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APOBEC3A/B deletion polymorphism and cancer risk

Liv B. Gansmo[1,2], Paal Romundstad[3], Kristian Hveem[4], Lars Vatten[3], Serena Nik-Zainal[5,6], Per Eystein Lønning[1,2] and Stian Knappskog[1,2,*]

[1]Section of Oncology, Department of Clinical Science, University of Bergen, Bergen, Norway; [2]Department of Oncology, Haukeland University Hospital, Bergen, Norway; [3]Department of Public Health, Faculty of Medicine and [4]Department of Public Health, Faculty of Medicine, K.G. Jebsen Center for Genetic Epidemiology, Norwegian University of Science and Technology, Trondheim, Norway; [5]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, UK and [6]Department of Medical Genetics, Addenbrooke's Hospital National Health Service (NHS) Trust, Cambridge, UK

*To whom correspondence should be addressed. Tel: +47-55976447; Fax: +47-55972046; Email: stian.knappskog@uib.no

Abstract

Activity of the apolipoprotein B mRNA editing enzyme, catalytic-polypeptide-like (APOBEC) enzymes has been linked to specific mutational processes in human cancer genomes. A germline *APOBEC3A/B* deletion polymorphism is associated with APOBEC-dependent mutational signatures, and the deletion allele has been reported to confer an elevated risk of some cancers in Asian populations, while the results in European populations, so far, have been conflicting. We genotyped the *APOBEC3A/B* deletion polymorphism in a large population-based sample consisting of 11 106 Caucasian (Norwegian) individuals, including 7279 incident cancer cases (1769 breast, 1360 lung, 1585 colon, and 2565 prostate cancer) and a control group of 3827 matched individuals without cancer (1918 females and 1909 males) from the same population. Overall, the *APOBEC3A/B* deletion polymorphism was not associated with risk of any of the four cancer types. However, in subgroup analyses stratified by age, we found that the deletion allele was associated with increased risk for lung cancer among individuals <50 years of age (OR 2.17, CI 1.19–3.97), and that the association was gradually reduced with increasing age (*P* = 0.01). A similar but weaker pattern was observed for prostate cancer. In support of these findings, the *APOBEC3A/B* deletion was associated with young age at diagnosis among the cancer cases for both cancer forms (lung cancer: *P* = 0.02; dominant model and prostate cancer: *P* = 0.03; recessive model). No such associations were observed for breast or colon cancer.

Introduction

Recent advances in cancer genome studies have identified several mutational signatures and mutational processes that point towards the molecular mechanisms behind mutations in cancer cell's DNA (1–3). One of the most abundant signatures has been found to emerge from the cytidine deaminase activity of proteins belonging to the apolipoprotein B mRNA editing enzyme, catalytic-polypeptide-like (APOBEC) family (1,4,5). The APOBEC mutational signatures observed in human cancers are particularly linked to the activity of the APOBEC3A and 3B proteins (6–8).

The APOBEC3 subfamily of proteins (APOBEC3A-G) is encoded by an APOBEC genomic cluster on chromosome 22 (9,10) and is known to protect human cells from viral infection by mutation of single-stranded DNA (10). While a link between the APOBEC3 genes and DNA damage was suggested already in the beginning of the 2000s (reviewed in (11)), it was more recently established that APOBEC3A is capable of hypermutating nuclear DNA and induce double-stranded DNA breaks (12,13). It has also been suggested, although to a lesser extent, that APOBEC3B is able to edit genomic DNA (14).

Recently, a common germline 29.5 kb deletion in the *APOBEC3* gene region was linked to an APOBEC-related mutational signature in breast tumors (15). The 29.5 kb deletion removes the 3′ end of the *APOBEC3A* gene and a large part of the *APOBEC3B* gene, creating a hybrid gene that transcribes an mRNA with the *APOBEC3A* coding region and the *APOBEC3B* 3′-untranslated regions (16). This hybrid transcript is more stable than the wild-type; therefore, it may lead to increased

Abbreviations

APOBEC	apolipoprotein B mRNA editing enzyme, catalytic-polypeptide-like
CI	confidence intervals
HRM	high resolution melting
MAF	minor allele frequency
ORs	odds ratios.

intracellular levels, with subsequent higher DNA damage caused by APOBEC3 activity (17). In population studies, the minor allele frequency (MAF) of the *APOBEC3A/B* deletion polymorphism has been estimated to 6% among individuals of European decent and 37% among individuals of Asian decent (16). Case–control studies in Asian populations have found that the *APOBCEC3A/B* deletion allele may be associated with increased risk for breast and ovarian cancer (18–20). In 2013, Xuan *et al.* also reported that the *APOBEC3A/B* deletion variant may be associated with increased risk for breast cancer among European women (21); however, this finding was not reproduced in a Swedish study (22).

In the present study, we analysed a large sample (*n* = 11 106) of the population-based cohort of Norway and assessed the impact of *APOBEC3A/B* deletion genotype on risk of cancer in the breast, colon, prostate and lung, using a case-control design.

Materials and methods

Study population

All samples analysed were drawn from the population-based cohort of Norway (23). In the present study, we included 11 130 individuals. Among these, the molecular analysis failed in 24 samples due to technical reasons, leaving 11 106 individuals for statistical analyses. These 11 106 included 7279 incident cancer cases (1769 breast, 1360 lung, 1585 colon, and 2565 prostate cancer) and a control group consisting of 3827 matched individuals without cancer (1918 females and 1909 males) from the same cohort.

The selected samples have been described previously in detail in germline genotyping studies (24–27). In our previous studies 10 830 out of 10 842 drawn samples were successfully analysed for *MDM2* and *MDM4* germline SNPs. Due to lack of DNA, 51 of the previous samples were not included in the present analyses, while 339 new samples were added, generating the total sample of 11 130 individuals.

The study was approved by the Regional Committee for Ethics in Medical Research (REK Midt-Norge), and all sample donors had provided written informed consent to anonymous genetic testing for scientific purposes.

Sample size

Given the fact that the *ABOBEC3A/B* deletion occurs at a lower frequency among Caucasians than among Asians, we performed power estimates to ensure that our sample set was large enough to detect differences between cases and controls. Few data are available for Caucasians, but we based our estimates on previously published data for breast cancer cases and controls among women of European ancestry. Based on the findings reported by Xuan *et al.* (21), and applying an α-value of 0.05, we found our sample sizes to yield the following β-values: 0.83 for breast cancer, 0.76 for lung cancer, 0.91 for prostate cancer and 0.80 for colon cancer. As such, we considered the sample sizes to be adequate for analysis.

APOBEC3 ins/del genotyping

Eleven thousand one hundred and six samples were successfully genotyped for the *ABOBEC3A/B* deletion on a LightCycler 480 II instrument (Roche Diagnostics, Basel, Switzerland) using separate primer pairs for the deletion and the wild-type allele (16) and with the following hybridization probes: 5′-LC640-TGTCCCAGCAGTACTCAAACT-PH and 5′-CATCCCTGGCGGTACACAA-FL for the wild-type allele and 5′-LC-640-TGTCCCAGCAGTGCTTAAATT-PH and 5′-CATCCCTGGTGGTCCACAA-FL for the deletion allele (TIB MOLBIOL Syntheselabor GmbH, Berlin, Germany). The amplifications of the wild-type and deletion allele were performed separately, in a final reaction volume of 10 μl, containing 1 μl LightCycler® FastStart DNA Master HybProbe mix (Roche Diagnostics, Basel, Switzerland), 3mM $MgCl_2$, 0.125 μM of each probe and 0.5 μM or 0.1 μM of each primer pairs, for the wild-type allele and the deletion allele, respectively, and finally, 0.05 U of Taq DNA polymerase (VWR) were added in the wild-type allele amplification. The thermocycling conditions were 10 min initial denaturation/activation at 95°C, followed by 45 or 50 cycles of denaturation at 95°C for 15 s, annealing for 10 s at 55°C or 59°C and an elongation step at 72°C for 15 or 25 s for the deletion and wild-type allele, respectively. Prior to the cooling step at 40°C for 30 s, the high resolution melting (HRM) step was performed, starting with an initial denaturation at 95°C for 30 s, followed by melting from 40 to 85°C with a ramp rate of 0.19°C/s. The HRM curve profiles were analysed applying the Melt Curve Genotyping module in the LightCycler® 480 II software version 1.5.

Subsequent to the HRM genotyping, the results from approximately 6% of all samples were validated by an independent PCR assay, described in (16), detecting only the wild-type allele.

Furthermore, 10% of all samples were genotyped for the SNP rs12628403, which is located in close proximity to the *ABOBEC3A/B* deletion, and reported previously to be in strong linkage disequilibrium with the deletion (28). The SNP was genotyped applying a custom LightSNiP assay (TIB-Molbiol) according to the manufacturer's recommendation. The thermocycling conditions were 10 min initial denaturation/activation at 95°C, followed by 45 cycles of denaturation at 95°C for 10 s, annealing for 10 s at 60°C and an elongation step at 72°C for 30 s. Prior to the cooling step at 40°C for 30 s, the HRM step was performed, starting with an initial denaturation at 95°C for 30 s, followed by melting from 40°C to 75°C with a ramp rate of 2.0°C/s. The melting curve profiles were analysed applying the Melt Curve Genotyping module in the LightCycler® 480 II software version 1.5. Out of the samples genotyped for rs12628403 (*n* = 1104), 16 revealed genotypes indicating recombination between this locus and the *ABOBEC3A/B* deletion. Four out of these 16 were reclassified when regarding the results from the two assays together. Accordingly, we observed recombination in 12 (1.09%) of individuals, corresponding to 0.54% of alleles. This recombination rate was in line with previous observations in an American cohort (28).

Statistics

Potential deviations from the Hardy-Weinberg equilibrium were determined by using the Chi-square test. Possible associations between the *APOBEC3A/B* polymorphism and risk for cancer of the breast, colon, lung or prostate were estimated by odds ratios (ORs) applying logistic regression analyses. All ORs are given with 95% confidence intervals (CI). For breast and prostate cancer, we used female and male controls for risk estimation, respectively, and the ORs were adjusted for age. For colorectal cancer, ORs were adjusted for age and sex. In addition, we here performed sex-specific sub-analyses, where female and male cases were compared to female and male controls. These sub-analyses were adjusted for age as co-variate. For lung cancer, ORs were adjusted for age, sex and smoking. In addition, we here performed sex-specific sub-analyses adjusted for age and smoking. When multiple adjustments were made, the interaction terms between the variables were also included in the models. The applied adjustments are given as footnotes in Table 1. Trends for ORs across age groups were estimated using binary logistic regression. Potential differences in age at onset of cancer were estimated by the Mann-Whitney rank test. The statistical analyses were performed using the IBM SPSS 22 software (IBM Corp, Armonk, NY, USA).

Results

Distribution of APOBEC3A/B genotypes

Among 3827 controls, we found 3148 individuals (82.3%) to be homozygous for the *APOBEC3A/B* insertion allele, 635 (16.6%) to be heterozygous, while 44 (1.2%) were homozygous for the deletion allele (Table 1). This resulted in an observed MAF of 0.094 and a genotype distribution that did not deviate from the Hardy-Weinberg

equilibrium (*P* > 0.4). The distributions of genotypes were also found to be in Hardy-Weinberg equilibrium within the groups of patients diagnosed with each of the four cancer types (all P-values > 0.4).

APOBEC3A/B genotypes and cancer risk

The distribution of the *APOBEC3A/B* genotypes in the different cancer types is given in detail in Table 1. We found no clear association between *APOBEC3A/B* genotype and risk of any of the four investigated cancer forms either applying the dominant or the recessive model (Table 1A; Figure 1).

For lung and colorectal cancer, we performed sub-analyses stratified according to sex but observed no association between the *APOBEC3A/B* variant and cancer risk for any of the sex-specific subgroups (Table 1A; Figure 1). For lung cancer, we performed additional analyses stratified by smoking status; the vast majority of lung cancer cases was confirmed smokers (87.3%), and the results in the smoker/non-smoker subgroups did not differ from the overall lung cancer analyses (data not shown). Similar results were obtained when assessing the allele distributions (Table 1B).

Table 1A. *APOBEC3A/B* genotype and cancer risk

Cases/controls	Genotype *n* (%)			OR (95% CI) Dominant[a]	*P*	OR (95% CI) Recessive[b]	*P*
	ins/ins	ins/del	del/del				
Controls	3148 (82.3)	635 (16.6)	44 (1.2)	1.00	–	1.00	–
Females	1576 (82.2)	322 (16.8)	20 (1.0)	1.00	–	1.00	–
Males	1572 (82.4)	313 (16.4)	24 (1.3)	1.00	–	1.00	–
Colon cancer[c]	1322 (83.4)	250 (15.8)	13 (0.8)	0.91 (0.77–1.08)	0.28	0.71 (0.37–1.36)	0.30
Females[d]	679 (84.2)	120 (14.9)	7 (0.9)	0.85 (0.67–1.08)	0.19	0.95 (0.37–2.42)	0.92
Males[e]	643 (82.5)	130 (16.7)	6 (0.8)	0.97 (0.77–1.22)	0.81	0.55 (0.22–1.38)	0.20
Lung cancer[f]	1101 (81.0)	240 (17.7)	19 (1.4)	1.13 (0.94–1.36)	0.20	1.03 (0.54–1.97)	0.93
Females[g]	405 (80.0)	98 (19.4)	3 (0.6)	1.22 (0.90–1.67)	0.20	0.84 (0.22–3.18)	0.80
Males[h]	696 (81.5)	142 (16.6)	16 (1.9)	1.08 (0.85–1.36)	0.54	1.11 (0.52–2.34)	0.79
Breast cancer[d]	1465 (82.8)	292 (16.5)	12 (0.7)	0.95 (0.80–1.13)	0.57	0.64 (0.31–1.31)	0.22
Prostate cancer[e]	2148 (83.7)	390 (15.2)	27 (1.1)	0.93 (0.78–1.10)	0.37	0.96 (0.53–1.74)	0.89

[a]Dominant model: del/del + ins/del versus ins/ins.
[b]Recessive model: del/del versus ins/del + ins/ins.
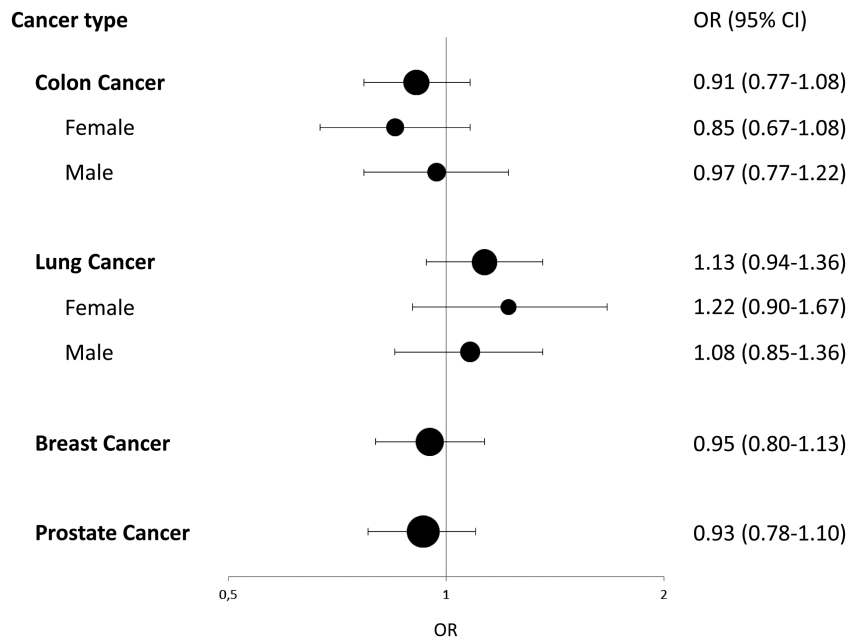[c]ORs adjusted for age and sex.
[d]ORs calculated against female controls and adjusted for age.
[e]ORs calculated against male controls and adjusted for age.
[f]ORs adjusted for age, sex and smoking.
[g]ORs calculated against female controls and adjusted for age and smoking.
[h]ORs calculated against male controls and adjusted for age and smoking.

Cancer type		OR (95% CI)
Colon Cancer		0.91 (0.77-1.08)
Female		0.85 (0.67-1.08)
Male		0.97 (0.77-1.22)
Lung Cancer		1.13 (0.94-1.36)
Female		1.22 (0.90-1.67)
Male		1.08 (0.85-1.36)
Breast Cancer		0.95 (0.80-1.13)
Prostate Cancer		0.93 (0.78-1.10)

Figure 1. *APOBEC3A/B* deletion and cancer risk. Forest plot illustrating the ORs for cancer of the colon, lung, breast and prostate, related to the *APOBEC3A/B* deletion polymorphism (dominant model).

In sub-analyses, we estimated the OR for cancer in different age groups (10 year intervals). For both lung and prostate cancer, applying the dominant model, we found that the association (OR) for the deletion allele decreased with age: For lung cancer, we found an increased risk among individuals <50 years of age (OR = 2.17; CI = 1.19–3.97; Figure 2), in addition to a gradual
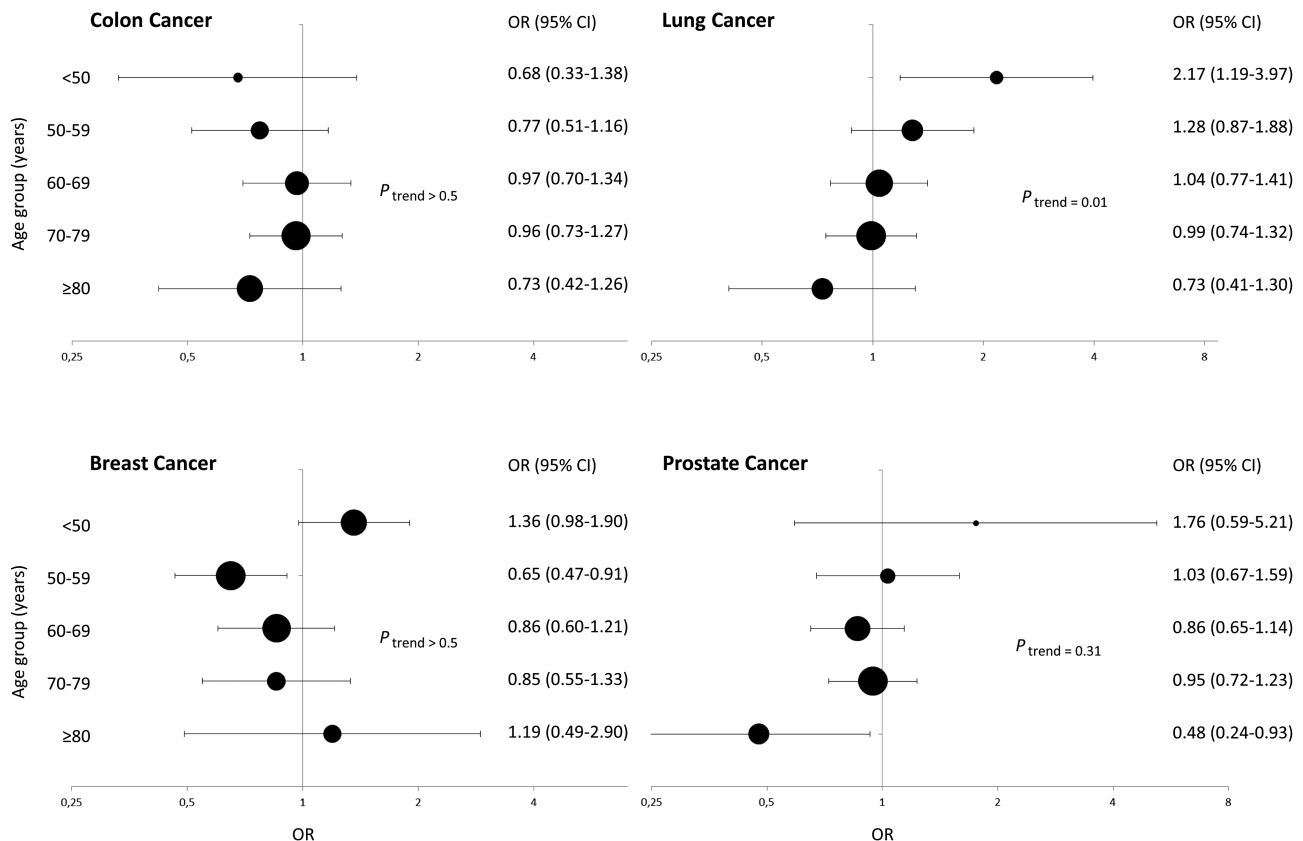
decrease in the OR with increasing age (*P* for trend = 0.01). Again, stratified analyses according to smoking status did not differ from the overall lung cancer analyses within age groups (data not shown). However, stratifying for gender, we found the association to be stronger among females (OR = 2.58; CI = 1.19–5.57) than among males (OR = 1.52; CI = 0.57–4.08; Supplementary Table S1, available at *Carcinogenesis* Online; *P* = 0.002 for the interaction between age and gender in a multivariate risk model). A similar but weaker pattern was observed for prostate cancer: here, the highest OR was present in men <50 years of age, followed by a reduction in the OR with increasing age. However, this trend did not reach statistical significance (*P* = 0.31: Figure 2) and neither did the interaction between age and gender (*P* = 0.12).

For breast and colorectal cancer, we found no similar patterns of risk associated with the deletion allele across age groups (Figure 2).

APOBEC3A/B genotypes and age at cancer onset

We also assessed whether the *APOBEC3A/B* genotype status of patients was associated with age at diagnosis within each of the four cancer groups.

Among patients diagnosed with lung cancer, age at diagnosis was lower among individuals harbouring the deletion allele, as compared to individuals with the homozygous insertion genotype (dominant model: *P* = 0.02, Mann-Whitney rank test; Table 2; Figure 3). Similar results were observed for prostate cancer, albeit here, the reduced age at diagnosis was observed in the recessive model (*P* = 0.03, Mann-Whitney rank test; Table 2; Figure 3). For breast and colon cancer cases, we observed no association of *APOBEC3A/B* status and age at diagnosis.

Table 1B. APOBEC3A/B alleles and cancer risk

	Alleles *n* (%)			
Cases/controls	ins	del	OR (95% CI)	P
Controls	6931 (90.6)	723 (9.5)	1.00	–
Females	3474 (90.6)	362 (9.4)	1.00	–
Males	3457 (90.5)	361 (9.5)	1.00	–
Colon cancer[a]	2894 (91.3)	276 (8.7)	0.91 (0.78–1.06)	0.21
Females[b]	1478 (91.7)	134 (8.3)	0.87 (0.69–1.09)	0.21
Males[c]	1416 (90.9)	142 (9.1)	0.94 (0.76–1.17)	0.58
Lung cancer[d]	2442 (89.8)	278 (10.2)	1.11 (0.94–1.32)	0.23
Females[e]	908 (89.7)	104 (10.3)	1.18 (0.89–1.57)	0.26
Males[f]	1534 (89.8)	174 (10.2)	1.07 (0.87–1.33)	0.52
Breast cancer[b]	3222 (91.1)	316 (8.9)	0.94 (0.82–1.08)	0.39
Prostate cancer[c]	4686 (91.4)	444 (8.7)	0.92 (0.80–1.05)	0.23

[a]ORs adjusted for age and sex.
[b]ORs calculated against female controls and adjusted for age.
[c]ORs calculated against male controls and adjusted for age.
[d]ORs adjusted for age, sex and smoking.
[e]ORs calculated against female controls and adjusted for age and smoking.
[f]ORs calculated against male controls and adjusted for age and smoking.

Figure 2. *APOBEC3A/B* deletion and age-related cancer risk. ORs for cancer of the colon, lung, breast and prostate, related to the *APOBEC3A/B* deletion polymorphism within age 10 years interval age groups (dominant model).

Table 2. *APOBEC3A/B* genotype and age at cancer diagnosis

Diagnosis	Genotype	n	Mean age (years)	P-value[a] (dominant model)	P-value[a] (recessive model)
Colon cancer	ins-ins	1322	70.9		
	ins-del	250	71.5		
	del-del	13	69.6	>0.5	>0.5
Lung cancer	ins-ins	1101	70.3		
	ins-del	240	68.3		
	del-del	19	71.0	0.02	>0.5
Breast cancer	ins-ins	1465	60.4		
	ins-del	292	60.1		
	del-del	12	62.1	>0.5	>0.5
Prostate cancer	ins-ins	2148	71.8		
	ins-del	390	71.6		
	del-del	27	67.6	>0.5	0.03

[a]Mann–Whitney rank test.

Discussion

In this population-based case-control study, we assessed whether the *APOBEC3A/B* deletion polymorphism is associated with the risk for cancer of the breast, colon, lung and prostate, using a large sample of Norwegian individuals. Although the Norwegian population is very homogenous and might not be representative for all Caucasians, our observation of a MAF of 0.094 is in line with previous observations in case-control studies performed on European cohorts (21,22). Overall, we found no association between the deletion polymorphism and cancer risk for any of the four cancer forms (breast, lung, colon or prostate). However, for lung cancer, we made interesting observations in different age groups, where an elevated cancer risk associated with the deletion allele was found in individuals younger than 50 years of age, and where the OR gradually decreased with increasing age. Similar but weaker findings were made for prostate cancer. These results were corroborated by the fact that for both cancers, the deletion allele was associated with younger
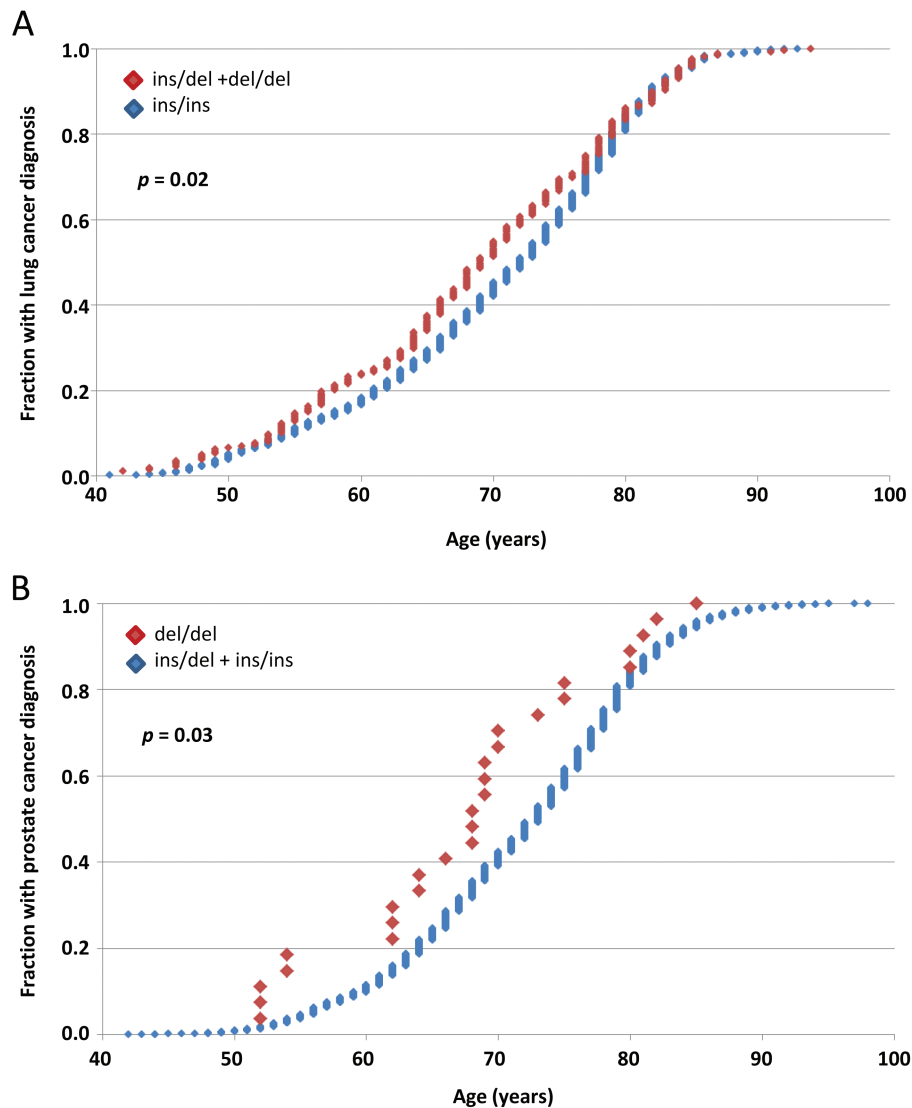

Figure 3. *APOBEC3A/B* deletion and age at diagnosis. (**A**) Cumulative fraction of patients with lung cancer diagnoses among individuals harbouring the *APOBEC3A/B* deletion allele (red diamonds) and individuals homozygous for the insertion allele (blue diamonds), plotted against age at lung cancer diagnosis. (**B**) Cumulative fraction of patients with prostate cancer diagnoses among individuals homozygous for the *APOBEC3A/B* deletion allele (red diamonds) and individuals heterozygous or homozygous for the insertion allele (blue diamonds), plotted against age at prostate cancer diagnosis.

age at diagnosis among the patients. Although these findings are striking, the underlying mechanisms are unknown.

Our finding that the *APOBEC3A/B* deletion may have a particular effect on lung cancer risk is in line with previous observations of the mutational signature linked to APOBEC activity in lung cancer genomes (1). However, while this signature has also been identified in breast cancer (1), and the magnitude of APOBEC-related mutation load in this cancer type has been linked to the *APOBEC3A/B* deletion (15), we did not observe any clear impact of the deletion variant on breast cancer risk.

While previous studies have reported the *APOBECA/B* deletion allele to be associated with increased risk for breast cancer (18,20,21), our observations are in line with a recent Swedish study reporting no association between *APOBECA/B* genotype and breast cancer risk (22). Notably, the discrepancy between studies could, at least partly, be due to ethnic differences since the Norwegian and Swedish populations are genetically very similar, while most positive studies (18,20) have been performed in Asian populations.

Although the hybrid transcript resulting from *APOBEC3A/B* deletion polymorphism has been found more stable than the wild-type transcript (17) and this indicate a real functional role of the polymorphism, the possibility exist that the *APOBEC* gene cluster also harbour other important polymorphisms and that haplotypes across several variants need to be taken into account when assessing germline genotype and cancer risk associated with APOBEC activity. Notably, there are several SNPs in the *APOBEC* gene family, including rs5750715, rs5757402 and rs17370615 that are also unequally distributed between ethnic groups, with MAFs of 0.27, 0.38, 0.29 and 0.47, 0.04, 0.04 among Caucasians and Asians, respectively (29). Recently, it was reported that the *APOBEC3A/B* deletion variant was associated with decreased risk of bladder cancer; however, after adjusting the risk estimates for the effect of SNP rs1014971 (a SNP found 20 kb upstream of *APOBEC3A*, this association) was lost (28). Of note, similar effects have been reported for other germline variants linked to cancer risk, e.g. the *MDM2* promoter polymorphism SNP309 rs2279744 (30), where the minor allele has been linked to increased risk of several cancers, particularly in Asian populations (31), while in Caucasian studies, the effect seems to be 'confounded' by other SNPs in the same region, which are only present in Caucasians (32,33).

In the present study, we performed several sub-analyses with stratification according to gender, and for lung cancer, we also stratified the data according to smoking status. While none of these sub-analyses revealed effects of the *APOBEC3A/B* deletion polymorphism on risk of colon or lung cancer, it may well be that further stratification of the four cancer types in the present study, if possible, could have revealed different results. Notably, the above mentioned APOBEC-related SNP rs1014971 has been found to affect the risk of estrogen receptor-positive breast cancers, in particular (28). However, such data were not available in the CONOR cohort.

In conclusion, we found that the *APOBEC3A/B* deletion polymorphism is associated with increased risk of lung cancer in individuals younger than 50 years of age and a younger age at diagnosis among lung and prostate cancer patients carrying this germline variant.

Supplementary material

Supplementary Table S1 can be found *Carcinogenesis* online.

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