

# Cancer and Noncancer Risk to Women in Agriculture and Pest Control: The Agricultural Health Study

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*The Agricultural Health Study is a collaborative effort involving the National Cancer Institute, the US Environmental Protection Agency, and the National Institute of Environmental Health Sciences. A goal of this investigation is to establish a large cohort of men and women that can be followed prospectively for 10 years or more to evaluate the role of agricultural exposures in the development of cancer, neurologic disease, reproductive difficulties, childhood developmental problems, and other chronic diseases. The study also will provide an opportunity to assess the role that diet, cooking methods, and other lifestyle factors have on the cause of cancer and other diseases. The cohort will be composed of approximately 112,000 adult study subjects, including 42,000 women, making this one of the largest cohorts of women ever assembled for an epidemiologic investigation of environmental and occupational exposures. Children of farm families also will be enrolled. The study will be conducted in Iowa and North Carolina. Enrollment will begin in December 1993 and continue for 3 years.*

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Surveys from around the world have noted excess risks for cancer of the lip, stomach, brain, prostate, connective tissues, skin, and lymphatic and hematopoietic systems among male farmers.<sup>1-4</sup> In the few studies including women, ovarian cancer has been linked to triazine herbicides,<sup>5</sup> breast cancer with insecticides,<sup>6,7</sup> soft-tissue sarcoma with phenoxy herbicides,<sup>8</sup> and various pesticides with multiple myeloma and non-Hodgkin's lymphoma.<sup>9,10</sup>

Specific agricultural agents that might be responsible for these cancer excesses, however, have not been clearly identified. Both men and women on farms have potential exposure to pesticides, animal viruses, mycotoxins, dusts, fuels and oils, engine exhaust, and fertilizers. The strongest links to date are with pesticides,<sup>11-16</sup> although non-Hodgkin's lymphoma also has been associated with fuels.<sup>15</sup>

Agricultural workers and their families are also exposed to many agents that are potential noncancer health hazards. Foremost among these are pesticides, many of which are known to be toxic to experimental animals. Potential health effects from systemic exposure to these chemicals include acute and chronic effects on the nervous, renal, respiratory, and reproductive systems of men and women.<sup>15,17</sup>

Farm families in Iowa and North Carolina are being evaluated in a long-term prospective study to: (1) identify and quantify cancer risks among women and men and whites and minorities associated with specific direct pesticide exposures and exposures to other agricultural agents; (2) evaluate noncancer health risks (including neurotoxicity, reproductive effects,

asthma, immunologic toxicity, kidney disease, birth outcomes, and growth and development among offspring) associated with exposure to pesticides and other potential agricultural exposures; (3) evaluate disease risks among spouses and children of farmers that may arise from indirect contact with agricultural chemicals (eg, ambient air drifts; pesticide residues on rugs, furniture, and other items; and transporting chemicals) and from nonoccupational exposures (eg, applications to pets, homes, or gardens); (4) assess agricultural exposures (both occupational and nonoccupational) using periodic interviews and environmental and biologic monitoring; (5) study the relationship between agricultural exposures, the occurrence of biomarkers of exposure, biologic effect, and biomarkers of preclinical disease and genetic susceptibility factors relevant to carcinogenesis; and (6) identify and quantify cancer and other disease risks associated with lifestyle factors such as diet, cooking practices, hair dye use, and physical activity.

### Methods

The Agricultural Health Study is a collaborative study between the National Cancer Institute, the National Institute of Environmental Health Sciences, and the US Environmental Protection Agency. To be conducted in Iowa and North Carolina, it has three major components: (1) a prospective cohort study; (2) nested case-control studies; and (3) exposure assessment and biologic marker studies.

#### Prospective Cohort Study

All persons in Iowa and North Carolina who wish to apply restricted-use pesticides must obtain pesticide applicator licenses through their state's Cooperative Extension Service or Department of Agriculture. There are two licensing categories: (1) private (eg, farmers, estimated to be 70% of licensed applicators); and (2) commercial (applicators used by pest-control companies and by businesses that use pesticides but whose primary functions are not pesticide application, eg, grain millers and warehouse operators).

We estimate that 75,000 applicators can be assembled over the 3-year cycle. Among farmer applicators and the 22,500 commercial applicators, approximately 6,000 applicators will be women, making this one of the largest cohorts of women occupationally exposed to pesticides ever assembled. For farmers, we also will enroll their spouses ( $n = 37,000$ ) and obtain information about their children.

A prospective approach provides the opportunity to evaluate many disease outcomes and to assess agricultural and other exposures periodically using a combination of methods, including questionnaires and ambient air monitoring, dermal deposition, contaminants in drinking water, and assays of biologic fluids and tissues or tissue levels. Periodic assessment of exposures before development of disease should improve recall and reduce nondifferential misclassification. Determining exposure before onset of disease will eliminate case-recall bias, thereby greatly enhancing the ability to make accurate links between environmental exposures and disease.

All pesticide applicators will be asked to complete a brief enrollment questionnaire at the licensing facility. This optically scannable questionnaire seeks identifying information as well as a brief history of pesticide use, crops and livestock grown (farm applicators only), smoking and alcohol consumption, and medical conditions. In addition, applicators will be given three take-home, optically scannable questionnaires. The applicator's questionnaire will seek detailed information on pesticide exposures, work practices, previous occupations, diet and cooking practices, other lifestyle factors, and selected health outcomes. A second questionnaire, the spouse questionnaire, will be given to farmers for completion by their spouses. This questionnaire will obtain necessary identifying information as well as details of pesticide exposures by the farmer's spouse. A third questionnaire for female applicators and spouses of male farmers, the female and family health questionnaire, will obtain information on reproductive histories and information on children.

The cohort will be linked annually with the National Death Index and state cancer registries to obtain information on mortality and cancer incidence. The health information on selected noncancer outcomes (ie, renal, neurologic, reproductive, developmental, and immunologic end points) obtained from questionnaires of applicators and their families will be compared with that of a national sample of the US population (eg, using data from the National Health and Nutrition Examination Survey). Incidence and prevalence of diseases and symptoms will be contrasted between persons exposed and unexposed to various factors of interest. Cross-sectional data will be used to identify groups for studies of special health end points (eg, childhood development, attention-deficit disorder, and childhood asthma) that could be conducted later.

#### Nested Case-Control Studies

During the course of the study, a series of nested case-control studies on a variety of diseases is anticipated. Initial plans call for case-control studies of non-Hodgkin's lymphoma, leukemia, and cancers of the prostate, brain, ovary, breast, lung, colon, and stomach. Control subjects will be selected from healthy cohort members. All patients and control subjects will receive an additional disease-specific questionnaire that will obtain information on etiologic issues not covered in the initial applicator and spouse questionnaires. Patients and control subjects will be asked to provide a peripheral blood sample to be analyzed for genetic susceptibility biomarkers to explore the interaction of exogenous exposures and genetic risk. Tumor tissue will be obtained from all patients for pathologic review.

#### Exposure Assessment Study

Exposure will be directly assessed by environmental and biologic monitoring for a sample of the cohort (approximately 200 families). Integrating monitoring and questionnaire data will make it possible to more effectively rank order cohort members by relative levels of exposure and to val-

idate questionnaire data on exposure. In addition, a subpopulation of the cohort with exposure to a specific pesticide will be extensively studied to link exposure information with biomarkers of internal dose, target dose, and biologic effect.

#### Advisory Groups

An ad hoc advisory panel composed of members of the National Cancer Institute's Division of Cancer Etiology Board of Scientific Counselors, other scientists, and farmers has been assembled to provide advice and oversight regarding the project to the collaborating agencies. The advisory panel will meet periodically to review study protocols, evaluate progress, and comment on analyses and reports. In addition, expert panels also have been established in Iowa and North Carolina using representatives from the state Department of Agriculture and Cooperative Extension Service. These expert panels provide insight on specific state agricultural issues and act as liaisons to state agencies.

#### Study Power

The total number of cancer cases by gender and anatomic site are shown in Table 1 for 5 and 10 years of follow-up, assuming no excess risk of cancer. After 10 years of follow-up, 1283 women with cancer (female pesticide applicators and female spouses) are expected, including 571 with breast cancer, 94 with lung cancer, 70 with colon and rectum cancer, and 66 with ovarian cancer.

This cohort will be exposed to a variety of pesticides and other agricultural substances. The portion of the cohort exposed to any particular agent, therefore, will vary considerably. For common exposures (defined here as 40% or more exposed), the study will be able to detect an approximate twofold excess risk for breast, lung, colon and rectum, ovarian, and non-Hodgkin's lymphoma after 5 years of follow-up. For less common exposures or less common cancers, a longer follow-up period will be necessary to identify risks of this magnitude with adequate power.

For common pesticide exposures, the study will be able to detect an

approximate twofold excess risk for prematurity, low birth weight (<2500 g), developmental delays, and attention-deficit hyperactivity disorders after 5 years of follow-up. For extreme low birth weight (<1500 g), a longer follow-up period will be necessary to identify risk at this level.

Excess neurologic symptoms and Parkinson's disease can be detected at a twofold excess risk after 5 years of follow-up in this cohort for common exposures. After 10 years of follow-up, excess Alzheimer's disease will be detectable at a relative risk of 1.9, and excess amyotrophic lateral sclerosis will be detectable at a relative risk of 2.6.

#### Discussion

The Agricultural Health Study should prove to be a landmark investigation of the role of pesticides in the cause of cancer and noncancer diseases in an important segment of the US population. Because of the size of the cohort and the large number of women included in the study, it will be possible to address important women's health issues in the first 5

TABLE 1  
Expected Numbers of Cancers for 5 Years\* and 10 Years† of Follow-Up

Cancers of Research Interest	Male Applicators (n = 68,475)			Female Applicators (n = 6,525)			Female Spouse (n = 37,012)			Total Adult Cohort (n = 112,012)	
	1-5 y	6-10 y	Total in 10 y	1-5 y	6-10 y	Total in 10 y	1-5 y	6-10 y	Total in 10 y	5 y	10 y
	Lung	39	159	198	3	11	14	16	64	80	58
Breast	1	3	4	25	61	86	140	345	485	166	575
Colon/rectum	25	100	125	3	8	11	13	46	59	41	195
Prostate	3	21	24	NA	NA	NA	NA	NA	NA	3	24
Pancreas	6	22	28	1	1	2	3	8	11	10	41
Melanoma of skin	33	66	99	3	6	9	18	32	50	54	158
Non-Hodgkin's lymphoma	28	61	89	1	3	4	8	20	28	37	121
Stomach	6	21	28	1	1	2	2	7	9	9	39
Leukemia	10	29	39	1	2	3	4	9	13	15	55
Brain	12	30	42	1	2	3	4	10	14	18	59
Ovarian	NA	NA	NA	2	8	10	13	43	56	15	66
Testis	16	18	34	NA	NA	NA	NA	NA	NA	16	34
Other cancers	124	325	449	10	82	92	69	173	242	203	783
Total	304	855	1,159	51	185	236	290	757	1,047	645	2442

\* US incidence rates for whites, data from Surveillance, Epidemiology, and End Results Program (1983 through 1987), assume average age 40 through 44 years.

† US incidence rates for whites, data from Surveillance, Epidemiology, and End Results Program (1983 through 1987), assume average age 45 through 49 years.

years of follow-up. Many of the findings from this investigation, particularly among family members who are not occupationally exposed, will have relevance to the urban population, where home use of and bystander exposure to pesticides have been of increasing concern.

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## Occupational Risk Factors I: Discussion Session V

This session on occupational risk factors was moderated by Dr Sandra Tillet of the Occupational Health Foundation, Washington, DC. Reports on cancer among women in agriculture, motor vehicle manufacturing, the high-nickel alloys industry, and fur hat manufacturing were presented.

Dr Kenneth Cantor asked Dr Helen McDuffie for the definition of "shallow well" used in her agricultural study and whether she had obtained measurements of nitrate levels in the well water. Dr. McDuffie defined shallow wells as wells that were dug as opposed to wells that were bored or drilled. Well water samples were not taken or analyzed. In response to a question from Dr John Vena concerning specific types of automotive jobs or plants that might be associated with excess cancer among women, Dr Elizabeth Delzell remarked that analyses are currently under way to evaluate

plant type and location within plant. There has been a preliminary observation of an increase of pancreatic cancer among assembly workers at one paint, plastic, and trim plant. Dr Vena also questioned Dr Vincent Arena about variation in results across the 13 plants included in his study of the high-nickel alloys industry. Dr Arena noted that most of the women were employed in only four of the 13 plants. Little variation in cancer mortality by plant was seen among women or white men. Among non-white men, however, more variation was seen. For example, there was a colon cancer excess in one plant that appeared to be attributable to hiring practices that placed nonwhite men in dirtier, dustier jobs than other employees. As requested by Dr Ellen Heineman, Dr Paolo Boffetta elaborated on the possible health worker effect in the women employed in fur hat manufacture in Italy. He believes

the healthy worker effect to be strong in this population because of the young age of the employees and the high degree of competition for the jobs, particularly during the 1960s and the 1970s, when the industry was shrinking. Dr Boffetta clarified his conclusions concerning lung and stomach cancer, as requested by Ms Caroline Freeman. The lung cancer excess could not be explained by smoking, asbestos exposure, or excess lung cancer in the local geographic area. It might be related to mercury, formaldehyde, other preservatives, or other occupational factors. On the other hand, the excess stomach cancer appeared to be similar to the excess for this tumor observed in the local geographic region and was unlikely to be occupationally related.

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