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The aggregation of early-onset melanoma in young Western Australian families

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ABSTRACT

Background: Few studies have examined the familial aggregation of melanoma or its co-aggregation with other cancers using whole-population based designs. This study aimed to investigate aggregation patterns in young Western Australian families, using population-based linked health data to identify individuals born in Western Australia between 1974 and 2007, their known relatives, and all incident cancer diagnoses within the resulting 1,506,961 individuals.

Methods: Cox proportional hazards regression models were used to compare the risk of melanoma for first-degree relatives of melanoma cases to that for first-degree relatives of controls, with bootstrapping used to account for correlations within families. The risk of (i) developing melanoma based on the number of first-degree relatives with other cancers, and (ii) developing non-melanoma cancers based on the number of first-degree relatives diagnosed with melanoma was also investigated.

Results: First-degree relatives of melanoma cases had a significantly greater incidence of melanoma than first-degree relatives of individuals not affected with melanoma (Hazard Ratio (HR) = 3.58, 95% bootstrap confidence interval (CI): 2.43–5.43). Sensitivity analyses produced a higher hazard ratio estimate when restricted to melanoma cases diagnosed before 40 years of age (HR = 3.77, bootstrap 95% CI: 2.49–6.39) and a lower estimate when only later-onset cases (>40 years) were considered (HR = 2.45, bootstrap 95% CI: 1.23–4.82). No significant evidence was found for co-aggregation between melanoma and any other cancers.

Conclusions: Results indicated a strong familial basis of melanoma, with the higher than expected hazard ratio observed likely to reflect early-age at onset cases in this young cohort, supported by the results of the sensitivity analyses. Exploratory analyses suggested that the determinants of melanoma causing the observed aggregation within families may be independent of other malignancies, although these analyses were limited by the young age of the sample. Determining familial aggregation patterns will provide valuable knowledge regarding improved clinical risk prediction and the underlying biological mechanisms of melanoma and other cancers.

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1. Introduction

A family history of melanoma is one of the key risk factors for the disease and is associated with an approximately two-fold increase in an individual's risk of melanoma development [1–3]. Mutations in *CDKN2A*, the primary high-penetrance susceptibility gene identified to date, account for only about 20–40% of inherited melanoma cases [4], and predisposing mutations in *CDK4* [5,6] and *MITF* [7,8] have been identified in a smaller number of families. Together, these mutations account for only a small proportion of the genetic risk in families, suggesting other genetic risk factors may exist. These unknown genetic factors may also be associated with the inheritance of other familial cancer types through pleiotropic or other mechanisms, as has been previously observed with known mutations. For example, co-aggregation between melanoma and pancreatic cancer has been noted specifically in melanoma families carrying *CDKN2A* mutations [9–12], and with kidney cancer in families with an *MITF* mutation [7,13]. Varying degrees of evidence exist for the familial co-aggregation of melanoma with other cancers [11,14–18]. Several studies have used large, population-based and genealogically linked datasets from the United States of America (Utah), Sweden and Iceland to investigate associations between cancer types [14–16,18,19]. However, the majority of studies have been conducted as family studies and often in small numbers of pedigrees [9,10,12,20–23].

Western Australia is one of the few places in the world that supports a comprehensive, population-based linkage system of health records [24]. The Western Australian Data Linkage System provides the infrastructure for the regular linkage of over 30 data collections, including a population-level genealogical system and population-based cancer registrations, enabling near total ascertainment of all incident cancer cases [24–26]. The availability of these data enables investigation into the familial patterns of disease on a large-scale in the population [24,25].

The current study therefore aimed to use linked health data to investigate the familial aggregation of melanoma in Western Australian families, by exploring the hypothesis that first-degree relatives of melanoma cases were at an increased risk of developing melanoma compared with first-degree relatives of melanoma-free controls. Exploratory analyses also investigated two hypotheses related to the co-aggregation of melanoma with other cancers. First, that individuals with a proportionally greater number of first-degree relatives affected with melanoma would be at an increased risk of developing cancers other than melanoma (non-melanoma cancers hereafter). Second, that individuals with a proportionally greater number of first-degree relatives affected with non-melanoma cancers would be at an increased risk of developing melanoma. Due to the young age of the cohort, these analyses were considered exploratory in nature, as a number of the cancers in question are known to occur most frequently in older individuals [27].

2. Materials and methods

2.1. Data linkage and study population definition

Data were extracted from the system of genealogical links (Western Australian Family Connections Genealogical System, "Family Connections" hereafter) and six statutory Western Australian Data Linkage System core datasets: Birth Registrations, Death Registrations, Midwives Notification System, Western Australian Electoral Roll, Hospital Morbidity Data System and Western Australian Cancer Registry [24,28]. Fig. S1 (Supplementary Data) illustrates the timeframe for the availability of data from each of these datasets.

Supplementary Fig. S1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2015.03.007.

Records relating to the same individuals across all datasets were linked using probabilistic matching protocols [26,29], with records from 1,530,147 individuals extracted in total. Probabilistic matching may result in some inaccuracies, although the error rate is generally considered too low to affect study outcomes [26,29]. Within the Western Australian system, the proportion of false positives and negatives due to matching errors were estimated to be as few as 0.11% in 1996 [26].

The study population comprised all births in Western Australia between 1974 (when electronic records commenced) and 2007 (when data were extracted), and all of their known relatives. Relatives were identified from Phase I of the Family Connections system, which uses available electronic birth records from 1974 onwards, marriages from 1984 and death records from 1969, to create a system of genealogical links [25]. Birth registrations are used as the primary source for creating the genealogy, as they directly define parent–offspring relationships [25]. Marriage, death and other registrations, such as Midwives Notification System records, are used to supplement the genealogy by confirming marital unions and name changes, and identifying additional relationships [25]. Degree of relatedness was subsequently calculated between genetically related individuals, identifying first-degree relatives (parents, siblings and offspring) for subsequent analyses.

Year of birth and sex were extracted for all individuals, using birth registrations or midwife notification records when available for people born in Western Australia since 1974 (68.0%), and other data sources (the Western Australian Electoral Roll, the Hospital Morbidity Data System, or Death Registrations, in that order) for the remaining cases (32.0%). The most recent record in each of these datasets was used if multiple records existed.

As death notifications are available from 1969 onwards in the linked data system, mortality data were extracted for any individual with a death record after this date. Duplicate death records were identified and excluded for 23 individuals. Cancer records were extracted for any individual with a cancer diagnosis recorded on the Western Australian Cancer Registry, which has received complete compulsory cancer notifications since 1982. An individual could have up to nine cancer diagnoses recorded. As detailed in Fig. 1, a number of cancer records were excluded for the purpose of this study such that of the initial 1,530,147 individuals extracted for the study, 28,976 had valid cancer records for analyses.

Discrepancies were noted between year of birth from demographic data and cancer record data for 1.0% of individuals diagnosed with cancer. This was considered an artefact of data collection error in one of the datasets. Cancer record data were therefore used preferentially for all individuals with a cancer record, as full date of birth and death data were available for use and could ensure more accurate and consistent age calculations.

Of the 1,530,147 individuals initially extracted from the system, 48 individuals had no sex information recorded and 18,666 individuals had no birth date available from any dataset, so were subsequently excluded. There were 2784 individuals with a date of death prior to 1982 who were also excluded, as they had died before a cancer diagnosis could be recorded on the Cancer Registry and were therefore not considered to be at risk of cancer in the current study. Similarly, three individuals who were older than 85 years in 1982 were excluded, as age variables for the study were censored at 85 years for analyses so that end-of-life increases in mortality did not bias estimates. There were 1685 individuals who had no relatives present in the sample and were also excluded, resulting in a final sample size of 1,506,961 individuals. Following these exclusions, there were 28,966 individuals in the final sample with at least one cancer diagnosis.