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Prospective study of Human Papillomavirus seropositivity and risk of Non-Melanoma Skin Cancer

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Abbreviations:

BCC – Basal Cell Carcinoma

CI – Confidence Interval

ERB – Ethical Review Board

GST - Glutathione S-Transferase

HPV – Human Papillomavirus

NMSC- Non-Melanoma Skin Cancer

OR – Odds Ratio

Q – Quartiles

SCC – Squamous Cell Carcinoma

SSMB – Southern Sweden Microbiology Biobank

UV- Ultra Violet

Running head: Human Papillomavirus and non-melanoma skin cancer

ABSTRACT

Cutaneous Human papillomaviruses (HPV) have been associated with squamous cell carcinoma (SCC) in case-control studies, but there is limited data from prospective studies assessing whether virus exposure is able to predict risk for future cancer development. Two major biobanks, the Southern Sweden Microbiology Biobank and the Janus Biobank in Norway, containing samples from 850,000 donors, were followed-up for incident skin cancer for up to 30 years using registry linkages. Altogether 2,623 donors with samples taken before diagnosis of SCC or basal cell carcinoma (BCC) of the skin were identified. Prediagnostic samples and samples from 2,623 matched controls were tested for antibodies against 33 HPV types. Baseline seropositivity to HPV types in genus *beta* species 2 was associated with SCC risk (OR 1.3, 95% CI: 1.1, 1.7), also for samples taken >18 years before diagnosis (OR 1.8, 95% CI: 1.1, 2.8). Type-specific persistent seropositivity had elevated point estimates of risk for SCC for 29 types and decreased point estimates for only three types. After multiple hypothesis adjustment, HPV 76 was significantly associated with SCC risk and HPV 9 with BCC risk. In summary, seropositivity to certain HPV types were associated with an increased risk for future development of SCC and BCC.

Keywords: DNA tumour viruses, beta papillomavirus,

Human Papillomaviruses (HPVs) belonging to the *beta*, *gamma*, *mu* and *nu* genera (1) infect healthy skin (2, 3, 4) and are commonly found in non-melanoma skin cancers (NMSC) (5, 6, 7, 8), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). In case-control studies, HPV of genus *beta* (7), genus *beta* species 2 (5, 8, 9), genus *beta* species 1 (6, 10) and the genus *gamma* (9) have been reported to associate with SCC, whereas not with BCC (5, 6, 10, 11). HPV types 5 (10), 8 and 38 (12) have also been reported in SCC. These studies have tested biopsies (5), plucked hair (7), archival tissue (6), swab samples (13), plasma (10), and serum (7, 11) and results of HPV analyses may vary depending on the sample tested (13, 14, 15) and the HPV test used (5, 7, 8, 16).

Ultraviolet (UV)-radiation is an established risk factor for NMSC (17). As HPV infection is more common on skin sites not covered by clothing (sun-exposed skin) (5, 10), confounding by UV light is possible. However, sunlight intensity does not affect HPV prevalence (2, 3) and adjustment for UV light does not affect associations between HPV and NMSC [14].

Prospective studies assessing whether exposure predicts future cancer risk are essential for causality inference. In studies using samples taken at or after diagnosis, the disease may have caused increased susceptibility or reactivation of HPV (reverse causality). Comparison of HPV seroprevalences before or after NMSC diagnosis found that many HPVs had higher seroprevalences in postdiagnostic than in prediagnostic samples (18). The association of common skin bacteria with NMSC in case-control studies also indicates that reverse causality must be considered as a possible pitfall in studies aiming to elucidate the etiology of NMSC (19).

Seropositivity for ano-genital HPVs is a marker of past or present infection (20) and prospective HPV seroepidemiology has been instrumental in providing prospective evidence supporting the causal association between HPV and cervical, anogenital and oropharyngeal cancers (20). High-throughput serology for a multitude of HPV types has been established (21). Although the performance of cutaneous HPV serology as a marker of skin HPV infection is not entirely clear (11, 18), the methodology has been useful in discovery of associations of HPV and disease (9, 10, 12).

Because our previous case-control study had found that HPV of genus *beta* species 2 were associated with SCC (5), we wished to follow up by performing a prospective serological

study of future SCC risk in relation to baseline presence of antibodies to HPV in genus beta species 2. We also explored the risk for SCC or BCC in relation to presence of prediagnostic antibodies to 33 individual HPV types.

MATERIALS AND METHODS

The study adhered to the Declaration of Helsinki and was approved by the Ethical Review Boards (ERB) at the Oslo University, Norway and Lund University, Sweden. For the Norwegian cohort, all 332,000 participants had signed a written informed consent at enrolment and the ERB decided that a renewed consent was not required at follow-up. In Sweden, the ERB decided that an "opt-out" method for consent should be used. The ERB decided that the information about the study should be given to the 524,000 subjects in the cohort by publishing an advertisement in the major newspaper of the population with clear instructions on how to decline and thus not be included in the study.

Cohorts

About 332,000 Norwegian volunteers donated about 493,000 serum samples to the Janus biobank, from 1972 and onwards. Population-registry-based invitations all over Norway enrolled most donors (90%), the remainder being blood donors (22, 23). Norway has about 4.8 million inhabitants.

About 524,000 individuals donated about 1.5 million serum samples to the Southern Sweden Microbiology Biobank (SSMB), which has a catchment area population of about 1 million inhabitants, from 1969 and onwards (22). The reasons for donating samples (*e.g.* microbiological screening of blood donors and of pregnant women) define sub-cohorts that are used when matching controls to the cases, to minimise biases by reason for donating sample. Similarly, the blood donor sub-cohort and the population-registry-based sub-cohort in the Janus Biobank are also used in matching.

Study design

The biobanks were followed-up using linkages to the national cancer registries in Norway and Sweden using the ICD7 code 191 for SCC and ICD7 code 189 for BCC. Cancer registration of NMSC is essentially complete for Norway (24). For Sweden, only SCC is registered. Cases had at least 1 serum sample taken at least 1 month before diagnosis. For each case, 1 control (alive and free of SCC or BCC (when known) when the case was diagnosed) was selected matched for age at first serum sampling (+/- two years), sex, county (in the Janus Biobank), sub-cohort, number of serial samples and length of follow-up. The first (oldest) sample for the control was matched with the first (oldest) sample of the case for date of sampling (+/- two months). If controls meeting matching criteria could not be found,

matching criteria were widened in successive steps of +/- one month of sampling date and +/- one year of age until a control was found. No samples taken after diagnosis were included.

The cancer registry linkage of the Janus biobank identified 497 eligible SCC cases and matched controls with 1,550 samples. When NMSC was diagnosed several times, only the first diagnosis was included. Forty-eight cases and controls were excluded from the SCC group and included as BCC, because of a BCC diagnosis preceding the SCC diagnosis. Conversely, 15 cases and controls from the BCC group were included as SCC because of an SCC diagnosis preceding the BCC diagnosis (Figure 1). Review of the different data sources obtained by the cancer registry (clinical reports, histopathology reports and death certificates) found two BCC cases previously diagnosed as SCC and four SCC cases previously diagnosed as BCC (Figure 1). Five cases and controls were excluded because the first sample of the case or control was donated after the diagnosis of the case (Figure 1). Fourteen serial samples were deleted because they were donated after the first NMSC diagnosis of the case. Four cases were re-diagnosed by the cancer registry as non-malignant and excluded (Figure 1). Eighty-eight cases diagnosed with non-melanoma skin cancers other than BCC and SCC were excluded as well as 16 cases of connective tissue tumours. Finally, 1,056 samples from 353 SCC cases, and the same number of controls, were included.

The Janus biobank identified 5,073 eligible BCC cases and selected 2,000 of these at random (2,000 cases was sufficient power for detection of an OR of 1.5 with 80% power for individual HPV types and OR of 1.3 with 80% power for species groups, both with a significance level of 0.05). Fifty extra cases were selected in case of missing samples and six of those were used. One sample was excluded since it lacked controls and one sample was handled incorrectly (Figure 1). Thirty-nine cases and controls (92 samples) were excluded because the first NMSC diagnosis was before the first sampling (Figure 1). Twenty-two serial samples were excluded because they were donated after the first NMSC diagnosis of the case. Re-diagnosed cases and cases with different first and last diagnosis mentioned for SCC resulted in exclusion of 19 and addition of 50 cases and controls (Figure 1). Finally, 6,145 samples from 1,990 BCC cases and the same number of controls were included.

The Swedish Cancer Registry has only recently registered BCC and no BCC cases were included from Sweden. The cancer registry linkage identified 419 SCC cases in SSMB. Fifty-six cases and controls had a missing or too low volume sample. Two cases and controls were

excluded because the control had had SCC before the case, two were excluded because of incorrect handling, one case and control were excluded because the first sample was not available and matching with the second sample was not possible (Figure 1). One case and control were excluded because the control donated the first sample after diagnosis of the case (Figure 1). Seventy-seven cases registered under ICD7 191 or 189 that had diagnoses other than BCC or SCC (e.g., Kaposi's sarcoma) were excluded. Finally, 280 SCC cases and the same number of controls were included from SSMB (2,059 samples).

Altogether the study contained 9,260 samples (3,115 samples from 633 SCC cases and the same number of controls, and 6,145 samples from 1,990 BCC cases and the same number of controls). In the serial samples analysis, there were 531 BCC cases and 256 SCC cases (and the same number of controls) that had at least 2 prediagnostic samples.

For the Swedish cases and controls life-time cumulative UV exposure was calculated using the yearly UV exposure at the locations where the subjects had resided, from birth until the cases were diagnosed. Information on the lifetime residential addresses down to the Zip-code level was retrieved from the Swedish Tax Agency and information on the yearly UV-index of those locations (as Commission Internationale de l'Éclairage weighted UV-radiation) was retrieved from the Swedish Meteorological and Hydrological Institute.

Serology

We tested for antibodies to the L1 protein of mucosal HPV types HPV 32 (*genus alpha species 1*) and HPV 13 (*genus alpha species 10*) and cutaneous HPV types HPV 3, 10 and 77 (*genus alpha species 2*), HPV 2 and 27 (*genus alpha species 4*), HPV 7 (*genus alpha species 8*), , HPV 5, 8, 20, 24 and 36 (*genus beta species 1*), HPV 9, 15, 17, 23 and 38 (*genus beta species 2*), HPV 49, 75 and 76 (*genus beta species 3*), HPV 92 (*genus beta species 4*), HPV 96 (*genus beta species 5*), HPV 4, 48, 50, 65 and 95 (*genus gamma*), HPV 1 and 63 (*genus mu*), HPV 41 (*genus nu*) as well as for the so far ungrouped types HPV 101 and 103. As specificity control, we also tested for antibodies against the VP1 protein of the JC virus. Antibody detection used multiplexed glutathione S-transferase (GST) capture ELISA in combination with fluorescent bead-based Luminex technology (21, 25, 26). The method has been found to have good reproducibility (10, 21) All serological testing was performed with the analysing laboratory blinded to any information about the samples.

Statistical methods

Relative risks estimated as odds ratios (OR) and 95% confidence intervals (CI) were estimated by conditional logistic regression with SAS 9.1 software (SAS Institute Inc., Cary, NC). If the asymptotic model did not converge, conditional maximum likelihood estimates of ORs were estimated by exact conditional logistic regression with LogXact 8 (Cytel Inc., Cambridge, MA). Heterogeneity in the OR estimates was assessed with a likelihood ratio test.

The raw data for multiple test adjustment consisted of 33 HPV type-specific p-values related to likelihood ratio test for adding the HPV variable with two or four categories to null model. The adjusted p-values were calculated controlling familywise error rate by the Holm method (27).

RESULTS

There were 432 males and 201 female SCC cases and 1,136 males and 854 female BCC cases. Distributions of age at first serum sampling are presented in table 1. SCC cases in SSMB are older compared to SCC case in Janus, because enrolment to the Janus biobank generally targeted younger subjects than the SSMB.

The median follow-up time (from the first sampling until diagnosis) was 12.6 years (quartiles (Q) 1=8.2 years and Q3=20.8 years) for the BCC cases. The median follow-up time for SCC cases was 8.9 years (Q1=4.4 years and Q3=18.3 years). Among BCC cases with serial samples the median follow-up time was 19.9 years (Q1=15.3 years and Q3=23.4 years). The median interval between the first and last prediagnostic sample was 9.2 years (Q1=5.0 years and Q3=10.1). Among SCC cases with serial samples the median follow-up time was 9.8 years (Q1=4.4 years and Q3=19.9 years). The median interval between the first and last prediagnostic sample was 5.0 years (Q1=1.3 years and Q3=9.6 years).

Baseline seropositivity for an HPV type in genus *beta* species 2 (HPV 9, 15, 17, 23 or 38) was associated with an increased risk for development of SCC (OR 1.3, 95% CI: 1.1, 1.7) (Table 2). HPV type-specific seropositivity was not significantly associated with SCC risk for any of the 33 investigated HPV types (Table 2). Four HPV types had point estimates of OR below unity, whereas 25 HPV types had OR estimates above unity.

Baseline type-specific HPV seropositivity associated with BCC for only 1/33 HPV types (Table 2). Ten HPV types had point estimates of OR below unity, whereas 14 HPV types had OR estimates above unity.

For 30/33 HPV types, seroprevalences were slightly higher for SCC cases than for BCC cases (Table 2). Seropositivity to JC virus had ORs close to unity for both SCC and BCC in all analyses (Table 2, 3a and 3b).

Among subjects with at least two samples, a significantly increased SCC risk with persistent seropositivity for HPV 76 (OR 3.9, 95% CI: 1.4, 10.3) was found, whereas previous (lost) seropositivity to HPV 76 was protective (OR 0.3, 95% CI: 0.1, 0.9) (Table 3). Persistent seropositivity for genus *beta* species 2 also had an elevated SCC risk (OR 1.5, 95% CI: 1.0, 2.3) (Table 3). Out of the 33 types tested, 29 had OR point estimates suggesting increased

SCC risk if persistently seropositive whereas only 3 had point estimates suggesting decreased risk. Previous (lost) seropositivity was associated with significantly increased SCC risk for only 1/33 tested HPV types (Table 3) and acquired seropositivity (seroconversion) was also associated with significantly increased SCC risk for only 1/33 tested HPV types (Table 3). Seropositivity at baseline regardless of serostatus at later time points found increased SCC risks for HPV 2, 23 and 95 (Table 3).

The BCC risk among subjects with at least two samples was increased if persistent seropositive for only 1/33 tested HPV types (Table 4). Previous (lost) seropositivity was also associated with BCC for only 1/33 HPV types (Table 4). Acquired seropositivity was associated with significantly increased BCC risk for three HPV types and with significantly decreased BCC risk for two HPV types (Table 4). For persistent seropositivity, ten types had OR estimates suggesting decreased BCC risk and 17 had ORs suggesting increased risk. Seropositivity at baseline regardless of serostatus at later time points found significantly increased BCC risks for HPV 15 and 95 (Table 4).

Adjustment for multiple comparisons for the 33 different HPV types, using a variable with 4 categories each, found that HPV76 was significantly associated with SCC and HPV9 associated with BCC, even after multiple testing adjustment.

Adjustment for UV-exposure was possible for the Swedish subjects, but had no effect on the results. Life-time cumulative sun-exposure could be reconstituted for 272 case-control pairs, with 95 pairs in the group with lowest UV-exposure, 106 in the medium group and 71 individuals in the group with highest UV-exposure (mean life-time UV-exposure for the cases in these groups was 9,938 mW/m², 1,0416 mW/m² and 1,0521 mW/m² respectively).

The effect of the time between the date of sampling until diagnosis was analysed for SCC for HPV 3, 38 (Table 5) and genus *beta* species 2 and for BCC for HPV 15 and genus *beta* species 2 (Table 6). These types were selected for analysis since they showed significant or nearly significant results in the analyses based on all samples (Table 2). Seropositivity for HPV genus *beta* species 2 in samples taken more than 18 years prior to diagnosis was significantly associated with SCC risk (OR 1.8, 95% CI: 1.1, 2.8). Seropositivity for HPV 3 was associated with increased SCC risk in samples taken more than eight years prior to diagnosis (OR 2.0, 95% CI: 1.1, 3.6) (Table 5). For BCC, an association of borderline

significance was seen in the intermediate lag time group for HPV genus *beta* species 2 and for HPV 15 (Table 6).

DISCUSSION

Our most consistent finding was the increased risk for future SCC associated with seropositivity for HPV genus *beta* species 2. The association was seen in analysis of all baseline samples, in analysis restricted to samples taken >18 years before diagnosis and in analysis restricted to subjects with persistent seropositivity and was also a pre-specified hypothesis, as both we and others had previously found an association of HPV genus *beta* species 2 with SCC, both in studies based on serological testing (9, 10) and on HPV DNA testing of tumour biopsies (5, 8)

Our prospective study design is particularly useful for addressing concerns about reverse causality. This concern is particularly relevant for skin cancer, as it has been shown that HPV seroprevalences increase in samples taken after diagnosis (18) suggesting that virus reactivation or increased susceptibility caused by the disease process could explain associations seen. However, an association with risk of cancer diagnosed >18 years later is unlikely to be attributable to reverse causality. Because cases and controls were derived from the same cohorts, followed using nationwide population-based cancer registries, the risk for selection biases is minimised. Additional strengths include sufficient study size to have statistical power to detect also weak associations and that this is the so far only study that, to our knowledge, has analysed NMSC risk in relation to persistence of HPV seropositivity in serial samples. We have looked at serum samples as seroconversion shows that presence of HPV is not merely contamination, i.e. it is evidence of an infection.

High throughput multiplexed GST-L1 serology allowed a comprehensive analysis of a broad spectrum of cutaneous HPV types. As all analyses were performed simultaneously comparability of results is ensured. However, serology for cutaneous HPV types is not as well validated as the serology for ano-genital HPV types (17). In particular, some cutaneous HPV types appear to have several serotypes (28) and studies correlating seroprevalences with presence of HPV DNA in the same subjects have found associations on the genus/species level rather than on the HPV type level (11). The possibility that some of the HPV seropositivities investigated may be attributed to cross-reactions with related HPVs therefore needs to be borne in mind.

Although we had access to near-complete data on life-time domiciles as well as to UV light exposure at the zip code level in Sweden and although we found essentially no difference in

risk estimates when adjusting for UV exposure, we cannot exclude confounding by UV light as the differences in average UV-exposure among the study participants were small and individual activities (e.g. outdoor sports and profession) might be more important determinants of UV exposure than place of residence. In Norway, place of residence (county) was included in the matching suggesting that average UV light exposure was controlled for.

HPV-type specific persistence of antibodies had a point estimate of SCC risk that was above unity for almost all the HPV types, suggesting that most cutaneous HPV types might confer a weakly increased risk for SCC. If so, the significant risk associated with genus beta species 2 might be attributable to improved statistical power when analysing several HPV types together. It is also possible that only some HPV types associate with SCC and that the tendencies for increased risk seen for related HPV types may be attributable to serological cross-reactivity. The point estimates for the specificity control, the unrelated JC virus, were close to unity in all analyses. The association between SCC and persistent seropositivity for HPV 76 is noteworthy, because a highly increased OR in case of persistence and decreased OR in case of clearance is the biologically expected pattern. This association remained significant also after controlling for multiple testing.

Our analysis of acquired seropositivity and lost seropositivity in relation to SCC risk are consistent with chance findings, although we note that the types with marginally significant associations (HPV 38 and 8) have transforming characteristics (29, 30, 31, 32) and that some (but not all (9)) previous studies have also suggested an NMSC association (12).

Chance is also a possible explanation for the few and weak associations seen between HPV and BCC risk, but for HPV 9 the risk increase was significant also after adjusting for multiple testing. Contrary to the association between genus *beta* species 2 and SCC, where multiple previous studies had pointed to an association, the HPV types with marginally significant associations with BCC in some of the analyses (HPV 15, 9 and 95) have not been reported to associate with BCC before. HPV seroprevalences were consistently slightly higher in SCC than in BCC (consistent with previous reports (11)), also suggesting that cutaneous HPVs associate with SCC rather than with BCC.

In conclusion, seropositivity for HPV in the genus *beta* species 2 was consistently associated with a long-term future risk for development of SCC. Future studies of how this biomarker is

related to the natural history of cutaneous HPV infections could lead to important insights into the aetiology of SCC.

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Table 1. Distribution of Age at First Serum Sampling Among Cases and Controls Presented as Median Age and Quartiles.

	Median age cases	Q1	Q3	Median age controls	Q1	Q3
BCC (all, Janus)	42.1	40.4	45.8	42.0	40.4	46.0
BCC (Janus, females)	41.7	40.3	43.3	41.6	40.3	43.3
BCC (Janus, males)	42.6	40.6	46.8	42.4	40.7	47.0
SCC (all)	49.3	42.8	66.4	48.8	42.5	66.3
SCC (females)	48.4	41.9	66.9	48.3	41.6	67.2
SCC (males)	49.3	44.3	66.0	49.0	43.6	66.0
SCC (SSMB, females)	65.9	50.4	74.7	65.7	49.3	74.8
SCC (SSMB, males)	66.6	54.3	74.0	65.9	53.4	74.0
SCC (Janus, females)	42.8	40.8	48.3	42.8	40.7	48.3
SCC (Janus, males)	46.8	42.1	49.5	46.4	41.8	49.3

Abbreviations used: BCC, basal cell carcinoma; Q, quartile; SCC, squamous cell carcinoma; SSMB, southern Sweden microbiology biobank.

Table 2. Seropositivity at Baseline and Risk for Non-Melanoma Skin Cancer.

HPV type (genus, species)	SCC				BCC			
	N	%	OR ^a	95% CI	N	%	OR ^b	95% CI
32 (α 1)	30	4.7	1.5	0.8, 2.6	60	3.0	0.8	0.6, 1.2
3 (α 2)	69	10.9	1.4	1.0, 2.1	170	8.5	0.9	0.7, 1.1
10 (α 2)	50	7.9	1.1	0.8, 1.7	97	4.9	0.9	0.7, 1.2
77 (α 2)	62	9.8	0.7	0.5, 1.0	170	8.5	1.0	0.8, 1.3
2 (α 4)	66	10.4	1.3	0.9, 1.9	107	5.4	0.9	0.7, 1.1
27 (α 4)	80	12.6	1.2	0.8, 1.6	233	11.7	1.1	0.9, 1.3
7 (α 8)	34	5.4	1.6	0.9, 2.8	58	2.9	0.9	0.6, 1.2
13 (α 10)	51	8.1	1.3	0.8, 1.9	111	5.6	0.8	0.6, 1.0
5 (β 1)	68	10.7	1.2	0.8, 1.7	128	6.4	1.0	0.8, 1.3
8 (β 1)	150	23.7	1.0	0.8, 1.3	413	20.8	1.1	0.9, 1.3
20 (β 1)	131	20.7	1.2	0.9, 1.6	279	14.0	1.0	0.8, 1.2
24 (β 1)	66	10.4	0.9	0.6, 1.3	160	8.0	0.9	0.7, 1.1
36 (β 1)	82	13.0	1.1	0.8, 1.5	185	9.3	1.0	0.8, 1.2
9 (β 2)	128	20.2	1.1	0.9, 1.5	317	15.9	1.0	0.8, 1.2
15 (β 2)	131	20.7	1.1	0.9, 1.5	342	17.2	1.2	1.0, 1.4*
17 (β 2)	146	23.1	1.2	0.9, 1.6	321	16.1	1.1	0.9, 1.3
23 (β 2)	83	13.1	1.3	0.9, 1.8	184	9.3	1.1	0.9, 1.4
38 (β 2)	130	20.5	1.3	1.0, 1.7	278	14.0	1.1	0.9, 1.3
49 (β 3)	134	21.2	1.1	0.8, 1.4	359	18.0	1.1	0.9, 1.3
75 (β 3)	75	11.8	1.1	0.8, 1.6	176	8.8	1.0	0.8, 1.2
76 (β 3)	63	10.0	1.3	0.9, 1.9	97	4.9	0.8	0.6, 1.1
92 (β 4)	59	9.3	1.3	0.9, 2.0	131	6.6	1.1	0.9, 1.5
96 (β 5)	100	15.8	1.0	0.8, 1.4	244	12.3	1.0	0.8, 1.2
4 (γ 1)	190	30.0	1.0	0.8, 1.2	646	32.5	1.1	0.9, 1.2
65 (γ 1)	188	29.7	1.1	0.9, 1.4	502	25.2	1.0	0.9, 1.2
95 (γ 1)	163	25.8	1.1	0.9, 1.5	414	20.8	1.0	0.9, 1.2
48 (γ 2)	123	19.4	1.2	0.9, 1.5	277	13.9	1.1	0.9, 1.3
50 (γ 3)	109	17.2	1.1	0.8, 1.5	277	13.9	1.1	0.9, 1.3
1 (μ 1)	142	22.4	0.9	0.7, 1.2	494	24.8	1.1	0.9, 1.2
63 (μ 2)	136	21.5	1.1	0.8, 1.4	399	20.1	1.1	0.9, 1.3
41 (ν)	72	11.4	0.7	0.5, 1.0	247	12.4	1.1	0.9, 1.3
101 (ungrouped)	30	4.7	1.0	0.6, 1.6	52	2.6	0.8	0.5, 1.1
103 (ungrouped)	47	7.4	1.4	0.9, 2.2	106	5.3	0.8	0.6, 1.1
Any α 2 type	115	18.2	0.9	0.7, 1.3	308	15.5	1.0	0.8, 1.2
Any α 4 type	106	16.8	1.2	0.8, 1.6	267	13.4	1.0	0.8, 1.2
Any β 1 type	234	37.0	1.1	0.9, 1.4	580	29.2	1.1	0.9, 1.2
Any β 2 type	259	40.9	1.3	1.1, 1.7*	649	32.6	1.1	1.0, 1.3
Any β 3 type	152	24.0	1.1	0.8, 1.4	404	20.3	1.1	0.9, 1.3
Any γ 1 type	287	45.3	0.9	0.8, 1.2	902	45.3	1.0	0.9, 1.2
Any α 2/4/8 type	210	33.2	1.1	0.9, 1.4	538	27.0	1.0	0.9, 1.2
JCV	512	80.9	1.0	0.8, 1.4	1581	79.5	0.9	0.8, 1.1

Abbreviations used: BCC, basal cell carcinoma; CI, confidence interval; HPV, human Papillomavirus; JCV, John Cunningham virus; N, number of positives; OR, odds ratio; SCC, squamous cell carcinoma

*P<0,05

^a Unadjusted ORs for 633 SCC cases and 633 controls.

^b Unadjusted ORs for 1,990 BCC cases and 1,990 controls.

Table 3. Seropositivity and Risk for SCC Based on Serostatus at the First and the Last Serum Sampling of 256 SCC Cases and Controls for Individuals With at Least Two Samples.

SCC (N=256) HPV type (genus, species)	1st sample				-/- ^a			-/+ ^a				+/- ^a				+/+ ^a			
	N	%	OR ^b	95% CI	N	%	Ref.	N	%	OR ^b	95% CI	N	%	OR ^b	95% CI	N	%	OR ^b	95% CI
32 (α1)	13	2.5	1.7	0.7, 4.4	238	93.0	1.0	5	2.0	1.3	0.4, 5.1	4	1.6	1.5	0.3, 6.7	9	3.5	1.9	0.6, 5.7
3 (α2)	28	5.5	1.7	0.9, 3.2	224	87.5	1.0	4	1.6	0.9	0.2, 3.5	8	3.1	2.1	0.6, 6.9	20	7.8	1.5	0.7, 3.2
10 (α2)	21	4.1	1.5	0.8, 3.0	230	89.8	1.0	5	2.0	1.7	0.4, 7.1	6	2.3	6.0	0.7, 50	15	5.9	1.2	0.6, 2.5
77 (α2)	26	5.1	0.7	0.4, 1.2	221	86.3	1.0	9	3.5	0.8	0.3, 2.0	4	1.6	0.3	0.1, 1.0	22	8.6	0.9	0.5, 1.6
2 (α4)	34	6.6	2.0	1.1, 3.8*	215	84.0	1.0	7	2.7	1.8	0.5, 6.4	11	4.3	2.3	0.8, 6.3	23	9.0	2.0	1.0, 4.1
27 (α4)	37	7.2	1.5	0.9, 2.69	205	80.1	1.0	14	5.5	1.4	0.6, 3.1	9	3.5	1.1	0.4, 2.7	28	10.9	1.9	1.0, 3.6
7 (α8)	17	3.3	1.3	0.6, 2.7	232	90.6	1.0	7	2.7	3.9	0.8, 19	6	2.3	2.4	0.6, 9.9	11	4.3	1.1	0.5, 2.6
13 (α10)	24	4.7	1.6	0.8, 3.2	224	87.5	1.0	8	3.1	3.5	0.7, 17	8	3.1	4.1	0.9, 19	16	6.3	1.3	0.6, 2.7
5 (β1)	24	4.7	1.4	0.7, 2.7	221	86.3	1.0	11	4.3	1.1	0.5, 2.8	7	2.7	2.4	0.6, 9.5	17	6.6	1.2	0.6, 2.5
8 (β1)	57	11.1	1.2	0.8, 1.8	182	71.1	1.0	17	6.6	1.1	0.5, 2.1	14	5.5	2.8	1.0, 7.9*	43	16.8	1.0	0.6, 1.6
20 (β1)	45	8.8	1.4	0.8, 2.3	201	78.5	1.0	10	3.9	0.8	0.3, 1.8	6	2.3	0.8	0.3, 2.3	39	15.2	1.6	0.9, 2.8
24 (β1)	22	4.3	1.0	0.5, 1.8	223	87.1	1.0	11	4.3	1.6	0.6, 4.1	3	1.2	0.4	0.1, 1.7	19	7.4	1.3	0.6, 2.6
36 (β1)	30	5.9	1.4	0.8, 2.5	212	82.8	1.0	14	5.5	2.1	0.8, 5.3	7	2.7	1.6	0.5, 5.3	23	9.0	1.4	0.7, 2.7
9 (β2)	50	9.8	1.2	0.8, 2.0	193	75.4	1.0	13	5.1	1.2	0.5, 2.8	8	3.1	1.2	0.4, 3.3	42	16.4	1.3	0.8, 2.1
15 (β2)	50	9.8	1.3	0.8, 2.0	195	76.2	1.0	11	4.3	1.3	0.5, 3.2	8	3.1	0.7	0.3, 1.9	42	16.4	1.6	1.0, 2.6
17 (β2)	50	9.8	1.1	0.7, 1.7	195	76.2	1.0	11	4.3	0.9	0.4, 2.1	6	2.3	0.8	0.3, 2.2	44	17.2	1.1	0.7, 1.8
23 (β2)	32	6.3	1.8	1.0, 3.3*	217	84.8	1.0	7	2.7	0.5	0.2, 1.4	10	3.9	3.3	0.9, 12	22	8.6	1.5	0.7, 2.9
38 (β2)	51	10.0	1.5	0.9, 2.4	189	73.8	1.0	16	6.3	2.7	1.0, 7.2*	7	2.7	2.6	0.6, 11	44	17.2	1.5	0.9, 2.4
49 (β3)	56	10.9	1.4	0.9, 2.1	189	73.8	1.0	11	4.3	0.9	0.4, 2.2	8	3.1	1.6	0.5, 5.0	48	18.8	1.3	0.9, 2.1
75 (β3)	31	6.1	1.3	0.8, 2.2	218	85.2	1.0	7	2.7	7.0	0.9, 57	6	2.3	0.7	0.2, 1.9	25	9.8	1.7	0.9, 3.3
76 (β3)	25	4.9	1.4	0.7, 2.6	228	89.1	1.0	3	1.2	0.7	0.2, 2.9	3	1.2	0.3	0.1, 0.9*	22	8.6	3.9	1.4, 10.3*
92 (β4)	18	3.5	1.3	0.6, 2.7	232	90.6	1.0	6	2.3	2.0	0.5, 8.0	7	2.7	1.5	0.4, 5.3	11	4.3	1.2	0.5, 2.9
96 (β5)	43	8.4	1.4	0.9, 2.4	205	80.1	1.0	8	3.1	1.0	0.4, 2.6	7	2.7	0.7	0.3, 1.9	36	14.1	1.7	1.0, 3.1

4 (γ 1)	66	12.9	0.8	0.5, 1.2	173	67.6	1.0	17	6.6	0.8	0.4, 1.6	11	4.3	0.9	0.4, 2.0	55	21.5	0.8	0.5, 1.2
65 (γ 1)	67	13.1	1.3	0.8, 1.9	172	67.2	1.0	17	6.6	1.4	0.6, 3.0	12	4.7	1.4	0.6, 3.4	55	21.5	1.3	0.8, 1.9
95 (γ 1)	60	11.7	1.6	1.0, 2.4*	175	68.4	1.0	21	8.2	1.4	0.7, 2.8	13	5.1	1.6	0.6, 3.8	47	18.4	1.6	1.0, 2.6
48 (γ 2)	52	10.2	1.2	0.8, 1.8	198	77.3	1.0	6	2.3	0.4	0.2, 1.2	12	4.7	1.3	0.5, 3.1	40	15.6	1.1	0.7, 1.8
50 (γ 3)	47	9.2	1.1	0.7, 1.8	202	78.9	1.0	7	2.7	0.5	0.2, 1.3	12	4.7	0.9	0.4, 1.9	35	13.7	1.2	0.7, 2.0
1 (μ 1)	66	12.9	1.4	0.9, 2.2	179	69.9	1.0	11	4.3	2.2	0.8, 6.6	11	4.3	1.4	0.5, 3.5	55	21.5	1.5	0.9, 2.4
63 (μ 2)	56	10.9	1.4	0.9, 2.2	185	72.3	1.0	15	5.9	1.0	0.5, 2.1	13	5.1	1.5	0.7, 3.6	43	16.8	1.4	0.8, 2.2
41 (ν)	29	5.7	0.9	0.5, 1.5	219	85.6	1.0	8	3.1	1.0	0.4, 2.7	5	2.0	0.5	0.2, 1.3	24	9.4	1.1	0.6, 2.1
101 (ungrouped)	7	1.4	0.6	0.2, 1.5	239	93.4	1.0	10	3.9	1.6	0.6, 4.5	2	0.8	0.4	0.1, 2.1	5	2.0	0.8	0.2, 2.6
103 (ungrouped)	17	3.3	1.3	0.6, 2.7	233	91.0	1.0	6	2.3	1.0	0.3, 3.1	6	2.3	1.5	0.4, 5.3	11	4.3	1.2	0.5, 2.9
Any α 2 type	47	9.2	1.0	0.6, 1.6	199	77.7	1.0	10	3.9	0.7	0.3, 1.7	7	2.7	0.4	0.2, 1.2	40	15.6	1.1	0.7, 1.9
Any α 4 type	49	9.6	1.5	0.9, 2.5	193	75.4	1.0	14	5.5	1.4	0.6, 3.1	13	5.1	1.6	0.7, 3.7	36	14.1	1.6	0.9, 2.8
Any β 1 type	86	16.8	1.2	0.8, 1.7	145	56.6	1.0	25	9.8	1.4	0.7, 2.5	15	5.9	1.1	0.5, 2.3	71	27.7	1.3	0.8, 1.9
Any β 2 type	99	19.3	1.5	1.0, 2.1*	134	52.3	1.0	23	9.0	1.4	0.7, 2.7	17	6.6	1.6	0.7, 3.7	82	32.0	1.5	1.0, 2.3*
Any β 3 type	64	12.5	1.3	0.9, 1.9	179	69.9	1.0	13	5.1	1.1	0.5, 2.5	8	3.1	0.8	0.3, 2.2	56	21.9	1.4	0.9, 2.2
Any γ 1 type	107	20.9	1.0	0.7, 1.4	125	48.8	1.0	24	9.4	1.4	0.7, 2.7	16	6.3	1.4	0.6, 3.2	91	35.6	1.0	0.7, 1.4
Any α 2, 4 and 8 type	89	18.4	1.2	0.8, 1.7	148	57.8	1.0	19	7.4	0.9	0.5, 1.9	16	6.3	0.8	0.4, 1.6	73	28.5	1.3	0.8, 2.0
JCV	204	49.3	0.8	0.5, 1.3	38	14.8	1.0	14	5.5	1.4	0.4, 4.0	5	2.0	0.5	0.2, 1.7	119	77.7	0.9	0.6, 1.4

Abbreviations used: CI, confidence interval; HPV, human Papillomavirus; JCV, John Cunningham virus; N, number of positives; OR, odds ratio; SCC, squamous cell carcinoma.

* $P < 0.05$.

^a Results are based on serostatus at the first and the last serum sampling of 256 SCC cases and controls.

^b Unadjusted OR.

Table 4. Seropositivity and Risk for BCC Based on Serostatus at the First and the Last Serum Sampling of 531 BCC Cases and Controls for Individuals With at Least Two Samples.

BCC (N=531) HPV type (genus, species)	1st sample				-/- ^b			-/+ ^b				+/- ^b				+/ ^b			
	N	%	OR ^c	95% CI	N	%	Ref.	N	%	OR ^c	95% CI	N	%	OR ^c	95% CI	N	%	OR ^c	95% CI
32 (α1)	13	1.2	0.8	0.4, 5.7	507	95.5	1.0	11	2.1	0.9	0.4, 2.3	3	0.6	∞	0.4, ∞	10	1.9	0.6	0.3, 1.5
3 (α2)	52	4.9	0.9	0.6, 1.3	468	88.1	1.0	11	2.1	0.8	0.4, 1.7	15	2.8	0.7	0.4, 1.5	37	7.0	1.0	0.6, 1.6
10 (α2)	26	2.5	1.0	0.6, 1.8	496	93.4	1.0	9	1.7	0.8	0.3, 1.8	8	1.5	1.3	0.5, 3.8	18	3.4	0.9	0.4, 1.7
77 (α2)	50	4.7	1.1	0.7, 1.7	462	87.0	1.0	19	3.6	1.0	0.5, 1.8	15	2.8	1.2	0.5, 2.5	35	6.6	1.1	0.7, 1.7
2 (α4)	25	2.4	0.6	0.4, 1.0	496	93.4	1.0	10	1.9	0.7	0.3, 1.5	6	1.1	0.6	0.2, 1.8	19	3.6	0.6	0.3, 1.1
27 (α4)	61	5.7	1.1	0.7, 1.6	454	85.5	1.0	16	3.0	0.8	0.4, 1.5	16	3.0	1.4	0.6, 3.2	45	8.5	1.0	0.6, 1.5
7 (α8)	11	1.0	0.8	0.4, 1.7	515	97.0	1.0	5	0.9	0.7	0.2, 2.3	5	0.9	1.2	0.3, 4.5	6	1.1	0.6	0.2, 1.7
13 (α10)	25	2.4	0.6	0.4, 1.1	494	93.0	1.0	12	2.3	1.3	0.5, 3.1	6	1.1	0.6	0.2, 1.7	19	3.6	0.7	0.4, 1.2
5 (β1)	31	2.9	0.9	0.5, 1.4	482	90.8	1.0	18	3.4	1.2	0.6, 2.4	11	2.1	0.9	0.4, 1.9	20	3.8	0.9	0.5, 1.7
8 (β1)	104	9.8	1.1	0.5, 2.1	394	74.2	1.0	33	6.2	1.0	0.6, 1.6	22	4.1	1.2	0.7, 2.3	82	15.4	1.1	0.7, 1.5
20 (β1)	64	6.0	1.0	0.7, 1.4	428	80.6	1.0	39	7.3	1.5	0.9, 2.5	15	2.8	1.3	0.6, 2.7	49	9.2	0.9	0.6, 1.3
24 (β1)	30	2.8	0.8	0.5, 1.4	477	89.8	1.0	24	4.5	2.3	1.1, 4.8*	5	0.9	0.5	0.2, 1.5	25	4.7	1.0	0.5, 1.7
36 (β1)	43	4.1	1.1	0.7, 1.8	468	88.1	1.0	20	3.8	1.2	0.6, 2.4	12	2.3	1.0	0.5, 2.3	31	5.8	1.1	0.6, 2.0
9 (β2)	81	7.6	1.1	0.8, 1.6	415	78.2	1.0	35	6.6	3.0	1.6, 5.9*	23	4.3	2.2	1.0, 4.5*	58	10.9	1.0	0.7, 1.5
15 (β2)	90	8.5	1.4	1.0, 2.0*	414	78.0	1.0	27	5.1	0.9	0.5, 1.5	18	3.4	1.5	0.7, 3.2	72	13.6	1.4	1.0, 2.0
17 (β2)	89	8.4	1.3	0.9, 1.8	410	77.2	1.0	32	6.0	1.0	0.6, 1.7	16	3.0	1.4	0.6, 3.0	73	13.8	1.2	0.9, 1.8
23 (β2)	38	3.6	1.0	0.6, 1.6	466	87.8	1.0	27	5.1	1.0	0.6, 1.7	13	2.5	1.2	0.5, 2.6	25	4.7	0.9	0.5, 1.6
38 (β2)	67	6.3	1.4	1.0, 2.1	434	81.7	1.0	30	5.7	2.0	1.1, 3.7*	11	2.1	2.8	0.9, 8.8	56	10.6	1.3	0.9, 2.0
49 (β3)	84	7.9	1.0	0.7, 1.4	416	78.3	1.0	31	5.8	1.2	0.7, 2.1	11	2.1	1.0	0.4, 2.3	73	13.8	1.0	0.7, 1.5
75 (β3)	44	4.1	1.4	0.9, 2.2	473	89.1	1.0	14	2.6	0.7	0.4, 1.4	10	1.9	1.1	0.5, 2.7	34	6.4	1.5	0.9, 2.5
76 (β3)	22	2.1	1.2	0.7, 2.3	498	93.8	1.0	11	2.1	1.0	0.4, 2.4	7	1.3	0.9	0.3, 2.4	15	2.8	1.5	0.7, 3.3
92 (β4)	25	2.4	1.4	0.7, 2.5	495	93.2	1.0	11	2.1	0.8	0.3, 1.8	7	1.3	1.0	0.4, 2.9	18	3.4	1.5	0.7, 3.3
96 (β5)	60	5.7	1.1	0.7, 1.6	462	87.0	1.0	9	1.7	1.2	0.5, 3.1	18	3.4	1.5	0.7, 3.2	42	7.91	1.0	0.6, 1.5

4 (γ 1)	169	15.9	1.0	0.8, 1.3	332	62.5	1.0	30	5.7	1.0	0.6, 1.7	26	4.9	0.8	0.5, 1.4	143	26.9	1.0	0.8, 1.4
65 (γ 1)	133	12.5	1.1	0.9, 1.5	367	69.1	1.0	31	5.8	0.6	0.4, 1.0*	23	4.3	1.2	0.6, 2.1	110	20.7	1.1	0.8, 1.5
95 (γ 1)	119	11.2	1.4	1.0, 1.9*	378	71.2	1.0	34	6.4	0.8	0.5, 1.2	18	3.4	1.1	0.5, 2.1	101	19.0	1.4	1.0, 2.0*
48 (γ 2)	75	7.1	1.2	0.8, 1.7	441	83.1	1.0	15	2.8	0.5	0.3, 0.9*	16	3.0	0.9	0.4, 1.8	59	11.1	1.2	0.8, 1.8
50 (γ 3)	74	7.0	1.3	0.9, 1.8	437	82.3	1.0	20	3.8	0.8	0.4, 1.5	28	5.3	1.7	0.9, 3.0	46	8.7	1.1	0.7, 1.7
1 (μ 1)	128	12.1	1.2	0.9, 1.6	381	71.8	1.0	22	4.1	1.2	0.6, 2.3	21	4.0	1.2	0.6, 2.4	107	20.2	1.2	0.9, 1.7
63 (μ 2)	97	9.1	1.1	0.8, 1.5	408	76.8	1.0	26	4.9	1.0	0.6, 1.8	20	3.8	0.9	0.5, 1.6	77	14.5	1.2	0.8, 1.7
41 (ν)	65	6.1	1.2	0.8, 1.7	444	83.6	1.0	22	4.1	1.3	0.7, 2.5	14	2.6	0.9	0.4, 1.9	51	9.6	1.3	0.8, 2.0
101 (ungrouped)	9	0.9	0.5	0.2, 1.0	516	97.2	1.0	6	1.1	0.5	0.2, 1.3	3	0.6	0.3	0.1, 1.2	6	1.1	0.6	0.2, 1.7
103 (ungrouped)	20	1.9	0.6	0.4, 1.1	502	94.5	1.0	9	1.7	0.6	0.3, 1.4	9	1.7	0.9	0.3, 2.1	11	2.1	0.5	0.2, 1.1
Any α 2 type	91	8.6	1.0	0.8, 1.4	416	78.3	1.0	24	4.5	0.8	0.4, 1.3	27	5.1	1.0	0.6, 1.7	64	12.1	1.0	0.7, 1.5
Any α 4 type	70	6.6	0.9	0.6, 1.3	442	83.2	1.0	19	3.6	0.6	0.3, 1.2	18	3.4	1.0	0.5, 2.0	52	9.8	0.9	0.6, 1.3
Any β 1 type	142	13.4	1.0	0.7, 1.3	339	63.8	1.0	50	9.4	1.0	0.6, 1.5	29	5.5	1.0	0.6, 1.7	113	21.3	0.9	0.7, 1.3
Any β 2 type	173	16.3	1.2	0.9, 1.6	295	55.6	1.0	63	11.9	1.2	0.8, 1.7	35	6.6	1.5	0.9, 2.6	138	26.0	1.2	0.9, 1.6
Any β 3 type	94	8.9	1.1	0.8, 1.5	403	75.9	1.0	34	6.4	1.2	0.7, 1.9	13	2.5	1.1	0.5, 2.4	81	15.3	1.1	0.8, 1.5
Any γ 1 type	246	23.2	1.0	0.8, 1.3	246	46.3	1.0	39	7.3	0.8	0.5, 1.3	37	7.0	0.9	0.6, 1.5	209	39.4	1.0	0.8, 1.3
Any α 2, 4 and 8 type	147	13.8	1.0	0.8, 1.3	349	65.7	1.0	35	6.6	0.7	0.4, 1.1	35	6.6	1.0	0.6, 1.6	112	21.1	0.9	0.7, 1.3
JCV	439	49.9	1.0	0.7, 1.4	79	14.9	1.0	13	2.5	0.8	0.4, 1.9	23	4.3	1.2	0.6, 2.4	416	78.3	1.0	0.7, 1.3

Abbreviations used: BCC, basal cell carcinoma; CI, confidence interval; HPV, human Papillomavirus; JCV, John Cunningham virus; N, number of positives; OR, odds ratio.

* $P < 0.05$.

^a Results are based on serostatus at the first and the last serum sampling of 531 BCC cases and controls.

^b Unadjusted OR.

Table 5. The Effect of Lag Time for SCC.

HPV type Lag time	OR	95% CI	Cases +/-all	Controls +/-all
HPV 3				
<4.25 yr	1.4	0.7, 3.0	18/156	13/156
4.25 – 8.83 yr	0.9	0.5, 1.7	17/159	19/159
8.83yr – 18.25 yr	3.8	1.4, 10.2*	20/159	6/159
>18.25y	1.2	0.5, 2.6	14/159	12/159
HPV 38				
<4.25 yr	1.9	1.0, 3.8	39/156	27/156
4.25 – 8.83 yr	1.0	0.5, 1.7	27/159	28/159
8.83yr – 18.25 yr	1.2	0.7, 2.1	36/159	31/159
> 18.25y	1.3	0.7, 2.4	28/159	22/159
Any β 2 type				
<4.25 yr	1.4	0.8, 2.3	68/156	56/156
4.25 – 8.83 yr	1.2	0.8, 1, 9	63/159	56/159
8.83yr – 18.25 yr	1.1	0.7, 1.7	61/159	59/159
>18.25y	1.8	1.1, 2.8*	67/159	46/159

Abbreviations used: CI, confidence interval; HPV, human Papillomavirus; OR, odds ratio; SCC, squamous cell carcinoma; yr, years.

* $P < 0.05$

Table 6. The Effect of Lag Time for BCC.

HPV type Lag time	OR	95% CI	Cases +/-all	Controls +/-all
HPV 15				
<12.5 yr	1.3	1.0, 1.7*	189/993	154/993
>12.5 yr	1.1	0.9, 1.4	153/997	138/997
Any β 2 type				
<12.5 yr	1.2	1.0, 1.5	354/993	314/993
>12.5 yr	1.0	0.8, 1.2	295/997	293/997

Abbreviations used: BCC, basal cell carcinoma; CI, confidence interval; HPV, human Papillomavirus; OR, odds ratio; yr, years.

* $P < 0.05$

Figure 1. Description of case inclusion and exclusion from the Southern Sweden Microbiology Biobank with about 524 000 donors.
Abbreviations: SCC, squamous cell carcinoma; ICD, international classification of diseases.

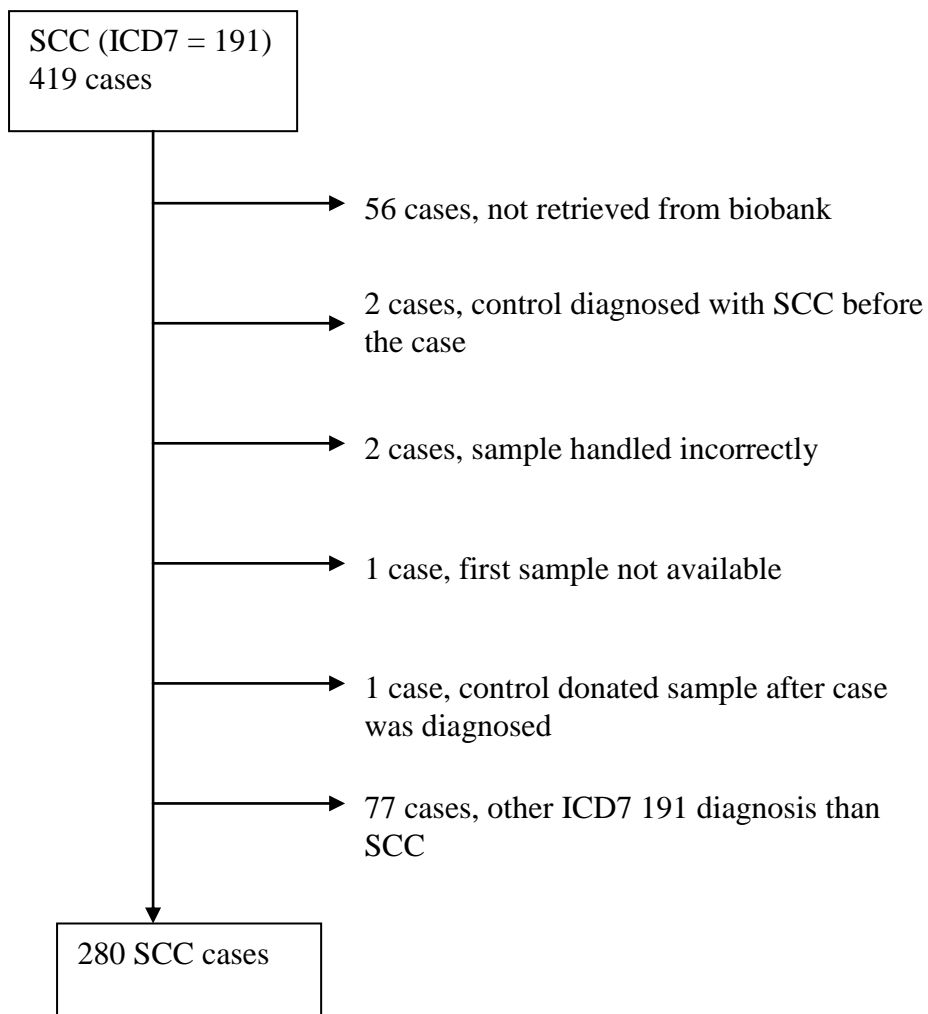


Figure 2. Description of case inclusion and exclusion from the Janus biobank with about 332 000 donors.
 Abbreviations: SCC, squamous cell carcinoma; BCC, basal cell carcinoma; ICD, international classification of diseases; NMSC, non-melanoma skin cancer.

