Familial Cancer
DOI 10.1007/s10689-016-9907-3

ORIGINAL ARTICLE

Increased incidence of bladder cancer, lymphoid leukaemia, and myeloma in a cohort of Queensland melanoma families

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Abstract Familial cancer risk has been proposed as a shared feature of many cancers, and overall susceptibility is influenced by combinations of low to moderate risk polymorphisms, rare high penetrance germline mutations, and modulation of risk by environmental and genetic factors. Clustering of melanoma occurs in approximately 10 % of families, and an over-representation of additional cancers has been noticed in some 'melanoma' families. The degree to which other cancers aggregate in families affected by melanoma has not been well defined. Therefore, this study aimed to assess the risk of cancers other than melanoma in a cohort of 178 'intermediate risk' melanoma families, not selected for specific genetic mutations. Families designated as 'intermediate risk' had two first degree relatives (FDRs) affected by melanoma when ascertained between 1982 and 1990, and were followed up over a 33 year period to assess new occurrences of cancer. We included 414 melanoma cases and 529 FDRs, comprising 25,264 person years of observation. Standardised incidence ratios and their 95 % confidence intervals were calculated for all invasive cancers, comparing observed to expected cases of cancer based on age and sex specific incidence rates for the Queensland population. Statistically significant increases were found for bladder cancer in females (observed, 7; expected, 1.99; SIR, 3.52; 95 % CI 1.41–7.25), lymphoid leukaemia in females (observed, 6; expected, 1.75; SIR, 3.43; 95 % CI 1.26–7.46), and myeloma in female melanoma cases (observed, 4; expected, 0.82; SIR, 4.89; 95 % CI 1.33–12.52). Over-representation of bladder cancer, lymphoid leukaemia, and myeloma in females of the cohort may suggest sex-dependent co-modifiers, and it is possible that specific combinations of polymorphisms predispose to certain cancer types.

Keywords Bladder cancer · Familial cancer · Lymphoid leukaemia · Melanoma · Risk

Introduction

In contrast to 'sporadic' cancer, occurring in the absence of family history or known risk genotype, the clustering of multiple cancers has been observed in some families. Familial risk has been proposed as a shared feature of many cancers, particularly for those diagnosed at a younger age and with multiple affected family members [1–4]. The degree to which certain cancers aggregate in families has been difficult to define, due to the heterogeneity of possible high penetrance germline mutations, low to moderate risk polymorphisms, genetic and environmental modifiers, and individual lifestyle factors [1, 4, 5]. However, it appears that risk of some cancers is more heritable than others [5, 6].

A positive family history is associated with increased risk of melanoma, and although familial melanoma prevalence varies by geographic region, approximately 10 % of Australian melanoma cases have an affected relative [7–9]. The cumulative risk of melanoma in first degree relatives (FDRs) of cases has been estimated at 6–7 % by the age of 80 years, with this risk rising to 10 % if the relative with melanoma was diagnosed before age 50 [10].

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Published online: 23 April 2016

The familial melanoma susceptibility gene *CDKN2A* is associated with an increased risk of cancers other than melanoma, particularly pancreatic and digestive tract cancers [11–14]. Other high-penetrance melanoma predisposition genes have also been linked to additional non-melanoma cancers, including a cancer syndrome comprising cutaneous melanoma, uveal melanoma, and mesothelioma associated with *BAP1* mutations; renal cell carcinoma with *MITF* and *BAP1*; glioma and *POT1* [15–25].

In some families affected by melanoma, additional 'over-represented' cancers continue to be observed. For both melanoma and other cancers, rare high penetrance loci cannot entirely explain observed familial rates, and it is likely that 'familial' cancer is influenced by the contribution of multiple low risk genes and modifiers inherited by susceptible individuals.

The combination of individual risk alleles may also be important, depending on whether the effects are additive or epistatic, and thus the number of inherited variants required for oncogenesis. Differences in populations with strong founder effects, different patterns of low-risk polymorphism inheritance, and specific environmental exposures, may result in different clusters of melanoma-associated cancer types between geographic regions [12].

At a population level, a unique underlying predisposition for cancer is likely conferred by the combined effects of many low risk loci and exposures, and it is possible that specific cancer types share similar combinations of polymorphisms that increase overall risk.

To investigate population level cancer risk for 'melanoma' families, the present study seeks to assess the risk of cancers other than melanoma in a cohort of families with at least two first-degree relatives affected by melanoma, not selected for specific genetic mutations.

Materials and methods

Study inclusion

The study cohort comprises 178 families originally ascertained between 1982 and 1990 as part of the Queensland Familial Melanoma Project (QFMP), designated as 'intermediate risk' due to confirmed cases of melanoma in two first-degree relatives [7]. Of the 415 families in the 'intermediate risk' group, these 178 families had not had further contact since a follow up study (The Queensland Study of Melanoma: environmental and genetic associations (Q-MEGA)) was completed between 2002 and 2005, when one or more individuals in each family answered a structured telephone interview relating to personal and family cancer information [26]. Melanoma cases and their FDRs were considered eligible for the current study if they had given written consent or had verified death information. First-degree relatives of all confirmed melanoma cases in each family were included, regardless of which individual was the proband.

For bilineal families, both family lines were considered, to account for possible polygenic inheritance. Individuals with confirmed melanoma who married into a 'melanoma' family were only considered if they had at least one child who had given written consent or had available death information. Individuals without a genetic link to any melanoma case were excluded (i.e. related only by marriage, adoption), as were all individuals who were not alive at any point during the study period regardless of melanoma status (for reason see below).

Study period

The study period (33 years) commenced in 1982, when it first became mandatory to notify all cancers in Queensland to the Queensland Cancer Registry (QCR), and concluded at the end of 2014.

Cancer verification

Information on cancer diagnoses were obtained and verified from the following sources: histopathology from the QCR or any other source; National Death Index (NDI); written confirmation from a doctor or medical professional; genetic clinic counselling information; and original medical records or cancer information sighted and transcribed by a research nurse. In the absence of any other confirmation, a self-reported melanoma excision scar of greater than 5 cm (as documented on a historical QFMP questionnaire) was considered acceptable. Any cancer reported by an individual or relative that was not supported by any of the above verification criteria was excluded.

Cancer type

Cancers were counted only for primary events, not for metastases, unless metastatic disease was the first cancer diagnosed. In the case of metastatic disease, events were counted for the histological subtype and not the organ with metastatic cancer. In this way, an individual with metastatic melanoma to the brain would only be counted for melanoma, not brain cancer. Different cancers of the same organ/type in a single individual were counted as separate events only if they were primary cancers and were histopathologically distinct. Cancers not reportable to the QCR, such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, were excluded.

Events were only counted for invasive cancers, in line with the cancer statistics reported by the QCR, defined as all invasive cancers with International Classification of Diseases for Oncology 3 (ICD-O3) site codes C00 to C80 (excluding C44 morphology codes M805 to M811, as these code for BCC and SCC) [27].

Sixteen benign or non-invasive neoplasms (i.e. with ICD-O behaviour codes of 0, 1, or 2) with histopathology confirmation were thus excluded.

Excluded neoplasms were two monoclonal gammopathies of unknown significance in two males both affected by melanoma, one parathyroid adenoma in a male FDR, one vulva intraepithelial neoplasia (VIN) III in a female FDR, one cervical intraepithelial neoplasia (CIN) I in a female FDR, one CIN II bordering on CIN III in a female affected by melanoma, and six cases of CIN III/cervical SCC in situ (five females affected by melanoma, and one FDR).

Four WHO grade I brain neoplasms were also excluded: one fibroblastic meningioma in a female FDR, one fibroblastic meningothelial meningioma in a male affected by melanoma, one meningothelial meningioma in a female FDR, and one haemangioblastoma cerebellum in a male FDR.

Cancer risk estimates

The Cancer Council Queensland publishes annual incidence of all invasive cancers, and also publishes a standardised incidence rate per 100,000 people for males, females, and total population. Annual crude incidence rates for each age and sex stratum are calculated and then applied to a standard reference population, to allow direct comparison and averages between years.

The standard population used for calculating age-standardised incidence rates by the Cancer Council Queensland is the 2001 Australian resident population, as published by the Australian Bureau of Statistics.

Based on differences in the availability of cancer incidence rates subdivided by age and sex for the study population at different periods of time, there are thus multiple valid ways that risk estimates can be derived. Cancer incidence rates are reported in the following ways: an average of incidence rates from 2008 to 2012, reported in 5 year age groups up to 85 years and over for males and females; and cancer incidence rates for each year from 1982 to 2012, reported in 15 year age groups from 35 years to 80 years and over in males and females for some cancers, and by sex only for remaining cancers. We present here data derived using two approaches: firstly based on the population statistics for the period 2008–2012; and secondly, for the period 1982–2012.

Method 1: 2008–2012

The expected number of cancers was calculated from age and sex specific published cancer incidence rates for Queensland. This was calculated first for all cancers using the 2008 to 2012 average incidence rate, age standardised in 5-year age groups from 0 up to 85 years and over [28]. Incidence rates expressed as a number of events per 100,000 people were divided by 100,000 and multiplied by the number of person years under observation in each age and sex specific stratum. The resulting numbers for each stratum were added to obtain 'expected' cancer events in the cohort and sub-groups for each cancer type.

Method 2: 1982–2012

The average of the cancer incidence over this time period was calculated, as the sum total divided by 31, reflecting 31 years of data [29]. As for Method 1, average incidence rates were divided by 100,000 and then multiplied by the number of person years in each age and sex stratum of the study cohort. For cancers where age stratified data were available (all invasive cancers, melanoma—used only in context of removing this number from total invasive cancers, breast, cervical, colorectal, lung, non-Hodgkin lymphoma (NHL), and prostate cancer), published cancer incidence rates per 100,000 persons for age groupings of age 35–49, age 50–64, age 65–79, and age 80 and over were used. No incidence rates were reported for the ages of 0–34. Therefore, to account for cancer events in persons aged 34 and younger, expected cancers for 0 to 34-year-olds were calculated by 5-year age groups from the published 2008-2012 incidence rates, and added to the total of expected cancers for age 35–80 years and over from 1982 to 2012 incidence rates.

For cancers where incidence rate data from 1982 to 2012 per 100,000 persons was only available for sex, and not stratified by age (bladder, brain, head and neck, gynaecological—combined group, ovarian, uterine, kidney, leukaemia—combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma—combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer), cancer risk estimates were obtained by multiplying the average total incidence for males and females by the number of person years under observation.

Statistical analysis

The standardised incidence ratio (SIR) was computed as the ratio of observed and expected cases of cancer. As above, expected cancers were based on age and sex specific incidence rates multiplied by the number of person years in each age and sex specific stratum. A person year was

defined as any part of a year under observation while the person was alive, with a maximum of 33 years from 1982 to 2014 inclusive. 95 % confidence intervals were computed to test the statistical significance of the SIRs, based on the Poisson distribution model. The difference between observed and expected cases was considered statistically significant if the 95 % confidence interval did not include the value of 1.

Expected versus observed cancers and 95 % confidence intervals were calculated by sex and by sub-group for individuals affected by melanoma and FDRs.

Age and sex standardized 'expected' events of melanoma were calculated for the purpose of subtracting these from the total number of expected invasive cancers, to obtain the expected number of invasive non-melanoma cancers. Melanoma risk was not analysed, as families were selected based on 'intermediate risk' melanoma status.

Results

A total of 943 individuals from 178 families were included, comprising 25,264 person years of observation. There were 414 individuals affected by melanoma, 192 males and 222 females, with 5244 and 6722 person years of observation, respectively. There were 529 FDRs of these individuals, 250 males and 279 females, contributing 5873 and 7425 person years, respectively.

Of the 178 families, 125 (70 %) had at least one individual diagnosed with non-melanoma cancer during the study period.

Of 414 individuals affected by melanoma, there were 128 non-melanoma cancer events in 102 (25 %) individuals. Of the FDRs, 134 (25 %) were also diagnosed with at least one non-melanoma cancer, with a total of 150 non-melanoma cancer events in this group.

The observed versus expected cancers were analysed in two different ways, as outlined in the methods.

2008–2012 incidence rates

Using the 2008 to 2012 incidence rates, in the overall cohort there was not a statistically significantly different number of total cancers observed than expected (observed, 278; expected, 291.43; SIR, 0.95; 95 % CI 0.85–1.07). Bladder, haematological, and thyroid malignancies were modestly increased (Table 1).

When separated by sex, no cancers reached statistical significance in males (Table 2). In females, increases in observed numbers of bladder cancer (observed, 7; expected, 1.99; SIR, 3.52; 95 % CI 1.41–7.25) and lymphoid leukaemia (observed, 6; expected, 1.75; SIR, 3.43; 95 % CI 1.26–7.46) were statistically significant (Table 3; Fig. 1).

Considering the individuals with melanoma separately, myeloma was statistically significant for the overall group (observed, 6; expected, 1.97; SIR, 3.04; 95 % CI 1.12–6.62). However, when separated by sex, myeloma was only significant for females (observed, 4; expected, 0.82; SIR, 4.89; 95 % CI 1.33–12.52). Bladder cancer was also statistically significant for females affected by melanoma (observed, 4; expected, 0.87; SIR, 4.59; 95 % CI 1.25–11.76). There were slightly more renal, haematological, and thyroid cancers than expected in melanoma cases, but these cancers did not reach statistical significance.

In FDRs of individuals with melanoma, either as a combined group or stratified by sex, no cancers reached statistical significance.

1982–2012 incidence rates

Comparing the study population to the average age and sex standardised incidence rates from 1982 to 2012, observed versus expected total non-melanoma invasive cancers was not significantly increased (observed, 278; expected, 267.30; SIR 1.04; 95 % CI 0.92–1.17).

For cancers with available age and sex standardised incidence rates, there were modest increases in observed events of NHL (16 observed, 9.71 expected) and female breast cancer (40 observed, 31.79 expected), however these differences were not statistically significant.

The remainder of cancers had incidence rates for males and females (available as an incidence rate by sex only) from 1982 to 2012. A number of cancers reached statistical significance for males and females combined—bladder, kidney, leukaemia, lymphoid leukaemia, lymphoma, myeloma, mesothelioma, pancreas, and thyroid (Table 1).

Statistically significant cancers with more than ten observed events each were bladder cancer (observed, 12; expected 3.93; SIR, 3.05; 95 % CI 1.58–5.33), leukaemia, mostly comprised of lymphoid leukaemia (observed, 12; expected 3.73; SIR, 3.22; 95 % CI 1.66–5.63), and lymphoma (observed, 17; expected 4.63; SIR, 3.68; 95 % CI 2.14–5.88).

The only cancers with at least five events to be statistically significant in males only were lymphoma, with 9 observed and 2.38 expected cases (SIR, 3.78, 95 % CI 1.73–7.18), and kidney cancer, with 7 observed and 1.85 expected cases (SIR, 3.78; 95 % CI 1.52–7.79) (Table 2; Fig. 2).

In females, bladder cancer (observed, 7; expected, 0.98; SIR 7.12; 95 % CI 2.86–14.66), thyroid cancer (observed, 5; expected, 1.30; SIR, 3.85; 95 % CI 1.25–8.99), and haematological malignancies were statistically significant. Leukaemia (observed, 7; expected, 1.59; SIR, 4.40; 95 % CI 1.77–9.07), including lymphoid leukaemia (observed, 6; expected, 0.77; SIR, 7.81; 95 % CI 2.87–17.00), lymphoma (observed, 8; expected, 2.21; SIR, 3.62; 95 % CI 1.56–7.14), and myeloma (observed, 4; expected, 0.62; SIR, 6.43; 95 % CI 1.75–16.47) were also all statistically significant (Table 3; Fig. 2).

Table 1 Observed versus expected invasive cancers, combined male and female

Cancer site/type	Observed	1982–2012*†			2008–2012		
		Expected	SIR	95 % CI	Expected	SIR	95 % CI
All invasive non-melanoma	278	267.30	1.04	0.92–1.17	291.43	0.95	0.85–1.07
Bladder	12	**3.93**	**3.05**	**1.58–5.33**	7.71	1.56	0.80–2.72
Brain	5	1.76	2.84	0.92–6.64	3.50	1.43	0.46–3.33
Breast	40	31.79	1.26	0.90–1.71	36.70	1.09	0.78–1.48
Colorectal	34	42.92	0.79	0.55–1.11	43.34	0.78	0.54–1.10
Gynaecological	8	6.17	1.30	0.56–2.56	12.66	0.63	0.66–1.95
Cervical	2	2.54	0.79	0.10–2.85	1.58	1.27	2.19–9.98
Ovarian	2	1.73	1.16	0.14–4.18	3.51	0.57	0.07–2.06
Uterine	3	2.17	1.38	0.28–4.04	5.90	0.51	0.10–1.49
Leukaemia (all)	12	**3.73**	**3.22**	**1.66–5.63**	9.25	1.30	0.67–2.27
Lymphoid leukaemia	8	**1.80**	**4.44**	**1.92–8.75**	4.37	1.83	0.79–3.61
Myeloid leukaemia	4	1.53	2.62	0.71–6.70	3.24	1.23	0.19–2.71
Lymphoma (all)	17	**4.63**	**3.68**	**2.14–5.88**	12.57	1.35	0.79–2.17
NHL	16	9.71	1.65	0.94–2.68	11.84	1.35	0.77–2.19
Myeloma	6	**1.39**	**4.32**	**1.59–9.40**	4.20	1.43	0.52–3.11
Head and neck	6	3.90	1.54	0.56–3.35	8.76	0.68	0.25–1.49
Kidney	9	**3.25**	**2.77**	**1.27–5.26**	9.38	0.96	0.44–1.82
Liver	2	0.89	2.26	0.27–8.15	3.51	0.57	0.07–2.06
Lung	27	31.45	0.86	0.57–1.25	32.35	0.83	0.55–1.21
Mesothelioma	3	**0.53**	**5.71**	**1.18–16.68**	2.35	1.28	0.26–3.73
Pancreatic	7	**2.50**	**2.80**	**1.13–5.78**	7.51	0.93	0.37–1.92
Prostate	49	44.29	1.11	0.82–1.46	54.53	0.90	0.66–1.19
Stomach	4	2.68	1.49	0.41–3.82	5.16	0.78	0.21–1.98
Thyroid	7	**1.57**	**4.45**	**1.79–9.17**	4.27	1.64	0.66–3.38

Bold type indicates statistical significance

SIR standardised incidence ratio, calculated as observed/expected; *NHL* non-Hodgkin lymphoma

* Expected cancers standardized by age and sex: all invasive cancers, breast, cervical, colorectal, lung, NHL, and prostate cancer

† Expected cancers standardised by sex only: bladder, brain, head and neck, gynaecological—combined group, ovarian, uterine, kidney, leukaemia—combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma—combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer

Lymphoid leukaemia was significant both for females affected by melanoma and female FDRs. Lymphoma and myeloma remained statistically significant when considering females affected by melanoma separately, but were not significant for FDRs.

Brain cancer was increased for females in the group (observed, 4; expected, 0.82; SIR 4.87; 95 % CI 1.33–12.46), mostly owing to female FDRs.

Discussion

This study investigated cancer in 178 'intermediate risk' melanoma families, not selected for genetic mutations. The main finding of this present analysis is the significance of bladder cancer and lymphoid leukaemia in females of the cohort, and myeloma in females affected by melanoma.

A greater number of other cancers were significant in the 1982–2012 analysis. However, the non-age standardised results must be interpreted with caution due to differences in the age distribution of the 2001 standard population and the study cohort population. While the 2008–2012 data is more precise due to narrower bands of age standardisation, the 1982–2012 method may reveal differences in cancer incidence and population trends over time that is more representative of the study population. Incidence counts of invasive cancer in Queensland have increased since 1982, and remain elevated even when standardised against a reference population to account for the changing demographics of an 'aging' population with more cancer events in older Australians [29]. Incidence rates of different

Table 2 Observed versus expected invasive cancers, males

Cancer site/type	Observed	1982–2012*†			2008–2012		
		Expected	SIR	95 % CI	Expected	SIR	95 % CI
All invasive non-melanoma	156	155.75	1.00	0.85–1.17	164.86	0.95	0.80–1.11
Bladder	5	2.94	1.70	0.55–3.97	5.77	0.87	0.28–2.02
Brain	1	0.91	1.10	0.03–6.13	1.88	0.53	0.01–2.96
Breast	2						
Colorectal	24	22.88	1.05	0.67–1.56	23.10	1.04	0.67–1.55
Leukaemia (all)	5	2.11	2.37	0.77–5.75	5.53	0.90	0.29–2.11
Lymphoid leukaemia	2	1.01	1.98	0.24–7.14	2.59	0.77	0.09–2.79
Myeloid leukaemia	3	0.84	3.55	0.73–10.39	1.85	1.62	0.33–4.74
Lymphoma (all)	9	**2.38**	**3.78**	**1.73–7.18**	6.94	1.30	0.59–2.46
NHL	8	5.15	1.55	0.67–3.06	6.58	1.22	0.52–2.40
Myeloma	2	0.77	2.59	0.31–9.37	2.40	0.83	0.10–3.01
Head and neck	4	2.70	1.48	0.40–3.80	6.19	0.65	0.18–1.65
Kidney	7	**1.85**	**3.78**	**1.52–7.79**	5.56	1.26	0.51–2.59
Liver	1	0.59	1.69	0.04–9.39	2.40	0.42	0.01–2.32
Lung	19	22.63	0.84	0.51–1.31	19.85	0.96	0.58–1.49
Mesothelioma	3	**0.49**	**6.18**	**1.27–18.06**	1.93	1.55	0.32–4.54
Pancreatic	4	1.29	3.11	0.85–7.97	3.73	1.07	0.29–2.75
Prostate	49	44.29	1.11	0.82–1.46	54.53	0.90	0.66–1.19
Stomach	3	1.74	1.72	0.36–5.04	3.34	0.90	0.19–2.62
Thyroid	2	0.37	5.46	0.66–19.71	1.16	1.72	0.21–6.23

Bold type indicates statistical significance

SIR standardised incidence ratio, calculated as observed/expected; *NHL* non-Hodgkin lymphoma

* Expected cancers standardized by age and sex: all invasive cancers, breast, cervical, colorectal, lung, NHL, and prostate cancer

† Expected cancers standardised by sex only: bladder, brain, head and neck, kidney, leukaemia—combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma—combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer

cancers have also varied over the study period, possibly reflecting environmental and screening factors [30]. It is likely that the 'real' value falls somewhere between the estimates from the two methods.

Significant cancers

Bladder

Reports of a possible association between risks of bladder cancer and melanoma are varied, although one population-based study found it to be the only significant non-melanoma cancer in relatives of individuals with multiple primary melanomas [1, 31]. Cases of bladder cancer have been documented in melanoma families affected by mutations in *MITF*, *TERT*, and *BAP1*, but a heritable link between these cancer types has not been proven [20, 25, 32]. Telomerase reverse transcriptase (*TERT*) gene promoter mutations initially described in melanoma have since been identified in bladder cancer, including a rare segregating variant initially found in a large melanoma family [32]. This T > G variant, located -59 base pairs from the ATG translation start site of *TERT*, generated binding motifs for Ets and ternary complex transcription factors, and has since been noted in a bladder tumour [33]. A recent study identified germline single nucleotide substitutions in the proximal promoter of *TERT* in more than 50 % of bladder tumours, including some that were also confirmed as somatic in distinct tumours [34]. The frequency (more than two-thirds) of somatic alterations in a variety of tumour stages suggests that *TERT* promoter alterations may be a common early event in bladder tumorigenesis [33–35]. Somatic alterations in *BAP1* were also recently detected in 15 % of bladder tumours [34]. Although multiple susceptibility loci have been proposed, segregating germline bladder cancer mutations are infrequently reported [36]. Several multiple-case bladder cancer families contain individuals with other cancers, but there seem no specific sites or inheritance modes [37]. In a two-case bladder cancer family, a novel germline balanced

Table 3 Observed versus expected invasive cancers, females

Cancer site/type	Observed	1982–2012*†			2008–2012		
		Expected	SIR	95 % CI	Expected	SIR	95 % CI
All invasive non-melanoma	122	115.24	1.06	0.88–1.26	126.14	0.97	0.80–1.15
Bladder	7	**0.98**	**7.12**	**2.86–14.67**	**1.99**	**3.52**	**1.41–7.25**
Brain	4	**0.82**	**4.87**	**1.33–12.46**	1.60	2.50	0.68–6.40
Breast	40	31.79	1.26	0.90–1.71	36.70	1.09	0.78–1.48
Colorectal	10	20.03	0.50	0.24–0.92	20.03	0.50	0.24–0.92
Gynaecological	8	6.17	1.30	0.56–2.56	12.66	0.63	0.27–1.25
Cervical	2	0.98	2.03	0.25–7.34	1.58	1.27	0.15–4.57
Ovarian	2	1.73	1.16	0.14–4.18	3.51	0.57	0.07–2.06
Uterine	3	2.17	1.38	0.28–4.04	5.90	0.51	0.10–1.49
Leukaemia (all)	7	**1.59**	**4.41**	**1.77–9.08**	3.69	1.90	0.76–3.91
Lymphoid leukaemia	6	**0.77**	**7.81**	**2.87–17.00**	**1.75**	**3.43**	**1.26–7.46**
Myeloid leukaemia	1	0.69	1.45	0.04–8.09	1.39	0.72	0.02–4.01
Lymphoma (all)	8	**2.21**	**3.62**	**1.56–7.14**	5.56	1.44	0.62–2.84
NHL	8	4.57	1.75	0.76–3.45	5.21	1.54	0.66–3.03
Myeloma	4	**0.62**	**6.43**	**1.75–16.47**	1.81	2.21	0.60–5.66
Head and neck	2	1.02	1.95	0.24–7.06	2.33	0.86	0.10–3.10
Kidney	2	1.34	1.49	0.18–5.39	3.72	0.54	0.07–1.94
Liver	1	0.27	3.70	0.09–20.63	1.04	0.96	0.02–5.36
Lung	8	9.23	0.87	0.37–1.71	12.55	0.64	0.28–1.26
Mesothelioma	0	0.89	–	–	0.43	–	–
Pancreatic	3	1.19	2.53	0.52–7.40	3.73	0.80	0.17–2.35
Prostate							
Stomach	1	0.92	1.09	0.03–6.07	1.78	0.56	0.01–3.13
Thyroid	5	**1.30**	**3.85**	**1.25–8.99**	3.32	1.51	0.49–3.51

Bold type indicates statistical significance

SIR standardised incidence ratio, calculated as observed/expected; *NHL* non-Hodgkin lymphoma

* Expected cancers standardized by age and sex: all invasive cancers, breast, cervical, colorectal, lung, and NHL

† Expected cancers standardised by sex only: bladder, brain, head and neck, gynaecological—combined group, ovarian, uterine, kidney, leukaemia—combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma—combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer

translocation affecting expression of *CDC91L1* at 20q11 was found in a 29-year-old male with bladder and renal pelvis transitional cell carcinoma [38]. In addition to a father with prostate cancer, the proband also had a brother who died at age 27 of metastatic melanoma. Given the young age of diagnosis in both brothers with bladder cancer and melanoma, it is plausible that this represents an extremely rare germline variant predisposing to both tumours. Over-expression of the cell division cycle 91-like 1 (CDC91L1) protein (75 %) and micro-RNA (30 %) in bladder cancer has subsequently been found in primary bladder carcinomas and cell lines [39]. In our study, more women than men were affected by bladder cancer, in contrast to higher population incidence in men worldwide. Tobacco smoke exposure that was historically biased toward men has now equalised, and despite the known vulnerability of bladder tissue to smoking, rates of male and female cancer have not matched modern smoking trends [40]. Causes of bladder cancer in women specifically have been inconclusive, with varying reports on parity, menopause, and hormone replacement therapy [41].

Lymphoid leukaemia

A bidirectional association between melanoma and leukaemia has been established, and melanoma risk following CLL appears particularly increased in the Australian population [42–45]. A host of factors including environmental ultraviolet light exposure, chronic immunosuppression, and genetic components have been proposed [42]. Although lymphoid leukaemia has a strong genetic component for concordant cancer, linkage studies have failed to account

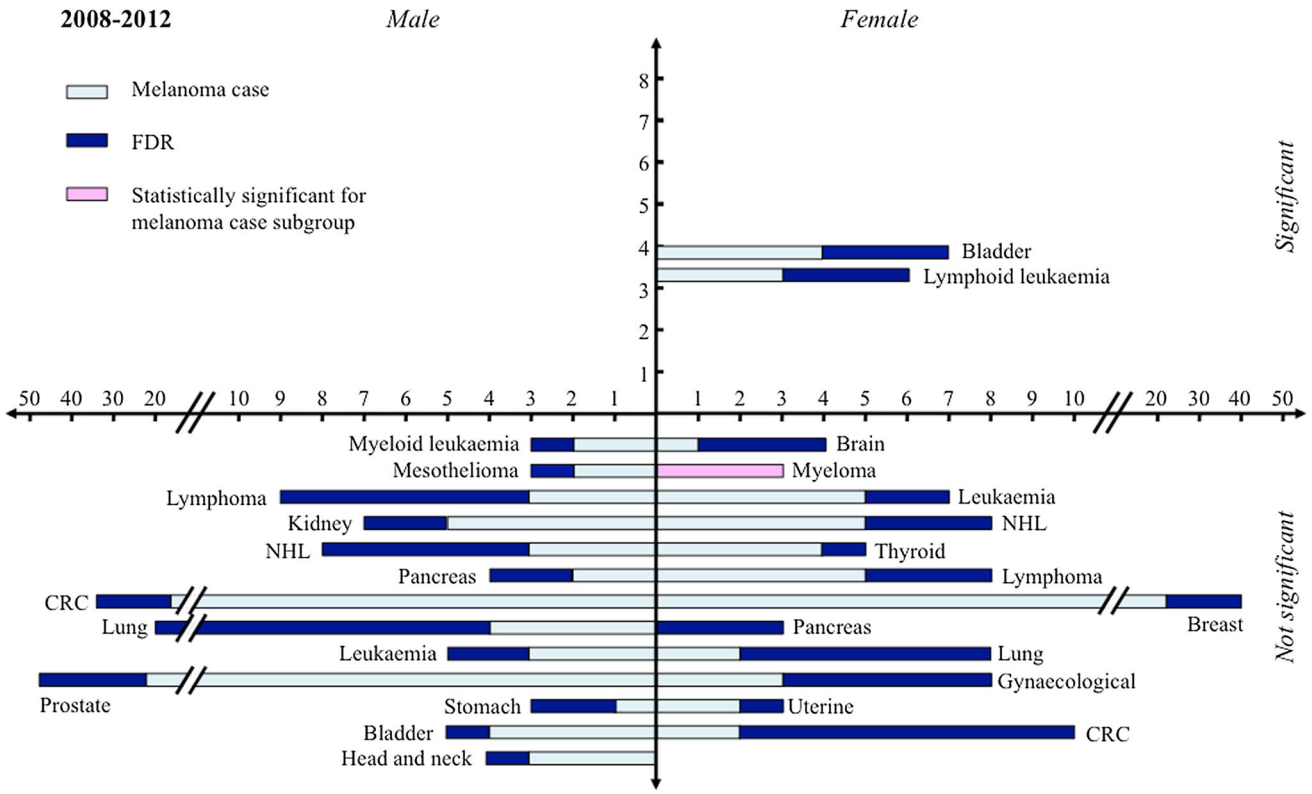

Fig. 1 Frequency of cancers with ≥3 observed events, for males and females, ranked in order of significance from 2008 to 2012 analysis. The position of statistically significant cancers corresponds to the odds ratios for each cancer type, indicated by numbered values on the positive *y* axis. Cancers that were not statistically significant are ranked in order of decreasing odds ratios on the negative *y* axis. The values on the *x* axis indicate frequency of cancer. *CRC* colorectal cancer, *NHL* non-Hodgkin lymphoma

for familial risk. However, a number of SNPs have demonstrated significance, and it is proposed that familial and sporadic CLL share many common elements. One novel variant allele, of *DAPK1* at chromosome band 9q22, was found to segregate with CLL in a six-case family, and was initially considered a private mutation until recent detection of germline *DAPK1* allele-specific expression in 14 % of tested CLL cases [46, 47]. A link between melanoma and CLL has been identified following the discovery of a shared mutation in *POT1,* in the germline of a melanoma family and somatically in CLL [21, 48]. One *POT1* germline mutation carrier had a history of both cancers, and it is possible that a common variant could influence cancer pathways for both melanoma and leukaemia [21, 22, 48]. Like *POT1*, the recently identified melanoma predisposition gene *ACD* is also involved in maintenance of telomere length as part of the shelterin complex, and the presence of both melanoma and leukaemia in an *ACD* mutation carrier could feasibly represent a shared link [49]. An over-representation of females with lymphoid leukaemia in our cohort may be explained by a finding of a greater affected proportion of females with familial CLL compared to sporadic CLL. It is projected that sex specific differences in penetrance or modifiers may be a feature of the discrepancy [50].

Myeloma

A significantly increased risk of myeloma for FDRs of melanoma cases has been noted in both the Utah and Swedish population databases, although the reverse has not been detected in familial multiple myeloma [1, 2, 51, 52]. Studies on familial clustering of myeloma have demonstrated increased risk of concordant cancer, as well as leukaemia (particularly CLL), and a common aetiologic pattern for the clustering of these cancers has been proposed [51, 52]. Other cancers linked to familial myeloma include colorectal, breast, non-thyroid endocrine, and prostate cancer [52]. A higher risk of myeloma has been identified for daughters of affected cases, with the highest risk in daughters of affected mothers (SIR 4.58) [51]. This sex correlation replicates previous results, and a female predilection possibly represents a heritable sex-specific modifier or common susceptibility, which may explain the findings of significance for females only in our cohort [51]. Most family studies suggest an autosomal dominant mode

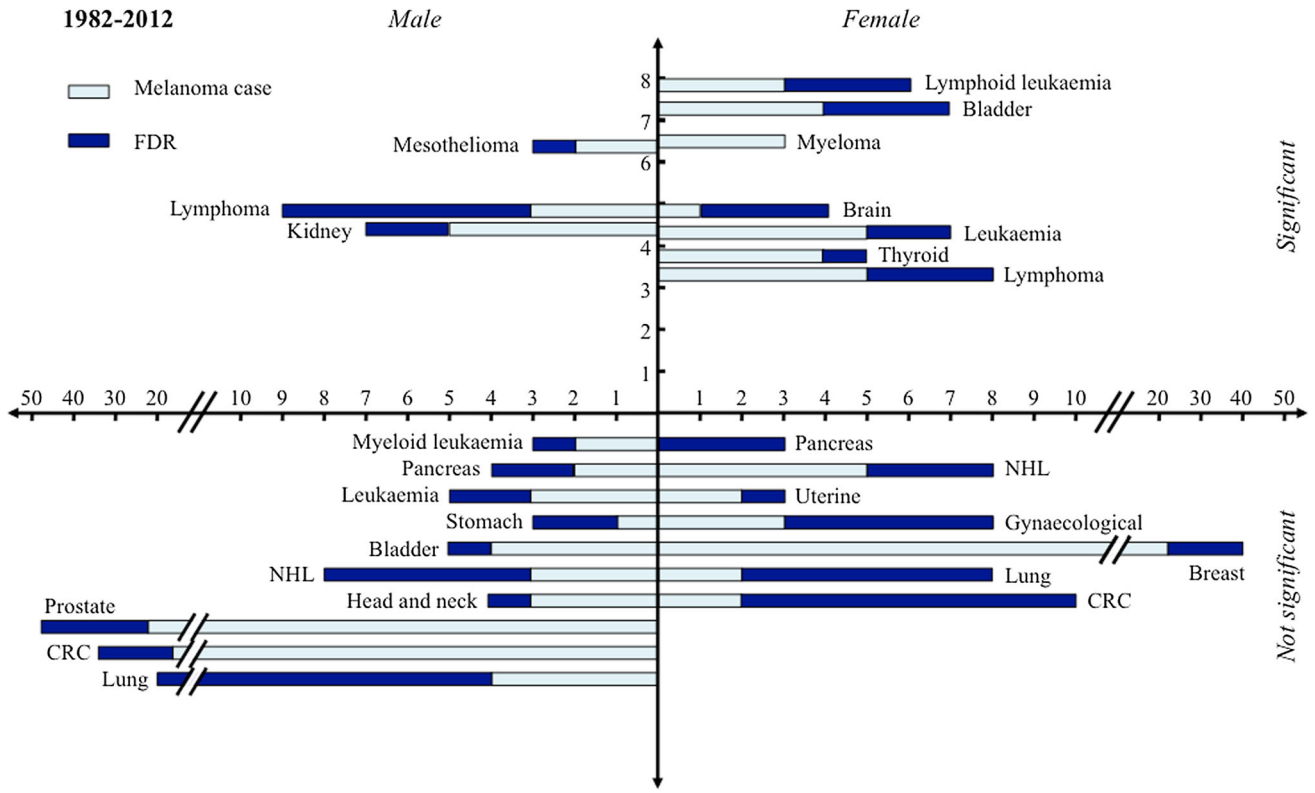

Fig. 2 Frequency of cancers with ≥3 observed events, for males and females, ranked in order of significance from 1982 to 2012 analysis. The position of statistically significant cancers corresponds to the odds ratios for each cancer type, indicated by numbered values on the positive *y* axis. Cancers that were not statistically significant are ranked in order of decreasing odds ratios on the negative *y* axis. The values on the *x* axis indicate frequency of cancer. *CRC* colorectal cancer, *NHL* non-Hodgkin lymphoma. Expected cancers standardized by age and sex: all invasive cancers, breast, cervical, colorectal, lung, NHL, and prostate cancer. Expected cancers standardised by sex only: bladder, brain, head and neck, gynaecological—combined group, ovarian, uterine, kidney, leukaemia—combined group, lymphoid leukaemia, myeloid leukaemia, lymphoma—combined Hodgkin lymphoma and NHL, myeloma, liver, mesothelioma, pancreatic, stomach, and thyroid cancer

of inheritance, with low penetrance for myeloma [52]. A genetic link between myeloma and melanoma has been established in one family, suggesting the high penetrance melanoma risk gene *CDKN2A* also acts as a low penetrance susceptibility gene for myeloma [53]. In this study, a germline *CDKN2A* mutation was present in four family members with melanoma and one with myeloma, and loss of heterozygosity studies on bone marrow of the individual affected by myeloma demonstrated loss of the wild-type *CDKN2A* allele in malignant plasma cells [53]. Of seven other risk loci predisposing to myeloma, two have possible links to melanoma [54–56]. A telomere link may be plausible via a SNP at 3q26.2 mapping 5′ to the gene encoding the telomere RNA component (*TERC*) that helps maintain telomere ends in combination with *TERT*, a known high penetrance melanoma gene [55]. A common mechanism via the p16INK4a/Rb and ARF/p53 pathways may also exist, as a SNP at 22q13.1 localising to chromobox homolog 7 (*CBX7*) influences these pathways through cooperation with the oncogene *MYC* [55]. A study of temporal associations between myeloma and other neoplasms identified 5 cases of melanoma and myeloma in the same individuals, with a median time of 5 years between melanoma and myeloma being diagnosed [57].

Additional neoplasms in the same individual are important to consider not only in the context of heritable risk factors, but also in relation to the possible contribution of the primary cancer to the development of a subsequent cancer. Field cancerisation from treatment with radiation and chemotherapy has been associated with ensuing haematological malignancies, and also radiation-sensitive tissue like breast and thyroid [58]. However, a radiation-induced effect in our cohort seems unlikely given that surgery is the main treatment for melanoma, and the relatively long time from melanoma to diagnosis of first haematological malignancy (median 18.5 years). The development of CLL or NHL in a study of melanoma patients treated with surgery only suggests that the association is unrelated to prior treatment, consistent with reports of CLL as non-radiogenic [59, 60]. Myeloma has

also not been reliably associated with radiotherapy [61]. It is likely that multiple neoplasms in the same individual are related to an underlying predisposition for cancer comprised of genetic and non-radiation environmental factors.

Multiple cancers

Further to statistically significant cancers, the presence of multiple cancers in some families and individuals is of interest. Fifteen individuals had three different types of cancer—at least one melanoma, and at least two other types of invasive cancer (Table 4). Relatively uncommon cancers that were observed in these individuals include renal cell carcinoma, mesothelioma, and cholangiocarcinoma (interestingly, all cancers that are associated with *BAP1* germline mutations), and thyroid cancer. Eight of 15 individuals had a haematological malignancy, including six leukaemias (three lymphoid leukaemia, and three myeloid leukaemia).

In sixteen melanoma-dense families, with four or more individuals affected by melanoma, 15 families had at least one individual affected by another type of invasive cancer. These cancers included bladder, breast, glioma, lymphoid leukaemia, lymphoma, mesothelioma, and kidney cancer. Although few in number, the presence of bladder cancer, lymphoid leukaemia, and myeloma in melanoma-dense families supports the possibility of common risk polymorphisms shared by these cancer types. Common polymorphisms predisposing to cancer in general are also supported by the presence of more common cancers in these families, in contrast to the cohort findings. Of the 16 families, eight had at least one case of prostate cancer, six had colorectal cancer, six had lung cancer, and five had breast cancer. Of three mesothelioma events in the cohort, two were in cancer-dense families (a five-case family, and a six-case family). Although the numbers are too few to be statistically relevant at a population level, the cancer density (and types) of these families warrants further investigation for potential germline mutations, particularly in *BAP1*.

Compared with cancer associations for known high penetrance melanoma genes, the seven observed pancreatic cancers were not significant by age standardised analysis, which contrasts with the frequency of pancreatic cancer in *CDKN2A* mutation-positive families. As *CDKN2A* is the most common high penetrance mutation, it seems that more pancreatic cancer would be expected, however this finding may be consistent with Australian data that demonstrates fewer cases of pancreatic cancer in *CDKN2A* families than international counterparts [1, 11, 12, 62]. It also echoes the findings of the Utah population database, where pancreatic cancer was not increased. Suggested contributing factors are the relatively low number of families affected by *CDKN2A* mutations, and the heterogeneity of pancreatic cancer predisposition in families that do carry *CDKN2A* mutations [1, 5].

Further to pancreatic cancer, the present study has not demonstrated associations for all significant cancer types found in population studies of melanoma families. It is possible that our sample size has been too small to detect

Table 4 Individuals affected by melanoma and at least two other invasive cancers, in order of diagnosis

First cancer	Second cancer	Third cancer	Fourth cancer	Fifth cancer
Females				
Melanoma	CLL	NHL	–	–
Melanoma × 4	Endometrial	Thyroid	–	–
Melanoma	Breast	Myeloma	–	–
Melanoma	Breast	CRC	–	–
Melanoma	NHL	CLL	–	–
Melanoma	Myeloma	CML	–	–
Males				
Thyroid	Melanoma	RCC	–	–
RCC	Prostate	Melanoma	–	–
Prostate	Breast	Parotid	Melanoma	–
Melanoma	Prostate	Mesothelioma	–	–
Melanoma	NHL	RCC	CRC	Prostate
Melanoma × 2	Hodgkin Lymphoma	CML	–	–
Melanoma	Prostate	NHL	CLL	–
Melanoma × 4	CRC	Gallbladder	–	–
Melanoma	CRC	AML	–	–

AML acute myeloid leukaemia, *CLL* chronic lymphocytic leukaemia, *CML* chronic myeloid leukaemia, *CRC* colorectal cancer, *NHL* non-Hodgkin lymphoma, *RCC* renal cell carcinoma

an association, but also that a difference in the low risk genetic polymorphisms and environmental exposures of the Queensland study population predisposes to specific cancer types. Although this study reflects population level cancer risk, it is also possible that some cancers may be attributed to a small number of families with undetected mutations in high-penetrance melanoma predisposition genes.

Limitations

The study is limited by searching only the Queensland Cancer Registry, and therefore we are unable to comment on the number of individuals who may have had cancers diagnosed in another state or country. We are also unable to comment on the possibility of unobtainable information, where records may have previously existed, or records that were unavailable. As the study is based in Queensland, Australia, the results may not be generalisable to other geographic regions.

Conclusion

This pilot hypothesis-generating study demonstrates a possible link between melanoma and other cancers in individuals affected by melanoma and their FDRs, particularly bladder cancer and lymphoid leukaemia in females, and multiple myeloma in females affected by melanoma. Associations we have found here for the above over-represented cancers require replication and validation in an independent data set.

An over-representation of other cancers in melanoma families hints at the possibility of common pathways for oncogenesis, including a likely multi-hit model of many low risk heritable polymorphisms and other modifiers that underpin susceptibility to invasive malignancies.

It is possible to conduct genetic testing for known high penetrance germline mutations predisposing to melanoma, however the low yield at a population level and likely polygenic risk modification raises questions about clinical utility. Although a polygenic risk score has been proposed, incomplete penetrance and multiple environmental modifiers and other lifetime exposure risks create difficulty in translating plausible associations to clinical benefit. The main implication for clinical application of familial cancer association research at the population level is likely in the field of primary health care, in providing appropriate counselling and information regarding cancer risk and prevention strategies for cancers linked to familial melanoma.

Acknowledgments This work was supported by the National Health and Medical Research Council (NHMRC) of Australia. NKH is the recipient of a Senior Principal Research Fellowship of the NHMRC. The authors are indebted to the families for their participation in this study and thank the investigators and researchers of the QFMP and Q-MEGA projects for their valued contributions.

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