International Journal of Occupational Medicine and Environmental Health, Vol. 14, No. 4, 339—348, 2001

CANCER RISK AMONG MALE FARMERS: A MULTI-SITE CASE-CONTROL STUDY

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Abstract. Farmers may experience exposure to several hazardous substances, and cancer risk in this occupational group is considered an important public health issue.
In order to examine the association between cancer and farming among male agricultural workers, a hospital-based case -control study was conducted in five Italian rural areas. The cancer sites selected for the study were: lip, oral cavity and oropharynx, oesophagus, stomach, colon, rectum, lung, skin melanoma, skin non-melanoma, prostate, bladder, kidney, and non-Hodgkin's lymphoma. In all, 1525 newly diagnosed cases, aged 20–75 years, were ascertained in hospital records, covering the period between March 1990 and September 1992, and for 1279 of them, a detailed exposure information was collected by a standard questionnaire. Data analyses were performed comparing each cancer site to a control group, including a subset of the other cancer sites in the study. Unconditional logistic regression models were used in the statistical analyses.
Increased risks of cancer associated with agricultural work were found for stomach (OR = 1.4, 95%CI:0.9–2.0), rectum (OR = 1.5, 95%CI:0.8–2.7), larynx (OR = 1.4, 95%CI:0.8–2.5), and prostate (OR = 1.4, 95%CI:1.0–2.1). The excess of prostate cancer was specifically related to application of pesticides (OR = 1.7, 95%CI:1.2–2.6).

Key words:
Case-control study, Male farmers, Crop grown, Pesticides, Cancer of prostate, stomach, rectum and larynx

INTRODUCTION

Agricultural activities may entail exposure to several hazardous substances, including pesticides. Some pesticides appear to be mutagenic in laboratory tests [1,2], and cytogenetic effects have been reported among exposed workers [3,4]. Furthermore, experimental studies have shown that different types of pesticides are able to exert immunotoxic effects [5], suggesting that such mechanisms may contribute to carcinogenic risks [6,7].

In spite of these potential hazards, male farmers and farm workers have usually been characterized by lower than expected incidence and mortality rates for all cancers, as well as for cancer of the oesophagus, colon, rectum, liver, lung, and kidney [8,9]. Increased risks for selected types of cancer, particularly some hematopoietic tumors, have been consistently reported in several studies [10,11]. The pattern of exposure to pesticides varies greatly among farmers and farm workers, therefore these groups of workers might be at different carcinogenic risks, if any. These circumstances may perhaps explain some exceptional observations on an excess of cancer of the lung [12–14], kidney [15], pan-

This work was partially supported by the Italian Ministry of Work, and the Italian National Research Council.
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creas [16], rectum [17], larynx [18], and bladder [19,20].

In the present case-control study, the association between farming among males and different types of cancer was evaluated, taking also account of different crops grown as a surogate of exposure.

METHODS

Study design and subjects

The study was carried out on men, aged 20–75 years, living in five areas with at least 10% of the occupationally active male population employed in farming, according to the 1971 and 1981 Italian Census. These areas included Asti in the Piedmont region, Pescia, Pistoia, and Grosseto in the Tuscany region, and Imola in the Emilia-Romagna region.

Cancer sites selected for the study included: lip, oral cavity and oropharynx, stomach, colon, rectum, larynx, lung, skin melanoma, skin non-melanoma, prostate, bladder, kidney, and non-Hodgkin's lymphoma (Table 1). Cases of the cancers diagnosed between March 1, 1990 and September 1, 1992, were identified through five district hospitals and three university hospitals, located in Turin, Pisa, and Siena. Histological confirmation was also required.

For each single cancer type, the control group consisted of the other cancers under study, excluding cancers that were anatomically contiguous (cancer of colon and rectum, and vice versa), arising from the same site (skin melanoma and skin non-melanoma), or sharing known etiologic factors (cancer of bladder was excluded from the reference group of lung cancer). Rectosigmoid subsites, including sigmoid colon and rectosigmoid junction (topography code 153.3 and 154.0, according to the 9th Revision of the International Classification of Diseases (ICD-9)) were excluded from the colon cancer and rectum cancer case series, respectively (Table 2). Lung cancer was excluded from all the control groups in order to avoid residual confounding due to the strength of the

Table 1. Number of cases ascertained and interviews performed for each site of cancer under study

Cancer site	Topography code (ICD-9)	No. of cases ascertained	No. of interviews	
			Direct (%)	Indirect (%)
Lip, oral cavity, oropharynx	140–141, 143–149	53	28 (70.0)	12 (30.0)
Stomach	151	140	88 (73.3)	32 (26.7)
Colon	153, except 153.3	120	86 (78.9)	23 (21.1)
Rectum	154, except 154.0	62	44 (83.0)	9 (17.0)
Larynx	161	73	45 (76.3)	14 (23.7)
Lung	162	252	137 (69.9)	59 (30.1)
Skin melanoma	172	25	21 (87.5)	3 (12.5)
Skin non-melanoma	173	348	249 (84.1)	47 (15.9)
Prostate	185	156	123 (87.9)	17 (12.1)
Bladder	188	182	136 (80.0)	34 (20.0)
Kidney	189.0, 189.1	48	31 (79.5)	8 (20.5)
Non-Hodgkin's lymphoma	200, 202	39	28 (84.8)	5 (15.2)

Table 2. Cancers analysed, sites excluded from each reference series, and variables included in the logistic regression models

Cancer site	Cancer sites excluded from the reference series	Variables in the model
Lip, oral cavity, oropharynx	Lung, larynx	Age, smoking habit, alcohol consumption, interview
Stomach	Lung	Education level, family history of stomach cancer, construction industry, place of residence (urban\rural)
Colon	Lung, rectum	Quetelet's index
Rectum	Lung, colon	Age, alcohol consumption
Larynx	Lung, lip, oral cavity, oropharynx,	Smoking habit, family history of cancer, textile industry
Lung	Larynx, bladder	Smoking habit, interview, construction industry, chemical industry, education level, place of residence (urban\rural)
Skin melanoma	Lung, skin non melanoma	Age, family history of skin melanoma
Skin non-melanoma	Lung, skin melanoma	Age
Prostate	Lung	Age, place of residence (urban/rural)
Bladder	Lung, kidney	Age, smoking habit
Kidney	Lung, bladder	Quetelet's index
Non-Hodgkin's lymphoma	Lung	–

association between this type of cancer and smoking. Furthermore, a sub-sampling procedure was applied in order to ensure that none of the single cancer sites constituted more than 20% of any control group.

Data collection

Trained personnel conducted questionnaire-based interviews with subjects, or with their next-of-kin. The questionnaire was designed to obtain information on socio-demographic characteristics, each job ever held, tobacco smoking, alcohol consumption, family history of cancer, and diet. For the subjects engaged in agricultural work, information on use of pesticides and protective equipment was collected, as well as the substantial characteristics of each farm where respondents were employed. Furthermore, 10 specific forms were included in the questionnaire in order to obtain details on each crop ever grown by individual subjects, with reference to historical periods, average acreage, crop diseases for which pesticides were applied, and tasks performed.

Response rates

We considered eligible for the study 1525 subjects with newly diagnosed cancer. For 1279 (85%) of them informed consent to participate in the study was obtained. In all, 1016 (79%) subjets were interviewed directly, and indirect interviews were conducted for 263 (21%) deceased or subjets unable to respond (Table 1).

Data analysis

The associations between different cancer sites, the job title of farmer and farm worker (if held for at least one year, and at least 15 years before the diagnosis of cancer), and farm-related factors were measured by maximum likelihood estimation of the odds ratio (OR). For each cancer site under study, an initial unconditional logistic model included known or suspected risk factors whose univariate test had a p value $\leq$0.25. These variables were subsequently removed if unable to change more than 10% of the coefficient for the independent variable of interest or to improve the log likelihood function.

Table 3 lists the variables considered as potential confounders and shows their stratification. Associations were estimated for three periods of employment in agriculture (1–5 years; 6–15 years; and 16 or more years). All ORs for farm-related factors were calculated considering as unexposed those persons who were not farmers and who had no contact with pesticides. The analyses were performed using the BMDP or STATA programs [21,22].

RESULTS

Table 4 shows the estimated risks for each cancer site under study in farmers. Ever being engaged in agricultural activities was associated with non-significant or borderline increase in cancer of the stomach (OR = 1.4, 95%CI:0.9–2.0), rectum (OR = 1.5, 95%CI:0.8–2.7), larynx (OR = 1.4, 95%CI:0.8–2.5), and prostate (OR = 1.4, 95%CI:1.0–2.1). The OR for lung cancer was close to unity. Risk estimates for stomach and larynx cancer showed a tendency to increase with duration of employment in agriculture, while risk estimates for lung cancer suggested a negative association. However, none of the observed trends was statistically significant.

As shown in Table 5, direct application of pesticides was associated with an increased risk for prostate cancer (OR = 1.7, 95%CI:1.2–2.6). The risk estimates for this type of cancer increased with number of years spent mixing and applying pesticides (p-value for trend = 0.003). A statistically non-significant stomach cancer excess was observed among those farmers and farm workers who had applied pesticides for at least 16 years (OR = 1.3, 95%CI:0.8–2.1) but also among those who had never been involved in such an activity (OR = 1.5, 95%CI:0.8–2.6). Similar results were obtained for rectal and laryngeal cancer (Table 5). Based on four exposed subjects, larynx cancer showed a particularly high risk for farmers aged at the time of diagnosis below 60 years and who had applied pesticides for 16 years or more (OR = 4.8, 95%CI:1.2–18.7).

The analyses by type of crops grown were limited to the crops reported in the questionnaire by at least 20% of the subjects with a previous history of farming. Since the majority of farmers grew both wheat and grapes, these crops were analyzed together. As shown in Table 6, a statistically nonsignificant increase in rectal cancer was found in farmers and farm workers growing wheat and grape (OR = 1.8, 95%CI:0.9–3.6), and vegetables (OR = 1.6, 95%CI:0.7–3.8). Stomach cancer was significantly associated with olive farming (OR = 2.0, 95%CI:1.2–3.3) and this type of cancer also showed slight increase in fruit growing (OR=1.3, 95%CI:0.7–2.4). Among fruit growers risk of prostate cancer was significantly increased (OR = 2.0, 95%CI:1.2–3.5).

Table 3. Variables considered as potential confounders

Variables	Categories
Age	Less than 60 yrs; 60 yrs or more
Quetelet's index	Less than 30 yrs; 30 yrs or more
Education level	Primary school; other
Marital status	Married; single
Interviews	Direct; indirect
Tobacco smoking:	
cigarette/day	For lung and bladder cancer the categories were defined according to the mean number of cigarettes smoked/day i.e. none; 1–19; 20 or more
Smoking habit	Nonsmokers; smokers
Place of residence	Urban; rural
Alcohol consumption	Less than 80 g/day; 80 g/day or more
Family history of cancer	Yes; no
Non - agricultural occupations	Any industrial activity held for at least one year and undertaken at least 15 years before cancer diagnosis
Diet :	
vegetables	Three or more times per week; less than three times per week
fruits	
cured meat	

Table 4. Risk estimates (OR) for different sites of cancer in farmers*

Cancer site	No. of cases (% in farming)	No. of referents (% in farming)	Length of employment (yrs)							
			Ever employed		1–5		6–15		≥16	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Lip, oral cavity, oropharynx	40 (35,0)	911 (38.6)	0.9	0.4–1.8	1.1	0.3–4.1	–	–	1.0	0.5–2.3
Stomach	119 (46.2)	899 (38.6)	1.4	0.9–2.0	0.9	0.3–3.1	1.2	0.6–2.3	1.5	1.0–2.3
Colon	109 (33.9)	859 (40.1)	0.8	0.5–1.2	0.4	0.1–1.4	0.9	0.4–2.0	0.8	0.5–1.2
Rectum	53 (50.9)	860 (40.5)	1.5	0.8–2.7	1.8	0.6–4.9	1.9	0.8–4.5	1.4	0.8–2.7
Larynx	59 (45.8)	909 (39.7)	1.4	0.8–2.5	0.9	01–7.4	1.1	0.4–2.9	1.6	0.9–2.9
Lung	196 (42.3)	833 (41.3)	1.1	0.8–1.7	1.6	0.7–4.1	1.1	0.6–1.9	1.0	0.6–1.4
Skin melanoma	24 (40.2)	824 (40.2)	1.1	0.5–2.5	-	–	1.1	0.2–4.9	1.1	0.4–2.9
Skin non-melanoma	296 (40.3)	823 (40.2)	0.9	0.6–1.1	1.8	0.8–3.9	0.9	0.5–1.5	0.8	0.6–1.1
Prostate	140 (48.6)	897 (38.7)	1.4	1.0–2.1	1.4	0.4–4.9	1.3	0.6–2.5	1.5	1.0–2.1
Bladder	170 (31.2)	816 (41.9)	0.8	0.5–1.2	0.7	0.2–2.5	0.6	0.2–1.2	1.0	0.9–2.1
Kidney	39 (46.1)	816 (41.2)	1.2	0.6–2.3	–	–	0.9	0.3–3.0	1.3	0.7–2.8
Non-Hodgkin's lymphoma	33 (30.3)	1003 (40.6)	0.6	0.3–1.3	–	–	0.9	0.3–3.3	0.5	0.2–1.2

* All ORs relative to risk for subjects who have never been farmers and never applied pesticides.

DISCUSSION

In the present case-control study, the influence of farming and agricultural activities on the risk of different types of cancer in men was evaluated. The main finding is an increased risk of prostate cancer in association with farming and application of pesticides. A farming-related excess of prostate cancer has been reported in several studies [10,17,23–29]. An increased risk of this type of cancer has also been observed in other groups of workers potentially exposed to pesticides, such as golf course superintendents [30], and pesticide applicators [31–33]. However, agriculture-specific exposures have rarely been considered. A Canadian study showed a relation between prostate cancer and number of acres sprayed with herbicidess [27]. Some authors have recently suggested that positive associations between prostate cancer and farming could be explained by exposure to hormonally active pesticides [29]. A recent *in vitro* study showed that different pesticides, including β-hexa-chlorocyclohexane, o,p-dichlorodiphenyltrichloroethane, heptachlor epoxide, trans-permethrin, and chlorotalonil, are able to induce progression of prostate cancer cells by activating protein tyrosine kinase [34]. This study showed an excess of prostate cancer especially among farmers who applied pesticides and among fruit growers. According to crop-exposure matrices, available for the areas under study [35], herbicides were applied once a year on all crops, and fruit growing was characterized by more frequent use of insecticides

Table 5. Risk estimates (OR) for different sites of cancer in farmers mixing and applying pesticides*

Cancer site	Employment in mixing and applying of pesticides											
	Never			≤15			≤16			Ever		
	No. of cases	OR	95%CI	No. of cases	OR	95%CI	No. of cases	OR	95%CI	No. of cases	OR	95%CI
Lip, oral cavity, oropharynx	3	1.0	0.3–3.0	1	0.6	0.1–4.6	8	1.2	0.5–2.8	9	0.9	0.4–2.0
Stomach	13	1.5	0.8–2.6	5	0.7	0.3–1.9	29	1.3	0.8–2.1	34	1.2	0.8–1.9
Colon	4	0.4	0.2–1.3	6	1.0	0.4–2.7	21	0.8	0.5–1.4	27	0.9	0.5–1.4
Rectum	5	1.3	0.5–2.9	5	1.8	0.6–5.1	15	1.5	0.8–2.9	20	1.6	0.8–2.9
Larynx	5	1.2	0.4–3.4	2	0.9	0.2–4.0	14	1.6	0.8–3.2	16	1.5	0.8–2.9
Lung	21	1.4	0.8–2.2	13	1.1	0.6–2.3	34	0.9	0.6–1.3	48	0.9	0.6–1.4
Skin melanoma	2	0.9	0.2–3.9	–			6	1.2	0.4–3.2	6	1.0	0.4–2.7
Skin non-melanoma	19	1.0	0.6–1.5	23	1.5	0.9–2.6	52	0.7	0.5–1.0	81	0.9	0.6–1.2
Prostate	11	1.1	0.5–2.2	7	1.3	0.5–2.9	44	1.9	1.2–2.9	51	1.7	1.2–2.6
Bladder	11	0.9	0.4–1.8	5	0.6	0.3–1.7	29	0.8	0.5–1.4	36	0.8	0.5–1.4
Kidney	4	1.0	0.3–3.4	1	0.4	0.1–3.3	11	1.3	0.6–2.9	13	1.1	0.5–2.3
Non - Hodgkin's lymphoma	4	0.9	0.3–2.7	2	1.0	0.2–4.3	4	0.4	0.1–1.3	6	0.5	0.2–1.3

* All ORs relative to risk for subjects who have never been farmers and never applied pesticides.

Table 6. Risk estimates (OR) for different cancer sites by the type of crops grown*

Cancer site	Crops grown											
	Wheat and grapes			Vegetables			Olives			Fruits		
	No. of exposed subjects	OR	95% CI	No. of exposed subjects	OR	95% CI	No. of exposed subjects	OR	95% CI	No. of exposed subjects	OR	95% CI
Lip, oral cavity, oropharynx	10	0.7	0.3–1.6	4	1.2	0.4–3.4	4	0.9	0.3–2.7	2	0.4	0.1–1.9
Stomach**	42	0.9	0.6–1.5	10	0.9	0.4–1.7	22	2.0	1.2–3.3	15	1.3	0.7–2.4
Colon	26	0.7	0.5–1.1	11	1.4	0.7–2.7	9	0.7	0.3–1.4	9	0.7	0.3–1.4
Rectum**	23	1.8	0.9–3.6	8	1.6	0.7–3.8	7	0.7	0.3–1.9	5	0.8	0.3–2.0
Larynx	15	0.9	0.5–1.7	5	0.9	0.4–2.5	15	1.0	0.4–2.5	6	1.0	0.4–2.5
Lung	65	1.2	0.8–1.7	19	1.2	0.6–2.1	19	0.8	0.4–1.4	18	0.9	0.5–1.5
Skin melanoma	8	1.3	0.5 - 3.1	–			3	1.3	0.4–4.0	4	0.3	0.1–0.7
Skin non-melanoma	83	0.9	0.6–1.2	27	1.0	0.6–1.6	37	1.2	0.8–1.8	26	0.7	0.5–1.2
Prostate**	61	1.2	0.8–1.9	11	0.9	0.4–1.7	20	0.9	0.5–1.6	27	2.0	1.2–3.5
Bladder	39	0.6	0.4–0.9	13	0.8	0.4–1.5	11	0.5	0.2–0.9	11	0.6	0.3–1.0
Kidney	14	0.8	0.3–2.0	1			4	0.8	0.3–2.4	8	2.1	0.8–5.3
Non-Hodgkin's lymphoma	7	0.6	0.2–1.4	3			1			2	0.5	0.1–2.1

* All ORs relative to risk for subjects who have never been farmers and never applied pesticides.
** OR adjusted by the other crops grown.

(five to eight times per year) as compared to the cultivation of other crops in question (one to five times per year). Increased risk of stomach cancer associated with agricultural occupations has been reported earlier [10,36], however, negative results have also been published [37]. In Italy, confounding by residence has been suggested to explain the cancer excess observed among farmers [38]. In the present study, an increase of 40% in risk of stomach cancer was related to the employment in agriculture, after adjustment by place of residence and other confounders. The observation that similar excess of stomach cancer was found in farmers and farm workers who applied pesticides, and in workers who had never used them, suggests that exposure to pesticides hardly represents a relevant risk factor for this disease in the areas under study. To explain this finding, it should also be considered that workers engaged in different agricultural activities could share other occupational exposures associated with gastric cancer, such as organic and inorganic dusts [39,40], combustion products [41] and fertilizers [37]. Furthermore, farming in the areas under study could be associated with exposures to non-occupational risk factors responsible for gastric cancer, such as lifestyle and dietary habits, not identified in the present study. It is worth noting, however, that a doubled risk of stomach cancer was observed in association with olive growing. In the areas under study, this type of cultivation is characterized by the use of a restricted number of pesticides. Among the pesticides used are copper compounds, widely applied to a variety of other crops, and more specifically, dimethoate, an organophosphate.

Similarly to the observations reported for stomach cancer, rectal and laryngeal cancers were increased among both agricultural pesticide users and non-users. With reference to rectal cancer, the available evidence suggests a limited role of environmental and occupational exposures in its etiology [42], and increased risks among farmers have only rarely been observed [17,43]. Long term physical work has been associated with an excess of rectal cancer and a reduction of colon cancer [42]. Considering agricultural activities as those demanding much physical effort, it is worth noting that in the present study a slightly reduced risk of colon cancer was related to farming while the opposite observation was reported for rectal cancer.

Smoking and alcohol consumption are well known and thoroughly investigated risk factors for laryngeal cancer [44]. Several occupations and occupational exposures have been positively associated with this disease, but only a limited number of studies have suggested increased risks for farmers or other groups of agricultural workers [45,46], and associated them with exposure to pesticides [47,48,49]. In the present study, both pesticide users and non-users were characterized by comparable excess of larynx cancer, but a particularly elevated risk was found in younger farmers and agricultural workers who had been involved in pesticide application for at least 16 years. This finding may deserve some attention since this result is comparable to that reported in a previous Italian study [23]. Over time changes in the use of pesticides and various agricultural practices, imply exposure to agricultural hazards in younger workers and for longer period of time. Such circumstances might help explain the observed risk.

In agreement with other studies, cancers of lung and bladder were not found to be increased in relation to agricultural activities. However, an excess of lung cancer was found in workers employed in agriculture for less than six years. Allowing in the analysis for the place of residence only partially reduced the observed increase (OR not adjusted by place of residence = 1.9; OR adjusted by place of residence = 1.6), suggesting that other factors, such as lifestyle and possible exposure to risk factors for lung cancer in subsequent occupational activities should also be considered.

A recent meta-analysis aimed at assessing cancer risk among farmers [9], pointed out that the results obtained for most cancers seemed to be a function of study design, and positive associations are more frequently reported in case-control and PMR studies in comparison to cohort studies. Furthermore, when using hospital controls, as in the present study, or deceased controls, the healthy worker effect may appear as reversed, namely as elevated risks because there is a relative lack of exposed subjects among this kind of controls as the healthy workers do not appear as cases of other diseases or deaths [50]. Considering these aspects, it

is nevertheless unlikely that the observed excess of certain cancer types in this study could be explained by the methods used. Also, recall and interviewer biases were minimized by the study design applied. In addition, a detailed information on known or suspected risk factors was collected for each cancer site, and the confounding potential was evaluated.

ACKNOWLEDGMENTS

We thank Benedetto Terracini, Paolo Boffetta, and Corrado Magnani for their contribution to the study design. We are highly indebted to Pietro Maiozzi for his support to the data management and analyses.
Thanks are also due to Alceste Masina, Alberto Andrion, Alberto Cappelli, Lucia Miligi, Lucia Bastianini, Rita Franzě, Rosanna Iannarilli, Cristiana Ivaldi, Luigi Luccoli, Letizia Sommani for their suggestions and assistance in the implementation of the study.

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Received for publication: April 9, 2001
Approved for publication: October 30, 2001