and health insurance coverage. The health insurance questions were repeated at the 2-year follow-up to permit examination of the relationship of insurance coverage to adherence to TBSEs at 2 years.

Baseline melanoma history. We confirmed the melanoma history of each participant at baseline through pathology reports, Utah Cancer Registry (a SEER Registry), and Utah Population Database.

Genetic testing result. Sequence analysis showed two pathogenic *CDKN2A/p16* mutations in our study population: V126D and 5′UTR-34G>T.

Adherence to annual TBSE. Participants reported at baseline and at 2 years whether they had received a TBSE in the last year.

SSE frequency and monthly SSE adherence metric. At baseline and 2 years, participants reported how many exams they had completed in the past 6 months by (i) estimating a number and (ii) endorsing a verbal description of frequency (e.g., monthly, weekly). The 2 question formats showed excellent correspondence and were converted to a monthly SSE average. Because reported performance of SSE was highly variable at both assessments, we created a monthly SSE adherence metric following consultation with dermatologists to characterize behavior with respect to the recommended standard of 1 exam/month. Participants who completed no skin exams in the past 6 months were characterized as extreme underscreeners (−2); 1 to 3 exams, underscreeners (−1); 4 to 8 skin exams, adherent (0); 9 to 24 exams, overscreeners (+1); and more than 24 exams, extreme overscreeners (+2).

SSE thoroughness. The thoroughness of SSEs was assessed by the number of body sites examined from a checklist of 11 sites, ranging from the scalp to the bottoms of the feet.

TBSE and SSE barriers. Perceived barriers to TBSE and SSE were assessed at baseline and 1 year. Participants completed 11 items assessing barriers to TBSE (1 = not at all, 5 = very much). On the basis of input from dermatologists and genetic counselors (at the time of study design, no complete scale of SSE or TBSE barriers had been published), we created three TBSE scales: logistics (time-consuming, expensive, inconvenient, and influenced by whether busy; baseline $\alpha = 0.79$, 1-year $\alpha = 0.81$), embarrassment (e.g., unpleasant, embarrassing; baseline $\alpha = 0.88$, 1-year $\alpha = 0.96$), and fear (e.g., scary, makes me worry about finding a melanoma; baseline $\alpha = 0.66$, 1-year $\alpha = 0.69$). Similar barriers were assessed for SSEs with minor exceptions: for logistic barriers, we added "hard to remember to do regularly" and removed expensive (baseline $\alpha = 0.83$, 1-year $\alpha = 0.81$). In addition, single items assessed SSE embarrassment and fear. A final item assessed low SSE confidence as a barrier to screening ("Conducting thorough skin exams is difficult because I don't know what to look for").

Explanation for over- and underscreening. If participants reported conducting SSEs more or less often than once per month at the 2-year follow-up, they were asked to explain why. Two independent raters coded responses (87.9% agreement).

Results

Overview of analyses

We examined the impact of melanoma genetic test reporting and counseling on adherence to TBSE and SSE guidelines by examining changes from baseline to 2 years in (i) the percentage of participants in each patient group reporting a TBSE in the past year, (ii) adherence to monthly SSE guidelines, and (iii) reported SSE thoroughness. We additionally examined barriers to TBSEs and SSEs and their association with adherence at 2 years.

Participant characteristics

Participants were on average 45.2 years old ($SD = 14.65$)[2]. All were White, 54.1% were male, 86.5% were married, 91.9% had greater than a high school education, 91.7% reported having some type of health insurance at baseline, and their median income was $60 to $69,000. There were no significant differences in age, sex, education, income, or baseline health insurance status (0 = no insurance, 1 = some type of insurance) among the 3 patient groups. At 2 years, however, unaffected noncarriers were less likely to report health insurance coverage than either of the carrier groups. Of the 31 participants providing insurance coverage data at 2 years, 61.5% of unaffected noncarriers versus 100% of unaffected and affected carriers reported insurance coverage ($\chi^2(2) = 8.25$, $P = 0.016$).

[2]Data concerning participants' demographics and baseline adherence reported here differ from those presented in our original report (7) because they reflect the 37 adults who completed the 2-year follow-up, rather than the 58 to 62 adults whose baseline data were presented in our initial report.

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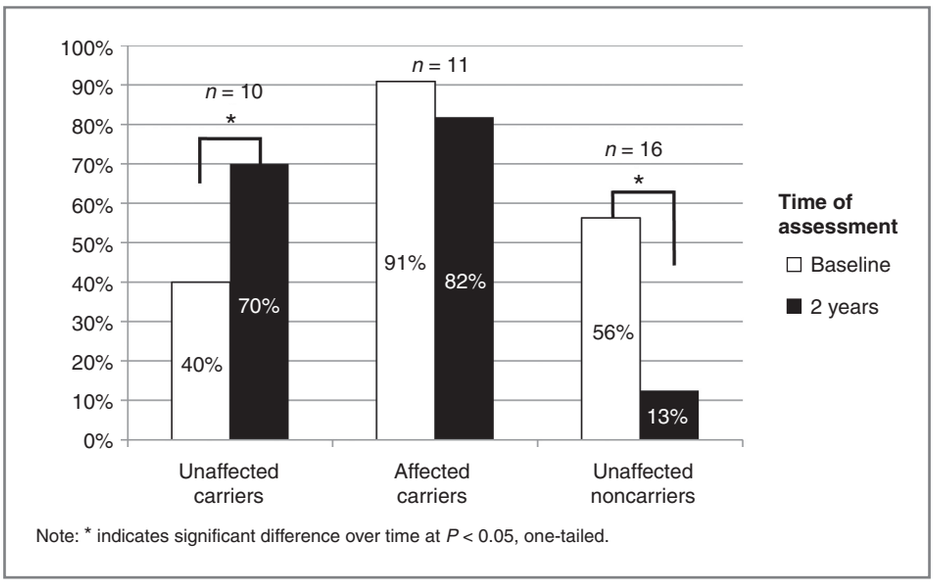

Figure 2. Percentage of unaffected carriers, affected carriers, and unaffected noncarriers reporting a TBSE in past year at baseline and 2 years following *p16* genetic counseling and test reporting.

Participants with a melanoma history ($n = 11$) had an average of 2.73 (SD = 2.45) past melanomas. Three participants, all with a personal history of melanoma at baseline, reported developing a new melanoma during the course of the study.

Changes from baseline in TBSE adherence 2 years following *p16* test reporting

Figure 2 displays adherence to TBSE at baseline and 2 years following *p16* genetic counseling and test reporting. At baseline, unaffected family members reported lower adherence to TBSE than affected family members (Fisher's exact test, $P = 0.002$). As shown in Fig. 2, unaffected carriers' TBSE adherence increased from 40% at baseline to 70% at 2 years, suggesting a benefit of *p16* test reporting and counseling, as unaffected carriers reported comparable adherence to affected carriers at 2 years (Fisher's exact test, $P = 0.635$). However, unaffected noncarriers' adherence decreased from 56% to 13% at 2 years, suggesting a decline in TBSE adherence among participants receiving negative melanoma genetic test results. The majority of affected carriers were adherent at both assessments (91% and 82%, respectively). A McNemar exact test indicated that both the increase in adherence among unaffected carriers ($P = 0.032$, one-tailed) and the decrease among unaffected noncarriers were significant ($P = 0.033$, one-tailed).

Demographic predictors of TBSE adherence. At baseline, there were no differences in TBSE adherence as a function of age, gender, income, education, or baseline health insurance status. However, participants with greater baseline income ($t(31) = 2.23$; $P < 0.04$), greater education ($t(35) = 1.83$; $P < 0.08$), and health insurance at 2 years were more likely to report a TBSE at 2 years (65.4% vs. 0%; $\chi^2(1) = 7.24$, $P < 0.012$). When analysis of TBSE performance at 2 years was restricted to the 26 participants who reported having health insurance at 2 years, the trend concerning decreased adherence among unaffected noncarriers remained similar (dropping from 50% at baseline to 25% at 2 years, $P = 0.344$, one-tailed; $n = 8$).

Changes from baseline in SSE frequency 2 years following *p16* test reporting

Monthly SSE adherence metric. As in our original report (7), the mean number of SSEs conducted in each group was uninformative due to extremely variability, ranging from 0 to 30.3 exams per month (overall M = 3.19; SD = 6.84; unaffected carriers, M = 5.69, SD = 8.47; affected carriers M = 3.15, SD = 6.67; unaffected noncarriers, M = 1.03, SD = 1.5). This variability precluded formal statistical analysis of the number of monthly exams. We instead present the percentage of respondents in each monthly SSE adherence category from extreme underscreening to extreme overscreening at each assessment (Fig. 3). First, as shown at the right of Fig. 3, 29.7% of respondents overall met the criteria for adherence to monthly SSEs at 2 years, compared to 13.5% at baseline. Of particular note, there was substantial prevalence of both overscreening (27.0%) and underscreening (43.2%) at 2 years[3]. Repeated measures ANOVAs on the adherence metric scores indicated no significant main effects or interactions of group or time of assessment (overall 2-year M = −0.19, SD = 1.20). Although there were no significant

[3]Because the adherence metric deliberately reduces variability in reported SSE frequency by assigning values from −2 to +2, it is easy to lose sight of the absolute degree of under- and overscreening reported by participants. Among underscreeners, participants reported approximately 1 to 2 exams in the past 6 months (M = 1.34, SD = 1.14), with no differences among groups [$F(2,15) = 1.04$, $P = 0.381$]. Of those underscreening, 13.5% completed no exams at 2 years and all 5 of these extreme underscreeners (4 unaffected noncarriers, 1 unaffected carrier) also reported that they did not obtain a TBSE in the previous year. Among overscreeners, participants reported approximately 62.7 exams in the past 6 months (SD = 19.59) or about 10 exams per month, with no differences among groups [$F(2,9) = 0.84$, $P = 0.473$].

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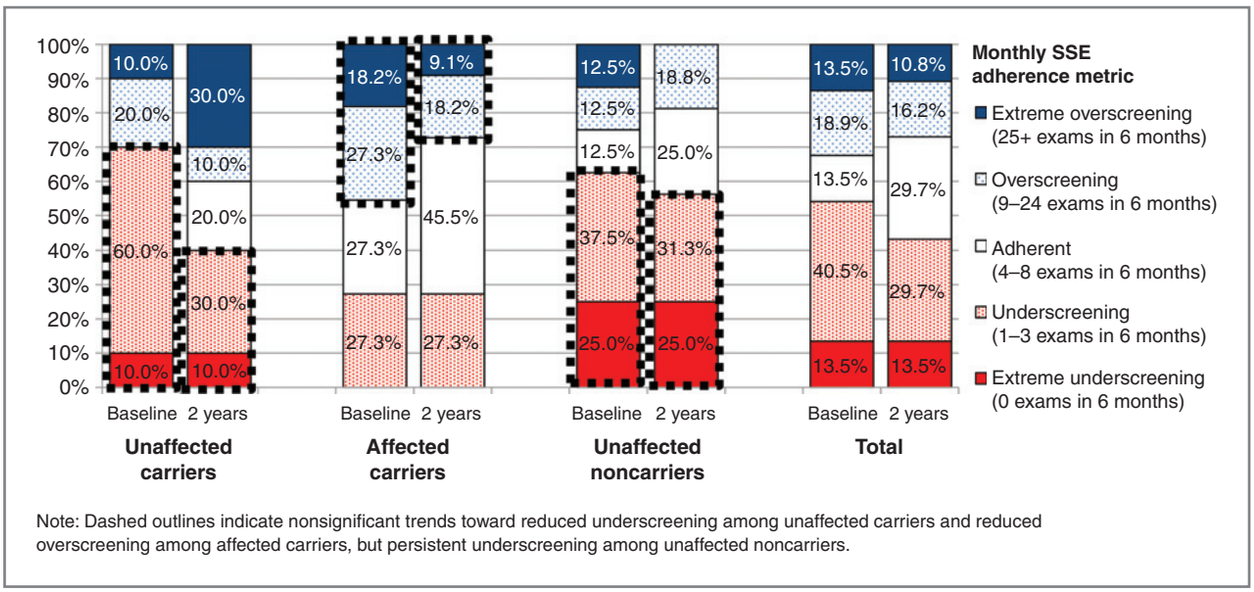

Note: Dashed outlines indicate nonsignificant trends toward reduced underscreening among unaffected carriers and reduced overscreening among affected carriers, but persistent underscreening among unaffected noncarriers.

Figure 3. Percentage of unaffected noncarriers, unaffected carriers, and affected carriers in each monthly SSE adherence category from extreme underscreening (red) to extreme overscreening (blue) at baseline and 2 years.

changes from baseline in the proportion of underscreeners in any of the 3 groups, we used black dashed outlines in Fig. 3 to characterize the trends in SSE frequency in each group following test reporting: (i) unaffected carriers' underscreening decreased from 70% to 40%, (ii) affected carriers' overscreening decreased from 45.5% to 27.3%, and (iii) unaffected noncarriers reported persistent underscreening at both assessments (62.5% and 56.3%). Last, we note that age, gender, income, and education were not significantly correlated with monthly SSE adherence or exam thoroughness at baseline or 2 years.

Number of body sites examined during SSE

Among the 32 respondents who reported at least one SSE in the past 6 months at 2 years, a main effect of time of assessment indicated that the number of body sites examined increased over time for all groups [$F(2,29) = 12.37$, $P = 0.001$]. As shown in Fig. 4, although the group $\times$ time interaction was not significant, simple effects tests indicated that unaffected carriers reported examining significantly more body sites at 2 years (M = 9.00) than at baseline (M = 6.44; $P = 0.003$), whereas unaffected noncarriers reported marginal improvement (baseline M = 7.67, 2-year M = 9.00; $P = 0.06$). Affected carriers reported examining high numbers of body sites at both assessments (baseline M = 9.36, 2-year M = 9.91, $P = 0.45$). A main effect of group [$F(2,29) = 3.96$, $P = 0.03$] indicated that affected carriers reported checking more body sites (M = 9.64) than unaffected noncarriers (M = 7.72; $P = 0.011$) and somewhat more body sites than unaffected carriers (M = 8.33; $P = 0.057$). For specific body sites checked at 2 years, participants were significantly more likely to check their feet [from 75.0%–96.9%, $F(1,29) = 10.72$, $P = 0.003$], shoulders [from 75.0%–93.8%, $F(1, 29) = 8.14$, $P = 0.008$], legs [from 84.4%–100%, $F(1, 29) = 6.93$, $P = 0.013$], and genitals [from 43.8%–68.8%, $F(1,29) = 6.71$, $P = 0.015$] and somewhat more likely to check their scalp [from 25.0%–43.8%, $F(1, 29) = 3.23$, $P = 0.083$], neck [from 84.4%–93.8%, $F(1, 29) = 3.07$, $P = 0.090$], and the bottoms of their feet [from 50.0%–62.5%, $F(1, 29) = 0.77$, $P = 0.097$].

Reported barriers to screening and their association with adherence at 2 years

We next examined reported barriers to TBSE and SSE and their relation to screening outcomes at 2 years. As shown in Fig. 5, reported barriers to screening were generally low and stable across time of assessment, with minor differences across groups. As shown in Fig. 5A, logistic barriers such as inconvenience and cost were the most highly endorsed barriers to TBSE, but did not differ by group [$F(2,26) = 2.52$, $P = 0.10$]. Perceived embarrassment about TBSEs received low ratings, with a marginal main effect of group [$F(2,26) = 2.65$, $P = 0.089$] indicating that unaffected noncarriers tended to report greater embarrassment (M = 2.71) than unaffected carriers (M = 1.40, $P < 0.06$; see Fig. 5B). As shown in Fig. 5C, reported fear as a barrier to TBSE performance was low, but tended to be greater among affected carriers than other participants [$F(2,26) = 3.14$, $P = 0.06$]. As shown in Table 1, logistic barriers at 1 year were significantly correlated with decreased adherence to annual TBSEs at 2 years[4].

[4]Although differences in the correlations with screening outcomes reported for perceived barriers at baseline and 1 year should be interpreted with caution due to the low sample sizes, it is likely that the perceived barriers at 1 year were more robust predictors of screening outcomes at 2 years because they were assessed more proximally in time to the outcomes.

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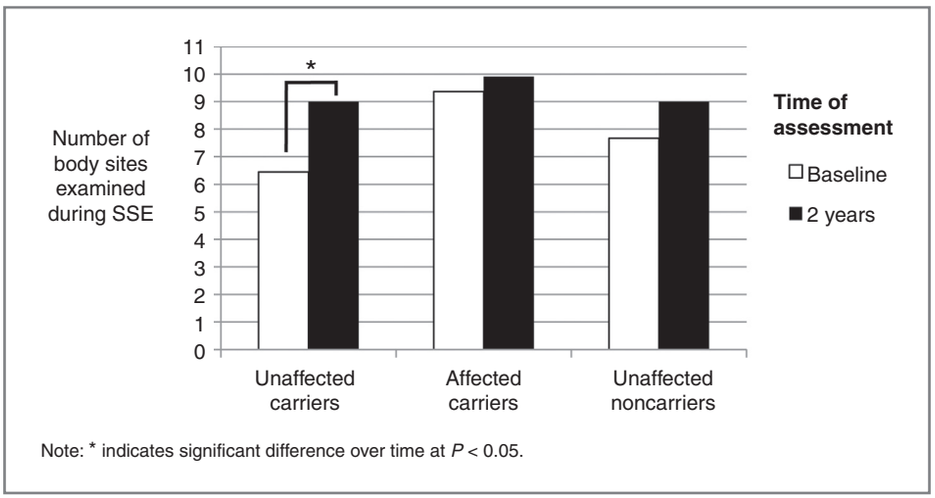

Figure 4. Number of body sites examined during SSE at baseline and 2 years following genetic test reporting in the 3 patient groups.

As shown in Fig. 5D, the only barriers to SSE substantially endorsed by any patient group were logistic barriers, for which there was a main effect of group [$F(2,21) = 5.28$; $P = 0.014$], such that unaffected noncarriers reported greater logistic barriers (M = 3.13) than affected carriers (M = 1.97; $P < 0.01$), with neither group significantly different from unaffected carriers (M = 2.60). As shown in Fig. 5E–G, there were no significant differences by group in embarrassment, fear, or low SSE confidence, respectively. For low SSE confidence, a marginal main effect of group [$F(2,25) = 3.13$, $P = 0.061$] suggested that unaffected noncarriers reported greater difficulty knowing what to look for (M = 1.82) than affected carriers (M = 1.13, $P < 0.019$), with unaffected carriers intermediate (M = 1.40). As shown in Table 1, perceived logistic barriers

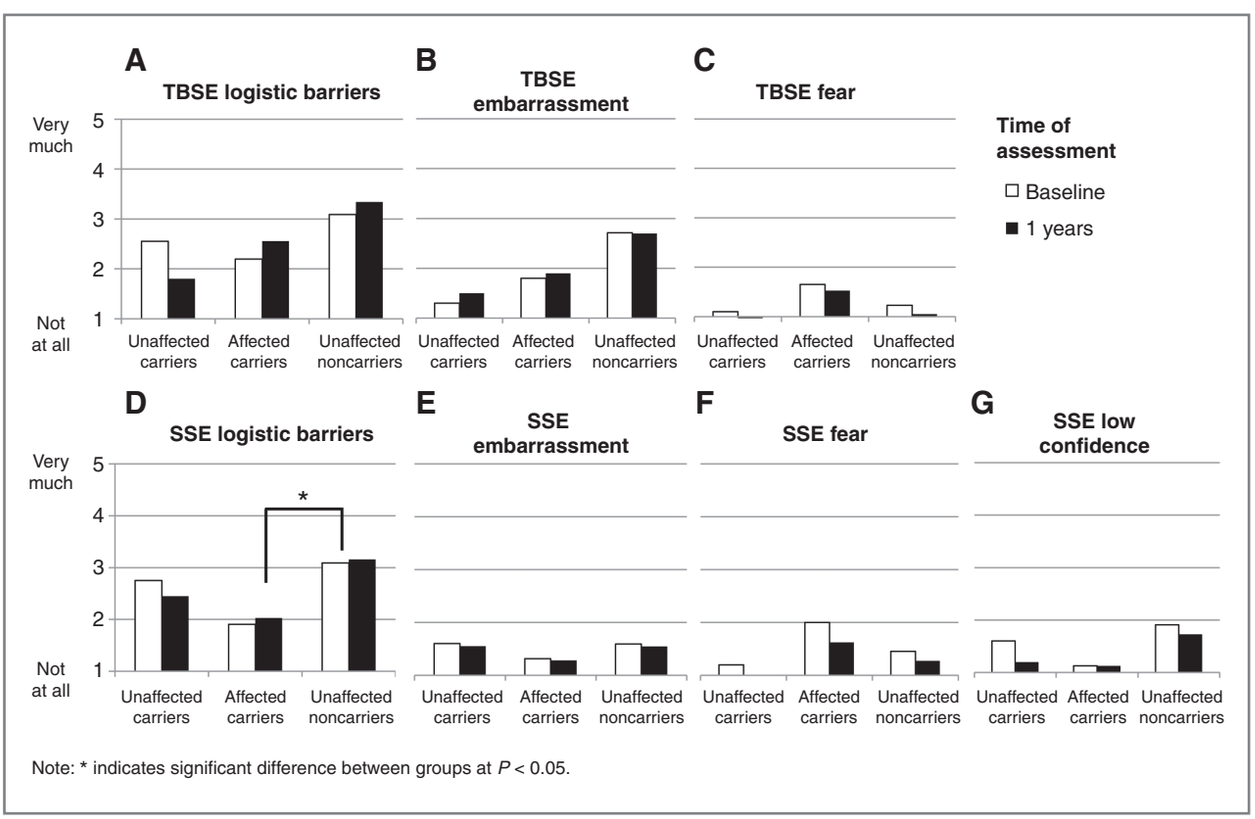

Figure 5. Perceived barriers to TBSE and SSE performance in the 3 patient groups at baseline and 1 year following genetic counseling and test reporting.

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Table 1. Correlations of barriers to TBSE and SSE at baseline and 1 year with screening adherence at 2 years, and corresponding partial correlations controlling for baseline adherence

			Adherence to skin self-exams at 2 years			
	TBSE performance at 2 years		Monthly SSE adherence metric (−2 to +2)		Number of body sites examined	
Barriers to Screening	Zero-order	Controlling for baseline	Zero-order	Controlling for baseline	Zero-order	Controlling for baseline
Baseline						
Logistic	−0.26	−0.26	−0.37*	−0.16	−0.37*	−0.43*
Embarrassment	−0.20	−0.20	−0.22	0.21	−0.12	−0.07
Fear	0.02	0.02	0.05	−0.12	−0.08	−0.10
Low confidence			−0.13	−0.09	−0.34	−0.31
1 year[a]						
Logistic	−0.59**	−0.59**	−0.58**	−0.46*	−0.37	−0.41
Embarrassment	−0.28	−0.28	0.13	−0.28	0.38	0.33
Fear	0.18	0.21	0.23	0.15	0.15	0.12
Low confidence			−0.29	−0.18	−0.05	0.09

[a]Correlations with barriers at 1 year are based on 25 participants. Correlations with number of body sites examined were conducted only for those participants who completed any SSEs at 2 years (21 participants).

*$P < 0.05$.

**$P < 0.01$.

to SSE at baseline and 1 year were significantly correlated with greater underscreening at 2 years on the monthly adherence metric, and perceived logistic barriers at baseline predicted fewer body sites checked at 2 years.

Patient-identified reasons for underscreening at 2 years. Fourteen of 16 (87.5%) participants classified as underscreeners at 2 years provided explanations. The most frequently reported reason was forgetting ($n = 6$, 42.9% of underscreeners who provided an explanation) or being too busy ($n = 5$, 35.7%). An additional subset ($n = 4$, 28.6%) reported that SSEs were too difficult or they felt unqualified and one participant reported being unaware of screening guidelines ($n = 1$, 7.1%). Finally, a minority of underscreeners ($n = 3$, 21.4%) indicated believing their risk was not high enough to warrant monthly exams.

Patient-identified reasons for overscreening at 2 years. Eight of 10 (80.0%) participants classified as overscreeners at 2 years provided explanations. Two (25.0%) indicated that they were reassured by frequent screening, whereas an additional 3 (37.5%) reported screening whenever they showered or bathed. High concern due to family history was reported by 2 (25%), and 2 (25%), reported high concern due to personal history or elevated personal risk. Finally, 2 participants (25%) reported overscreening because they believed a high level of screening would be effective and 1 (10%) reported overscreening when noticing skin changes.

Discussion

Unaffected carriers report improved adherence to screening

Unaffected carriers have the greatest potential to benefit from early detection, given both their poor baseline adherence and lack of a personal diagnosis of melanoma to motivate increased screening. Two years following melanoma genetic counseling and test reporting, unaffected carriers reported improvements in adherence to annual TBSEs and thoroughness of SSEs. Importantly, both TBSE adherence and the number of body sites examined during SSE at the 2-year follow-up were nearly as high for unaffected carriers counseled about positive *p16* test results as for those family members with a personal history of melanoma. Although the persistence of underscreening with respect to the standard of 1 SSE per month among 40% of unaffected carriers suggests room for improvement, 60% reported conducting SSEs at least monthly at 2 years. These findings, coupled with the lack of evidence for adverse psychological outcomes (depression, anxiety, or cancer worry) in the current sample (16), suggest a net benefit of melanoma genetic testing for unaffected carrier members of *p16* families.

To bolster potential positive health behavior outcomes, it will be beneficial to understand changes in health cognitions that may result from learning one's genetic risk for disease. Motivation to adhere to screening recommendations may also depend on one's specific genetic test

Published OnlineFirst August 15, 2013; DOI: 10.1158/1055-9965.EPI-13-0422

result. As noted earlier, all of the patients in the present study had received prior family history-based counseling regarding the importance of consistent SSEs and annual TBSEs. A positive test result may motivate unaffected carrier family members to perceive screening as more urgent and important. It is also possible that genetic counseling improves patient perceptions that annual TBSEs and monthly SSEs will be effective in detecting melanoma in its earlier, more treatable stages. Further studies are needed to distinguish the impact of receiving genetic test results from the impact of additional counseling and education.

Affected carriers maintain high levels of adherence to screening

For participants with a melanoma history, the goal of genetic testing may not be to increase screening, as these patients were largely adherent at baseline. Following test reporting and counseling, affected carriers maintained high levels of adherence to TBSEs and SSEs. Affected carriers also reported high rates of overscreening at both assessments. It will be important to understand whether weekly or even daily skin exams serve to reassure participants with a melanoma history that they are not having a recurrence. It will also be important to understand the impact of such frequent self-examination on early detection. Specifically, it is possible that highly frequent examination of specific lesions (weekly or even daily) may make it more difficult to detect changes in those lesions. At present, there are no data on the impact of especially frequent surveillance on screening outcomes (such as tumor thickness) in the melanoma literature either in general or specifically for members of families with *p16* mutations. Thus, an examination of the psychological and clinical outcomes of heightened vigilance to screening is needed in future research. It is important to note that we obtained no evidence that overscreening was a long-term consequence of melanoma genetic testing; instead, overscreening was reported at baseline by participants in all 3 patient groups.

Unaffected noncarriers report decreased adherence to TBSE but gains in SSE thoroughness

A long-standing concern in evaluating the impact of melanoma genetic testing is the potential for negative test results to provide a false sense of security to unaffected noncarrier members of high-risk families and thereby reduce vigilance to recommendations concerning early detection (19). For melanoma, a negative test result indicates greatly reduced risk. However, unaffected noncarriers may still be at approximately twice population risk, because *p16* families with multiple cases of melanoma may have additional phenotypic and behavioral risk factors that confer elevated risk. Unaffected noncarriers in this study were counseled to have annual TBSEs and to conduct monthly SSEs, but at present, standards of care for individuals at this magnitude of risk have not been well defined and standardized recommendations do not exist. This study found mixed evidence as to whether melanoma genetic test reporting improves screening for unaffected noncarriers. Most importantly, TBSE performance dropped sharply from baseline to 2 years. While part of this decline may be due to lack of health insurance coverage at 2 years among unaffected noncarriers, this trend for decreased adherence nonetheless suggests a need for continued follow-up and intervention to promote annual exams. In addition, at 2 years unaffected noncarriers reported exams of comparable thoroughness to those of unaffected carriers, checking an average of 9 of 11 potential body sites. However, underscreening remained prevalent in this group and a small minority of unaffected noncarriers reported neither conducting SSEs nor obtaining a TBSE at 2 years. Importantly, among unaffected noncarriers who reported underscreening, few indicated that they thought their risk was too low to warrant monthly SSEs; instead, logistic difficulties in adhering to both SSE and TBSE guidelines were reported.

Limitations and directions for future research

Although the present study is the largest to date, with 21 mutation carriers and 16 unaffected noncarriers followed over 2 years, the modest sample size is its primary limitation. This limitation was compounded by the high level of variability in reported SSE frequency. However, given the striking differences in baseline adherence among members of high-risk families, we do not believe it is optimal or desirable to combine unaffected and affected carriers in analyses of long-term adherence outcomes. Furthermore, analyzing unaffected carrier family members separately gives an improved understanding of clinical outcomes in this key group. The conclusions presented in this study await data from larger studies powered to analyze complex changes in SSE frequency in each patient group.

The high degree of prior research involvement of all patients in the present study should also be noted. Participants had not only received extensive prior counseling, but also showed considerable commitment to melanoma research by participating in two prior studies over a period of several years. With respect to the possibility that participants were especially motivated, we obtained very high levels of participation in the initial test-reporting phase of the study, along with a 2-year follow-up rate of 64.9%. We believe this response rate to be relatively high, as there were no clinic visits following the initial in-person session to motivate continued participation in multiple follow-up assessments and only modest nonmonetary compensation for participants. Thus, it is unknown whether members of high-risk families without prior research participation would respond similarly to melanoma genetic counseling and test reporting. With respect to the possibility of differential attrition, although there were no differences in baseline adherence to screening between completers and noncompleters of the 2-year assessment, it is possible that other differences among patients may have influenced continued participation in

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the study. For example, unaffected noncarriers may have been less likely to continue research participation if they thought the study was less important to them; however, there was no evidence of differential attrition among the three patient groups. Finally, we note that patients in all groups reported considerable nonadherence to screening recommendations at both baseline and 2 years. Thus, while participants likely differed from other potential samples in their demonstrated degree of commitment to melanoma research, they did not seem to be especially adherent to screening recommendations nor did there seem to be differential attrition among the groups.

The prevalence of persistent under- and overscreening in all 3 patient groups raises questions as to the underlying psychological processes and the corresponding information, motivation, and support patients from high-risk families may need to meet the monthly standard. As suggested earlier, overscreening may serve to reassure affected family members that they are not experiencing a recurrence, but it remains unknown whether overscreening reduces the effectiveness of SSEs. Both groups of unaffected family members (40% of unaffected carriers, 34% of unaffected noncarriers) reported some degree of overscreening at 2 years. With respect to the unaffected noncarriers, a study of the outcome of FAP testing indicated that 42% of unaffected noncarriers were not reassured by testing negative for the mutation and intended to continue screening (20). Although such lack of confidence in genetic test results is infrequently reported in the literature, it is possible that low-risk status may be especially difficult for a subset of unaffected noncarrier family members to accept, given their experience growing up in a family with high rates of melanoma. Furthermore, unaffected noncarriers were specifically counseled that phenotypic and behavioral factors might independently confer melanoma risk, regardless of *p16* mutation status. Thus, screening frequency may also be related to other phenotypic and behavioral risk factors, such as fair skin tone, blonde or red hair, or a personal history of sunburns. Future research may examine whether specific events following melanoma genetic testing reporting, such as diagnosis of additional family members or having a biopsy of a suspicious mole, prompt increases in SSE frequency, regardless of mutation status or melanoma history. We examined both melanoma history and genetic test result as moderators, but were underpowered to examine the impact of phenotypic, behavioral, or situational factors in conjunction with these factors. Future research may profitably do so.

Targets for intervention

As it may not be possible to prevent melanoma in some patients at high genetic risk for melanoma, screening is perhaps the most important behavior to target for improved adherence. Our findings concerning perceived barriers to SSEs suggest several targets for intervention in high-risk families. Specifically, low confidence in how to conduct SSEs, embarrassment and fear received low endorsement. Instead, logistic barriers such as inconvenience and cost may be more urgent targets for intervention in such education efforts than informational or emotional barriers. Interventions to remind participants to receive annual TBSEs and to make TBSEs more affordable and accessible (such as referrals to no- or low-cost screenings) should improve performance. For patients who forget to conduct SSEs, interventions might use automated monthly reminders, perhaps through applications on smart phones. If patients report being too busy to conduct exams, psychological interventions might target ways that participants can prioritize screening. Future work should test whether booster counseling sessions can effectively impart this sense of priority and urgency to unaffected patients. Furthermore, given the familial nature of the melanoma risk, counseling sessions and interventions might involve multiple family members, who can work to support each other in behavior change attempts. These partners, children, or parents might help the patient to prioritize these behaviors and offer reminders as needed to meet the monthly recommendation.

Conclusion

Consistent with the findings concerning the outcomes of genetic counseling and testing for other hereditary cancer syndromes (21), unaffected carrier members of *p16* families reported improvements in TBSE and SSE performance in the 2 years following melanoma genetic counseling and test reporting, whereas affected carriers maintained high levels of adherence. However, despite some gains in SSE thoroughness among unaffected noncarriers, reported TBSE performance among family members receiving negative test results decreased sharply. Because of the multifactorial nature of melanoma risk, some of these individuals may still be at a moderately increased risk and future interventions should focus on how to continue to promote appropriate adherence in the context of a negative genetic test result. Future investigations to distinguish the impact of receiving genetic test results from general genetic education and counseling is needed to determine how these different types of information affect adherence and motivation. Intervention efforts should also target logistic barriers to screening.

Disclosure of Potential Conflicts of Interest

W. Kohlmann and S.A. Leachman are consultant/advisory board to Myriad Genetics & Laboratories (Salt Lake City, UT). No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: L.G. Aspinwall, S.A. Leachman
Development of methodology: L.G. Aspinwall, S.A. Leachman
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W. Kohlmann, S.A. Leachman
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.G. Aspinwall, J.M. Taber, W. Kohlmann, S.A. Leachman
Writing, review, and/or revision of the manuscript: L.G. Aspinwall, J.M. Taber, S.L. Leaf, S.A. Leachman
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.M. Taber
Study supervision: L.G. Aspinwall, S.A. Leachman

Published OnlineFirst August 15, 2013; DOI: 10.1158/1055-9965.EPI-13-0422

Acknowledgments

The authors thank all of the family members in this study for their generous participation, without which this project would not have been possible; Marybeth Hart, Erin Dola, and Lisa Wadge for their contributions to the development of the study; Amber Kostial, Emily Bullough, Michelle Welch, Hoda Wali, Candace Larson, and Taylor Haskell for their service as study and/or clinic coordinators; Angela Newman for assistance with preparation of the manuscript; and two anonymous reviewers for helpful comments on prior versions of the manuscript.

Grant Support

This work was supported by a Funding Incentive Seed Grant, Office of the Vice President for Research, University of Utah, and a Cancer Control and Population Sciences Pilot Project Award from the Huntsman Cancer Institute (to L.G. Aspinwall and S.A. Leachman). Support was also received from the Huntsman Cancer Foundation (HCF), the Tom C. Mathews, Jr. Familial Melanoma Research Clinic endowment, the Pedigree and Population Resource of Huntsman Cancer Institute, and the Utah Population Database. This research was supported by the Utah Cancer Registry, which is funded by contract N01-PC-35141 from the National Cancer Institute (NCI) SEER Program with additional support from the Utah State Department of Health and the University of Utah. The authors acknowledge the use of core facilities supported by the NIH through National Cancer Institute Cancer Center Support Grant 5P30CA420-14 awarded to Huntsman Cancer Institute, the genetic counseling core facility supported by the Huntsman Cancer Foundation, and National Center for Research Resources grant 1KL2RR025763-01 awarded to the University of Utah by the National Institutes of Health Office of the Director. The authors were supported in part in the preparation of this article by Award Number R01 CA158322-01 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

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Received April 23, 2013; revised August 1, 2013; accepted August 5, 2013; published OnlineFirst August 15, 2013.

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Published OnlineFirst August 15, 2013; DOI: 10.1158/1055-9965.EPI-13-0422

Cancer Epidemiology, Biomarkers & Prevention

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Cancer Epidemiol Biomarkers Prev 2013;22:1687-1697. Published OnlineFirst August 15, 2013.