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Influence of family history on risk of second primary cancers and survival in patients with squamous cell skin cancer

S. Chattopadhyay,[1,2,3] G. Zheng,[1,2,3] A. Hemminki,[4,5] A. Försti,[1,6,7,8] K. Sundquist,[8,9,10] J. Sundquist[8,9,10] and K. Hemminki[1,2,8,11]

[1]Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580 D-69120, Heidelberg, Germany
[2]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580 D-69120, Heidelberg, Germany
[3]Faculty of Medicine, University of Heidelberg, Heidelberg, Germany
[4]Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland
[5]Cancer Gene Therapy Group, Translational Immunology Research Program, University of Helsinki, Helsinki, Finland
[6]Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany
[7]Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, Germany
[8]Center for Primary Health Care Research, Lund University, 205 02, Malmö, Sweden
[9]Department of Family Medicine and Community Health, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY, U.S.A
[10]Center for Community-based Healthcare Research and Education (CoHRE), Department of Functional Pathology, School of Medicine, Shimane University, Japan
[11]Faculty of Medicine and Biomedical Center in Pilsen, Charles University in Prague, 30605, Pilsen, Czech Republic

Summary

Background Patients with squamous cell skin cancer (SCC) have an excellent prognosis but second primary cancers (SPCs) weaken survival prospects. Family history is a known risk factor for cancer but whether it is a risk factor for SPC in patients with SCC is not known.

Objectives To quantify the risk of family history on SPCs in patients with SCC and estimate survival probabilities of patients with SPCs depending on family history.

Methods With 13 945 histologically verified SCCs, relative risks (RRs) were estimated for family history using a generalized regression model. For survival analysis, hazard ratios (HRs) were assessed using a multivariable Cox proportional-hazards model.

Results Family history of invasive SCC increased risk of second invasive SCC [RR = 42·92, 95% confidence interval (CI) 33·69–50·32] compared with risk without family history (RR 19·12, 95% CI 17·88–21·08). Family history of any nonskin cancer in invasive SCC increased risk of the same cancers to be diagnosed as SPC (RRF_H = 1·48, 95% CI 1·35–1·61 vs. $RR_{no\ FH}$ = 1·40, 95% CI 1·32–1·48); significant increases were observed for seven different nonskin cancers. Most results were replicated for *in situ* SCC. SPC was deleterious for survival irrespective of family history; HR for patients with SPC was 4·28 (95% CI 3·83–4·72) vs. those without SPC (1·04).

Conclusions Family history of nonskin cancer was associated with approximately a doubling of risk for SPCs in patients with SCC. SPC increases the death rate in patients with SCC 3–4 times, irrespective of family history. Taking family history into account at SCC diagnosis may help prevention or early detection of SPCs.

What's already known about this topic?

- Second primary cancers (SPCs) are frequently diagnosed in patients with invasive and *in situ* squamous cell carcinoma (SCC); some epidemiological studies suggest a link to immune dysfunction.

Correspondence
Kari Hemminki.
E-mail: k.hemminki@dkfz.de

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Conflicts of interest
A.H. is a shareholder in Targovax ASA, and an employee of and shareholder in TILT Biotherapeutics Ltd. The other authors have no conflicts of interest to declare.

K.H. and S.C. were responsible for design; J.S. and K.S. for acquisition of data; S.C., G.Z., K.H., J.S., K.S., A.F. and A.H. for statistical analysis and interpretation; and K.H. and all other authors for manuscript writing. All authors were responsible for approval of the final text.

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- Family history of cancer is a risk factor for practically all first primary cancers but whether it also influences risk of SPCs in patients with SCC is not known.
- The possible influence of family history on survival in patients with SCC remains to be established.

What does this study add?

- Of 8·8 million individuals, 2743 (20%) of 13 945 patients with invasive SCC developed SPC.
- Family history of a cancer increased the risk of that cancer being diagnosed as SPC approximately twofold on top of the overall elevated risk of SPC; diagnosis of SPC increased death rate approximately 3–4 times vs. patients with SCC without SPC.
- Family history influenced survival indirectly by increasing the number of SPCs.

Squamous cell skin carcinoma (SCC) and its precursor, *in situ* SCC (Bowen disease), are common cancers with generally increasing incidence rates in fair-skinned populations.[1–3] The 10-year absolute survival in SCC was 73% according to a large German study; survival rate was best for women and younger individuals.[4] Risk factors for skin SCC include cumulative exposure to ultraviolet radiation, sun-sensitive skin, immunosuppression, and exposures to arsenic, glucocorticoids and polycyclic hydrocarbons.[3] The importance of the first two risk factors is underlined by the fact that SCC of the skin is overwhelmingly diagnosed on the face.[1,4]

Family history is an often forgotten risk factor, although the familial risk for SCC of about 2·0 between first-degree relatives is approximately as high as among other common cancers.[5–7] However, familial risk of SCC may increase up to 15-fold when several family members are affected; the risk can even be noted among patients diagnosed beyond age 90 years.[8,9] Invasive and *in situ* SCCs share familial risks between them.[6] SCC is additionally associated with some other cancers in families, most notably with cutaneous melanoma.[10] Counting any cancers among the first-degree relatives of patients with SCC, 7% have SCC and 54% have any other cancer.[11] SCC is a manifestation of some very rare cancer syndromes, including xeroderma pigmentosum, Fanconi anaemia, and Bloom and Werner syndromes.[3,12] Genome-wide association studies on SCC have identified some 20 low-risk loci, many of which function in pigmentation, immune regulation or oncogenic pathways.[3,13,14] As survival in SCC is good, patients are often at risk of developing second primary cancers (SPCs). A systematic review summarized results from 10 studies reporting on SPCs after skin SCC and found significant increases for salivary gland, lip, mouth and pharynx, and lung cancer, and for melanoma and non-Hodgkin lymphoma.[15] In our previous study, we found that the risks for SPCs were quite similar between invasive and *in situ* SCC.[16]

The aim of the present study was to estimate the influence of family history on the risk of SPCs in patients with primary invasive or *in situ* SCC. We also hypothesized that family history of cancer X increases the risk for cancer X to be an SPC, as has been observed for some other cancers.[17–21] We additionally tested if family history of skin cancer increases risk of second SCC after nonskin cancer. Some recent results on prostate, breast and ovarian cancers suggest that the cause of death in patients with SPC is often the SPC;[18,19,22] therefore, we assessed survival in patients with SCC who were diagnosed with SPC and whether survival is influenced by family history of SPC.

The study was approved by the Ethical Committee of Lund University, Sweden, without requirement for informed consent, and was conducted in accordance with the tenets of the Declaration of Helsinki. The project database is located at the Center for Primary Health Care Research in Malmö, Sweden. Before the database construction, it was advertised in major newspapers to offer people an option for withdrawal.

Patients and methods

Study population

Data for the study were obtained from the Swedish Family-Cancer Database, which includes information on the residents of Sweden organized in families and linked to the Swedish Cancer Registry, which was started in 1958.[23] The Cancer Registry records cancers according to the International Classification of Diseases 7th revision (ICD-7) and later revisions. By the end of 2015 more than two million cancers were recorded among 16·1 million living and dead individuals, with 8·8 million individuals belonging to the 0–83-year-old offspring generation (born after 1931) for which relative risks (RRs) were calculated. Everyone in Sweden is assigned a unique identifier at birth. The Multigeneration Register uses these identifiers to link newborns to their parents and in the Family-Cancer Database these data are used to assemble families. In the present analysis two generations were used: offspring with siblings and parents.

Data collection

We followed newly diagnosed patients with SCC from 1 January 1981 to 31 December 2015 for diagnosis of any of 28 different SPCs; only invasive SPCs were considered, except that *in situ* SCC was also considered. Family history was attributed in two separate designs, firstly as nonskin cancer family history, if at least one relative was diagnosed with the same nonskin SPCs as the patient; and secondly as invasive skin cancer family history, when at least one relative was diagnosed with SCC. Family history was recorded from the beginning of cancer registration in Sweden from the year 1958 onwards. Follow-up was initiated in 1981, year of birth, diagnosis of first cancer or immigration, whichever occurred latest, and was terminated at diagnosis of SPC, emigration, death, or 31 December 2015 (when the oldest individuals reached age 83 years), whichever occurred earliest. If *in situ* SCC and SCC were diagnosed in a person at the same time, SCC was given precedence.

Statistical analysis

Incidence rates were computed for each stratum over vectored categories of sex, age group, calendar period, residential area and socioeconomic status. Familial and nonfamilial RRs of SPC were estimated by comparing risk (incidence rate) of SPC among patients with SCC, with or without prior family history, against risk of that cancer in the general population. Waiting time distribution with Poisson assumption was employed to estimate RRs and corresponding confidence intervals (CIs) at a 5% level of significance. RRs were calculated for the offspring generation. A generalized linear multivariate model was used with regressor variables including age group, sex, calendar period, residential area and socioeconomic status as adjustment for potential confounding.

For the sensitivity analysis, a test of trend was constructed for comparing statistically significant difference between two risk strata. This was achieved by constructing Pearson χ^2 statistics between the groups, taking two separate bootstrapped samples with 100 000 resamples. All tests were considered to be statistically significant at $P < 0{\cdot}05$, although significance of RRs was additionally indicated for $P < 0{\cdot}01$ and $P < 0{\cdot}001$.

Overall survival was modelled with multivariable Cox regression analysis, subject to conformity to the proportional-hazards assumption. The model was adjusted for sex, age group, residential area and socioeconomic status. Observations were censored for diagnosis of cancer other than SCC. Separate analyses were performed for invasive and *in situ* SCC, considering diagnosis of a nonskin SPC and presence of family history of any cancer. Assessment of survival probabilities and hazard ratios (HRs) of patients with SCC was performed for patients without SPC and no family history as the baseline hazard. All statistical analyses were implemented in R version 3·4[24] and SAS V9·4 (SAS Institute Inc., Cary, NC, U.S.A.).

Results

Individuals belonging to the offspring generation were followed from 1981 to 2015, and 13 945 invasive SCCs and 15 797 *in situ* skin cancers were recorded. Among the people with invasive SCCs, there were 1325 nonskin SPCs [median (interquartile range) follow-up in 3 years (1–7)], 1418 second invasive SCCs [2 (0–6)] and 1232 second *in situ* SCCs [4 (1–8)]. Median age at diagnosis of first invasive SCC was 68 years (58–72). After first invasive SCC, median age at diagnosis of nonskin SPCs was 72 years (68–76); for second invasive SCCs it was 69 years (67–72) and for second *in situ* SCCs, 72 years (69–77). In patients with *in situ* SCC, there were 1455 nonskin SPCs [5 (1–8)], 885 second invasive SCCs [1 (0–3)] and 1226 second *in situ* SCCs [2 (1–5)]. Median age at diagnosis for first *in situ* SCC was 68 years (61–74), for nonskin SPCs it was 72 years (69–76), for second invasive SCCs it was 69 years (68–72) and for second *in situ* SCCs it was 69 years (67–73). Median follow-up times from a nonskin cancer as first cancer to second invasive and *in situ* SCC were both 7 years.

Table 1 shows the influence of family history on the risk of SPC in patients diagnosed with invasive and *in situ* SCC. When invasive SCC was the first cancer, the RR of second invasive SCC increased when there was a family history of invasive SCC [$RR_{no\ FH}$ = 19·12 (95% CI 17·88–21·08); $RR_{FH\ of\ SCC}$ = 42·92 (95% CI 33·69–50·32)]. The RR for second *in situ* SCC [$RR_{no\ FH}$ = 16·92 (95% CI 15·42–18·83)] also increased if there was a family history of invasive SCC [$RR_{FH\ of\ SCC}$ = 32·16 (95% CI 21·40–41·79)]. A similar increase in RR was noted for second invasive SCC after *in situ* SCC [$RR_{no\ FH}$ = 6·82 (95% CI 4·39–8·24) vs. $RR_{FH\ of\ SCC}$ = 15·61 (95% CI 8·18–20·59)]. Likewise, for second *in situ* SCC, the RR also increased in the presence of family history [$RR_{no\ FH}$ = 11·85 (95% CI 10·29–13·27) vs. $RR_{FH\ of\ SCC}$ = 21·83 (95% CI 17·41–25·16)]. All RRs in Table 1 were significant at the 0·1% level and trend-test P-values were < 0·001.

Table 2 shows risks for discordant (nonskin) SPC after SCC, stratified over family history of the discordant cancer (we abbreviate this as 'SCC – cancer X, FH of cancer X'). When the first cancer was invasive SCC (upper part of Table 2), 11 SPCs had their risk increased given family history of the SPC, as judged from the trend test. Overall risk for nonskin SPC was increased [RR_{FH} = 1·48 (95% CI 1·35–1·61) vs. $RR_{no\ FH}$ = 1·40 (95% CI 1·32–1·48), significant at the 5% level or lower]. Note that the overall risk considered only concordant family histories: e.g. for second colorectal cancer a family member was diagnosed with colorectal cancer. The RRs for familial SPCs vs. RRs without family history were increased approximately one-and-a-half-fold for colorectal cancer [$RR_{FH\ of\ colorectal}$ = 2·26 (95% CI 1·18–4·35) vs. $RR_{no\ FH}$ =1·34 (95% CI 1·15–1·57)] and non-Hodgkin lymphoma (NHL), and twofold for prostate cancer, melanoma and leukaemia. Increases greater than twofold were observed for lung, bladder and pancreatic cancers. The trend test was significant for all sets of comparisons except for the two

Table 1 Risk of second primary skin cancers among patients with skin cancer stratified over family history of skin cancer

	Number of first-degree relatives with cancer				
	≥ 1		0		Trend test
	n	RR (95% CI)	n	RR (95% CI)	P-value
First cancer: invasive skin cancer					
Second cancer:					
Invasive skin	143	42·92 (33·69–50·32)	1275	19·12 (17·88–21·08)	< 0·001
In situ skin	109	32·16 (21·40–41·79)	1123	16·92 (15·42–18·83)	< 0·001
First cancer: *in situ* skin cancer					
Second cancer:					
Invasive skin	83	15·61 (8·18–20·59)	802	6·82 (4·39–8·24)	< 0·001
In situ skin	207	21·83 (17·41–25·16)	1019	11·85 (10·29–13·27)	< 0·001

RR, Relative risk; CI, confidence interval. All RRs significant at $P < 0·001$.

haematological cancers. The lower part of Table 2 shows results for SPCs following *in situ* SCC. SPCs were included only when the trend test for family history was significant; these included second colorectal, lung, breast and prostate cancers.

Table 3 shows RRs for second primary SCCs after nonskin cancers under the influence of family history of SCC (cancer X – SCC, FH of SCC). The upper part of Table 3 shows the increased risks for SPCs, depending on family history, for seven SPCs, including upper aerodigestive tract, colorectal, breast and prostate cancers, melanoma, NHL and leukaemia. RRs between SPCs, with and without family history, were increased approximately twofold for most familial patients with SCC. For all patients with nonskin cancer, an overall increase was also noted [$RR_{FH\ of\ SCC} = 4·27$ (95% CI 3·41–5·33) vs. $RR_{no\ FH} = 2·10$ (95% CI 2·01–2·19); $P < 0·001$]. The lower part of Table 3 summarizes a similar analysis conducted for *in situ* SCC. The trend test for family history of SCC was statistically significant due to increased RRs in familial second primary SCCs after colorectal, breast, endometrial and prostate cancers, melanoma and leukaemia.

Figure 1 depicts Kaplan–Meier survival curves for patients with SCCs grouped over SPCs with or without family history of any concordant cancer; SCC was not included as SPC in survival analysis. Patients with SCC without SPC and/or family history of cancer were considered as the reference group. Under the assumption of independent proportional hazards, HRs for patients with SPC were greatly increased, irrespective of family history [$HR_{SPC,\ any\ FH} = 4·28$ (95% CI 3·83–4·72), $P < 0·001$ vs. $HR_{SPC,\ no\ FH} = 3·65$ (95% CI 3·06–4·28), $P < 0·001$]. Furthermore, family history had no influence on

Table 2 Risk of second primary nonskin cancer after skin cancer stratified over family history of the nonskin cancer

	Number of first-degree relatives with cancer				
	≥ 1		0		Trend test
	n	RR (95% CI)	n	RR (95% CI)	P-value
Second cancer after invasive skin cancer					
Colorectum	9	2·26 (1·18–4·35)*	129	1·34 (1·15–1·57)**	< 0·001
Pancreas	3	21·15 (6·82–65·62)*	22	1·13 (0·79–1·62)	0·01
Lung	9	4·14 (2·15–7·96)**	108	1·46 (1·23–1·74)**	< 0·001
Breast	10	1·66 (0·90–3·09)*	133	1·42 (1·21–1·66)**	0·03
Prostate	35	2·15 (1·55–3·00)**	279	1·11 (0·99–1·23)	< 0·001
Bladder	4	5·58 (2·09–14·87)**	53	1·54 (1·22–1·94)**	0·03
Melanoma	9	7·41 (3·85–14·25)**	126	3·04 (2·59–3·57)**	0·04
Non–Hodgkin lymphoma	2	5·05 (1·26–20·20)**	89	3·04 (2·50–3·71)**	0·13
Leukaemia	1	4·31 (0·61–30·60)	49	2·14 (1·67–2·74)**	0·21
All (except skin)	99	1·48 (1·35–1·61)**	1226	1·40 (1·32–1·48)**	0·02
Second cancer after *in situ* skin cancer					
Colorectum	8	1·94 (1·10–3·42)**	152	1·03 (0·90–1·18)	0·02
Lung	5	2·45 (1·23–4·91)**	99	1·00 (0·85–1·19)	< 0·001
Breast	16	2·01 (1·31–3·08)**	193	1·12 (0·98–1·27)	< 0·001
Prostate	33	2·05 (1·56–2·69)**	308	1·10 (1·00–1·21)*	< 0·001
All (except skin)	78	1·61 (1·50–1·73)**	1377	1·02 (0·97–1·10)	< 0·001

RR, Relative risk; CI, confidence interval. *$P < 0·05$, **$P < 0·01$.

Table 3 Risk of primary skin cancer as a second tumour after a nonskin cancer primary, stratified over family history of skin cancer

	Number of first-degree relatives with skin cancer				
	≥ 1		0		Trend test
	n	RR	n	RR	P-value
Primary nonskin, followed by invasive skin cancer					
Upper aerodigestive tract	4	7·68 (2·88–20·47)**	112	5·69 (4·84–6·67)**	< 0·001
Colorectal	6	3·52 (1·58–7·83)**	141	1·51 (1·31–1·73)**	< 0·001
Breast	13	4·47 (2·59–7·71)**	277	1·61 (1·45–1·79)**	< 0·001
Prostate	14	2·62 (1·55–4·42)**	423	1·51 (1·39–1·64)**	< 0·001
Melanoma	10	6·60 (3·55–12·27)**	260	3·81 (3·41–4·25)**	< 0·001
Non-Hodgkin lymphoma	6	9·62 (4·32–21·42)**	171	5·23 (4·58–5·99)**	0·13
Leukaemia	8	20·49 (10·24–40·99)**	189	7·58 (6·66–8·64)**	< 0·001
All (except skin)	78	4·27 (3·41–5·33)**	2100	2·10 (2·01–2·19)**	< 0·001
Primary nonskin, followed by *in situ* skin cancer					
Upper aerodigestive tract	3	3·56 (1·15–11·05)*	132	3·49 (3·01–4·05)**	0·18
Colorectum	8	2·77 (1·39–5·55)**	187	1·09 (0·96–1·24)	< 0·001
Breast	21	3·36 (2·19–5·16)**	560	1·44 (1·33–1·55)**	< 0·001
Endometrium	4	2·89 (1·09–7·71)*	109	1·29 (1·10–1·53)**	0·01
Ovary	3	4·25 (1·37–13·18)*	44	1·25 (0·97–1·60)	0·18
Prostate	15	2·33 (1·40–3·87)**	601	1·48 (1·37–1·59)**	< 0·001
Melanoma	18	6·59 (4·15–10·46)**	586	4·90 (4·56–5·26)**	< 0·001
Leukaemia	11	17·56 (9·72–31·71)**	175	6·70 (6·01–7·46)**	0·001
All (except skin)	106	3·45 (2·85–4·18)**	2993	1·95 (1·88–2·01)**	< 0·001

RR, Relative risk; CI, confidence interval. *P < 0·05, **P < 0·01.

survival in patients without SPC [$HR_{no\ SPC,\ no\ FH}$ = 1·04 (95% CI 0·91–1·26), P = 0·59]. However, detrimental effects of SPC combined with family history was observed for patients with *in situ* SCC [$HR_{SPC,\ any\ FH}$ = 6·15 (95% CI 5·28–7·19), P < 0·001], while HRs for SPC with no or any family history were both nominal and statistically insignificant ($HR_{SPC,\ no\ FH}$ = 1·02 and $HR_{no\ SPC,\ any\ FH}$ = 1·04).

Discussion

Our findings demonstrated that risks for second SCC after a primary SCC are very high and not very different for invasive (RR 19·12) and *in situ* SCC (RR 11·85), as previously reported.[16] We showed also that a concordant family history was associated with almost twice the increased risk for SPC, with 42·92 for invasive and 21·83 for *in situ* SCC. Familial risks for concordant invasive and *in situ* SCCs are known to be approximately 2·0 or somewhat higher.[6,11] Thus we suggest, as a novel hypothesis, that the results on familial SPC can be rationalized by a multiplicative interaction between SPC (RR approximately 20) and familial risk (RR approximately 2). We further assessed whether multiplicative interactions may also apply to discordant associations, as discussed below.

Previous studies have shown that family history may increase the risk of some SPCs after Hodgkin lymphoma, multiple myeloma, prostate cancer and melanoma.[17,20,21,25] We showed here that family history of seven cancers was associated with an increased risk of their being diagnosed as SPCs after invasive SCC, and for four SPCs the results were replicated for the first *in situ* SCC (SCC – cancer X, FH of cancer X). We observed that most familial risks for SPCs increased the RRs about twofold over the RRs for SPC. As concordant familial risks for most cancers are about twofold, the multiplicative interactions appear to describe the result quite satisfactorily.[11]

We showed also that the risk for second primary SCC was increased when there was a family history of SCC (cancer X – SCC, FH of SCC). The first cancers were upper aerodigestive tract, colorectal, breast and prostate cancers, melanoma, NHL and leukaemia, and of these all but NHL were replicated for second *in situ* SCC. The increase in RR was also about twofold. These two sets of results can be rationalized by hypothesizing that a family history of nonskin cancer will manifest itself irrespective of first SCC, and family history of SCC will manifest itself irrespective of first nonskin cancers.

The qualification to the above statement is that the associated nonskin cancers appeared to be a defined set that consistently included colorectal and prostate cancers, melanoma and leukaemia. Breast cancer, including other hormone related female cancers, upper aerodigestive tract cancer and NHL were also often present as significant partners. One obvious common denominator for these nonskin cancers is that they were common, and thus least limited by statistical power to manifest the familial risk. Some of these cancers also share risk factors with skin cancer, including melanoma (ultraviolet radiation), and NHL, leukaemia and upper aerodigestive tract cancer (infections and immune deficiency).[26–29]

Although patient-related diagnostic information was not available to explore the mechanistic links underpinning the results, a main strength of the study was nationwide coverage

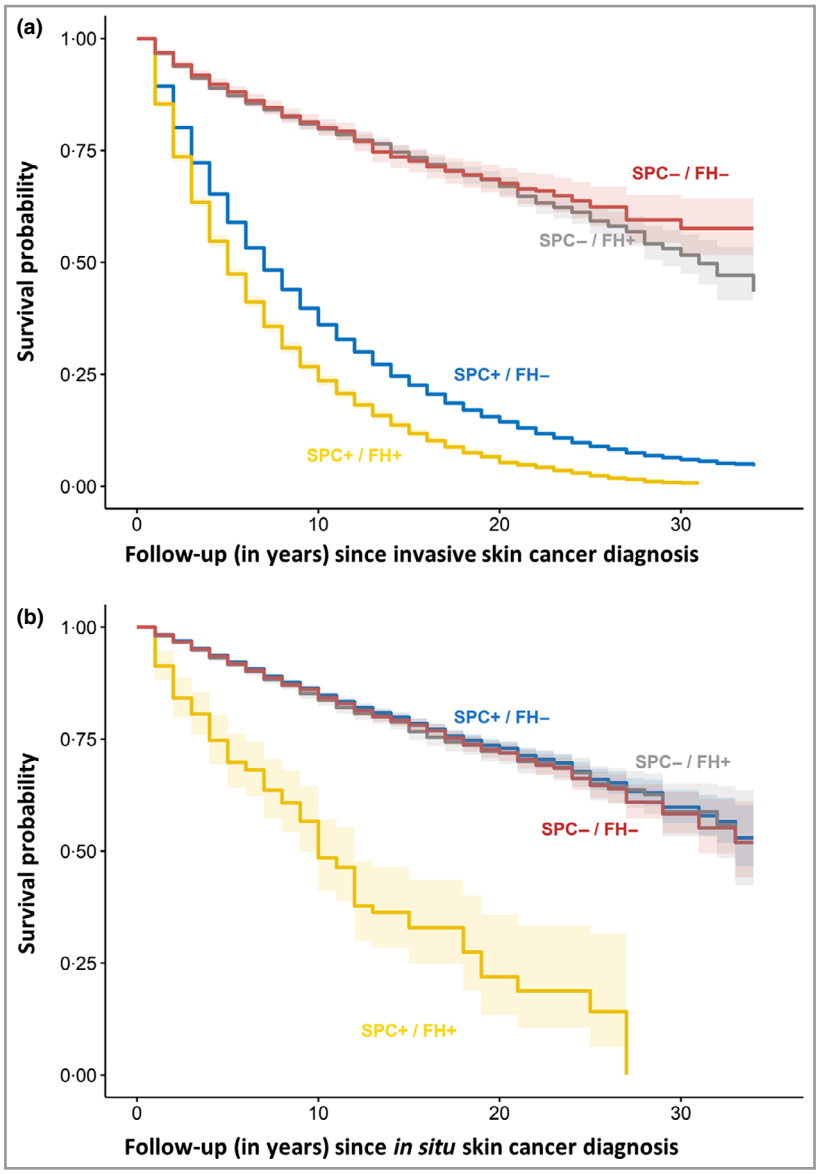

Fig 1. Kaplan–Meier survival curves for patients with squamous cell carcinoma (SCC): (a) invasive SCC and (b) *in situ* SCC, with and without second primary cancer (SPC), grouped over presence or absence of family history (FH) of any cancer. The shaded area around the curves shows 95% confidence intervals.

of cancers from a high-quality cancer registry, which, in contrast to most other cancer registries, also collects data on *in situ* SCC. In addition, the high confidence in the proper distinction of tumour types is granted due to histological classification of tumours. Moreover, for the reporting of SPC, there is a tradition mandated by requirement for the clinicians to report any cancers, irrespective of their order.

Our novel findings demonstrated detrimental survival probabilities for patients with SCC who have a SPC, and further showed that family history had no effect on survival. A three- to fourfold increased HR was both observed for patients with invasive and *in situ* SCC with family history, indicating that SCC of excellent prognosis is, on diagnosis of SPC, converted to SCC of critical and unpredictable prognosis. Although family history had no direct effect on survival for invasive SCCs, it predisposes patients with SCC to SPCs with approximately a twofold increase in risk, thus increasing the proportion of patients with SPC. As the SPCs with a family history included colorectal, lung and breast cancers as well as melanoma, vigilant monitoring of family history at SCC diagnosis may prompt recommendations for prevention (e.g. advice about smoking for lung cancer) or early detection of SPCs (colorectal and breast cancers and melanoma), and thus improve survival in patients with SCC. Finally, our findings suggest that SCC may be a useful 'canary in the coal mine' for highlighting underlying genetic predisposition to various types of epithelial cancers. Further work is needed to dissect the contributing mechanisms.

However, families with high numbers of SCC and non-SCC cancers could prove useful in this regard.

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References

1 Hussain SK, Sundquist J, Hemminki K. Incidence trends of squamous cell and rare skin cancers in the Swedish national cancer registry point to calendar year and age-dependent increases. *J Invest Dermatol* 2010; **130**:1323–8.

2 Rees JR, Zens MS, Gui J *et al.* Non melanoma skin cancer and subsequent cancer risk. *PLOS ONE* 2014; **9**:e99674.

3 Green AC, Olsen CM. Cutaneous squamous cell carcinoma: an epidemiological review. *Br J Dermatol* 2017; **177**:373–81.

4 Eisemann N, Jansen L, Castro FA *et al.* Survival with nonmelanoma skin cancer in Germany. *Br J Dermatol* 2016; **174**:778–85.

5 Hemminki K, Zhang H, Czene K. Time trends and familial risks in squamous cell carcinoma of the skin. *Arch Dermatol* 2003; **139**:885–9.

6 Hussain SK, Sundquist J, Hemminki K. The effect of having an affected parent or sibling on invasive and *in situ* skin cancer risk in Sweden. *J Invest Dermatol* 2009; **129**:2142–7.

7 Frank C, Fallah M, Ji J *et al.* The population impact of familial cancer, a major cause of cancer. *Int J Cancer* 2014; **134**:1899–906.

8 Hemminki K, Zhang H, Czene K. Familial invasive and *in situ* squamous cell carcinoma of the skin. *Br J Cancer* 2003; **88**:1375–80.

9 Kharazmi E, Fallah M, Sundquist K, Hemminki K. Familial risk of early and late onset cancer: nationwide prospective cohort study. *BMJ* 2012; **345**:e8076.

10 Hemminki K, Sundquist J, Brandt A. Do discordant cancers share familial susceptibility? *Eur J Cancer* 2012; **48**:1200–7.

11 Frank C, Sundquist J, Yu H *et al.* Concordant and discordant familial cancer: familial risks, proportions and population impact. *Int J Cancer* 2017; **140**:1510–16.

12 Rahman N. Realizing the promise of cancer predisposition genes. *Nature* 2014; **505**:302–8.

13 Chahal HS, Lin Y, Ransohoff KJ *et al.* Genome-wide association study identifies novel susceptibility loci for cutaneous squamous cell carcinoma. *Nat Comm* 2016; **7**:12048.

14 Siiskonen SJ, Zhang M, Li WQ *et al.* A genome-wide association study of cutaneous squamous cell carcinoma among European descendants. *Cancer Epidemiol Biomarkers Prev* 2016; **25**:714–20.

15 Wheless L, Black J, Alberg AJ. Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2010; **19**:1686–95.

16 Hemminki K, Dong C. Subsequent cancers after in situ and invasive squamous cell carcinoma of the skin. *Arch Dermatol* 2000; **136**:647–51.

17 Sud A, Thomsen H, Sundquist K *et al.* Risk of second cancer in Hodgkin lymphoma survivors and the influence of family history. *J Clin Oncol* 2017; **35**:1584–90.

18 Zheng G, Hemminki A, Försti A *et al.* Second primary cancer after female breast cancer: familial risks and cause of death. *Cancer Med* 2019; **8**:400–7.

19 Zheng G, Chattopadhyay S, Försti A *et al.* Familial risks of second primary cancers and mortality in ovarian cancer patients. *Clin Epidemiol* 2018; **10**:1457–66.

20 Chattopadhyay S, Yu H, Sud A *et al.* Multiple myeloma: family history and mortality in second primary cancers. *Blood Cancer J* 2018; **8**:75.

21 Chattopadhyay S, Hemminki O, Försti A *et al.* Impact of family history of cancer on risk and mortality of second cancers in patients with prostate cancer. *Prostate Cancer Prostatic Dis* 2019; **22**:143–9.

22 Chattopadhyay S, Zheng G, Hemminki O *et al.* Prostate cancer survivors: risk and mortality in second primary cancers. *Cancer Med* 2018; **7**:5752–9.

23 Hemminki K, Ji J, Brandt A *et al.* The Swedish Family-Cancer Database 2009: prospects for histology-specific and immigrant studies. *Int J Cancer* 2010; **126**:2259–67.

24 R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. Available at: www.r-project.org/ (last accessed 2 January 2020).

25 Chattopadhyay S, Hemminki A, Försti A *et al.* Familial risks and mortality in second primary cancers in melanoma. *JNCI Cancer Spectrum* 2019; **2**:pky068.

26 Birkeland S, Storm H, Lamm LU *et al.* Cancer risk after renal transplantation in the Nordic countries, 1964–1986. *Int J Cancer* 1995; **60**:183–9.

27 Zur Hausen H. The search for infectious causes of human cancers: where and why. *Virology* 2009; **392**:1–10.

28 Bottomley MJ, Thomson J, Harwood C, Leigh I. The role of the immune system in cutaneous squamous cell carcinoma. *Int J Mol Sci* 2019; **20**:2009.

29 Hortlund M, Arroyo Mühr LS, Storm H *et al.* Cancer risks after solid organ transplantation and after long-term dialysis. *Int J Cancer* 2017; **140**:1091–101.