Cohort studies on melanoma and keratinocyte skin cancer: a systematic review

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ABSTRACT

The incidence of cutaneous malignancies is increasing worldwide, presenting an important public health burden and concern. Cohort studies can provide high quality data on the epidemiology of these cancers, and are invaluable for deriving measures of disease burden used to inform public health policy in relation to their control. We conducted a systematic review of the literature to summarise the characteristics of cohort studies that have published one or more papers describing the epidemiology of melanoma and/or keratinocyte cancers. Eligible studies were population-based cohort studies that have published findings on incidence or etiology of melanoma or keratinocyte cancer (including associations with phenotypic, environmental and genetic factors). We excluded clinical cohorts focused on survivorship outcomes, and other restricted prospective cohorts. We searched MEDLINE 1950 (U.S. National Library of Medicine, Bethesda, MD, USA), the ISI Science Citation Index (1990 to present) and the reference lists of retrieved articles, imposing no language restrictions. We identified 21 eligible cohorts studies of which 19 had published on melanoma, and 12 on keratinocyte cancer; nine were conducted in the United States, ten in Europe, and two in Australia. There was substantial variability in terms of cohort size, risk factor information recorded at baseline, and other data collected (e.g. health services, genetic). Only three studies were specifically designed to examine skin cancers as study endpoints, and only two cohorts pre-specified both melanoma and keratinocyte cancer endpoints. Our summary provides a resource for skin cancer researchers conducting investigations into the causes, burden and prevention of these important cancers.

INTRODUCTION

The incidence of skin cancer, both cutaneous melanoma and the more common keratinocyte cancers (KC) - basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) - is rising in most fair-skinned populations across the world.[1,2] Strategies to control these cancers include primary prevention and early detection, both of which are dependent on knowledge of the important factors that confer increased risk. To date, most of our knowledge about the risk factors for melanoma and keratinocyte cancers derives from case-control studies, which are prone to various inherent biases. Risk estimates free from bias and confounding are essential for causal inference. They are also essential for quantifying derived measures that are used to inform public health policy (e.g. population attributable fractions and potential impact fractions). Authoritative international cancer agencies that provide advice regarding strength of association for cancer risk factors are increasingly using data derived exclusively from prospective studies.[3]

Our aim was to summarise the characteristics of cohort studies that have reported findings on the epidemiology of melanoma and/or keratinocyte cancers.

METHODS

We conducted a systematic review to identify population-based prospective studies that have published one or more papers on melanoma or keratinocyte cancer. Eligibility criteria for study inclusion were pre-specified, as were the specific data elements to be extracted from each identified cohort study.

Data sources and searches

Eligible studies published up to January 4, 2019, were identified by searching the MEDLINE 1950 (U.S. National Library of Medicine, Bethesda, MD, USA), the ISI Science Citation Index (1990 to present) and by hand-searching the reference lists of retrieved articles. We did not impose any language restrictions on the search. We did not search for conference abstracts, unpublished studies, or other grey literature.

For computer searches, we used the following medical subject heading (MeSH) terms or text words: “melanoma”, “keratinocyte cancer”, “basal cell carcinoma”, “BCC”, “squamous cell carcinoma”, “SCC”, “cohort study”, “prospective”, “longitudinal”.

We read the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine if they met the study inclusion criteria.

Inclusion and exclusion criteria

We included population-based cohort studies that have published on incidence or aetiology of melanoma or keratinocyte cancer (including associations with phenotypic, environmental and genetic factors).

Data extraction

A single reviewer (CO) abstracted data from identified studies using a standardized data abstraction form. The following information was recorded: cohort name; geographic location; numbers of participants by sex (male/female/both); years of follow-up; number of cases (melanoma/KC; taken from the most recent report); baseline assessment of phenotype (pigmentation factors etc.), nevi, sun exposure and sun protection; case definition (i.e.

histological confirmation); linkage to pathology data; linkage to health services and costings data; collection of biological specimens; and whether repeatability or validation studies had been conducted.

Data synthesis and analysis

We conducted a qualitative synthesis of the identified cohort studies.

RESULTS

We found 379 published reports from which we identified 21 relevant cohort studies: 19 cohort studies had published at least one paper on melanoma[4-21] (Table 1) and 11 had published at least one paper on keratinocyte cancer[4,7,10,12,14,16,19-23] (Table 2) (nine cohorts had published at least one paper on both outcomes[4,7,10,12,14,16,19-21]).

Of the 19 cohorts that published on melanoma, 11 included both men and women; seven included women only and the remaining cohort included men only; nine were conducted in the US, eight in Europe, and two in Australia (Table 1). Of the 12 cohorts that have published on KC, six included both men and women; five included women only and the remaining cohort included men only; three were conducted in the US, seven in Europe and two in Australia (Table 2).

Histological confirmation of cases (melanoma/KC) was ascertained in most of the cohorts. Biological samples suitable for genetic analyses were collected in approximately half of the cohort studies identified, mostly for a sub-set of the full cohort.

Only three of the cohorts were established specifically to investigate skin cancer endpoints;[5,12,21] the remaining cohorts did not capture important aspects of phenotype (e.g. skin type, nevi, hair color, tanning ability) and/or environmental risk (e.g. sun exposure, sun protection) at baseline. The three purpose-designed skin cancer cohorts were the Nambour Study (n=1621),[12] MISS (Melanoma Inquiry in Southern Sweden, n=29,508 women only)[5] and the QSkin Sun and Health Study (QSkin; n=43,794).[21] Both the Nambour Study and MISS collected comprehensive baseline data on risk factors, but because of either small size (Nambour) or low incidence (Swedish women), they have very few melanoma events despite nearly 30 years follow-up (Nambour = 33 melanomas; MISS = 155 invasive, 60 *in situ*). Only the Nambour study and the QSkin cohort have data on both melanoma and KC as study endpoints. Neither Nambour nor MISS have linked their cohorts to other datasets to capture health services events or health costings data, and neither has published genotype data. The QSkin cohort reported 316 invasive and 466 *in* situ melanoma cases after a mean of 4.4 years, and is the only cohort study with linked health services data as well as genotype data.

DISCUSSION

Cohort studies are powerful tools for epidemiologic discovery, and for developing and implementing public health measures and practices;[24] their impact on public health is unquestioned. They have distinct advantages over case-control studies by characterizing exposures and risk factors prior to disease onset, which reduces important biases. They are also valuable for understanding the genetic basis of complex diseases. The breadth and reliability of prospectively ascertained environmental exposure data also allows the examination of potentially important and clinically relevant gene-environment interactions.

In this systematic review of the literature, we identified 21 population-based cohorts that published on the incidence or etiology of melanoma and/or KC, of which 19 reported on melanoma and 11 on KC. BCCs and SCCs are not registered in many parts of the world, so prospective data for these cancers is scarcer than for melanoma.

Most of the cohort studies identified were not established specifically to examine skin cancer outcomes and thus did not collect information about important risk factors and potential confounding factors at baseline. Conversely, the three studies that were purposely designed to investigate skin cancer collected tailored information at baseline to meet the study goals.[5,12,21] Two of these cohorts can provide value through the examination of all skin cancer outcomes simulataneously.[12,21] Notwithstanding their primary focus on cancers of the skin, all three of those 'specialized' cohorts can also provide valuable insights for other disease endpoints, particularly those that might share risk factors.

This study is novel in systematically summarizing the characteristics of all population-based cohort studies with data on melanoma and KCs. We believe we have identified all informative reports from prospective cohort studies that have published on skin cancer outcomes. We specifically excluded clinical cohorts of skin cancer patients established to assess survivorship and other clinical outcomes; similarly, we excluded other selective cohorts that imposed restrictive exclusion criteria on participants that limited generalizability. Our review highlights the small number of cohorts that have collected comprehensive skin cancer risk factor information in the correct temporal sequence, and as such provides a resource for skin cancer researchers conducting investigations into the causes, burden and prevention of these important cancers.

FUNDING STATEMENT

This study was supported in part by the National Health and Medical Research Council (NHMRC) of Australia (grant number 552429). DCW and REN are supported by fellowships from the NHMRC.

Table 1. Characteristics of population-based cohort studies that have published data on melanoma

COHORT	ACRONYM	FOLLOW-UP	SEX	GEOGRAPHIC LOCATION	NUMBER OF CASES	PHENOTYPE AT BASELINE	NEVI	UV/SUN EXPOSURE	SUN PROTECTION	HISTOLOGICAL CONFIRMATION OF CASES	PATHOLOGY	BIOLOGICAL SPECIMENS	HEALTH SERVICE DATA	COSTING DATA	REPEATIBILITY/ VALIDITY
NURSES HEALTH STUDY (I AND II)[4]	NHS	1976-present	Female	US	2439 up to 2011/2012 for NHS/HPFS	1982 survey for NHS, 1991 survey for NHS II	1982 survey for NHS, 1991 survey for NHS II	Average July ambient erythemal UV radiation	Not at baseline	Self-reported, confirmed by medical records	No	200,000 participants across all three cohorts	No	No	Not reported
HEALTH PROFESSIONALS FOLLOW-UP STUDY[4]	HPFS	1986-present	Male	US	2439 up to 2011/2012 for NHS/HPFS	1988 survey	1988 survey	Average July ambient erythemal UV radiation	Not at baseline	Self-reported, confirmed by medical records	No	200,000 participants across all three cohorts	No	No	Not reported
MELANOMA INQUIRY OF SOUTHERN SWEDEN[5]	MISS	1990-present	Female	Sweden	155 invasive, 60 *in situ*	Yes	Yes	Yes	Yes	Yes	No	DNA collection began in 2011	No	No	Yes (Westerdahl et al., 1994)
NORWEGIAN WOMEN AND CANCER STUDY[6]	NOWAC	1991-present	Female	Norway	1374	Yes	Yes	Yes	Yes	Yes	No	Blood collected for 60,000/170,000 women	No	No	Yes (Veierod et al., 2008)
FRENCH TEACHERS COHORT[7]	E3N	1992-present	Female	France	539	Yes	Yes	In a nested-case contrl study only (2008)	In a nested-case contrl study only (2008)	Yes	No	47,000 saliva samples; not all genotyped	No	No	Yes

COHORT	ACRONYM	FOLLOW-UP	SEX	GEOGRAPHIC LOCATION	NUMBER OF CASES	PHENOTYPE AT BASELINE	NEVI	UV/SUN EXPOSURE	SUN PROTECTION	HISTOLOGICAL CONFIRMATION OF CASES	PATHOLOGY	BIOLOGICAL SPECIMENS	HEALTH SERVICE DATA	COSTING DATA	REPEATIBILITY/ VALIDITY
EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION[8]	EPIC	1992-present	Both	Europe	1221	No	No	No	No	Yes	No	Blood collected from 385,747/519,978	No	No	Yes (diet only)
UNITED STATES RADIOLOGIC TECHNOLOGISTS COHORT[9]	USRT	1983-present	Both	US	207	No (second survey	No	Yes	No	Self-reported; some validated through medical record review	No	No	No	No	Not reported
JANUS COHORT[10]		1972-present	Both	Norway	2570	No	No	Yes - 1972-1991 only, ambient	No	Yes	No	Yes - serum	No	No	Not reported
THE MULTIETHNIC COHORT[11]		1993-present	Both	US	581 invasive, 412 *in situ*	Yes	No	No	No	Yes	No	Blood/urine on 70,000/215,000 collected in 2001-2005	No	No	Yes (diet only)
THE NAMBOUR SKIN CANCER PREVENTION TRIAL[12]		1992-2006	Both	Australia	33	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes (diet only)
CANCER PREVENTION STUDY-3 COHORT[13]	CPS-3	2006-present	Both	US	60	Not reported	Not reported	Not reported	Not reported	Self-reported in 2011; registry linkage confirmed 42/60		Blood	No	No	Not reported

COHORT	ACRONYM	FOLLOW-UP	SEX	GEOGRAPHIC LOCATION	NUMBER OF CASES	PHENOTYPE AT BASELINE	NEVI	UV/SUN EXPOSURE	SUN PROTECTION	HISTOLOGICAL CONFIRMATION OF CASES	PATHOLOGY	BIOLOGICAL SPECIMENS	HEALTH SERVICE DATA	COSTING DATA	REPEATIBILITY/ VALIDITY
THE DIET, CANCER AND HEALTH COHORT[14]		1993-present	Both	Denmark	357	Yes	Yes	No	No	Yes	No	Not reported	No	No	Not reported
NIH-AARP DIET AND HEALTH STUDY[15]	NIH-AARP	1995-present	Both	US	310 invasive, 171 *in situ*	No	No	Yes	No	Yes	No	Not reported	No	No	Not reported
THE MILLION WOMENS' COHORT[16]	MWS	1996-present	Female	UK	Not reported	No (12 year survey subset)	No	No	No	Yes	No	5% sample only (blood)	Yes	?	Yes
VITAMINS AND LIFESTYLE (VITAL) COHORT STUDY[17]	VITAL	2000-present	Both (48% male)	US	309 invasive, 257 *in situ*	Yes	Yes	No	No	Yes	No	No	No	No	Yes (diet only)
CANCER PREVENTION STUDY II (CPS-II) AND CPS-II NUTRITION COHORT[18]	CSP-II	1982-present	Both	US	1238	No	No	No	No	Yes	No	No	No	No	Not reported
NORWEGIAN-SWEDISH WOMEN'S LIFESTYLE AND HEALTH COHORT STUDY/WOMEN'S LIFESTYLE AND HEALTH COHORT STUDY[19]		1991-2005	Female	Norway, Sweden	412	Yes	Yes	Yes	No	Yes	No	No	No	No	Not reported
WOMEN'S HEALTH INITIATIVE[20]	WHI	1993-present	Female	US	280 invasive and 252 *in situ*	Yes	No	Not at baseline - year 4 survey	Not at baseline - year 4 survey	Yes	No	No	No	No	Yes (diet and other characteristics; not phenotype or sun exposure)

COHORT	ACRONYM	FOLLOW-UP	SEX	GEOGRAPHIC LOCATION	NUMBER OF CASES	PHENOTYPE AT BASELINE	NEVI	UV/SUN EXPOSURE	SUN PROTECTION	HISTOLOGICAL CONFIRMATION OF CASES	PATHOLOGY	BIOLOGICAL SPECIMENS	HEALTH SERVICE DATA	COSTING DATA	REPEATIBILITY/ VALIDITY
QSKIN SUN AND HEALTH STUDY[21]	QSKIN	2010-present	Both	Australia	316 invasive and 466 *in situ*	Yes	Yes	Yes	Yes	Yes	Yes	Saliva collected on 17,965 participants; all genotyped	Yes	Yes	Yes (Morze et al., 2012)

Table 2. Characteristics of population-based cohort studies that have published data on keratinocyte cancers

COHORT	ACRONYM	FOLLOW-UP	SEX	GEOGRAPHIC LOCATION	NUMBER OF CASES	PHENOTYPE AT BASELINE	NEVI	UV/SUN EXPOSURE	SUN PROTECTION	HISTOLOGICAL CONFIRMATION OF CASES	PATHOLOGY	BIOLOGICAL SPECIMENS	HEALTH SERVICE DATA	COSTING DATA	REPEATIBILITY/ VALIDITY
WOMEN'S HEALTH INITIATIVE[20]	WHI	1993-present	Female	US	9593 KC (not differentiated)	Yes	No	Not at baseline - year 4 survey	Not at baseline - year 4 survey	No	No	No	No	No	Yes (diet and other characteristics; not phenotype or sun exposure)
THE NAMBOUR SKIN CANCER PREVENTION TRIAL[12]		1992-2006	Both	Australia	281 BCC; 188 SCC	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes (diet only)
NURSES HEALTH STUDY (I AND II)[4]	NHS	1976-present	Female	US	17,556 BCC, 2233 SCC	1982 survey for NHS, 1991 survey for NHS II	1982 survey for NHS, 1991 survey for NHS II	Average July ambient erythemal UV radiation	Not at baseline	Self-reported, confirmed by medical records	No	200,000 participants across all three cohorts	No	No	Not reported
HEALTH PROFESSIONALS FOLLOW-UP STUDY[4]	HPFS	1986-present	Male	US	13,092 BCC 1756 SCC	1988 survey	1988 survey	Average July ambient erythemal UV radiation	Not at baseline	Self-reported, confirmed by medical records	No	200,000 participants across all three cohorts	No	No	Not reported
THE DIET, CANCER AND HEALTH COHORT[14]		1993-present	Both	Denmark	3,465 BCC, 341 SCC	Yes	Yes	No	No	Yes	No	Not reported	No	No	Not reported
THE MILLION WOMENS' COHORT[16]	MWS	1996-present	Female	UK	48,666 BCC; 6699 SCC	No (12 year survey subset)	No	No	No	Yes	No	5% sample only (blood)	Yes	No	Yes

COHORT	ACRONYM	FOLLOW-UP	SEX	GEOGRAPHIC LOCATION	NUMBER OF CASES	PHENOTYPE AT BASELINE	NEVI	UV/SUN EXPOSURE	SUN PROTECTION	HISTOLOGICAL CONFIRMATION OF CASES	PATHOLOGY	BIOLOGICAL SPECIMENS	HEALTH SERVICE DATA	COSTING DATA	REPEATIBILITY/ VALIDITY
FRENCH TEACHERS COHORT[7]	E3N	1992-present	Female	France	1027 BCC; 165 SCC	Yes	Yes	In a nested-case contrl study only (2008)	In a nested-case contrl study only (2008)	Yes	No	47,000 saliva samples; not all genotyped	No	No	Yes
SUPPLÉMENTATION EN VITAMINES ET MINÉRAUX ANTIOXYDANTS (SU.VI.MAX) COHORT[22]	SU.VI.MAX	1994-2007	Both	France	106 BCC, 18 SCC	Yes	No	Yes	Yes	Yes	No	Blood sample for 1760/13.017 trial participants	No	No	Yes (diet only)
NORWEGIAN-SWEDISH WOMEN'S LIFESTYLE AND HEALTH COHORT STUDY[19]		1991-2009	Female	Norway, Sweden	141 SCC	Yes	Yes	Yes	No	Yes	No	No	No	No	Not reported
JANUS COHORT[10]		1972-present	Both	Norway	1191 BCC, 633 SCC	No	No	Yes - 1972-1991 only, ambient	No	Yes	No	Yes - serum	No	No	Not reported
ROTTERDAM STUDY[23]		1990-present	Both	Holland	1528 BCC	Yes	No	Yes	Yes	Yes (GWAS)		No	Yes	No	No
QSKIN SUN AND HEALTH STUDY[21]	QSKIN	2010-present	Both	Australia	316 invasive and 466 *in situ*	Yes	Yes	Yes	Yes	Yes	Yes	Saliva collected on 17,965 participants; all genotyped	Yes	Yes	Yes (Morze et al., 2012)

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