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Baptiste Vesper Guillon

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UNIVERSITÉ GRENOBLE ALPES
UFR DE MÉDECINE DE GRENOBLE

Année : 2019

**DIGESTIVE CANCER RISK AND OCCUPATIONAL EXPOSURE IN FRENCH
FARMERS: RESULTS FROM MUTUALITE SOCIALE AGRICOLE (MSA)
MEDICO-ADMINISTRATIVE DATABASES**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Baptiste VESPER GUILLON

[Données à caractère personnel]

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**ÉVALUATION DU RISQUE DE CANCERS DIGESTIFS SELON L'EXPOSITION
PROFESSIONNELLE CHEZ LES AGRICULTEURS FRANÇAIS, D'APRÈS LES
DONNÉES MÉDICO-ADMINISTRATIVES DE LA MUTUALITÉ SOCIALE
AGRICOLE (MSA)**

RÉSUMÉ

Introduction : Les travailleurs agricoles ont un plus faible risque de cancer digestif. Il s'agit pourtant d'une population fréquemment exposée à de nombreux risques professionnels, parmi lesquels figuraient certains agents classés cancérigènes certains par le CIRC, et figurent toujours certains agents classés cancérigènes probables ou possibles, avec des variabilités d'exposition au sein des différentes activités agricoles. Le but de cette étude était d'évaluer le risque de cancer digestif en fonction de l'exposition professionnelle chez les agriculteurs français.

Méthodes : L'ensemble des exploitants agricoles ayant cotisé au moins une fois à la MSA entre 2006 et 2016 a été étudié. Les déclarations de cancers digestifs en ALD 30, au sein de cette population, ont été relevées de 2012 à 2016, en précisant le sous-type de cancer selon la classification CIM-10. A l'aide de modèles logistiques, permettant l'ajustement sur le sexe, l'âge et d'autres variables, les associations entre déclaration de cancers digestifs et activités agricoles ont été étudiées et exprimées sous forme d'Odds Ratio. Une correction (Benjamini-Hochberg) a été effectuée pour prendre en compte les tests multiples.

Résultats : Sur les 899 212 exploitants agricoles étudiés, 4438 cancers digestifs ont été déclarés. Le risque de cancer digestif était augmenté chez les viticulteurs (OR=1.28 [95% CI 1.16-1.42], $p<0.00005$), principalement lié à une augmentation du risque de cancer colorectal (OR=1.21 [95% CI 1.09-1.35], $p=0.01$). Une tendance à l'augmentation du risque de cancer du grêle a également été mise en évidence (OR=2.19 [95% CI 1.31–3.67], proche de la significativité ($p=0.07$ après application de la correction concernant les tests multiples). Par ailleurs, une diminution du risque de cancer digestif a été retrouvée chez les producteurs céréaliers (OR=0.87 [95% CI 0.8–0.95]), sous-tendue par une diminution de risque de cancer de l'estomac (OR=0.6 [95% CI 0.45–0.81]).

Conclusion : Nos résultats montrent une augmentation de risque de déclaration en ALD de cancer digestif et principalement de cancer colorectal chez les viticulteurs français. Il est également retrouvé une diminution du risque de cancer digestif chez les producteurs céréaliers, principalement une diminution de risque de cancer de l'estomac.

MOTS CLÉS : Cancers digestifs ; Agriculteurs ; Exposition professionnelle ; Facteurs de risque ; Cohorte

FILIÈRE : Gastro-entérologie, hépatologie et oncologie digestive, CHU Grenoble Alpes, France

**DIGESTIVE CANCER RISK AND OCCUPATIONAL EXPOSURE IN FRENCH
FARMERS: RESULTS FROM MUTUALITE SOCIALE AGRICOLE (MSA)
MEDICO-ADMINISTRATIVE DATABASES**

ABSTRACT

Introduction - Farmers are at lower risk to present with digestive cancer. However, this population is frequently exposed to carcinogens, with exposure variability depending on the agricultural activity. The aim of our study was to evaluate the risk of digestive cancer according to agricultural activity among French farmers.

Methods - We included all farmers recorded at least once in the social security system of French agricultural workers “Mutualité sociale agricole” (MSA) between January 2006 and December 2016. We recorded the digestive cancers in this population reported as Long Term Disease (LTD) from January 2012 to December 2016. We specified for each case the cancer subtype according to the ICD-10 classification. The association between digestive cancer and agricultural activity was studied with logistic models, and expressed as Odds Ratio

Results - 4,438 digestive cancers were reported among 899,212 included farmers. The risk of presenting with digestive cancer was increased in wine growers (OR=1.28 [95% CI 1.16-1.42]), mainly an increased risk of colorectal cancer (OR=1.21 [95% CI 1.09-1.35]). An increased risk of small bowel cancer was also identified but with a limited statistical significance (OR=2.19 [95% CI 1.31-3.67], p=0.08). Furthermore, a lower risk of digestive

cancer was identified among cereal crop farmers (OR=0.87 [95% CI 0.8-0.95]), supported by a lower risk of stomach cancer (OR=0.6 [95% CI 0.45-0.81]).

Conclusion - Our results suggest an increased risk of digestive cancer among French wine growers, mainly colorectal cancer. We also found a lower risk of digestive cancer among cereal crop farmers, mainly gastric cancer.

KEYWORDS - Gastrointestinal Neoplasms; Farmers; Risk Factors; Occupational Exposure; Cohort Studies

ABRÉVIATIONS

AGRICAN: AGRiculture and CANcer cohort

AHS: Agricultural Health Study

CI: Confidence Interval

IARC: Agency for Research on Cancer

ICD-10: International Classification of WHO Diseases, 10th edition

LTD: Long Term Disease

MCE: Matrice Culture Exposition

MSA: Mutualité Sociale Agricole

OR: Odds Ratio

ARTICLE

DIGESTIVE CANCER RISK AND OCCUPATIONAL EXPOSURE IN FRENCH FARMERS: RESULTS FROM MUTUALITE SOCIALE AGRICOLE (MSA) MEDICO-ADMINISTRATIVE DATABASES

INTRODUCTION

Cancer epidemiology

France has one of the highest incidence of cancer among European countries: 382,000 new cases were reported in 2018 [1]. Globally, it is estimated that one in five men and one in six women will develop cancer during their lifetime [2]. In terms of mortality, 157,000 deaths were cancer related in France, in 2018, making it the leading cause of specific mortality, regardless of gender, before cardiovascular diseases and infectious causes, despite recent and ongoing progress in early detection and treatment [1].

Digestive cancers

The incidence of digestive cancers is high in France, with colorectal cancer ranking first. The aging population, improved screening techniques, but also changes in lifestyle such as increased level of inactivity, have probably led an increased incidence since the 1980s. In 2017, there were an estimated 45,000 new cases per year of colorectal cancer, making it the second most common cancer in women and the third most common in men [3]. It is also one of the deadliest since it is ranked third in men and second in women in terms of mortality [3][4]. A rapid and poorly explained increase in the incidence of pancreatic cancer has also been reported over the past ten years (+ 2.7% per year in men and + 3.8% in women between

1990 and 2018), while these figures have not increased similarly in other industrialized countries [3] [5] [6].

Risk factors and occupational exposures

A study by the International Agency for Research on Cancer (IARC) in 2000 shows that about 35% of incident cancers could be preventable if exposure to risk factors had been at the optimal level or reference level [7]. Numerous published IARC monographs list the various types of known or suspected carcinogens, whether chemical, physical, viruses, dust, ionizing radiation, but also new lifestyle factors such as food quality. Tobacco and alcohol are the best-known and incriminated risk factors, accounting respectively for 20% and 8% of incident cancers [8][9]. Food consumption and obesity both account for 5.4% of the fractions attributable to new cases. Regular physical activity could be a protective factor [10]. 3.6% of incident cancers are attributable to occupational exposure and 12% of employees have been exposed at their workplace to at least one carcinogen (chemical or non-chemical), for occupational medicine [7]. More specifically for digestive cancers, the attributable fractions to occupational exposure were respectively 4% for stomach, 2% for colon-rectum, and 3.7% for liver cancer [9]. Studies focusing on a relationship between occupational exposure and cancer risk are valuable tools for prevention campaigns and the legal framework of product use.

Agricultural workers

The relationship between cancer and agriculture has been studied often since the early 1980s and has led to several meta-analyses [11] [12]. The authors of previous major studies have reported a reduction of cancer risk in this population compared to the global population, concerning digestive cancers [13]. Two major agricultural cohorts have allowed confirming

this: the Agricultural Health Study (AHS) among US private pesticide applicators from North Carolina and Iowa [14][15] and the AGRICulture and CANcer (AGRICAN) cohort among French farmers [16]. Possible explanations were a lower rate of tobacco consumption in this population high levels of occupational physical activity, and possibly a safer diet (higher fruits and vegetables intake). In the AGRICAN cohort, however, there was a slightly increased risk of stomach cancer in female farmers and in those who never used pesticides.

However, farmers are frequently exposed to many potentially carcinogenic agents such as pesticides, cristalline silica, ultraviolet rays, and viruses.[17].

Monitoring diseases in this exposed population is crucial for the identification and prevention of the new threats. Using insurance data for the detection of these risks, complementary to conventional epidemiological studies, could improve early detection.

The Mutualité Sociale Agricole (MSA) is a social security system covering all French agricultural workers for the following issues : diseases, family, occupational health and retirement. The MSA has undertaken to use its medico-administrative data for research purposes mainly on occupational risks vigilance. We decided to use these medico-administrative databases in our study to identify, without any prior assumption, any association between various agricultural activities and the occurrence of digestive cancers.

METHODS

Agreements

The massive data mining project in which this study is integrated was approved by the French Data Protection Authority CNIL (MMS/SBM/AE171001).

Study Population

The authors of a pilot study demonstrated the feasibility and relevance of MSA medico-administrative database use to assess risks among agricultural workers [18]. We used this cohort by focusing specifically on digestive cancers. MSA is the French national health insurance for every agricultural worker. It groups two different statuses of agricultural workers: farm owners and farm salaried workers, whether active or retired. They can be farmers, breeders, but also less frequent occupations such as beekeepers, foresters, shellfish farmers, and even tertiary workers serving the agricultural population (bank, insurance and MSA workers themselves). In 2016, 3.3 million people were affiliated with the MSA. We included all adults 18 of age or more, men and women, active farm owners, recorded in the MSA at least once between 2006 and 2016 (Table 1). Farm workers (employees) were not included in the analysis as a large proportion of them have either seasonal jobs, or move shortly from one contract to another, which introduce a higher variability in their occupations, and makes the assessment of occupational activity more complex and less accurate, so less relevant for our analysis. We did not take into account farm owners retired before 2006 since we have no information about occupational activity for them.

Data collection

Data collected from the MSA records was divided in two different categories: administrative database and medico-administrative database. The administrative database was implemented in 2006 and included sex, date of birth, region of residence, socio-economic status, first year of activity and agricultural activity as defined by the MSA thesaurus (Table 2). Each individual had to report his agricultural activity once a year and was regularly controlled.

The medico-administrative database was implemented in 2012. We identified all Long-Term Disease (LTD) declarations and the corresponding disease sub-category following the International Classification of WHO Diseases (ICD-10) (Table 3) for every year in this

database. Chronic diseases such as cancers are reported to the health insurance system, in France, by family practitioners as LTDs so that patients can have free medical care adapted to the disease. LTD 30 is the code for malignant tumors. We collected all ICD-10 codes from C15 to C26 (digestive cancers) in the database, reported between January 2012 and December 2016. We decided to group some ICD-10 codes because of their clinical and epidemiological similarity, with the aim to increase statistical power. Malignant neoplasms of the colon were grouped with rectosigmoid junction and rectum neoplasms (C18, C19, and C20 respectively); gallbladder neoplasms were grouped with other and unspecified biliary tract neoplasms (C23 and C24 respectively).

Statistical analysis

Two matrices were generated with ICD-10 codes on one hand and occupational activities on the other hand, studied as binary variables. Each association between one ICD-10 code and one occupational activity was studied with a specific model build with stepwise selection of variables. Because of the great number of tests, it was essential to control the potentially false identifications and highlight the relevant associations. We chose the Benjamini-Hochberg procedure, stable but little conservative, to adjust p-values. We calculated p-values for each association, with an alpha risk of 0.05. P-values <0.05 , after correction for multiple testing, were considered as statistically significant. Results were computed as Odds Ratio (OR) expressed with a 95% confidence interval (CI), adjusted on age, sex, year of first installation, matrimonial status, affiliation status, region, exploitation administrative area, and history of any LTD. All statistical analyses were performed using R statistical software.

RESULTS

Study Population

The main characteristics of the study population are listed in Table 1. 899,212 farm-owners were identified; mostly men (70.2%) with a median age of 50.2 years (± 12.9 for men and ± 13.5 for women), median year of first installation in 1995 (1940 to 2016), and 69.5% were exclusively working in agriculture. We identified, for the five main activities, 226,607 (23%) people working in cereal crops, 136,146 (13.8%) in dairy cattle, 104,128 (10.6%) in winegrowing, 101,711 (10.3%) in beef cattle, and 112,983 (11.5%) in mixed crops and breeding.

Occupational exposure and cancer risk

We identified 4,438 digestive cancers (Table 4) between January 2012 and December 2016. Colorectal cancer was the most frequent subtype (n=2,930; 66%), followed by pancreatic cancer (n=434; 9.8%), gastric cancer (n=314; 7%), esophagus cancer (n=290; 6.5%), and liver and intrahepatic bile ducts cancer (n=260; 5.9%). The associations between occupational activities and occurrence of digestive cancer are listed in Table 5 and Table 6

Winegrowing

Winegrowing was associated with an overall increased risk of digestive cancer of nearly 30% (OR=1.28, 95%CI 1.16–1.42; $p < 0.00005$). The risk increase was preponderant for colorectal cancer, nearly 20%, resistant to correction of multiple tests (OR=1.21, 95%CI 1.09–1.35; $p = 0.01$). We found a higher risk of small intestine cancer for winegrowing before multiple test correction (OR=2.19, 95%CI 1.31–3.67), still nearly significant, after Benjamini-Hochberg correction ($p = 0.07$). The high level of statistical significance for all cancers OR estimate is partly due to the fact that, except for esophagus, all cancer risks estimates were above 1, even if none of them, except for colorectal cancer, was statistically significant by itself.

Cereal crop

We found an overall lower risk for all digestive cancers in cereal crop farmers, of nearly 13% (OR=0.87, 95%CI 0.8–0.95; p=0.02) and more specifically a significantly lower risk of 40% of stomach cancer (OR=0.6, 95%CI 0.45–0.81; p=0.02).

Negative but non-significant associations were identified for cereal crop farmers: esophagus cancer (OR=0.97, 95%CI 0.73–1.28), colorectal cancer (OR=0.95, 95%CI 0.87–1.04), liver and intrahepatic bile duct cancer (OR=0.9, 95%CI 0.67–1.23), and pancreatic cancer (OR=0.97, 95%CI 0.77–1.23).

Other occupational activities

No significant difference in risk was identified for other cancer sites such as esophagus, liver and bile ducts, pancreas, anal canal, regardless of occupational activity.

DISCUSSION

This large-scale study highlighted an increased risk of digestive cancer and more specifically of colorectal cancer among French winegrowers. It also highlighted a reduction in the risk of stomach cancer in cereal crop farmers.

Limitation and strength of our study

The first strength of this study was the great number of farmers of both genders included, and the diversity in activity. It was also the extensive data collection for farm-owners since the MSA is the only social regimen for these professionals in France.

The follow-up period was long, since the median year of installation was 1995 and the first recorded agricultural activity went back to 1940. Cancer declarations have been recorded since 2012, allowing for a delay between professional exposure and occurrence of cancer consistent with the current data on carcinogenic processes [19][20][21][22][23].

We performed a robustness test, to avoid the risk of over-adjustment, by limiting the number of adjustment variables. We kept only age, sex, year of installation, health regimen, and geographic region. The results obtained were the same as in the main analysis, reinforcing the power of our study.

Our study however, had several limitations. The occupational activity was assessed as an exposed / not exposed dichotomous form. Our data prevent us to take into account the duration of activity and thus the duration of exposure, whereas we suppose that the real risk depend on cumulative exposure, and that exposure might have change over successive periods (change in pesticides use, etc).

We were unable to include tobacco abuse status in the adjustment variables since this data was not present in the MSA records. However, it is well known that tobacco abuse among farmers is lower than in the global population (21% vs. 34% respectively), which would tend to support our results [24].

We chose to include only farm-owners because they were considered as more stable in their professional activity, whereas it was difficult to establish a work time threshold for farm-salaried-workers that could be qualified as "stable". In the Maugard pilot study, 75% of employees had to be excluded because they did not meet the criteria for stable employment

(>1,014h / year) [18]. The AGRICAN cohort, however, showed a slightly increased cancer risk in the farm-worker subgroup compared to farm-owners (+ 14%). Not taking this subpopulation into account was therefore a limitation of our study, but a database review is ongoing to include them in the near future.

Differences between observed and predicted incidence using the LTD variable were assessed in French administrative subdivision using a cancer registry [25]. This method was chosen to estimate the overall incidence of colorectal cancer in France from data in administrative subdivision with a cancer registry, with a relative error of prediction inferior to 15%. The authors showed that the use of French National Hospital Information System (PMSI, Programme de Médicalisation des Systèmes d'Information) data combined with LTD allowed improving the quality of incidence prediction for pancreatic, esophagus, and stomach cancer. It is therefore possible that incidence for these locations are higher than the occurrence found in our study, which could decrease the risk estimate for these cancers. Completing our study with hospital PMSI data could improve our results. Furthermore, the MSA medico-administrative database also contains data on medicine consumption. Integrating this data with the LTD declaration could help identify more patients with cancer.

Winegrowing

Published data concerning associations between winegrowing and digestive cancer risk is scarce. Some authors have shown an increased risk of rectosigmoid junction carcinoma among residents of a German winegrowing community (area under wine cultivation >20% of community area), but with no excess of cancer of either colon, rectum, or colon and sigmoid and rectum all together [26]. Thus, this result might be due to chance. This population was also characterized by an overall lower risk of digestive cancers. Winegrowing is the

agricultural activity in which pesticides are the most used in France (20% of pesticides for only 3% of the country's agricultural area). One of the main reasons for this increased risk could be the use of arsenic. Arsenical pesticides have been banned since 1973, except for winegrowing where they were allowed until 2001. It is estimated that between 1979 and 2001, from 60,000 to 100,000 winegrowers used this type of pesticide [27]. Inorganic arsenic is classified as carcinogenic to humans (group 1) by IARC and several authors have well documented the link between its use and the risk of skin, lung, bladder, prostate, and liver cancer [28][29][30]. A decreased incidence of colorectal cancer was reported after decreasing arsenic levels in drinking water but an increased risk of cancer was reported in individuals exposed to high levels of arsenic in drinking water [31][32]. Several animal and in vitro models support the potential carcinogenic role of arsenic in colorectal cancer [33][34]. In contrast, research has highlighted the therapeutic potential of arsenical derivatives in the treatment of digestive cancers [35][36].

Cereal crops

We observed a lower risk of digestive cancers and mainly gastric cancers in cereal crop growers. The AGRICAN cohort has already proved a lower risk of gastric cancer among male farm-owners. The link with occupational exposure is not established and it is likely that the environment, especially dietary patterns, play a role in this risk variability. Several protective associations for gastric cancer have already been demonstrated such as the consumption of fruits, vegetables, and dietary flavonoids [37][38]. In contrast, high salt intake or red and processed meat consumption may be associated with an increased risk of gastric cancer [39][40].

Research perspectives

The MSA administrative database includes the region of activity for each farmer. We could study the geographical distribution of cancer declaration rates and compare them with data published by the National Public Health Agency (*Santé Publique France*).

Moreover, winegrowing has a strong north-south distribution gradient in France. It would be interesting to know if this gradient could be identified in the occurrence of colorectal cancer in our study.

Finally, this exploratory preliminary study could be extended by identification of phytosanitary product use by farmers. The Graphical Terrain Register (Registre Parcellaire Graphique) lists all French agricultural areas and their main cultures. Furthermore, the Crop Exposure Matrices (MCE) of the Matphyto project of the National Public Health Agency (*Santé Publique France*) allows the evaluation of retrospective phytosanitary product exposure according to agricultural specialty [41]. We could evaluate the association between phytosanitary product use and digestive cancer by associating these tools with our study models [42]. We could thus improve vigilance for phytosanitary product use among farmers.

CONCLUSION

We found a positive association between winegrowing and the occurrence of LTD digestive cancers among French farm-owners, most often colorectal cancer. We question the use of arsenic as a pesticide until 2001 in this population to be one of the possible risk factors. We also highlighted a reduction in the risk of stomach cancer in cereal crop farmers.

The evaluation of occupational exposure is a major challenge to detect new risks and protect agricultural workers. Further studying the associations between phytosanitary product use and cancer risk could provide crucial answers to these topical issues.

Table 1

Main characteristics of study population made of French self-employed agricultural workers

Characteristics	N	%
Overall	899,212	-
Gender		
Men	631,560	70.2
Women	267,652	29.8
Mean age		
Men	48.7	-
Women	53.8	-
Year of first installation		
Median	1995	-
Minimum	1940	-
Maximum	2016	-
Health regimen		
Exclusive	625,139	69.5
Principal	42,077	4.7
Liberal	10,463	1.2
Employees	16,959	1.9
Others	204,574	22.8
Matrimonial status		
Single	350,942	39.0
Married	532,732	59.2
Widowed	37,940	4.2
Divorced	48,366	5.4

¹Health regimen: exclusive: 100% incomes from agriculture. Principal: > 50% incomes from agriculture. Liberal: < 50% incomes from agriculture. Others: simultaneous assignment to another health regimen

Table 2

Agricultural activities as defined by MSA thesaurus for self-employed workers

Value	Name
1	Vegetables, flowers
2	Fruit trees
3	Plant nursery
4	Cereals
5	Winegrowing
6	Forestry
7	Other specialized crops
8	Dairy cattle farmers
9	Beef farmers
10	Mixed dairy and beef cattle
11	Sheep and goat
12	Pigs
13	Horses
14	Other big animals
15	Poultry and rabbits
16	Other small animals
17	Horse riding club
18	Shellfish farming
19	Non-specialized and/or mixed crops and breeding
20	Salt marshes
21	Wood working
22	Sawmills
23	Agricultural company
24	Landscaping
25	Local agricultural health insurance agents

Table 3
ICD-10 classification for malignant digestive neoplasms

Code	Name
ICD-15	Malignant neoplasm of esophagus
ICD-16	Malignant neoplasm of stomach
ICD-17	Malignant neoplasm of small intestine
ICD-18	Malignant neoplasm of colon
ICD-19	Malignant neoplasm of rectosigmoid junction
ICD-20	Malignant neoplasm of rectum
ICD-21	Malignant neoplasm of anus and anal canal
ICD-22	Malignant neoplasm of liver and intrahepatic bile ducts
ICD-23	Malignant neoplasm of gallbladder
ICD-24	Malignant neoplasm of other and unspecified parts of biliary tract
ICD-25	Malignant neoplasm of pancreas
ICD-26	Malignant neoplasm of other and ill-defined digestive organs

Table 4 - Number of cancer cases following occupational exposures

	Vegetables, flowers	Fruit trees	Plant nursery	Cereal	Winegrowing	Forestry	Other specialized crops	Dairy cattle farmers	Beef farmers	Mixed dairy and beef	Sheep and goat	Pigs	Horses	Other big animals	Poultry and rabbits	Other small animals	Horse riding club	Shellfish	mixed crops and breeding	Salt marshes	Wood working	Sawmill	Agricultural company	Landscaping	Insurance agents	Rural artisans	
	185	125	16	1211	644	12	26	661	596	153	177	74	44	6	88	40	28	7	517	2	38	1	62	116	6	1	
ICD-15 esophagus	290	18	6	1	75	30	1	3	38	35	12	9	6	7	2	10	0	1	0	39	1	2	1	2	8	0	0
ICD-16 stomach	314	8	9	2	63	39	1	3	59	51	12	19	5	2	0	9	4	2	1	35	0	5	0	2	10	1	0
ICD-17 small intestine	83	3	3	0	18	19	0	0	13	15	3	1	0	2	0	1	1	1	0	6	0	0	0	0	2	1	0
ICD-18 colon	1935	71	54	7	560	275	4	10	293	240	58	76	34	16	2	32	18	12	3	220	0	12	0	30	45	2	0
ICD-19 rectosigmoid junction	220	9	7	0	61	42	0	3	28	30	8	4	3	4	0	3	3	1	0	20	0	3	0	5	6	0	0
ICD-20 rectum	824	43	19	2	221	117	6	3	114	119	25	26	15	3	0	21	7	3	1	95	0	7	0	11	18	1	1
ICD-21 Anus and anal canal	54	2	1	0	14	8	0	0	4	4	4	2	1	0	0	0	0	2	0	9	0	1	0	1	2	1	0
ICD-22 liver and intrahepatic bile ducts	260	9	7	1	66	36	0	0	35	31	13	11	3	3	0	6	1	2	2	32	1	6	0	5	6	0	0
ICD-23 gallbladder	24	1	0	0	9	4	0	0	3	6	0	1	0	2	0	0	0	0	0	1	0	0	0	0	1	0	0
ICD-24 other and unspecified parts of biliary tract	63	1	1	0	13	8	0	0	11	14	3	2	1	1	0	1	0	1	0	6	0	0	0	1	3	0	0
ICD-25 Pancreas	434	19	16	3	108	63	0	4	60	47	14	26	5	4	2	5	6	3	0	53	0	2	0	4	14	0	0
ICD-26 other and ill-defined digestive organs	20	1	2	0	3	3	0	0	3	4	1	0	1	0	0	0	0	0	0	1	0	0	0	1	1	0	0

Table 5 - Corrected p-values (Benjamini-Hochberg test) for associations between occupational exposures and digestive cancers

	ICD-15	ICD-16	ICD-17	ICD-18-19-20	ICD-21	ICD-22	ICD-23-24	ICD-25	ICD-26	ICD-15-26
Vegetables, flowers	2.52E-01	6.53E-01	0.998	0.791555556	0.998	0.998	0.998	0.984	0.999	0.788666667
Fruit trees	9.95E-01	9.64E-01	0.998	0.791555556	0.998	0.998	0.998	0.972	0.999	0.1235
Plant nursery	9.95E-01	9.64E-01		0.462222222		0.998		0.984		0.537333333
Cereal	9.95E-01	1.85E-02	0.998	0.496	0.998	0.998	0.998	0.984	0.999	0.02158
Winegrowing	9.31E-01	9.64E-01	0.07748	0.010972	0.998	0.998	0.998	0.972	0.999	0.0000455
Forestry	0.9308	0.964		0.182866667						0.432545455
Other specialized crops	0.51025	0.65288889		0.889473684		0.972				0.432545455
Dairy cattle farmers	5.10E-01	5.10E-01	0.998	0.481	0.7605	0.998	0.998	0.972	0.999	0.2496
Beef farmers	9.31E-01	5.10E-01	0.875333333	0.902	0.998	0.998	0.13754	0.972	0.999	0.869916667
Mixed dairy and beef	9.95E-01	9.64E-01	0.998	0.4732	0.7605	0.998	0.998	0.984	0.999	0.87
Sheep and goat	9.31E-01	5.10E-01	0.875333333	0.434571429	0.998	0.998	0.998	0.972		0.432545455
Pigs	9.31E-01	9.64E-01		0.434571429	0.998	0.998	0.998	0.984	0.999	0.2496
Horses	2.52E-01	9.53E-01	0.875333333	0.23595		0.998	0.5668	0.984		0.865913043
Other big animals	0.25168		0.434571429		0.972					0.537333333
Poultry and rabbits	2.52E-01	7.25E-01	0.998	0.902		0.998	0.998	0.972		0.437666667
Other small animals		9.64E-01	0.998	0.902		0.998		0.984		0.87
Horse riding club	9.31E-01	9.64E-01	0.998	0.7176	0.4251	0.998	0.998	0.984		0.537333333
Shellfish		0.964		0.599857143		0.998				0.432545455
Mixed crops and breeding	9.95E-01	9.64E-01	0.875333333	0.182866667	0.998	0.998	0.998	0.984	0.999	0.068986667
Salt marshes	0.25168		0.2977							0.6682
Wood working	0.995	0.65288889		0.902	0.998	0.2977		0.984		0.537333333
Sawmill	0.51025									0.537333333
Agricultural company	0.768444444	0.65288889		0.462222222	0.998	0.998	0.998	0.974	0.999	0.587052632
Landscaping	9.95E-01	9.64E-01	0.998	0.902	0.998	0.998	0.998	0.984	0.999	0.865913043
Insurance agents		0.5564	0.10647	0.791555556	0.11596					0.537333333
Rural artisans				0.481						0.432545455

Table 6 - Non-corrected p-values for associations between occupational exposures and digestive cancers

	ICD-15	ICD-16	ICD-17	ICD-18-19-20	ICD-21	ICD-22	ICD-23-24	ICD-25	ICD-26	ICD-15-26
Vegetables, flowers	4.84E-02	0.192	0.839	0.548	0.873	0.63	0.428	0.688	0.834	0.637
Fruit trees	6.66E-01	0.764	0.469	0.529	0.755	0.998	0.438	0.132	0.0479	0.019
Plant nursery	6.63E-01	0.855		0.16		0.726		0.667		0.372
Cereal	8.28E-01	0.00071	0.577	0.248	0.924	0.518	0.575	0.809	0.317	0.00166
Winegrowing	4.95E-01	0.822	0.00298	0.000422	0.628	0.429	0.699	0.17	0.751	0.00000175
Forestry	0.46	0.59		0.0211						0.152
Other specialized crops	0.13	0.226		0.65		0.257		0.154		
Dairy cattle farmers	1.57E-01	0.0785	0.721	0.209	0.0971	0.54	0.904	0.241	0.875	0.0492
Beef farmers	5.37E-01	0.0427	0.169	0.706	0.262	0.664	0.00529	0.267	0.318	0.803
Mixed dairy and beef	7.57E-01	0.713	0.89	0.182	0.117	0.158	0.951	0.709	0.786	0.87
Sheep and goat	4.16E-01	0.0761	0.202	0.117	0.829	0.91	0.735	0.0914		0.178
Pigs	3.98E-01	0.701		0.0843	0.767	0.823	0.88	0.56	0.248	0.0576
Horses	1.38E-02	0.403	0.158	0.0363		0.869	0.0436	0.801		0.766
Other big animals	0.048		0.109		0.299		0.372			
Poultry and rabbits	4.51E-02	0.279	0.531	0.779		0.463	0.579	0.125		0.202
Other small animals		0.687	0.766	0.856		0.304		0.459		0.837
Horse riding club	5.35E-01	0.768	0.563	0.414	0.0327	0.938	0.6	0.84		0.279
Shellfish		0.889		0.323		0.184		0.123		
Mixed crops and breeding	8.67E-01	0.447	0.121	0.0193	0.421	0.757	0.18	0.638	0.301	0.00796
Salt marshes	0.0249		0.0229		0.514					
Wood working	0.701	0.187		0.771	0.362	0.0155		0.464		0.343
Sawmill	0.146		0.346							
Agricultural company	0.266	0.217		0.155	0.652	0.777	0.931	0.337	0.178	0.429
Landscaping	9.59E-01	0.939	0.967	0.887	0.617	0.392	0.145	0.623	0.494	0.759
Insurance agents		0.107	0.00819	0.523	0.00446		0.335			
Rural artisans		0.222		0.183						

Table 7 - Odds Ratio for associations between occupational exposures and digestive cancers

	ICD-15	ICD-16	ICD-17	ICD-18-19-20	ICD-21	ICD-22	ICD-23-24	ICD-25	ICD-26	ICD-15-26
Vegetables, flowers	1.63 [1-2.64]	0.63 [0.31-1.27]	0.89 [0.28-2.81]	1.06 [0.88-1.28]	0.89 [0.22-3.66]	0.85 [0.43-1.67]	0.57 [0.14-2.31]	1.1 [0.69-1.75]	1.24 [0.17-9.29]	1.04 [0.87-1.24]
Fruit trees	0.83 [0.37-1.89]	1.11 [0.57-2.17]	1.53 [0.48-4.87]	1.08 [0.85-1.37]	0.73 [0.1-5.29]	1 [0.46-2.17]	0.46 [0.06-3.29]	1.48 [0.89-2.48]	4.42 [1.01-19.31]	1.28 [1.04-1.58]
Plant nursery	0.64 [0.09-4.66]	1.14 [0.28-4.65]		0.61 [0.31-1.21]		0.7 [0.09-5.19]		1.29 [0.4-4.11]		0.78 [0.45-1.35]
Cereal	0.97 [0.73-1.28]	0.6 [0.45-0.81]	0.86 [0.5-1.48]	0.95 [0.87-1.04]	1.03 [0.54-1.95]	0.9 [0.67-1.23]	0.86 [0.52-1.44]	0.97 [0.77-1.23]	0.52 [0.14-1.87]	0.87 [0.8-0.95]
Winegrowing	0.87 [0.6-1.28]	1.04 [0.74-1.46]	2.19 [1.31-3.67]	1.21 [1.09-1.35]	1.21 [0.57-2.57]	1.16 [0.81-1.66]	1.13 [0.61-2.08]	1.21 [0.92-1.59]	1.22 [0.36-4.2]	1.28 [1.16-1.42]
Forestry	2.1 [0.29-15.02]	1.72 [0.24-12.26]		2.09 [1.12-3.9]			1.62 [0.84-3.12]			
Other specialized crops	2.42 [0.77-7.57]	2.02 [0.65-6.33]		1.13 [0.67-1.9]			1.8 [0.65-5.01]		1.37 [0.89-2.11]	
Dairy cattle farmers	0.78 [0.55-1.1]	1.3 [0.97-1.73]	0.9 [0.49-1.63]	0.93 [0.84-1.04]	0.42 [0.15-1.17]	0.89 [0.62-1.29]	1.04 [0.58-1.85]	0.85 [0.64-1.12]	0.91 [0.26-3.15]	0.91 [0.82-1]
Beef farmers	0.89 [0.62-1.28]	1.37 [1.01-1.85]	1.48 [0.85-2.6]	1.02 [0.91-1.14]	0.56 [0.2-1.55]	0.92 [0.62-1.35]	2.05 [1.24-3.38]	0.84 [0.62-1.14]	1.75 [0.58-5.27]	1.01 [0.91-1.13]
Mixed dairy and beef	1.1 [0.61-1.97]	1.12 [0.62-1.99]	0.92 [0.29-2.93]	0.86 [0.69-1.07]	2.27 [0.81-6.34]	1.51 [0.85-2.66]	0.96 [0.3-3.06]	0.9 [0.53-1.55]	1.32 [0.18-9.98]	0.98 [0.82-1.19]
Sheep and goat	0.76 [0.39-1.48]	1.53 [0.96-2.44]	0.28 [0.04-1.99]	0.85 [0.69-1.04]	0.86 [0.21-3.52]	1.04 [0.56-1.92]	0.82 [0.26-2.6]	1.42 [0.95-2.13]		0.88 [0.73-1.06]
Pigs	1.42 [0.63-3.21]	1.19 [0.49-2.89]		1.29 [0.97-1.72]	1.35 [0.19-9.84]	0.88 [0.28-2.77]	0.86 [0.12-6.2]	0.77 [0.31-1.87]	3.32 [0.43-25.37]	1.29 [0.99-1.67]
Horses	2.64 [1.22-5.73]	0.55 [0.14-2.23]	2.77 [0.67-11.38]	0.62 [0.39-0.97]		1.1 [0.35-3.51]	3.32 [1.04-10.61]	0.88 [0.33-2.38]		0.95 [0.66-1.35]
Other big animals	4.24 [1.01-17.73]		0.29 [0.07-1.31]				2.16 [0.5-9.3]		0.6 [0.19-1.86]	
Poultry and rabbits	1.92 [1.01-3.63]	1.45 [0.74-2.82]	0.53 [0.07-3.84]	0.96 [0.73-1.26]		1.36 [0.6-3.08]	0.57 [0.08-4.13]	0.5 [0.2-1.21]		0.84 [0.65-1.1]
Other small animals		1.23 [0.45-3.33]	1.35 [0.19-9.84]	1.04 [0.7-1.53]		0.35 [0.05-2.57]		1.37 [0.6-3.13]		0.96 [0.66-1.4]
Horse riding club	0.54 [0.07-3.84]	0.81 [0.2-3.28]	1.79 [0.25-13.04]	0.81 [0.49-1.34]	4.78 [1.14-20.11]	1.06 [0.26-4.34]	1.7 [0.23-12.33]	0.89 [0.28-2.8]		0.77 [0.49-1.23]
Shellfish		1.15 [0.16-8.33]		0.6 [0.22-1.65]		2.71 [0.62-11.79]		0.41 [0.13-1.27]		
Mixed crops and breeding	1.03 [0.73-1.45]	0.87 [0.61-1.24]	0.52 [0.23-1.19]	0.87 [0.77-0.98]	1.34 [0.65-2.75]	0.94 [0.64-1.38]	0.59 [0.27-1.28]	0.93 [0.7-1.25]	0.35 [0.05-2.59]	0.86 [0.77-0.96]
Salt marshes	9.59 [1.33-69.17]					9.91 [1.37-71.53]		1.59 [0.4-6.41]		
Wood working	0.76 [0.19-3.08]	1.82 [0.75-4.44]		1.07 [0.69-1.64]	2.54 [0.34-18.81]	2.78 [1.21-6.35]		0.59 [0.15-2.4]		1.19 [0.83-1.71]
Sawmill	4.31 [0.6-30.88]						0.39 [0.05-2.77]			
Agricultural company	0.45 [0.11-1.83]	0.41 [0.1-1.68]		1.26 [0.92-1.73]	1.58 [0.22-11.55]	1.14 [0.45-2.88]	0.92 [0.13-6.64]	0.61 [0.22-1.68]	4.07 [0.53-31.34]	1.13 [0.83-1.54]
Landscaping	0.98 [0.47-2.03]	1.03 [0.53-1.97]	0.97 [0.23-4.06]	1.02 [0.79-1.31]	1.45 [0.34-6.31]	0.69 [0.3-1.61]	2.17 [0.77-6.17]	1.15 [0.66-2.01]	2.07 [0.26-16.6]	1.04 [0.83-1.29]
Insurance agents		5.06 [0.7-36.33]	14.75 [2.01-108.38]	1.45 [0.46-4.52]	18.37 [2.47-136.58]		1.62 [0.61-4.36]			
Rural artisans		0.29 [0.04-2.1]					0.26 [0.04-1.88]			

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THÈSE SOUTENUE PAR : Baptiste VESPER GUILLON

TITRE :

Evaluation du risque de cancers digestifs selon l'exposition professionnelle chez les agriculteurs français, d'après les données médico-administratives de la Mutualité Sociale Agricole (MSA)

CONCLUSION :

Les travailleurs agricoles ont un plus faible risque de cancer digestif. Il s'agit pourtant d'une population fréquemment exposée à des agents cancérigènes, avec des variabilités d'exposition au sein des différentes activités agricoles. Le but de cette étude était d'évaluer le risque de cancer digestif en fonction de l'exposition professionnelle chez les agriculteurs français.

L'ensemble des exploitants agricoles ayant cotisé au moins une fois à la MSA entre 2006 et 2016 a été étudié. Les déclarations de cancers digestifs en ALD 30, au sein de cette population, ont été relevées de 2012 à 2016, en précisant le sous-type de cancer selon la classification CIM-10. A l'aide de modèles logistiques, les associations entre déclaration de cancers digestifs et activités agricoles ont été étudiées et exprimées sous forme d'Odds Ratio.

Sur les 899 212 exploitants agricoles étudiés, 4438 cancers digestifs ont été déclarés. Le risque de cancer digestif était augmenté chez les viticulteurs (OR = 1.28 [95% CI 1.16-1.42]), principalement lié à une augmentation du risque de cancer colorectal (OR = 1.21 [95% CI 1.09-1.35]). Une augmentation du risque de cancer du grêle a également été mise en évidence mais de significativité statistique limite (OR = 2.19 [95% CI 1.31-3.67]). Par ailleurs, une diminution du risque de cancer digestif a été retrouvée chez les producteurs céréaliers (OR = 0.87 [95% CI 0.8-0.95]), sous-tendue par une diminution de risque de cancer de l'estomac (OR = 0.6 [95% CI 0.45-0.81]).

Nos résultats montrent une augmentation de risque de déclaration de cancer digestif et principalement de cancer colorectal chez les viticulteurs français.

VU ET PERMIS D'IMPRIMER

Grenoble, le :

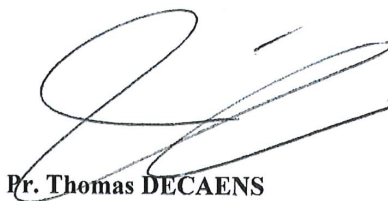
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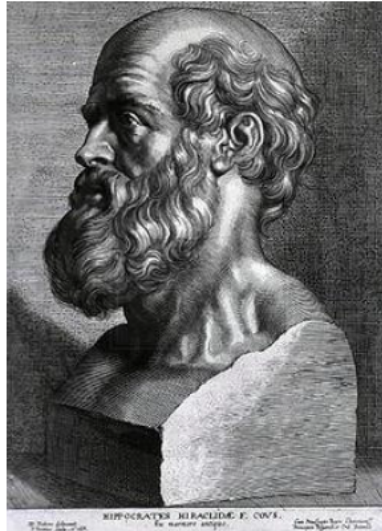


Pr. Patrice MORAND
Pour le Président
et par délégation
Le Doyen de Médecine
Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE



Pr. Thomas DECAENS



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.