

SUPPLEMENTAL MATERIALS

Patients and Study Overview

Full details regarding the participants and methods for the Genes, Environment, and Melanoma (GEM) study have been described previously.(Begg et al., 2006) In brief, the GEM study involves the population-based ascertainment of incident cases of melanoma in nine geographic regions of the world: New South Wales (Australia); Tasmania (Australia); British Columbia (Canada); Ontario (Canada); Torino (Piemonte, Italy); California (Orange County and San Diego, USA); Michigan (USA); New Jersey (USA); North Carolina (USA). The total sample size was 3,579.

Risk factors of interest were measured by data collected from a self-administered questionnaire, a telephone interview, and by testing DNA from buccal cells or blood. The study protocol was approved by the Coordinating Center's Institutional Review Board (at Memorial Sloan-Kettering Cancer Center in New York), and by those at each of the contributing sites. Physician approval was obtained prior to subject contact. Research staff obtained informed consent and a self-administered questionnaire to obtain basic demographic data, pigmentary characteristics, and residence, occupation and vacation history. Subsequently, a telephone interview lasting approximately one hour was conducted in which detailed information was obtained on the family history of melanoma and other cancers, including non-melanoma skin cancer. Pathology slides were obtained and were reviewed by one of three central pathologists (or by two if there was disagreement between the original diagnosis and that of the first review pathologist). All data were collected and sent to the Coordinating Center on a routine basis and maintained in a database. Research staff at the Coordinating Center carried out data quality assurance. Data from the self-administered questionnaire and telephone interview were transferred either by machine-scannable forms or electronically.

In the present analysis, only patients with single primary cutaneous melanoma were studied. To minimize reverse causality, patients with second or higher order invasive melanoma (n=1,110), dying within 6 months of enrollment (n=3) or missing data (n=1) were excluded, for a final analytic cohort of 2,465. Vital status was followed through 2007 or 2008.(Begg et al., 2006) Date and cause of death were obtained from National Death Indexes, cancer registries, and municipal records.(Thomas et al., 2014)

Tumor Clinicopathology and Molecular Features

Standardized pathology review assessed histologic subtype, Breslow thickness, mitosis rate, ulceration, and radial or vertical growth phase. Melanomas were classified according to histopathology criteria. Solar elastosis was evaluated on histopathologic slide review as absent or present.(Berwick et al., 2014) Degree of tumor infiltrating lymphocytes (TILs) was scored as absent, nonbrisk, or brisk.(Thomas et al., 2013) Finally, tumor sections from a random sample of 912 patients were analyzed for *NRAS* and *BRAF* mutations.(Begg et al., 2006)

Exercise Exposure Assessment

At enrollment, participants reported the frequency and duration of various exercise activities (e.g., biking, walking, jogging) participated in at least 10 days, between the hours of 9am and 5pm over the 12 months prior to diagnosis. Standardized MET values(Ainsworth et al., 2011) were assigned to each activity; ‘dose’ was calculated by multiplying the frequency of sessions per week by average session duration, weighted by the standardized activity MET. Individual activities were summed to derive a total MET-hours per week (MET-hrs·wk⁻¹). Total MET-hrs·wk⁻¹ was categorized via an unbiased quartile split (≤ 3 , >3 to ≤ 20.2 , >20.2 to ≤ 48.4 , and >48.4 MET-hrs·wk⁻¹).

Statistical Analysis

The associations between patient clinicopathologic characteristics and exercise dose were summarized using the frequency and percent and differences across groups were tested with the Chi-square test. The Kaplan-Meier method estimated overall survival (OS) and melanoma specific survival (DSS); DSS was calculated from the date of diagnosis to death from melanoma or the end of follow-up (censored patients). Cox regression models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age, sex, and study center. Melanoma treatment was not included since the follow-up period ended before recent approvals of new systemic agents.(Thomas et al., 2014) Exploratory, hypothesis-generating Cox regression models were used to estimate the age, sex, and center--adjusted HR and 95% CI for tests of interactions between dichotomous exercise dose (≤ 9 and >9 MET-hrs·wk⁻¹) and DSS on the basis of select tumor clinicopathologic or molecular features. We also conducted analyses adjusted for sun exposure (data not presented). A p-value of <0.05 was considered statistically significant. For interaction analyses, a p-value of <0.1 would be considered promising. All statistical analyses were conducted using R software version 3.2.5 (R Core Development Team, Vienna, Austria).