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High risk of tobacco-related cancers in *CDKN2A* mutation-positive melanoma families

Hildur Helgadóttir,¹ Veronica Höiom,¹ Göran Jönsson,² Rainer Tuominen,¹ Christian Ingvar,² Åke Borg,² Håkan Olsson,² Johan Hansson¹

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¹Department of Oncology and Pathology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

²Department of Oncology, Lund University and Skåne University Hospital, Lund, Sweden

Correspondence to

Dr Hildur Helgadóttir, Department of Oncology and Pathology, Karolinska Institutet, Karolinska University Hospital, Solna, Stockholm 171 76, Sweden; hildur.helgadottir@karolinska.se

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ABSTRACT

Background Germline mutations in the tumour suppressor gene *CDKN2A* occur in 5–20% of familial melanoma cases. A single founder mutation, p.Arg112dup, accounts for the majority of *CDKN2A* mutations in Swedish carriers. In a national program, carriers of p.Arg112dup mutation have been identified. The aim of this study was to assess cancer risks in p.Arg112dup carriers and their first degree relatives (FDRs) and second degree relatives (SDRs).

Methods In this prospective cohort study, cancer diagnoses in carriers (n=120), non-carriers (n=111), carriers' FDRs (n=275) and SDRs (n=321) and controls (n=3976) were obtained from the Swedish Cancer Registry. Relative risks (RRs) for cancers were calculated (number of cancers/person years). Two-sided 95% CIs were calculated for all RRs.

Results In carriers prospective RR for non-melanoma cancers was 5.0 (95% CI 3.7 to 7.3), for pancreatic cancer 43.8 (95% CI 13.8 to 139.0), for cancers in upper digestive tissues 17.1 (95% CI 6.3 to 46.5), and in respiratory tissues 15.6 (5.4 to 46.0). In FDRs and SDRs RRs were significantly elevated for cancers in pancreas, respiratory and upper digestive tissues. In ever-smoking carriers compared with never-smoking carriers, the odds ratio (OR) of cancers in pancreas, respiratory or upper digestive tissues was 9.3 (95% CI 1.9 to 44.7).

Conclusions *CDKN2A* p.Arg112dup mutation carriers from melanoma-prone families and their FDRs and SDRs have elevated risk for pancreatic, lung, head and neck and gastro-oesophageal carcinomas. These cancers were mainly seen in ever-smoking carriers. Germline *CDKN2A* mutations may confer an increased sensitivity to carcinogens in tobacco smoke. *CDKN2A* mutation carriers should be counselled to abstain from smoking.

INTRODUCTION

It is estimated that approximately 10% of all cases of cutaneous malignant melanoma occur in kindreds with hereditary predisposition for melanoma.^{1–2} Among melanoma families 5–20% carry a germline mutation of the *CDKN2A* gene on chromosome 9p21 coding for the cell cycle inhibitors and tumour suppressors p16-INK4A and p14-ARF.³ In Swedish melanoma families, occurrence of *CDKN2A* mutations has been analysed in studies from Southern Sweden and from Stockholm and were found in 19% and 8% of the families, respectively.^{4,5} In Sweden a single *CDKN2A* mutation, NM_000077.4: c.335_337dup, p.Arg112dup is the predominant mutation in melanoma families. The mutation inserts (duplicates) an arginine at codon

112 in one of the ankyrin repeats of p16-INK4A, disrupting its binding to CDK4/6. The mutation is located in *CDKN2A* exon 2 in a region that is also part of a second transcript with alternative reading frame, giving rise to a duplication of Ser-127 in p14-ARF, still of unknown functional consequence.^{4,5} This mutation, which has only been detected in Sweden is a founder mutation estimated to have arisen in Sweden approximately 2000 years ago, and it is possible (but not confirmed) that the mutation may have spread with Swedish emigration to European and North American countries.⁶ Individuals with p.Arg112dup and several other *CDKN2A* mutations also have an increased risk of developing pancreatic carcinoma.^{4,7–10} Several studies have reported an excess risk of other cancer types in *CDKN2A* mutated families, including gastrointestinal, breast, lung, central nervous system (CNS), gynaecological, childhood, head and neck, non-melanoma skin cancers and uveal melanomas,^{4,7,11–19} but these cancer risks are not as well established, nor as consistently observed as the increased risks of melanoma and pancreatic cancer. In *CDKN2A* carriers, melanoma risk has been positively associated with sun exposure,²⁰ but apart from this there have been no studies so far investigating the association of exposures to carcinogens, such as those in tobacco smoke, on cancer risk in *CDKN2A* carriers from melanoma-prone families.

In 1987 the Swedish Melanoma Study Group initiated a national program to identify kindreds with familial cutaneous malignant melanoma and to provide the members of these families with the possibility to participate in a preventive program.²¹ The original criteria for participation were two or more blood relatives (including first degree relatives (FDRs), second degree relatives (SDRs) and third degree relatives) with histopathologically confirmed melanoma. Later these criteria have been narrowed according to more recent guidelines from the International Melanoma Genetics Consortium to include only kindreds with two FDRs with melanoma or three or more melanomas in at least two blood related individuals. Since 1995, *CDKN2A* mutation analysis has been available for family members; to date at least one member in 455 families has undergone testing. Protein altering mutations have been found in 35 families, corresponding to 8% of the analysed families (unpublished data). Of these, 29 families are carriers of the p.Arg112dup founder mutation. The first aim of the study was to prospectively determine the risks in p.Arg112dup carriers for non-melanoma cancers

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(all combined) and also risk for individual cancer types. Second, we tested independently if the risks seen in confirmed carriers were also seen in the carrier's non-genotyped FDRs and SDRs.

MATERIALS AND METHODS

Participants, register linkages and questionnaire

The cohorts of carriers ($n=120$) and non-carriers ($n=111$) of the Swedish *CDKN2A* p.Arg112dup founder mutation were identified in 28 melanoma-prone families, of which 12 have previously been described.^{4 5 13 22} All known p.Arg112dup families were included in the study, except one. This family was excluded because several family members are also carriers of a *BRCA1* mutation and a high occurrence of breast cancer had been observed in family members. Informed consent was obtained before family members underwent germline *CDKN2A* analysis and the study was approved by Lund University Ethical Committee.

To extend the families the unique 10-digit personal identity numbers of the carriers were linked with the Swedish Multi-Generation registry which contains connections between all individuals born after 1931 and their biological parents that have been registered in Sweden after 1960.²³ This allowed identification of carriers' FDRs (parents, siblings and children) and SDRs (grandparents, uncles/aunts, half-siblings, nieces/nephews and grandchildren). Since the individuals within a family are related, an individual that is a known carrier also could be identified as a FDR or SDR to another known carrier. In this study each individual was assigned only to one group; known carriers were only accounted for as carriers even when they had been identified as FDRs or SDRs to other known carriers; FDRs were only accounted for as FDRs even if they had also been identified as SDRs. In this manner 275 FDRs and 321 SDRs of mutation carriers were identified. This extension of the families showed that two of the p.Arg112dup families are closely related, but in none of the other families there were shared FDRs or SDRs.

An age-matched and sex-matched control population for the carriers was obtained from the Swedish Civil Registry ($n=360$). FDRs ($n=1586$) and SDRs ($n=2030$) of controls were obtained from the Multi-Generation Registry. In the age-matched and sex-matched control group for the carriers ($n=360$) there were so few cancer occurrences that relative risks (RRs) for several cancer types became non-calculable and interpretations of risks uncertain. To increase power of the analysis, the control groups were combined ($n=3976$). An analysis was performed to calculate the power to detect significant ($p<0.05$; two-sided test) RRs in carriers compared with the prespecified control group and the combined control group. When assessing risks for all cancers combined (set at 10% in the control population), both control groups had 80% power to significantly detect twofold RRs. When assessing risks for rare cancer types (set at 0.2% in the control population), using the prespecified control group, there was 80% power to detect 20-fold RRs, whereas using the combined control groups there was 80% power to detect 10-fold RRs. This analysis demonstrated that the combination of the control groups was helpful in increasing the power in the analysis of RRs of rare cancer types. In the prespecified control groups the age and sex distributions were similar (see online supplementary table S1). The analysis based on the combined control groups did not alter the trends observed using specific control groups.

Cancer diagnoses in carriers, non-carriers, FDRs, SDRs and controls were obtained from the Swedish Cancer registry. Reporting to this registry, established in 1958, is compulsory for clinicians and pathologists/cytologists diagnosing a cancer.

Completeness of the register in 2011 was estimated to 97%.²⁴ All cancers registered from start of registry in 1958 to 31 December 2011 were obtained. ICD7 codes and histology codes (WHO/HS/CANC/24.1) were used to identify cancer types.

Information on tobacco smoking habits among carriers was obtained from questionnaires that were distributed to members of melanoma families with germline *CDKN2A* mutations. In the questionnaire it was asked how many years they had smoked and how many cigarettes they smoked per day on average. Ever-smoker was defined as in lifetime having smoked 100 cigarettes or more. Never-smoker was defined as having smoked less than 100 cigarettes in lifetime. For the deceased carriers, smoking history was retrieved from medical records.

DNA isolation, PCR and direct sequencing of PCR products

See online supplementary materials and methods.

Follow-up

In carriers and non-carriers follow-up started the date the first blood sample was taken for *CDKN2A* analysis in each family. When the controls were compared with the carriers, follow-up started the date the blood sample was taken for *CDKN2A* analysis in the carriers they were controls for. For FDRs and SDRs follow-up started at their date of birth. When the controls were compared with FDRs and SDRs, follow-up started at the controls' date of birth. The rationale behind having different definitions of start of follow-up for carriers and non-carriers versus FDRs and SDRs was twofold. First, using the start of follow-up date determined in the carriers for the FDRs and SDRs meant that there were too few events for a risk analysis, many cancer occurrences that had occurred in the older generations were then left out. Second, there was no apparent sign of ascertainment bias for other cancers than melanoma, and since the risk of carriers and their relatives for non-melanoma cancers was the main aim of the study we found this approach acceptable. For all individuals follow-up ended at date of death, emigration or census date of 31 December 2011.

Statistics

For the genotyped p.Arg112dup carriers and non-carriers median age was calculated for age at study inclusion and age at first melanoma diagnosis. RR for all non-melanoma cancers and for specific cancer types was calculated from incidence rates (number of cancers/person years). In individuals with multiple occurrences of the same cancer diagnosis, each diagnosis was only counted once in every individual. To estimate age-specific cumulative cancer incidence in carriers, the incidence of cancer was analysed in 10 year intervals from 0 year to 80 years of age (number of cancers/persons alive in each interval). Odds ratio (OR) was calculated for smoking status (ever/never) and having been diagnosed with cancer in pancreas, respiratory and upper digestive tissues (yes/no). Two-sided 95% CIs were calculated for all RRs. Database handling and statistical calculations were done in Microsoft Office Excel 2007 and StatSoft Statistica V.10.

RESULTS

Table 1 shows baseline characteristics of *CDKN2A* p.Arg112dup mutation carriers and non-carriers. At study inclusion, 39 carriers had been diagnosed with melanoma, and of those 20 had been diagnosed with multiple primary melanomas. Among non-carriers, five had been diagnosed with melanoma, whereof none had multiple primary melanomas. The median age at diagnosis of first melanoma was 39 years for carriers and 45 years for

Table 1 Baseline characteristics of carriers and non-carriers from *CDKN2A* p.Arg112dup mutated families*

	Carriers (n=120)	Non-carriers (n=111)
Sex (men/women)	56/64	54/57
Age at study inclusion (years; median, range)	35 (7–80)	33 (3–69)
No. diagnosed with melanoma	39	5
No. diagnosed with multiple primary melanomas	20	0
Age at first melanoma diagnosis (years; median, range)	39 (16–64)	45(24–68)
No. diagnosed with non-melanoma tumours	13	3
Gynaecological	4	2
Digestive—upper	2	0
Haematopoietic or lymphatic	2	0
Breast	1	1
Respiratory	1	0
Skin (non-melanoma)	1	0
Digestive—lower	1	0
Endocrine	1	0
Pancreas	0	0

*Baseline is defined as the date when each family's index case was tested for mutation.

non-carriers. At baseline 13 carriers and 3 non-carriers had been diagnosed with non-melanoma tumours.

Prospective RRs for all cancers in p.Arg112dup carriers compared with non-carriers and controls are shown in [table 3](#). Carriers contributed 1657, non-carriers 1837 and controls 51 952 person years. Observed cases of each cancer type for carriers are shown. In non-carriers and controls, numbers of expected cases are calculated to correspond to equal person years as for carriers. Prospective RRs for all non-melanoma cancers in mutation carriers compared with controls was 5.0 (95% CI 3.7 to 7.3). The RR for melanoma was 64.8 (95% CI

36.9 to 117.9), for pancreatic cancer 43.8 (95% CI 13.8 to 139.0), for primary cancers in upper digestive tissues (oral cavity, tongue, pharynx, oesophagus, stomach, liver, gall bladder) 17.1 (95% CI 6.3 to 46.5), for primary cancers in respiratory tissues (lung, bronchi, larynx) 15.6 (95% CI 5.4 to 46.0), for gynaecological cancers 8.8 (95% CI 3.8 to 20.4) and for non-melanoma skin cancer 3.3 (95% CI 1.0 to 10.7). Compared with non-carriers there was a significantly higher risk in carriers for all non-melanoma cancers and for melanoma. In non-carriers there were no cases of pancreatic cancers or cancers in upper digestive tissues and one case of lung cancer, indicating a marked excess risk for these tumours in carriers compared with non-carriers. In [tables 1–3](#) cancers in upper digestive tissues are shown separately from pancreatic cancer, since this tumour is of special interest being previously known to be more common in *CDKN2A* mutation carriers.

Relative cancer risks for FDRs and SDRs are shown in [table 3](#), FDRs contributed 12 683, SDRs 15.525 and controls 187.179 person years. RRs for all non-melanoma cancers was significantly elevated in FDRs, 2.1 (95% CI 1.6 to 2.7) but not in SDRs, 1.0 (95% CI 0.8 to 1.4). RRs for pancreatic cancer was significantly elevated in FDRs, 21.6 (95% CI 9.1 to 49.9) and in SDRs, 3.8 (95% CI 1.1 to 14.9). RRs for primary cancers in respiratory tissues were significantly elevated in FDRs, 6.0 (95% CI 2.8 to 13.1) and in SDRs, 2.8 (95% CI 1.0 to 7.2). RRs for primary cancers in upper digestive tissues were significantly elevated in FDRs, 3.3 (95% CI 1.5 to 7.6) and in SDRs, 2.3 (95% CI 1.0 to 5.6). Specification of all cancer occurrences and RRs in carriers, FDRs and SDRs compared with controls are shown in online supplementary table S2. The following cancers were significantly more frequent in the p.Arg112dup families compared with controls; cutaneous melanoma, cancer of the tongue, oral cavity, oesophagus, stomach, pancreas, larynx, lung, breast and cervix.

Age-specific cumulative incidence in p.Arg112dup carriers of all non-melanoma cancers and combined for cancers in pancreas, upper digestive and respiratory tissues is shown in [figure 1](#). The numerical values of the cumulative incidences used for [figure 1](#) are shown in online supplementary table S3.

Table 2 Prospective risk of cancers in *CDKN2A* p.Arg112dup carriers (n=120) compared with non-carriers (n=111) and controls (n=3976)

Tumour type	p.Arg112dup observed	Non-carriers expected*	RR (95% CI)	Controls expected*	RR (95% CI)
Melanoma	35	3.61	9.7 (3.5 to 27.2)	0.54	64.8 (36.9 to 117.9)
Pancreas	7	0	NA†	0.16	43.8 (13.8 to 139.0)
Digestive—upper	6	0	NA†	0.35	17.1 (6.3 to 46.5)
Respiratory	5	0.90	5.6 (0.7 to 47.4)	0.32	15.6 (5.4 to 46.0)
Gynaecological	7	3.61	1.9 (0.6 to 6.6)	0.80	8.8 (3.8 to 20.4)
Haematopoietic or lymphatic	2	0	NA†	0.51	3.9 (0.6 to 10.6)
CNS	1	0	NA†	0.29	3.4 (0.4 to 27.5)
Skin (non-melanoma)	3	0.90	3.3 (0.3 to 31.9)	0.92	3.3 (1.0 to 10.7)
Breast	3	0.90	3.3 (0.3 to 31.9)	0.99	3.0 (0.9 to 9.9)
Endocrine	1	0	NA†	0.35	2.9 (0.4 to 22.1)
Urinary	3	0.90	3.3 (0.3 to 31.9)	1.75	1.7 (0.5 to 5.5)
Digestive—lower	1	0	NA†	0.96	1.0 (0.1 to 7.7)
Connective tissue	0	0	NA†	0.03	0.0
Unknown primary tumour	0	0	NA†	0.29	0.0
All non-melanoma cancers	39	8.12	4.8 (2.4 to 10.1)	7.78	5.0 (3.7 to 7.3)

*In non-carriers and controls, numbers of expected cases are calculated to correspond to equal person years as for carriers.

†NA=RR not calculable since 0 cases of cancer type in non-carriers.

RR, Relative risk.

Table 3 Lifetime risk of all cancers in *CDKN2A* p.Arg112dup carriers FDRs (n=275) and SDRs (n=321)

	FDRs	Expected*	RR (95% CI)	SDRs	Expected*	RR (95% CI)
Melanoma	28	1.36	20.6 (11.6 to 36.7)	8	1.66	4.8 (2.1 to 10.9)
Pancreas	13	0.6	21.6 (9.1 to 49.9)	3	0.8	3.8 (1.1 to 14.9)
Respiratory	9	1.5	6.0 (2.8 to 13.1)	5	1.8	2.8 (1.0 to 7.2)
Digestive—upper	7	2.1	3.3 (1.5 to 7.6)	6	2.6	2.3 (1.0 to 5.6)
Haematopoietic or lymphatic	2	1.8	1.1 (0.3 to 4.6)	2	2.2	0.9 (0.2 to 3.8)
Gynaecological	7	6.7	1.0 (0.5 to 2.2)	8	8.2	1.0 (0.5 to 2.0)
Endocrine	4	1.4	2.9 (1.0 to 8.6)	0	1.7	0.0
Skin (non-melanoma)	4	2.9	1.4 (0.5 to 3.9)	0	4.3	0.0
Breast	8	4.2	1.9 (0.9 to 4.0)	7	5.1	1.4 (0.6 to 3.0)
CNS	3	1.4	2.1 (0.6 to 7.1)	0	1.7	0.0
Digestive—lower	5	4.3	1.2 (0.5 to 2.9)	2	5.3	0.4 (0.1 to 1.5)
Urinary	8	7.3	1.1 (0.5 to 2.9)	12	8.9	1.3 (0.7 to 2.5)
Connective tissue	1	0.3	3.3 (0.3 to 25.3)	1	0.4	2.5 (0.3 to 20.6)
Unknown primary tumour	3	1.2	2.5 (0.8 to 8.9)	0	1.4	0.0
All non-melanoma cancers	74	35.7	2.1 (1.6 to 2.7)	46	44.4	1.0 (0.8 to 1.4)

*In controls, numbers of expected cases are calculated to correspond to equal person years as for carriers. FDR, first degree relative; RR, relative risk; SDR, second degree relative.

Among carriers at age 50 years, 20% had been diagnosed with non-melanoma cancers and 7% with cancers in pancreas, upper digestive and respiratory tissues. At age 80 years, 76% had been diagnosed with non-melanoma cancers and 53% with tumours in pancreas, upper digestive and respiratory tissues.

In table 4 the numbers of members in each family (p.Arg112dup carriers, FDRs and SDRs) with cancers in respiratory, upper digestive tissues and pancreas are shown. Pancreatic cancer, cancer in respiratory and upper digestive tissues was seen in 16, 12 and 12 families, respectively. In all families with more than 16 family members at least one subject was diagnosed with these cancers.

In the carriers, FDRs and SDRs we observed significantly elevated risks for pancreatic, lung, head and neck and gastro-oesophageal malignancies. In a normal population these cancer types are highly associated with tobacco smoke and to some extent other agents such as alcohol, chewing tobacco, certain foods, pollution and human papillomavirus (HPV). Although

not a predefined aim in this study we found it important to address if the elevated risks of the observed cancers among carriers and their relatives was dependent primarily on the genotype or if environmental factors contributed to the phenotype observed. For this reason data on cigarette smoking was collected among all carriers that had reached the age of 29 years, which was the youngest age when any of the cancers described above had been diagnosed. Of the 116 carriers that had reached that age, information on smoking history was retrieved from 60% of the individuals (67% in carriers with any of these cancers and 57% in carriers without), in 61 individuals information was obtained from questionnaires and in 11 from medical records. In ever-smoking carriers compared with never-smoking carriers, the OR of cancers in pancreas, respiratory or upper digestive tissues was 9.3 (1.9 to 44.7) (table 5). Among ever-smokers that had the diagnoses, the following cancers were observed: pancreatic cancer (three cases), tongue cancer (three cases), lung cancer (three cases), cancer of oral cavity (one case), larynx cancer (one case), oesophageal cancer (one case). The median age at end of follow-up of smokers that had been diagnosed with cancers in pancreas, upper digestive or respiratory tissues was 70 years while in smokers that had none of these diagnoses, the median age at end of follow-up was 50 years.

DISCUSSION

In this study we studied melanoma kindreds and investigated the cancer risks in carriers of the Swedish p.Arg112dup *CDKN2A* founder mutation and their FDRs and SDRs. We found a significantly elevated risk in carriers and FDRs for all non-melanoma cancers combined. More specifically, in carriers, FDRs and SDRs, there were significantly elevated risks for cancers in pancreas, upper digestive and respiratory tissues. At age 80 years, 53% of the carriers had one of these diagnoses. Cancers in pancreas, upper digestive and respiratory tissues were found in the majority of families and not limited to a small subset of kindreds, indicating that it is unlikely that the association between the mutation and these cancers is confounded by other genetic causes. Interestingly among carriers that had ever smoked cigarettes, the risk for pancreatic, respiratory and upper digestive cancers was significantly elevated compared with non-smokers. The difference in median age at the

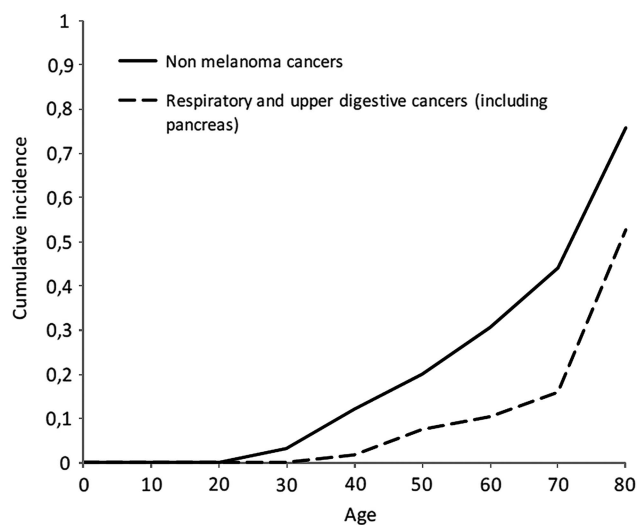


Figure 1 Age-specific cumulative incidence of non-melanoma cancers and for cancers in respiratory and upper digestive tissues (including pancreas) among the cohort of *CDKN2A* p.Arg112dup carriers (n=120).

end of observation between smokers that had these cancers compared with those that did not was 20 years, indicating that younger smokers are at increased risk to develop these cancer types later in life.

In a study by de Snoo *et al.*,⁷ specific cancer risks in melanoma families with the Dutch founder mutation (p16-Leiden) in *CDKN2A* were analysed. In this study, the 221 mutation carriers from 22 melanoma families had a significantly increased risk for cancers of the pancreas, respiratory tissues, lip, mouth and pharynx, digestive tissues (not specified if upper or lower), female genital tissues and eye/brain (only two cases). Interestingly, the specific cancers with increased risks were largely the same among carriers of the p16-Leiden and the p.Arg112dup mutations. These mutations have the following in common: they are founder mutations identified in a number of families and have originated in North European countries (Netherlands and Sweden). The mutations are both located in exon 2 of the gene, and both are set in ankyrin repeats 3–4, where significantly higher risks of pancreatic cancers have been reported compared with mutations in ankyrin repeats 1–2 of the gene.²⁵ In the report by de Snoo *et al.*, there was no data or statement on a possible association with tobacco smoking, but

Table 4 Numbers of subjects per *CDKN2A* p.Arg112dup positive family diagnosed with cancers in pancreas, respiratory and upper digestive tissues

Family ID	Family size no.*	Pancreas no. w/diagnosis	Respiratory tissues no. w/diagnosis	Upper digestive tissues no. w/diagnosis
3998	10			1
8508	14	1	1	1
8512	31	1		
8523	48	2		1
8528	13			
8551	9	1	1	1
8581	21		3	
8601	35	1	1	
8611	17	1		
8621	40		1	3
8793	10	1	1	
8795	34	2		
8839	18	1		
8866	11		1	1
12 519	13			
12 546	15			
12 551	18			1
13 502	143	2	5	6
13 509	34	2		2
13 512	12			2
13 531	49	1	2	
13 545†	9	3	1	
13 549†	23		2	
13 562	4			
13 569	5	1		
13 581	28	1		1
13 592	16			
13 616	38	2	1	1

*Total numbers of carriers, FDRs and SDRs per family.

†Families 13 545 and 13 549 were found to have shared SDRs.

FDR, First degree relative; SDR, second degree relative.

Table 5 Smoking status among *CDKN2A* p.Arg112dup carriers* diagnosed with cancers in respiratory or upper digestive tissues (including pancreas)

	Total no.	Diagnosed with cancers in respiratory or upper digestive tissues		
		Yes	No	OR (95% CI)
Never-smoker	37	2	35	1.0 (reference)
Ever-smoker	35	12	23	9.3 (1.9 to 44.7)

*Only carriers that had reached the age of 29 years were included in this analysis. OR, odds ratio.

since there were increased risks for mainly the same specific cancers as were observed in our study, it is likely that carriers of the p16-Leiden mutation, and possibly also of other *CDKN2A* mutations perturbing ankyrin repeats 3–4, have increased risk for smoking induced cancers compared with the wild type population.

The *CDKN2A* encoded proteins p16-INK4A and p14-ARF are cell cycle inhibitors and tumour suppressors, where p16-INK4A is an inhibitor of CDK4/CDK6 in the retinoblastoma pathway and p14-ARF through its inhibition of HDM2, is a regulator of p53. Notably, germline mutations in *TP53* and *RB1* genes are associated with high risks for lung cancer (and other specific cancers, in particular retinoblastomas in *RB1* mutated and sarcomas in *TP53* mutated).^{26 27} In *RB1* and *TP53* mutated the elevated risks for lung cancers are mainly observed in smokers.^{27 28} Thus, it seems that carriers of *CDKN2A* mutations, and of mutations in tumour suppressors linked to p16-INK4A and p14-ARF, are at elevated risks for smoking induced cancers.

Upper digestive tissues (including pancreas) and respiratory tissues are derived from foregut endoderm²⁹ and are known to be sensitive to exposures from certain carcinogens, in particular a strong association with cancers in these tissues and tobacco smoke and/or alcohol has been established.^{30 31} In three separate case reports of *CDKN2A* mutation carriers that were smokers and/or alcohol consumers, cancers of the tongue, oral cavity, pharynx and lung have been reported.^{12 17 19} Loss of the wild type *CDKN2A* allele was observed in tumours from these individuals, supporting the role of inactivation of this tumour suppressor gene in these tumours.^{17 19} Another study showed that among subjects that ever smoked, the risk for pancreatic cancer was higher for *CDKN2A* mutation carriers compared with non-carriers, but among non-smokers the risk for pancreatic cancer was not significantly different in carriers and non-carriers. Although interesting, this study was limited by a low number of confirmed carriers (n=9), which were all carriers of different *CDKN2A* mutations.³² Somatic *CDKN2A* alterations are frequently observed in pancreatic, lung, head and neck, oesophageal and gastric cancers, where they are believed to be driver mutations.^{33–36} In lung and head and neck cancers it has been shown that somatic alterations in the *CDKN2A* gene are associated with tobacco smoke and/or alcohol exposure.^{37–39} In a rodent model it has been demonstrated that exposure to a tobacco smoke derived carcinogen (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) induces tumours with hypermethylation of the p16 gene promoter leading to loss of p16 expression.⁴⁰ In a recent study of mutational processes in multiple human cancers, it was reported that of the 30 different tumour types analysed, melanoma, lung, oesophageal, head and neck and gastric cancers were all among the tumour types that had most acquired

mutations.⁴¹ Digestive and respiratory organs are highly exposed to multiple carcinogens in our environment in analogy to the skin being exposed to ultraviolet radiation, and it has been shown that melanoma penetrance in *CDKN2A* mutation carriers is associated with the environmental ultraviolet (UV) exposure in the country of residence.²⁰ In melanoma tumours, UV-B signature DNA changes are commonly observed in the *CDKN2A* gene.⁴² In carriers we also found an increased risk of gynaecological malignancies, largely due to cervical carcinomas (see online supplementary table S2). It will be of interest to follow whether this increase is abolished by the introduction of prophylactic HPV vaccination. Our findings support the concept that germline *CDKN2A* mutations may confer an increased sensitivity to carcinogens, resulting in the observed pattern of increased cancer risks.

In p.Arg112dup carriers, three adolescents were diagnosed with melanoma, but no melanomas or other tumours were seen in young children, in FDRs there was one case of CNS tumour at age 9 years and in SDRs one case of leukaemia at age 2 years (data not shown). Although these are more cases than would be expected in the general population, they are too few for statistical analysis and the association previously reported for childhood cancer¹⁵ in p.Arg112dup families cannot be confirmed nor refuted in this study. For breast cancer, the RR was moderately elevated in carriers, FDRs and SDRs but not significantly increased. Higher risk for breast cancer has previously been reported in p.Arg112dup carriers.⁴ In the study by Borg *et al*, nine p.Arg112dup families were analysed, but it was later discovered that in one family (excluded from the current study) with a high burden of breast cancer, family members had a germline mutation in the *BRCA1* gene in addition to the *CDKN2A* mutation, which may have contributed to the conclusion that there was a marked increase in breast cancer risk. Also carriers might be more likely to participate in population screening programs for breast and cervical cancer, possibly increasing the incidence of these cancer types in this group.

A few limitations of our study deserve attention. The *CDKN2A* p.Arg112dup carriers are identified solely from melanoma-prone families and we have limited knowledge on the mutation frequencies in other populations. Therefore we cannot automatically draw conclusions that all carriers of this mutation have the risks found in this study. But in Stockholm we have previously tested sporadic melanoma cases and controls for *CDKN2A* p.Arg112dup mutations and found mutations in 0.2% (n=526) and 0% (n=663), respectively, indicating that the mutation frequency in the population is low and likely mainly observed in melanoma-prone families.⁴³ In studies as this one there is always a risk for ascertainment bias, and for melanoma we cannot exclude that there is some ascertainment bias since there are more melanoma cases than would be expected in the non-carriers from the mutation carrying families. This is to some degree expected when individuals are selected solely for belonging to families with multiple melanoma cases. In this study the main aim was the risk for non-melanoma cancers, and by observing the frequencies of non-melanoma cancers in non-carriers, we cannot see an obvious tendency of ascertainment bias for non-melanoma tumours (tables 1 and 2). In addition to assessing the combined risk for all non-melanoma cancers we also intended to assess the risks for tissue-specific cancers. This is a highly relevant issue, since for the families it is important to recognise the total risk and the risk for certain cancer types. Although we have included all the known families carrying the p.Arg112dup mutation in our study, the size of the cohorts is

too small for an adjustment of statistical significance for multiple outcomes. To still address this issue we have done comparisons in multiple groups, first comparing carriers with non-carriers and with controls and also independently comparing FDRs and SDRs with controls. In online supplementary table S2 we also compare all individuals in p.Arg112dup mutation families (except the non-carriers) with the total control population. We only draw conclusions on an association between certain cancer forms and the mutation when we have seen significantly elevated risks in all comparisons. When smoking history was collected in mutation carriers, data was missing from 33% of carriers with cancers in pancreas, upper digestive and respiratory tissues and 43% of those not diagnosed with these cancer types. This difference was likely mostly explained by that in those that had died being diagnosed with lung, head and neck, pancreatic or gastro-oesophageal cancers there was more often information on smoking history in medical records, than in deceased carriers that had not been diagnosed with these cancer types. We cannot rule out that there might have been an issue of misclassification with respect to smoking status from data collected from medical records or from the questionnaires, but it is very unlikely that the marked association seen between smoking and these cancers, would only have been due to information bias.

The strength of this study is that it involved the hitherto largest number of families with the same germline *CDKN2A* mutation, with long time follow-up for occurrence of cancer. We have investigated independently the cancer risks in carriers and their FDRs and SDRs by linkage to national registries with near-complete coverage. We found high risks among carriers for cancers in pancreas, respiratory and upper gastrointestinal tissues. In a gene-dose manner we confirmed elevated risks for the same cancer types in FDRs and SDRs as were observed in carriers. By collecting information on smoking history, we show in mutation carriers, a previously not recognised association between tobacco smoking and cancers in pancreas, respiratory and upper gastrointestinal tissues.

We conclude that the risk for non-melanoma cancers in *CDKN2A* p.Arg112dup mutation carriers is not limited to pancreatic cancer and the phenotype should be extended to include tumours in respiratory and upper digestive tissues. As has been reported for pancreatic cancer, it is not unlikely that the risk for cancers in respiratory and upper gastrointestinal tissues may vary significantly between carriers of specific germline *CDKN2A* mutations.²⁵ This emphasises the need for further collaborative analyses of cancer occurrence among carriers of specified *CDKN2A* germline mutations. Further molecular and epidemiological studies should be done to examine the relation between carcinogens and cancers in *CDKN2A* mutation carriers. *CDKN2A* p.Arg112dup mutation carriers should be strongly advised to abstain from tobacco smoking. Moreover, families with multiple cases of melanoma as well as cancers in respiratory and upper digestive tissues should be regarded as candidates for *CDKN2A* mutation screening. We propose that, particularly in mutation carriers who smoke, screening for lung, head and neck, and gastro-oesophageal malignancies should be considered.

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Contributors All authors of this paper have participated/contributed to this work as follows: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Novelty and Impact Statements In this study we describe in members of melanoma-prone families with germline *CDKN2A* mutation, a significantly increased risk of pancreatic, lung, head and neck and gastro-oesophageal cancers. We show a positive association between tobacco smoking and these non-melanoma cancers among mutation carriers. This is the first study that shows association between smoking history and cancer diagnoses in *CDKN2A* mutation carriers. Our study has important implications for counselling and monitoring of members of melanoma-prone families with germline *CDKN2A* mutations.

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High risk of tobacco-related cancers in *CDKN2A* mutation-positive melanoma families

Hildur Helgadóttir, Veronica Höiom, Göran Jönsson, Rainer Tuominen, Christian Ingvar, Åke Borg, Håkan Olsson and Johan Hansson

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