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Powering a prospective melanoma chemoprevention trial in high-risk cohorts

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Dear Editor,

Although daily sunscreen use can reduce melanoma risk,¹ there is considerable interest in developing chemoprevention strategies that could be used as an adjunct to sunscreen. While several agents have shown promise in early phase trials, no prospective randomized trial with melanoma as the endpoint has been performed.² Testing candidate agents is problematic given the latency of melanoma development and its relatively low incidence which may require long monitoring times and large numbers of subjects depending on their melanoma risk. However, examining a high-risk population with a higher individual risk of melanoma would allow for a smaller number of subjects to be required in such a chemoprevention trial. Designing a prospective randomized controlled chemoprevention trial with melanoma as the endpoint thus requires a reasonable estimation of melanoma risk (i.e. rate of melanoma development per person per year) in the proposed study group.

We reviewed the literature and found several studies that describe the rate of melanoma development in high-risk cohorts (Table 1). However, there is significant disparity in the observed melanoma rate among studies that is likely related to the prevalence of various melanoma risk factors among the subjects, although differences in number of subjects and length of follow-up may also have been a factor.^{3–7} Melanoma incidence rates (IR) per subject per year ranged from 0.0023 to 0.007 in low-risk subjects with self-reported risk factors and atypical nevi, to 0.015–0.019 in medium-risk subjects with personal or family history of melanoma and numerous nevi, to 0.08 in high-risk subjects including those with multiple primary melanomas and melanoma-predisposing germline mutations (Table 1). Three additional studies in high-risk cohorts reported that 12.6%,⁸ 11.5%,⁹ and 22.8%¹⁰ of

patients were diagnosed with melanoma over median follow-up periods of 8.0, 3.7 and 6.9 years, respectively, although calculation of melanoma IR per year was not provided.

Using this range of reported melanoma incidence rates from Table 1, we determined the minimum number of subjects required for a controlled trial of a candidate chemoprevention agent with 80% power to detect a 20–50% reduction in melanoma, assuming subjects would be randomized 1:1 into control and intervention arms and have five years of follow-up (Table 2). Power calculations were performed for two-sample test for proportions at the 0.05 significance level (two-sided), with new melanoma diagnosis during a 5-year follow-up period as outcome variable. An Australian sunscreen trial randomized 1621 subjects and had 10 years of clinical follow-up after the intervention period.¹ Using the 50% reduction in melanoma incidence they observed as a benchmark, 4059 low-risk subjects (with IR 0.023) per arm (or 8118 total) would be required for 80% power to detect a 50% difference in melanoma development for a single test agent (Table 2). Alternatively, 592 medium-risk subjects (with IR 0.015) per arm (or 1184 total) would be required to detect a 50% difference in melanoma development. Finally, only 82 high-risk subjects (with IR 0.08) per arm (or 164 total) would be required to achieve the same power. Fewer subjects would be needed for a study period exceeding 5 years. Reductions of 20–40% would also be clinically significant, but more subjects would be required at each risk level (Table 2). While fewer subjects from higher risk groups are needed, they are less common and thus may take longer to recruit adequate numbers.

Thus, while over 8000 low-risk subjects would be required for a randomized controlled trial of a candidate chemoprevention agent with 80% power to detect a 50% reduction in melanoma over a 5-year period, only 164 high-risk subjects would be required. Given the generally accepted lifetime risk of melanoma for U.S. Caucasians of 1–2%, it is likely that <1% of the general population is high-risk. This relatively low estimate of risk for the general population underlies the rationale for focusing a chemoprevention trial on a population subset which is high-risk. This analysis provides the information needed to determine feasibility and costs of a prospective chemoprevention trial for melanoma in high-risk subjects.

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Table 1

Reported calculations of melanoma risk from observational studies

References	Total subject #	Risk factors (number of subjects)	Surveillance period (y)	Melanoma rate ^a
Rat (2015) ⁶	3923	• Elevated risk based on self-assessment of melanoma risk score	1	0.0023
Halpern (1993) ⁴	153	• Clinically atypical nevi or history of nevi showing melanocytic dysplasia	7.8	0.007
Truong (2016) ⁷	926	• Personal history of melanoma (363) • Family history of melanoma (207) • 50 nevi (676)	5	0.015
Banky (2005) ³	309	• Personal history of melanoma (219) • Family history of melanoma (87) • 100 nevi (255) • >10 atypical nevi (165)	2.8	0.019
Moloney (2014) ⁵	311	• Personal history of melanoma and dysplastic nevus syndrome (219) • Personal history of melanoma and family history of melanoma (52) • Personal history of at least 2 melanomas (146) • Confirmed <i>CDKN2A</i> or <i>CDK4</i> germline mutation (17)	3.5	0.080

^aNumber of observed melanomas per person per year.

Table 2

Sample size estimates for prospective randomized controlled trial

Melanoma rate ^a	Reduction in melanoma diagnoses (%)	Sample size per arm (80% Power) ^b
0.0023 (low-risk)	20	30,394
	30	12,765
	40	6,762
	50	4,059
0.015 (medium-risk)	20	4,391
	30	1,850
	40	983
	50	592
0.08 (high-risk)	20	564
	30	244
	40	133
	50	82

^aNumber of expected melanomas per person per year.^bPower calculations were performed using the “power.prop.test” function in R (R Foundation for Statistical Computing, Vienna, Austria, version 3.2.0). The calculations assume no drop-ins (participants randomized to placebo control who are exposed to drug in the same class) or participant drop-out due to death from other causes, lack of adherence, etc. The general effect of both drop-ins and drop-outs would be to reduce the difference between the treatment and control groups with the intent to treat analysis. An increased sample size would be required to compensate.