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Exposure to farm animals and lung cancer risk in the AGRICAN cohort

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Footnote page

Abbreviations

HR, hazard ratio; CI, confidence interval; AGRICAN, Agriculture and Cancer Study; AHS, Agricultural Health Study; MSA, Mutualité Sociale Agricole; ADK, adenocarcinoma; SCC, squamous cell carcinoma.

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Running head

Exposure to farm animals and lung cancer risk

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Abstract

Epidemiological studies have found lower risks of lung cancer in farmers. However, little is known about the types of agricultural activities concerned. In the AGRICAN cohort, we assessed the relationship between animal farming and lung cancer by investigating the type of animals, tasks and timing of exposure. Analyses included 170,834 participants from the AGRICAN cohort. Incident lung cancers were identified through linkage with cancer registries from enrollment (2005–2007) to 2011. A Cox model, adjusted for pack-years of cigarette smoking, was used to calculate hazard ratios and 95% confidence intervals. Lung cancer risk was inversely related to duration of exposure to cattle (≥40 years: hazard ratio=0.60, 95% confidence interval: 0.41, 0.89, *P* for trend=0.04) and to horse farming (≥20 years: hazard ratio=0.64, 95% confidence interval: 0.35, 1.17, *P* for trend=0.08), especially for adenocarcinomas, but not with poultry or pig farming. More pronounced decreased risks were reported among individuals who had cared for animals, undertaken milking and who had been exposed to cattle in infancy. Our study provides strong evidence of an inverse association between cattle and horse farming, and lung cancer. Further research is warranted to identify the etiologic protective agents and biological mechanisms.

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As in several other occupational settings (cotton-textile (1) and incineration (2) industries, occupations with contact with water-based metalworking fluids (3)), most epidemiologic studies in farming have found lower rates of lung cancer compared to the general population (4-6), as supported by large cohorts of farmers from incidence data in the United States (Agricultural Health Study, AHS) (7) and in Nordic European countries (8) and from mortality data in France (Agriculture and Cancer study, AGRICAN) (9). Risks were decreased by 40% to 60% but the estimates were not controlled for smoking, which is known to be less prevalent in farm owners than in the general population (7, 9, 10). Few studies considered the types of farming associated with lung cancer risk (11-22). Some of them did not control for individual smoking data (14-16, 19-22) or had a low statistical power to analyze specific farming activities (12-14, 18). Studies were based on job title (11-15, 18, 20, 21) or on farm characteristics (16, 17, 19, 22) as a proxy for individual exposure. Most studies reported lower risks for some types of animal farming (13-22). The AHS cohort found lower lung cancer incidence in poultry farming and large-scale livestock farming, after adjustment for smoking (17). Only one small study (23 deaths by lung cancer) investigated the relation between duration of exposure of one type of animal farming and lung cancer mortality, without adjustment for smoking, and found a lower mortality in long–term exposed dairy farmers (14). Their updated analysis adjusted for smoking also suggested the reversibility of the protective effect (18). Analyses by histological subtypes have been seldom performed. After adjustment for smoking, Mastrangelo et al. found similar results between squamous cell carcinomas (22 deaths) and other or unknown lung carcinomas (23 deaths) (18). To date, no study has attempted to identify which tasks in animal farming could be particularly protective and if early exposure to a farm environment (*in utero*, childhood) might play a role in

protection, as shown for other respiratory outcomes (allergic sensitization and atopic diseases) (23).

In several occupational settings including farming, lower risks of lung cancer have been previously attributed to potential exposure to endotoxins (lipopolysaccharide), a component of the outer membrane of gram–negative bacteria present in organic dust (24). High levels of exposure to dusts and endotoxins were measured in animal farming especially among swine and poultry farming (25). Some proposed anti–carcinogenic mechanisms involve endotoxin–induced inflammation leading to immune system upregulation, but they remain poorly understood and evidence from human studies is limited (24). On the other hand, some recent studies did not support the protective effect of endotoxins in the occurrence of lung cancer. Checkoway et al. reported a possible promotion of lung cancer with increasing time since first exposure to endotoxins in the cotton textile industry (26). Pooled analyses of population-based case–control studies on lung cancer did not report lower risks for high exposure to endotoxins as assessed with a job–exposure matrix, and they even reported increased risks of lung cancer among livestock and dairy farmers (27-28). These contradictory findings reflect our lack of knowledge about the possible protective effects of certain farming activities against lung cancer. A better understanding of which agricultural activities, tasks and temporal courses of exposure are associated with lower lung cancer risk could help in identifying protective agents and the period of susceptibility to risk.

The prospective cohort AGRICAN offers the opportunity to evaluate the risk of lung cancer, overall and by subtypes, associated with individual exposure to different types of animal farming, considering periods of exposure (childhood, adulthood) and the type of tasks performed and taking smoking history into account.

METHODS

Study population

The AGRICAN cohort is a prospective cohort of 181,842 active and retired agricultural subjects (9). Individuals were included if they were at least 18 years old, affiliated for at least three years to the *Mutualité Sociale Agricole* (MSA), the French health insurance scheme in agriculture, living in one of the 11 French areas covered by a population-based cancer registry at the time of enrollment (*Côte-d'Or, Doubs, Gironde, Isère, Loire-Atlantique, Manche, Bas-Rhin, Haut-Rhin, Somme, Tarn* and *Vendée*) and returned a self–administered questionnaire for enrollment (1 November 2005–31 December 2007). The cohort was mainly composed of participants who had already worked on a farm during their lifetime (87%, referred hereafter as farming population), but also some participants who had never been exposed to a farming environment (such as some office workers, referred hereafter as non-farming population) (12%). The study protocol was reviewed and approved by the Advisory Committee on Information Processing for Health Research (CCTIRS) (Reference: 01.148) and by the French data protection authority (CNIL) (Reference: 05.1292). Place of residence and affiliation to the health insurance scheme are checked annually by the MSA files to identify cohort members being lost to follow-up. Vital status and causes of death were obtained annually using the MSA files and the French National Death Index. For identification of primary incident lung tumours**,** the AGRICAN database is matched every two years to all the general cancer registries covered by the study areas. Lung cancer cases were coded according to the International Classification of Diseases for Oncology, 3rd edition (ICD–O–3 code: C34). We identified 768 incident lung cancer cases (619 male, 149

117 female) with a mean age at diagnosis of 72.6 years (±10.4 years). Cases were grouped according
118 to morphology codes: 38.8% of cases were adenocarcinomas (ADK) and 28.8% were squamous
119 cell carcinomas (SCC). Other subtypes were small cell lung carcinomas (10.3%), large cell
120 carcinomas (4.3%), other carcinomas (9.9%) and cases with unknown histological types (8.2%).
121 One lung sarcoma was excluded from the analyses.

122

123 Exposure data and potential confounders

124 The enrollment questionnaire collected a complete job calendar with a lifetime history of
125 agricultural activities and information whether participants lived on a farm during their first year
126 of life (with indication of the type of animals and crops on the farm and duration of living in that
127 place). Detailed information on individual exposure was available for five types of animals:
128 cattle, poultry, pigs, horses and sheep and/or goats, and the main tasks performed for each type of
129 animal (animal care, use of insecticide, milking and disinfection of milking equipment (for cattle
130 and sheep/goats), disinfection of barns (for cattle, sheep/goats, poultry and pigs)), with year of
131 beginning and end for each task, and the number of animals concerned for care, milking and
132 insecticide use.

133 Other collected data included demographic characteristics, smoking (age at beginning, duration,
134 intensity: number of cigarettes, cigars and pipes per day), diet, some respiratory conditions (self–
135 reported diagnosis of chronic bronchitis or emphysema), weight and height.

136 Statistical analyses

137 For the present analysis, exclusion criteria were: living in an area with no registry for lung
138 tumours (*Côte–d'Or*) (n=10,875); suffering from lung cancer before the date of enrollment and

after the date of implementation of the most recent registry in the study area (1st January 2005) (n=87) and with no follow–up (n=45). Individuals were followed from the date of enrollment (date of reception of the questionnaire) until incident lung cancer diagnosis, date of death, date they left the study areas covered by the cohort, date they were lost to or ended follow–up (31 December 2011), whichever came first. We fitted Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (95% CI), adjusting for smoking history (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, smoking of pipes and/or cigars), with attained age as the underlying time metric.

For each type of animal, we assessed associations between lung cancer (overall and separately for ADK and SCC) and each component of exposure (ever/never, duration of work, number of animals, tasks). We considered two reference groups. The first, used in all the main analyses, consisted of farmers not exposed to the types of animals studied. The second consisted of the non–farming population. Associations were mutually adjusted for other animal exposures associated with lung cancer risk in our analyses. We used categorical variables for duration of exposure (10-year interval) and number of animals (quartiles). Tests for trend used median of categories as a continuous variable in the model. We additionally assessed the role of occupational exposure to cattle in stratified analyses by smoking (ever/never smoked), childhood exposure to cattle farming in the first year of life (yes/no), and by number of years since last exposure (≤5 years, 6–10 years, 11–15 years, 16–20 years, 21–25 years and ≥ 26 years).

To assess the robustness of associations, we performed complementary analyses adjusted for other potential confounders (gender, education, body mass index, daily consumption of fruits and self–reported diagnosis of chronic bronchitis or emphysema, pesticide use on crops) and using other smoking metrics (duration: non-smoker, <10, 10-19, 20-29, 30-39, ≥40 years and smoking

status combined with tertiles of number of pack-years of cigarette smoking: never smoker, former smoker and pack-years<5, former smoker and pack-years [5,15[, former smoker and pack-years ≥15, current smoker and pack-years <7, current smoker and pack-years [7,17[, current smoker and pack-years ≥17). We also performed multiple imputation by chained equations (MICE) to handle incomplete information (50 imputations) on smoking (missing data: 12%), job history (incomplete data: 13%) and occupational exposure to cattle (ever worked in cattle farming: missing data: 14%, duration of work in cattle farming: missing data: 34%) (29). Estimates of parameters and variances were pooled using multiple imputation rules (30). Statistical analyses were performed using SAS (version 9.3) and for multiple imputation STATA (version 13.1).

RESULTS

The population was mainly composed of men (54%). The median age at enrollment was 67 years. Half of the population had a level of education lower than middle school. Half of the men had ever smoked during their life while only 13% of women had ever smoked (Table 1). Associations between smoking history (smoking status and number of pack-years of cigarette smoking) and lung cancer incidence (overall, ADK and SCC) are available in Web Table 1. Smoking history was significantly associated with increased lung cancer risk, for both men and women, with higher risks among men for SCC than ADK. People ever worked on a farm were more often men, older, less educated, never smokers, overweight or obese, born on a farm and with a higher prevalence of non-cancer respiratory diseases (Table 1).

The most frequent type of animals raised was cattle (78% of farmers). Median duration of work was higher in cattle and poultry farming. The median numbers of animals were three (for horses), 35 to 45 (for pig, poultry and cattle) and 50 (for sheep/goats). Care for animals was performed by

74% of farmers in poultry farming to 88% in cattle farming. Almost 80% of cattle farmers performed milking (vs. 35% for sheep and/or goats). Insecticides on animals were used by 16% of horse farmers (men: 17%, women: 12%) to 36% of cattle farmers (men: 51%, women: 16%) (Table 2).

Cattle farming

After adjustment for smoking, occupational exposure to cattle was significantly associated with an overall reduced lung cancer risk (HR=0.72, 95% CI: 0.58, 0.90) with a significant linear inverse relationship with duration of exposure to cattle (*P* for trend=0.04), compared to farmers not exposed to cattle. The deficit was more pronounced for ADK (≥40 years: HR=0.50, 95% CI: 0.26, 0.97, *P* for trend<0.01) than for SCC (≥40 years: HR=0.70, 95% CI: 0.36, 1.37, *P* for trend=0.18). The number of cattle was not significantly associated with lung cancer risk after adjustment for smoking and duration of exposure to cattle (Table 3). Lower risks associated with exposure to cattle were more pronounced among non-smokers (HR=0.39, 95% CI: 0.25, 0.62) than smokers (HR=0.75, 95% CI: 0.59, 0.96, *P* for interaction=0.01). We found a lower risk for longer duration of work with cattle among non-smokers (≥40 years: HR=0.25, 95% CI: 0.12, 0.56, *P* for trend<0.0001) than among smokers (≥40 years: HR=0.59, 95% CI: 0.40, 0.87, *P* for trend<0.001, *P* for interaction=0.24) (Table 4). Inverse associations with exposure to cattle and overall lung cancer risk were slightly less pronounced and not statistically significant when compared to the non-farming population of the cohort. Whatever the reference group (farming or non-farming), associations with adenocarcinoma risk were however of the same magnitude. Inverse relationships with duration of cattle farming remained significant for overall lung cancer risk and for adenocarcinomas (Web Table 2). Adjustment for other potential confounders did not substantially modify the associations between duration of exposure to cattle and overall lung cancer risk (≥40 years: H=0.73, 95% CI: 0.47, 1.15, *P* for trend=0.04) and ADK (≥40 years:

HR=0.59, 95% CI: 0.28, 1.25, *P* for trend=0.03). Analyses using multiple imputation did not provide substantial changes in prevalence of exposure to cattle and confirmed the inverse relationship between duration of cattle farming and lung cancer risk (Web Table 3).

Exposure to other types of animals

We found a lower lung cancer risk associated with exposure to horses (≥20 years: HR=0.64, 95% CI: 0.35, 1.17, *P* for trend=0.08), after adjustment for smoking and duration of exposure to cattle. There was a significant strong inverse relation between increasing duration of exposure to horses and lung ADK (≥10 years: HR=0.38, 95% CI: 0.15, 0.97, *P* for trend=0.03) (Table 3). Associations between duration of horse farming and ADK remained unchanged, although non-significant, compared to the non-farming population (Web Table 2).

Non-significant increased risks of lung cancer were observed for poultry and pig farming and only for SCC for sheep or goats farming. We did not report significant exposure-relationships with duration for these three types of animal farming. We observed significant increased risk between lung cancer and number of animals only for pig farming (≥50 pigs: HR=1.69, 95% CI: 1.05, 2.73; *P* for trend=0.03), after adjustment for smoking and duration of exposure to cattle and horses (Web Table 4).

Associations between tasks and lung cancer risk

The five tasks performed by farmers who raised cattle were inversely related to lung cancer risk, but only for ADK (Table 5). Lower ADK risks were observed among those performing only care (HR=0.58, 95% CI: 0.31, 1.10) or only milking (HR=0.54, 95% CI: 0.23, 1.27) or both (HR=0.62, 95% CI: 0.39, 1.00). Interestingly, lung cancer risk was increased with use of insecticides on cattle among those not performing care for animals or milking, overall (HR=2.71, 95% CI: 1.19, 6.18) and for both subtypes (data not shown). No substantial change in estimates was observed after adjustment for pesticide use on crops (overall lung cancer risk: HR=2.87, 95%

CI: 1.16, 7.12). A decreased ADK risk was observed among farmers who provided care for horses (HR=0.65, 95% CI: 0.41, 1.03) and for sheep and/or goats (HR=0.56, 95% CI: 0.30, 1.08), after adjustment for cattle exposure. No clear association was found with specific tasks in poultry and pig farming, apart from an increased risk for SCC associated with insecticide use on pigs (Table 5).

Role of exposure to cattle during early life

Decreased risk of lung cancer was observed only among farmers who had been exposed to cattle both in their first year of life and in their occupational life (HR=0.64, 95% CI: 0.49, 0.84, compared to other farmers who had never been exposed to cattle in childhood and in their occupational life (Figure 1, part A). No significant trend was observed between duration of occupational exposure to cattle and lung cancer risk among those without early exposure to cattle (*P*–trend=0.35), contrary to farmers who did (*P*–trend<0.0001) (Figure 1, part B).

Role of time since cessation of occupational exposure to cattle

Whatever the time since last exposure to cattle, decreased risks of lung cancer (HR=0.48 to 0.63) were observed in relation to occupational exposure to cattle, except for participants who had worked less than 20 years and stopped more than 26 years before enrollment (Figure 2).

DISCUSSION

This analysis in the AGRICAN cohort provides evidence of an inverse association between lung cancer and duration of exposure to cattle. This inverse relationship was restricted to ADK, was still present long after cessation of exposure and found only in those born on a farm with cattle, after taking smoking history into account. Some tasks (care for animals and milking) were associated with a greater decrease in risk. Interestingly and in contrast, insecticide use on cattle increased the lung cancer risk whatever the subtypes of cancer. Decreased risks of adenocarcinomas were also suggested in horse and sheep/goat farming with an inverse relation with duration of work only in horse farming. Slight increased risks were observed for poultry and pig farming, with a significant increased risk among pig farmers raising more than 50 pigs.

Our study has some strengths. First, the prospective design with collected information before diagnosis based on almost 800 primary incident cases through linkage to population-based cancer registries limits the differential information bias. Second, the good quality of follow-up of this cohort (less than 1% of the participants lost to follow-up for cancer incidence) limits selection bias. Our results, relying on an average follow-up time of 5 years, need however to be replicated with longer duration of follow-up. Third, we controlled for smoking history. Associations between smoking history and lung cancer risk (overall and by subtypes) were in line with estimates from pooled analyses of population-based case–control studies (31) and estimates from the AHS cohort (32). These smoking data allowed us to adjust or stratify our analyses on different metrics of active smoking without any changes in association observed. Moreover, a decreased risk seemed to be more pronounced among never smokers. Fourth, adjustment for other collected potential confounders (level of education, BMI, history of chronic respiratory

diseases, consumption of fruits, use of pesticides on crops) did not change the results. Fifth, missing information was a matter of concern particularly for the duration of farming activities. However, the prevalence of exposures and associations between exposure to cattle and lung cancer risk did not change after using an accurate method for imputation (29). Sixth, the availability of years of beginning and ending exposures allowed us to take into account latency without significant changes in the results. Seventh, since we created our cohort thanks to the MSA which includes all people working in the field of agriculture, we also had a non-farming population as reference category. Thus, lower risks associated to cattle farming did not seem to be totally driven by potential high-risk exposure in the reference farming population as inverse associations were also reported when compared to the non-farming population.

Few studies have estimated associations between lung cancer and some particular types of farming (11-22). Some of them were large epidemiologic studies (15-17, 19-22) and based on incidence data (11-13, 16, 17, 22). However, a few studies controlled for individual smoking data (11-13, 17, 18). The prospective AHS cohort of North Carolina and Iowa farmers found a decreased risk of lung cancer incidence associated with poultry (HR=0.6, 95% CI: 0.4, 1.0) and among farmers raising more than 1000 animals (HR=0.5, 95% CI: 0.3–1.0; *P* for trend=0.04) after adjusting for smoking (17). Working in dairy cattle was associated with a decreased risk among men only in France (13), but with an increased risk among men in Germany (11). Moreover, increased risks were observed with beef cattle farming in New Zealand (12) and among animal keepers in Germany (11). Most studies in the literature did not investigate the role of duration of exposure, except a small historical cohort of dairy cattle farmers in Italy that found a decreased, but reversible, risk with longer duration of exposure and an increased number of dairy cattle (14, 18). In Finland, lung cancer incidence was lower among dairy farmers continuing this farming activity, compared to the general population, but less pronounced and statistically

298 non-significant among those who had changed to another type of farm production, suggesting the
299 reversibility of the potential protection. However, associations were not adjusted for smoking and
300 dairy farmers who had quit farming had still a lower lung cancer incidence than the general
301 population (22). Contrary to Mastrangelo's findings, exposure to cattle was still associated with a
302 decrease in risk several decades after cessation of exposure in our analyses, and we did not find
303 any inverse association with the number of cattle. Exposure to endotoxins has been proposed as a
304 potential explanation for the inverse associations found in the literature. The number of cattle has
305 not been strongly related to levels of exposure to organic dust and endotoxins which were
306 measured in a few field studies in dairy cattle farming (25). Levels of exposure to dusts and
307 endotoxins in animal farming might be much higher in poultry and pig farming than in cattle or
308 horse farming (25, 33). On the contrary, in our analyses we found lower lung cancer risks in
309 cattle and horse farming and increased risks associated with pig and poultry farming, statistically
310 significant among those raised a high number of pigs. The determinants of exposure to dusts and
311 endotoxins have not been extensively studied. They could include some tasks in cattle farming
312 (handling of feed and seeds in barns, distribution of bedding and type of bedding, milking) and
313 stable characteristics (type of slurry systems, type of milking installation) (25, 34). Whereas no
314 study to date has investigated the role of specific tasks on lung cancer risk, we found that care for
315 cattle and milking were associated with lower risks of lung cancer. From the enrollment
316 questionnaire, we could not disentangle the role of all tasks included under the heading "care for
317 animals" (feeding, distribution of bedding, use of some veterinary products). However, we found
318 an increased risk with insecticide use on cattle among farmers not performing care or milking,
319 which has received very little attention among farmers, even if some insecticides used heavily on
320 crops are also used on cattle like organochlorines (lindane), organophosphates (diazinon) and
321 pyrethroids (permethrin). The AHS cohort did not report any significant association between lung

cancer and permethrin use on animals (32). Our findings suggestive of lower risks in horses and sheep and/or goat farming were not reported in previous studies and need to be confirmed.

Our results also suggest that exposure in early life could play a role in the occurrence of lung cancer in farmers, in combination with occupational exposure. Indeed, the decrease in risk was more pronounced in farmers who lived on a farm with cattle during the first year of life. Interestingly, early exposure to a farm environment (*in utero* and/or during the first year of life) has been shown to be inversely associated with allergic sensitization and atopic diseases through exposure to endotoxins and/or other components of organic dusts such as fungal spores, glucans or indicators of the diversity of microbial exposure, which were inversely related to asthma among children living on a farm (23, 35).

This prospective cohort enables us to confirm some assumptions (lower risk in cattle farming, including in dairy farming), to disconfirm others (reversibility of inverse associations, lower risk in pig and poultry farming), and to formulate new ones (tasks of care and milking in cattle farming inversely related to lung cancer risk, lower risk in horse farming, potentially protective exposure in infancy, more pronounced decreased risks for adenocarcinomas, increased risk associated with insecticide use on cattle).

Understanding the reason for the lower risk of lung cancer in farmers, which is observed independently of smoking habits, could provide important clues to the etiology of this disease and help for prevention. Biological mechanisms, including immunological pathways, possibly related to exposure to endotoxins, need to be further elucidated. Our results suggest that the farming environment appears to encompass various components that act in opposite directions:

some could reduce the risk while others like pesticides could increase it. The challenge for future studies will be to disentangle these effects and to understand their underlying mechanisms.

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Table 1. General Characteristics of Study Population at Enrollment, AGRICAN, 2005-2007

	All n=170,834	Farming population n=128,387	Non-farming population n=17,528
Gender, % of men	54.2	56.1	49.8
Age, years			
Q2 (Q1–Q3)	67 (53–76)	68 (55–77)	57 (45–66)
Education[a], %			
Middle school or less	50.4	55.4	18.4
High school	40.0	37.7	56.0
More than high school	9.6	6.9	25.6
Missing	(7.4)		
Pack–years of cigarette smoking[a], %			
Non-smokers	65.9	67.8	52.2
<20	22.5	21.2	32.5
20–39	6.3	6·0	8.6
40–59	1.4	1.4	1.9
≥60	0.6	0.5	0.8
Other smokers, pipes and/or cigars	3.3	3.1	4.0
Missing	(12.1)		
Body Mass Index, kg/m^{2a}, %			
<18·5	1.5	1·3	2.0
18·5–24·9	41.9	40.2	49.6
25–29·9	41.9	43.2	36.5
≥30	14.7	15.2	11.9
Missing	(15.4)		
Consumption of fruits[a], %			
Daily	44.6	45.1	47.3
Missing	(8.6)		
Lifetime history of chronic bronchitis or emphysema[a], %			
Yes	11.0	11.9	6.4
Missing	(17.7)		
Ever worked on a farm[a], %			
Yes (farming population)	86.7	–	–
No, but ever worked in other agricultural sectors[b]	1.5		
No (non-farming population)	11.8		
Incomplete job history	(13.4)		
Ever lived on a farm during 1st year of life[a], %			
Yes	68.8	77.9	30.5
Missing	(10.2)		

Ever lived on a farm with cattle during 1st year of life[a], %				
	Yes	52.3	60.3	21.8
	Missing	(13.4)		

[a] Missing values were excluded from percentage

[b] Other agricultural sectors included jobs with potential exposure to agricultural hazards (such as forestry/aquaculture/service provided for agricultural work…)

Table 2. Description of Occupational Exposures to Animals at Enrollment Among the Farming Population, AGRICAN, 2005-2007

	Cattle	Poultry	Pig	Horse	Sheep and/or goat
N (%)	85,970 (77.5)	40,597 (37.5)	30,790 (28.1)	23,160 (21.4)	14,420 (13.2)
Nb of years, Q2 (Q1–Q3)	28 (12–40)	24 (10–40)	17 (8–32)	13 (7–24)	15 (7–28)
Nb of animals, Q2 (Q1–Q3)	45 (20–86)	45 (22–300)	35 (20–70)	3 (2–5)	50 (12–150)
Tasks, %					
Care	87.8	73.6	86.1	79.2	82.1
Insecticides	36.1	21.2	18.2	15.5	24.4
Building disinfection	35.0	34.3	35.7	NA	28.2
Milking	78.4	NA	NA	NA	34.5
Milking machine disinfection	40.8	NA	NA	NA	17.1

Abbreviations: NA, Not Applicable; Nb, number

Table 3. Associations Between Exposure to Cattle and Horse Farming and Lung Cancer Risk, Overall and by Subtypes, Among the Farming Population, AGRICAN, 2005-2011

			All subtypes				Adenocarcinomas				Squamous cell carcinomas			
			N	HR	95% CI	*P* for trend	N	HR	95% CI	*P* for trend	N	HR	95% CI	*P* for trend
Cattle	Ever[a]		287	**0.72**	**0.58, 0.90**		103	**0.64**	**0.45, 0.92**		90	0.97	0.63, 1.50	
	Duration[b]	Never exposed	99	1.00		**0.04**	39	1.00		**<0.01**	27	1.00		0.18
		<10 years	52	1.04	0.73, 1.49		19	1.08	0.61, 1.92		20	1.26	0.71, 2.26	
		10–19 years	33	0.85	0.57, 1.28		12	0.86	0.45, 1.65		13	1.13	0.58, 2.20	
		20–29 years	21	0.72	0.45, 1.17		9	0.77	0.37, 1.59		8	1.02	0.46, 2.25	
		30–39 years	32	**0.63**	**0.42, 0.95**		10	**0.49**	**0.25, 1.00**		12	0.90	0.45, 1.78	
		≥40 years	38	**0.60**	**0.41, 0.89**		12	**0.50**	**0.26, 0.97**		13	0.70	0.36, 1.37	
	Number of Animals[b]	Never exposed	99	1.00		0.81	39	1.00		0.91	27	1.00		0.20
		<20	26	0.83	0.51, 1.33		9	0.90	0.41, 2.00		9	1.00	0.44, 2.26	
		20–44	47	1.20	0.79, 1.83		14	1.14	0.56, 2.35		19	1.63	0.82, 3.26	
		45–84	45	1.42	0.89, 2.27		16	1.71	0.79, 3.67		19	1.98	0.92, 4.24	
		85–149	10	0.69	0.33, 1.45		9	1.32[c]	0.52, 3.36		6	0.88[‡]	0.31, 2.53	
		≥150	10	1.14	0.54, 2.40									
Horse	Ever[a]		120	0.96	0.77, 1.21		37	0.83	0.56, 1.22		39	0.99	0.66, 1.48	
	Duration[b]	Never exposed	224	1.00		0.08	90	1.00		**0.03**	61	1.00		0.80
		<10 years	24	0.82	0.52, 1.30		6	0.54	0.22, 1.29		10	1.04	0.50, 2.17	
		10–19 years	15	0.80	0.46, 1.37		5	**0.38**[d]	**0.15, 0.97**		7	1.08	0.47, 2.49	
		≥20 years	12	0.64	0.35, 1.17						5	0.84	0.32, 2.18	
	Number of Animals[b]	Never exposed	224	1.00		0.21	90	1.00		0.35	61	1.00		0.44
		<5	20	0.74	0.41, 1.35		4	0.60	0.16, 2.16		7	0.60	0.27, 1.34	
		≥5	15	1.36	0.68, 2.72		4	1.55	0.41, 5.89		7	1.46	0.66, 3.26	

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

[a] For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), exposure to cattle (ever/never), and exposure to horses (ever/never); for SCC: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥ 60, other tobacco) and exposure to cattle (ever/never)

[b] For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), duration of work on cattle and duration of work on horses; for SCC: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), duration of work on cattle

[c] HR for the category ≥85 cattle

[d] HR for the category ≥10 years

Table 4. Associations Between Occupational Exposure to Cattle and Lung Cancer Risk, Stratified by Smoking, Among the Farming Population, AGRICAN, 2005-2011

	Non-Smokers			Smokers			*P* for interaction
	N	HR	CI 95%	N	HR	CI 95%	
Ever							
Never exposed to cattle	29	1.00		88	1.00		**0.01**
Exposed to cattle	57	**0.39**	**0.25, 0.62**	240	**0.75**	**0.59, 0.96**	
Duration							
Never exposed to cattle	29	1.00		88	1.00		0.24
<10 years	6	0.52	0.22, 1.25	54	1.00	0.71, 1.41	
10–19 years	6	0.44	0.18, 1.06	33	0.84	0.56, 1.25	
20–29 years	7	0.56	0.24, 1.27	18	0.65	0.39, 1.08	
30–39 years	6	**0.25**	**0.10, 0.60**	28	**0.59**	**0.39, 0.91**	
≥40 years	8	**0.25**	**0.12, 0.56**	39	**0.59**	**0.40, 0.87**	
P for trend		**<0.0001**			**<0.001**		

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

Table 5. Associations Between Tasks Performed in Animal Farming and Lung Cancer Risk, Overall and by Subtypes, Among the Farming Population, AGRICAN, 2005-2011

	All subtypes			Adenocarcinomas			Squamous cell carcinomas		
	N	HR[a]	95% CI	N	HR[a]	95% CI	N	HR[b]	95% CI
Cattle									
Care	261	**0.74**	**0.59, 0.93**	89	**0.63**	**0.43, 0.90**	87	1.04	0.67, 1.60
Milking	222	**0.74**	**0.59, 0.94**	79	**0.65**	**0.44, 0.94**	72	1.05	0.67, 1.64
Insecticides on cattle	112	**0.68**	**0.52, 0.89**	43	0.66	0.43, 1.01	35	0.86	0.52, 1.43
Barn disinfection	115	**0.70**	**0.54, 0.92**	42	0.66	0.43, 1.01	37	0.91	0.55, 1.50
Milking machine disinfection	116	**0.74**	**0.57, 0.96**	46	0.72	0.47, 1.09	38	1.03	0.63, 1.70
Horses									
Care	87	0.84	0.66, 1.08	24	0.65	0.41, 1.03	30	0.90	0.58, 1.39
Insecticides on horses	20	1.04	0.66, 1.64	7	1.03	0.48, 2.23	7	1.11	0.51, 2.42
Sheep and/or goats									
Care	43	0.86	0.62, 1.19	10	0.56	0.30, 1.08	19	1.25	0.76, 2.05
Milking	13	0.77	0.44, 1.35	4	0.66	0.24, 1.79	4	0.83	0.31, 2.27
Insecticides on sheep/goats	15	0.88	0.52, 1.48	7	1.18	0.55, 2.55	8	1.47	0.71, 3.03
Barn disinfection	20	1.00	0.64, 1.58	8	1.18	0.57, 2.42	9	1.42	0.71, 2.81
Milking machine disinfection	8	0.96	0.47, 1.94	3	1.00	0.32, 3.16	3	1.24	0.39, 3.93
Poultry									
Care	92	0.97	0.75, 1.25	33	1.00	0.66, 1.51	24	0.90	0.56, 1.45
Insecticides on poultry	30	0.94	0.64, 1.46	12	1.11	0.60, 2.04	12	1.23	0.67, 2.29
Barn desinfection	43	0.86	0.62, 1.19	16	0.94	0.55, 1.61	11	0.74	0.39, 1.39
Pigs									
Care	102	1.06	0.83, 1.37	32	1.03	0.67, 1.59	38	1.40	0.92, 2.13
Insecticides on pigs	22	0.94	0.60, 1.46	6	0.81	0.35, 1.86	13	**1.85**	**1.01, 3.39**
Barn disinfection	44	0.96	0.68, 1.34	13	0.90	0.49, 1.63	20	1.45	0.86, 2.42

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

[a] Adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), work on cattle (ever/never) and work on horses (ever/never)

[b] Adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), and work on cattle (ever/never)

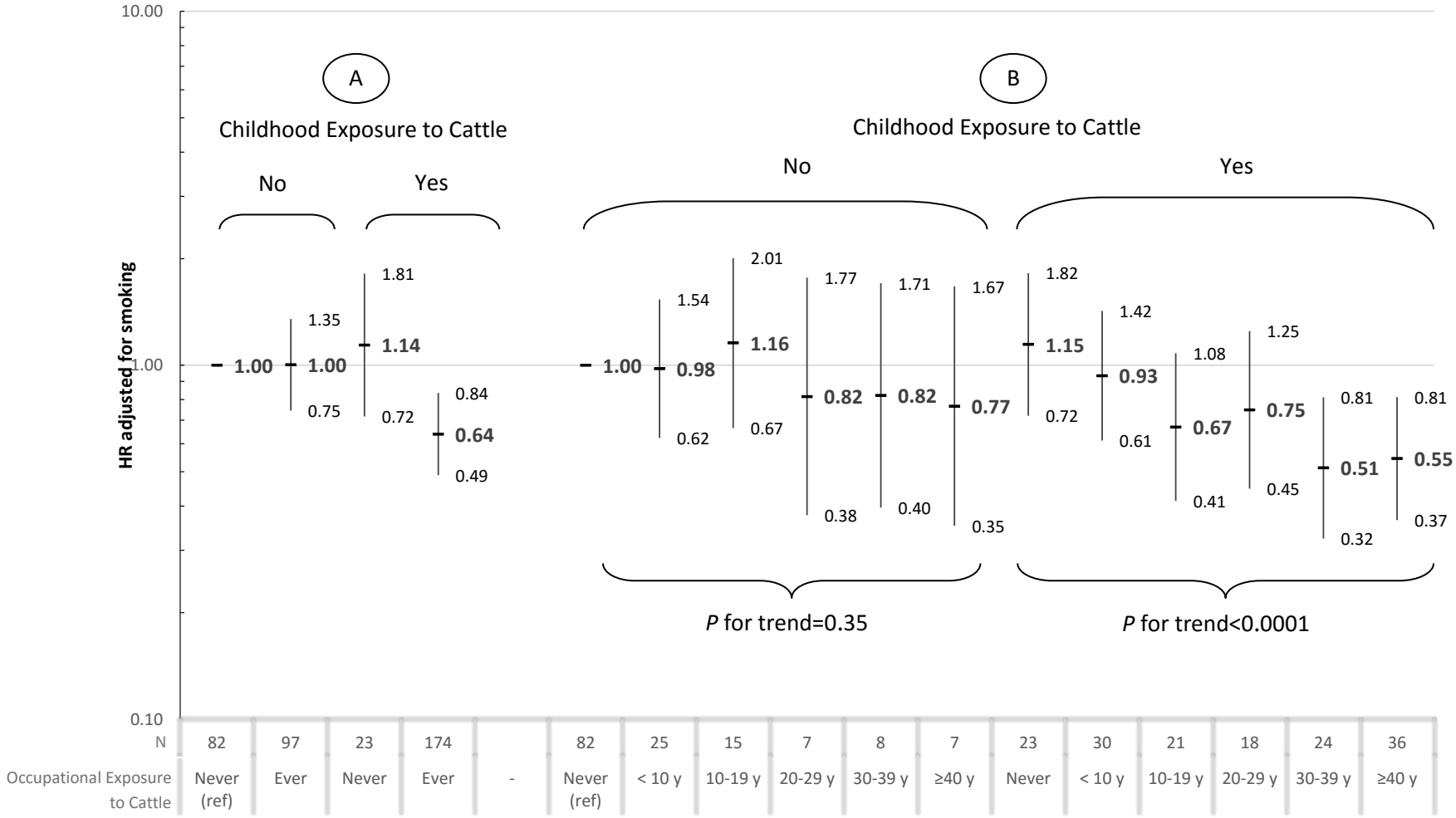

Figure 1. Associations Between Lung Cancer Risk and Occupational Exposure to Cattle (A: Ever/Never; B: Duration of Exposure), Stratified by Childhood Exposure to Cattle (First Year of Life), Among the Farming Population, AGRICAN, 2005-2011. Abbreviations: HR, hazard ratio; N, number of cases; ref, reference; y, year. Bars, 95% confidence interval.

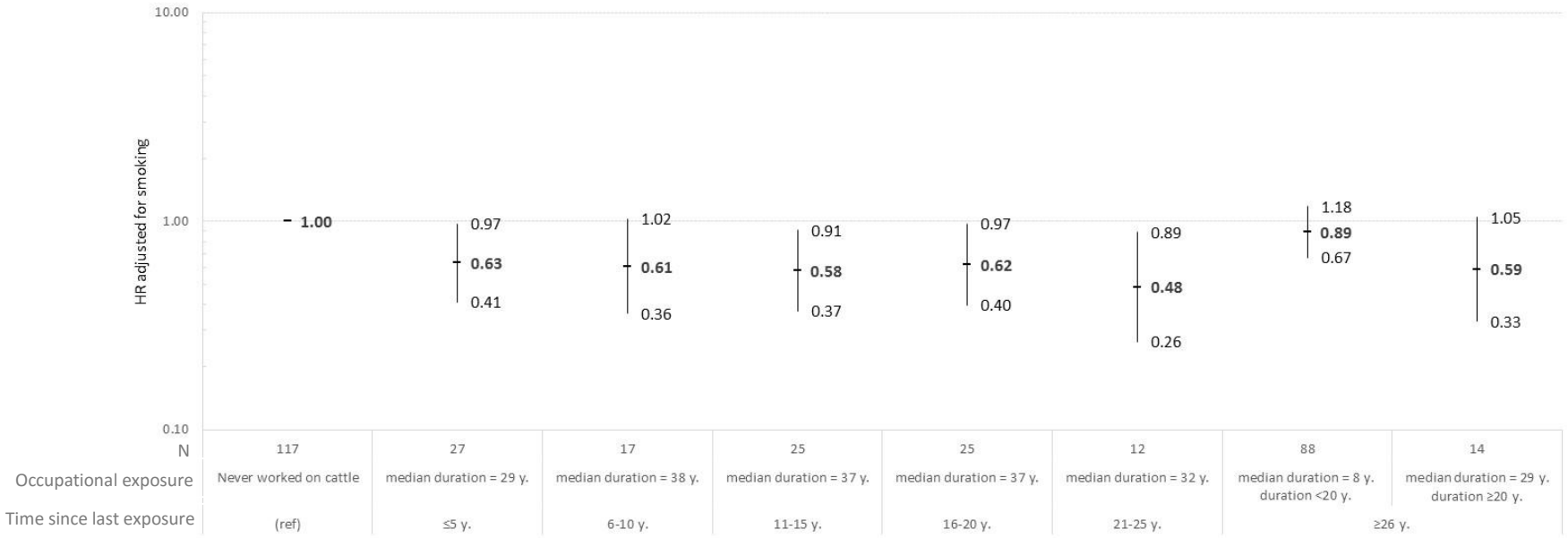

Figure 2. Impact of Time Since Last Exposure to Cattle (≤5 years, 6–10 years, 11–15 years, 16–20 years, 21–25 years, ≥26 years) on Relation Between Occupational Exposure to Cattle (for Time Since Last Exposure ≤ 25 years: Ever vs. Never Worked on Cattle; for Time Since Last Exposure ≥26 Years: Duration of Work<20 Years and ≥20 Years vs. Never Worked on Cattle) and Lung Cancer Risk, Among the Farming Population, AGRICAN, 2005-2011. Abbreviations: HR, hazard ratio; N, number of cases; ref, reference; y, year. Bars, 95% confidence interval.

Web Tables

Web Table 1. Associations Between Smoking and Lung Cancer Risk in AGRICAN Cohort, 2005-2011

	All subtypes			ADK			SCC		
	N	HR	IC95%	N	HR	IC 95%	N	HR	IC 95%
Smoking history									
Men									
Non-smokers	41	1.00		17	1.00		5	1.00	
Former smokers	275	**8.66**	**6.24, 12.02**	107	**8.12**	**4.87, 13.55**	90	**23.21**	**9.43, 57.12**
Current smokers	154	**28.84**	**20.35, 40.87**	45	**18.36**	**10.42, 32.34**	58	**96.41**	**38.52, 241.32**
Other types of smoking	71	**13.07**	**8.90, 19.20**	19	**8.39**	**4.36, 16.14**	22	**33.14**	**12.55, 87.51**
Women									
Non-smokers	83	1.00		53	1.00		2	1.00	
Former smokers	14	**4.34**	**2.39, 7.86**	9	**3.70**	**1.74, 7.87**	2	-	- -
Current smokers	22	**16.53**	**9.44, 28.95**	11	**9.85**	**4.56, 21.31**	7	-	- -
Other types of smoking	4	**15.34**	**5.58, 42.15**	1	-	- -	1	-	- -
Pack-years of cigarette smoking									
Men									
Non-smokers	41	1.00		17	1.00		5	1.00	
<20	143	**5.98**	**4.22, 8.46**	52	**5.16**	**2.98, 8.93**	50	**17.31**	**6.90, 43.41**
20-39	161	**17.65**	**12.52, 24.87**	65	**16.96**	**9.93, 28.95**	49	**44.08**	**17.56, 110.67**
40-59	73	**30.76**	**20.97, 45.12**	22	**22.42**	**11.89, 42.26**	27	**92.28**	**35.53, 239.73**
≥60	37	**37.40**	**23.97, 58.36**	9	**22.37**	**9.96, 50.25**	16	**132.22**	**48.41, 361.13**
Other types of smoking	71	**13.11**	**8.92, 19.26**	19	**8.45**	**4.39, 16.27**	22	**32.91**	**12.46, 86.95**
Women									
Non-smokers	83	1.00		53	1.00		2	1.00	
<20	17	**4.21**	**2.36, 7.52**	11	-	- -	4	-	- -
20-39	13	**19.57**	**10.48, 36.55**	8	-	- -	2	-	- -
40-59	3	**27.96**	**8.70, 89.82**	1	-	- -	1	-	- -
≥60	2	**56.02**	**13.57, 231.25**	0	-	- -	1	-	- -
Other types of smoking	4	**14.56**	**5.30, 40.05**	1	-	- -	1	-	- -

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

Web Table 2. Associations Between Exposure to Farm Animals and Lung Cancer Risk, Compared to the Non-farming Population, AGRICAN, 2005-2011

			All subtypes				ADK				SCC			
			N	HR	95% CI	*P* for trend	N	HR	95% CI	*P* for trend	N	HR	95% CI	*P* for trend
Cattle	Ever[a]	Never worked on a farm	90	1.00			36	1.00			27	1.00		
		Ever worked on cattle	287	0.86	0.66, 1.12		103	0.71	0.47, 1.07		90	0.90	0.57, 1.42	
	Duration[b]	Never worked on a farm	90	1.00		**0.02**	36	1.00		**0.03**	25	1.00		0.15
		<10 years	52	1.21	0.83, 1.76		19	1.12	0.62, 2.01		20	1.19	0.66, 2.14	
		10-19 years	33	0.99	0.64, 1.51		12	0.92	0.47, 1.80		13	1.04	0.53, 2.05	
		20-29 years	21	0.84	0.51, 1.37		9	0.79	0.38, 1.66		8	0.94	0.42, 2.09	
		30-39 years	32	0.73	0.48, 1.11		10	0.52	0.25, 1.05		12	0.82	0.41, 1.65	
		≥40 years	38	0.69	0.46, 1.04		12	0.52	0.26, 1.03		13	0.64	0.32, 1.27	
Horses	Ever[a]	Never worked on a farm	90	1.00			36	1.00			25	1.00		
		Ever worked on horses	120	1.14	0.80, 1.61		37	0.92	0.53, 1.53		39	0.88	0.46, 1.69	
	Duration[b]	Never worked on a farm	90	1.00		0.52	36	1.00		0.46	25	1.00		0.89
		<10 years	24	0.94	0.55, 1.60		6	0.55	0.21, 1.46		10	1.01	0.41, 2.49	
		10-19 years	15	0.90	0.49, 1.67		5	0.40[c]	0.15, 1.11		7	1.02	0.38, 2.73	
		≥20 years	12	0.73	0.38, 1.42						5	0.79	0.26, 2.34	
Poultry	Ever[a]	Never worked on a farm	90	1.00			36	1.00			25	1.00		
		Ever worked on poultry	142	1.29	0.92, 1.81		55	1.31	0.78, 2.21		44	1.06	0.57, 1.99	
	Duration[b]	Never worked on a farm	90	1.00		0.99	36	1.00		0.28	25	1.00		0.37
		<10 years	15	1.04	0.55, 1.95		9	0.98[d]	0.42, 2.26		7	0.61[d]	0.23, 1.60	
		10-19 years	11	0.97	0.48, 1.95									
		20-29 years	6	0.99	0.41, 2.37		8	1.00[e]	0.41, 2.39		7	0.76[e]	0.29, 2.00	
		30-39 years	8	1.25	0.57, 2.72									
		≥40 years	12	1.28	0.64, 2.56									
Pigs	Ever[a]	Never worked on a farm	90	1.00			36	1.00			25	1.00		
		Ever worked on pigs	123	1.31	0.90, 1.90		45	1.34	0.75, 2.40		44	1.28	0.66, 2.48	
	Duration[b]	Never worked on a farm	90	1.00		0.83	36	1.00		0.22	25	1.00		0.69
		<10 years	24	1.37	0.78, 2.41		6	0.91	0.33, 2.51		9	1.10	0.43, 2.78	

		10-19 years	12	1.04	0.52, 2.11		4	1.10	0.34, 3.53		7	1.39	0.51, 3.85		
		≥20 years	23	1.48	0.84, 2.59		8	1.55	0.63, 3.83		8	1.13	0.43, 2.93		
Sheep or goats	Ever[a]	Never worked on a farm	90	1.00			36	1.00			25	1.00			
		Ever worked on sheep/goats	55	1.11	0.75, 1.65		16	0.85	0.44, 1.66		20	1.03	0.51, 2.06		
	Duration[b]	Never worked on a farm	90	1.00		0.53	36	1.00		0.37	25	1.00		0.80	
		<20 years	13	0.88	0.47, 1.64		2	0.36	0.08, 1.55		9	1.39	0.59, 3.28		
		≥20 years	10	1.21	0.60, 2.41		3	0.93	0.27, 3.16		4	1.12	0.36, 3.46		

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

[a] For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), exposure to cattle (ever/never), and exposure to horses (ever/never); for SCC: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥ 60, other tobacco) and exposure to cattle (ever/never)

[b] For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), duration of work on cattle and duration of work on horses; for SCC: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), duration of work on cattle

[c] HR for the category ≥10 years

[d] HR for the category <20 years

[e] HR for the category ≥20 years

Web Table 3. Associations Between Exposure to Cattle Farming and Lung Cancer Risk After Multiple Imputation, Among the Farming Population, AGRICAN, 2005-2011

A. Description of Prevalence of Exposure to Cattle

	Complete case analysis	From 50 imputed datasets	
		Proportion / mean	95% CI
Work on a farm, %	86.7	86.7	86.5 86.8
Cattle farming, among those working on a farm, %	77.5	75.8	75.5 76.0
Duration of cattle farming, mean number of years	26.7	27.1	27.0 27.2
Tasks among cattle producers, %			
Care	87.9	83.3	83.0 83.6
Milking	80.2	76.7	76.5 77.0
Insecticides	36.9	39.7	39.3 40.0
Building disinfection	35.8	34.3	33.9 34.6
Milking machine disinfection	41.8	45.3	45.0 45.6

Abbreviations: CI, confidence interval.

B. Associations Between Exposure to Cattle and Lung Cancer Risk, Overall

	Complete case analysis			From 50 imputed datasets		
	HR*	95% CI	*P*–trend	HR*	95% CI	*P*–trend
Ever	**0.70**	**0.57, 0.87**		**0.69**	**0.57, 0.84**	
Duration						
Never exposed	1.00		**<0.0001**	1.00		**<0.0001**
<10 years	0.94	0.68, 1.28		0.93	0.70, 1.25	
10–19 years	0.78	0.54, 1.13		0.79	0.58, 1.07	
20–29 years	0.68	0.44, 1.05		**0.70**	**0.51, 0.95**	
30–39 years	**0.54**	**0.36, 0.79**		**0.58**	**0.43, 0.78**	
≥40 years	**0.55**	**0.39, 0.78**		**0.57**	**0.42, 0.76**	

Abbreviations: CI, confidence interval; HR, hazard ratio.
* Adjusted for pack–years of smoking

Web Table 4. Associations Between Exposure to Other Animals and Lung Cancer Risk, Overall and by Subtypes, Among the Farming Population, AGRICAN, 2005-2011

			All subtypes				Adenocarcinomas				Squamous cell carcinomas			
			N	HR	95% CI	*P*– trend	N	HR	95% CI	*P*– trend	N	HR	95% CI	*P*– trend
Sheep or goat	Ever/Never[a]		57	0.93	0.63, 1.23		16	0.76	0.45, 1.28		20	1.12	0.69, 1.81	
	Duration[b]	Never exposed	245	1.00		0.62	92	1.00		0.51	78	1.00		0.50
		<20 years	13	0.73	0.42, 1.30		2	0.34	0.08, 1.39		9	1.48	0.73, 3.00	
		≥20 years	10	1.03	0.54, 1.94		3	0.89	0.28, 2·82		4	1.21	0.44, 3.34	
	Number of Animals[b]	Never exposed	245	1.00		0.63	92	1.00		0.69	78	1.00		0.47
		<50	8	0.76	0.37, 1.54		1	0.30	0.00, 2.18		5	1.26	0.51, 3.14	
		50–149	6	1.00	0.44, 2.25		1	0.47	0.07, 3.41		3	1.49	0.47, 4.73	
		≥150	5	0.80	0.33, 1.94		2	0.86	0.21, 3.49		3	1.42	0.45, 4.52	
Poultry	Ever[a]		148	1.10	0.88, 1.37		55	1.22	0.85, 1.73		44	1.23	0.83, 1.80	
	Duration[b]	Never exposed	188			0.84	70	1.00		0.97	60	1.00		0.64
		<10 years	15	0.91	0.52, 1.61		9	0.95[c]	0.46, 1.97		7	0.68[c]	0.30, 1.53	
		10–19 years	11	0.86	0.45, 1.63									
		20–29 years	6	0.88	0.38, 2.01		8	0.99[d]	0.46, 2.14		7	0.88[d]	0.39, 1.97	
		30–39 years	8	1.11	0.54, 2.31									
		≥40 years	12	1.16	0.62, 2.16									
	Number of Animals[b]	Never exposed	188	1.00		0.90	70	1.00		0.41	60	1.00		0.24
		<45	14	0.76	0.43, 1.33		3	0.52	0.16, 1.68		5	0.72	0.28, 1.82	
		≥45	20	0.96	0.60, 1.53		9	1.31	0.65, 2.66		4	0.54	0.19, 1.49	
Pig	Ever/Never[a]		121	1.12	0.88, 1.42		45	1.27	0.86, 1.87		44	1.42	0.95, 2.12	
	Duration[b]	Never exposed	199			0.35	75	1.00		0.30	61	1.00		0.47
		<10 years	24	1.19	0.73, 1.94		6	0.91	0.37, 2.27		9	1.15	0.53, 2.49	
		10–19 years	12	0.91	0.48, 1.73		4	1.09	0.37, 3.18		7	1.51	0.64, 3.60	
		≥20 years	23	1.30	0.80, 2.09		8	1.54	0.70, 3.37		8	1.24	0.56, 2.74	
	Number of	Never exposed	199	1.00		**0.03**	75	1.00		0.07	61	1.00		0.16

Animals[b]	<49	30	1.12	0.73, 1.72		9	1.15	0.54, 2.42		10	0.93	0.46, 1.88
	≥50	19	**1.69**	**1.05, 2.73**		8	2.00	0.95, 4.19		7	1.74	0.79, 3.86

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

[a] For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), exposure to cattle (ever/never), and exposure to horses (ever/never); for SCC: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥ 60, other tobacco), and exposure to cattle (ever/never)

[b] For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), duration of work with cattle and duration of work with horses; for SCC: adjusted for smoking (never smokers, pack–years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), and duration of work with cattle

[c] HR for the category < 20 years

[d] HR for the category ≥ 20 years