



Cancer incidence in the Agricultural Health Study after 20 years of follow-up

Catherine C. Lerro¹ · Stella Koutros¹ · Gabriella Andreotti¹ · Dale P. Sandler² · Charles F. Lynch³ · Lydia M. Louis¹ · Aaron Blair¹ · Christine G. Parks² · Srishti Shrestha² · Jay H. Lubin⁴ · Paul S. Albert⁴ · Jonathan N. Hofmann¹ · Laura E. Beane Freeman¹

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Abstract

Purpose To evaluate cancer incidence in the Agricultural Health Study (AHS), a cohort of private pesticide applicators, their spouses, and commercial applicators, based on 12,420 cancers, adding 5,989 cancers, and 9 years of follow-up since last evaluation.

Methods We calculated age, year, sex, and race-adjusted standardized incidence ratios (SIR) and 95% confidence intervals (CI) for cancer sites in the AHS relative to the general population.

Results Overall AHS cancer incidence was lower than the general population ($SIR_{\text{private}} = 0.91$, CI 0.89–0.93; $SIR_{\text{spouse}} = 0.89$, CI 0.86–0.92; $SIR_{\text{commercial}} = 0.83$, CI 0.76–0.92), with notable deficits across applicators and spouses for oral cavity, pancreas, and lung cancers. Cancer excesses included prostate cancer, lip cancer, certain B-cell lymphomas (e.g., multiple myeloma), acute myeloid leukemia (AML), thyroid cancer, testicular cancer, and peritoneal cancer. The lung cancer deficit was strongest among applicators reporting potential exposure to endotoxin at study enrollment (tasks such as raising animals and handling stored grain).

Conclusions Although an overall deficit in cancer was observed, there were notable exceptions, including newly observed excesses for AML, thyroid, testicular, and peritoneal cancers. Furthermore, endotoxin exposure may, in part, account for observed lung cancer incidence deficits. Cancer incidence patterns in the AHS suggest farm exposures' relevance to cancer etiology.

Keywords Farming · Cancer · Incidence · Pesticides · Endotoxin

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✉ Catherine C. Lerro
catherine.lerro@nih.gov

- ¹ Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6E116, 9609 Medical Center Drive, Rockville, MD 20850, USA
- ² National Institute of Environmental Health Sciences, 111 T.W. Alexander Drive, Research Triangle Park, NC 27709, USA
- ³ Department of Epidemiology, University of Iowa, 145 N. Riverside Drive, Iowa City, IA 52242, USA
- ⁴ Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850, USA

Background

Agricultural populations in Western countries have lower overall risks of cancer than the general population [1, 2], likely due to lifestyle factors such as lower rates of smoking and a higher level of occupational physical activity. In addition, the healthy worker effect is also thought to, in part, explain observed cancer and mortality deficits in occupational cohorts including agricultural populations [3]. However, excesses of certain types of cancer have been reported among agricultural workers and more broadly in farming populations, including prostate, brain, and lip cancer, lymphoma, multiple myeloma, leukemia, and melanoma [1, 4–12]. Several farming-related exposures may contribute to these divergent patterns, such as pesticides, diesel engine

exhaust, ultraviolet radiation, biologically active dusts, and viral and bacterial exposures via farm animals [13–16].

The Agricultural Health Study (AHS) cohort is a large prospective study of pesticide applicators (mostly male), including private pesticide applicators from Iowa (IA) and North Carolina (NC), USA (mostly farmers), their spouses (mostly women), and commercial pesticide applicators from IA. Cancer incidence in the cohort compared with the general population has been evaluated twice for cancers diagnosed from enrollment through 2002 and through 2006, [4, 7]. In these evaluations, overall cancer risk was consistently lower than that in the general population, particularly for smoking-related cancers including esophagus, pancreas, lung, bladder, and kidney. Excesses have also been observed, including cancers of the prostate, ovaries (among female applicators only), and lip, multiple myeloma, and marginal zone lymphoma (MZL) [4, 7]. Agricultural exposures and cancer risk have been evaluated extensively within the AHS. For example, certain pesticide exposures have been associated with elevated cancer risk, including prostate cancer [17] and multiple myeloma [18]. Additionally, exposure to animals, (e.g., number of livestock) thought to be a proxy for endotoxin exposure, has been inversely associated with lung cancer risk in the AHS [19]. Endotoxin, a component of Gram-negative bacteria cell walls, is often present in high concentrations in biologically active dusts found in grain elevators and animal containment facilities [20].

We have updated the evaluation of cancer incidence in the AHS cohort compared to the general population, extending follow-up 9 years and adding 5,989 cancer cases for a total of 12,420.

Methods

The AHS cohort has been described in detail [21]. Briefly, from 1993 to 1997, 52,394 private pesticide applicators (IA and NC) and 4,916 commercial pesticide applicators (IA only) were recruited and completed enrollment questionnaires when they renewed their restricted-use pesticide licenses (82% applicator response rate). A total of 32,346 spouses of private pesticide applicators in IA and NC (an estimated 75% of spouses of married applicators) completed and returned enrollment questionnaires. At enrollment, all study participants provided detailed information about farm and pesticide exposures (e.g., types of crops and animals, self-reported lifetime use of 50 pesticides), demographic information (e.g., age, race), and lifestyle factors (e.g., cigarette smoking, alcohol consumption). AHS study questionnaires are available at <https://aghealth.nih.gov/collaboration/questionnaires.html>. The study protocol, including implied

consent for completion of questionnaires, was approved by all relevant institutional review boards.

AHS cancer ascertainment and classification

We obtained incident cancer cases via linkage with IA and NC state cancer registries. We analyzed malignant first primary cancers diagnosed from enrollment through date of death, movement out of state, or last study follow-up (31 December 2015 for IA, 31 December 2014 for NC), whichever was earliest. Only 3.4% ($n = 3,201$) of study participants moved out of state; person-time was censored on the date they moved. Cancer site was classified according to the International Classification of Diseases for Oncology, third revision (ICD-O-3) [22]. Lymphoid malignancies were classified according to the 2008 Surveillance, Epidemiology, and End Results (SEER) Lymphoma Subtype Recode [23]. Myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN) diagnosed after 2001, when these cancers became reportable to the US central cancer registries, were classified according to ICD-O-3 [22].

Statistical methods

We calculated standardized incidence ratios (SIRs) and 95% confidence intervals (CI) to compare the cancer experience in the AHS cohort to the general populations of IA and NC. We first obtained site-specific rates for first primary cancers in IA and NC using the latest releases of the SEER and North American Association of Central Cancer Registries (NAACCR) Cancer in North America (CiNA) public use data [24], respectively, by 5 year age and calendar year (1995–2015) categories, sex (male, female), and race (white, all other) strata.

We created an AHS data set with the same stratification variables (age, sex, year, race) and the number of AHS person-years contributed to each stratum. We used the STDRATE command in SAS version 9.4 (SAS Institute, Cary, NC) to calculate age, sex, year, and race-adjusted expected cancer cases for each site. We compared the ratio of observed incident cases within the cohort to the expected number of cases to calculate the SIR. Confidence intervals were calculated using the Breslow and Day method [25].

Previous analyses demonstrated fewer cancers than expected within the cohort [4, 7]. To account for this deficit in cancer incidence, we calculated relative SIRs (RSIR) as follows using a modified version of relative SMR methods to account for the comparison of site-specific cancer risks [25–27], where “site” is the specific cancer of interest and “all sites” are all cancers combined:

$$RSIR = \frac{Observed_{Site} / Expected_{Site}}{(Observed_{AllSites} - Observed_{Site}) / (Expected_{Allsites} - Expected_{Site})}$$

We calculated SIRs separately for IA and NC for private applicators and spouses; all commercial applicators were from IA (21). For lung cancers, we stratified SIRs by smoking and potential endotoxin exposure at study enrollment to explore the separate contributions of each. Smoking was classified as never (< 100 lifetime cigarettes) or ever (100+ lifetime cigarettes). Potential exposure to endotoxin was classified using self-reported farm tasks known to be associated with elevated levels of endotoxin [20]. For applicators, this included raising livestock or exposure to grain dust, and for spouses, having direct contact with animals in the past year or occupational grain dust exposure in an off-farm job [16]. No information was available for spouses regarding grain dust exposure on the farm. Tests for heterogeneity were calculated using the Breslow and Day method [25]. We additionally compared selected characteristics from the AHS, such as current tobacco use, alcohol consumption, and body size, to data from a representative sample of IA and NC adults (ages 18+) in the 1995 Behavioral Risk Factor Surveillance System (BRFSS) [28]. All tests were two-sided with $\alpha=0.05$.

Results

Table 1 describes selected characteristics of the cohort. In general, NC applicators and spouses were older than their IA counterparts, including commercial applicators. Commercial applicators were younger than private applicators and spouses. Applicators were predominantly male, and spouses were predominantly female. NC study participants were more racially diverse and reported fewer years of education. Commercial applicators were most likely to report current smoking and drinking at least once per month at enrollment. IA applicators (private and commercial) were more likely to report alcohol consumption compared to NC applicators. Usual adult body mass index (BMI) for AHS participants ranged from 26 for spouses to 27.6 for applicators. Self-reported lifetime pesticide use (i.e., herbicides, insecticides, fungicides, fumigants) varied by state and applicator type; patterns observed by state were similar for applicators and spouses, though spouses reported less pesticide use. IA private applicators were more likely to be exposed to endotoxin (94.6%) compared to NC private applicators (54.5%) and commercial applicators (49.4%). Similarly, IA spouses were more likely to be exposed to endotoxin (60.4%) compared to NC spouses (31.1%).

We compared lifestyle characteristics of the AHS participants with a representative sample of IA and NC adults aged 18+ (Supplemental Table 1) [28]. For context, the BRFSS sample is similar in age for IA private applicators and spouses, younger than NC participants, and older than commercial applicators. AHS study participants were less

likely to be current smokers, more were never smokers, and a similar proportion were former smokers compared with the general population. Current smokers in the AHS reported similar numbers of cigarettes/day compared with the general population. Private applicators and spouses were slightly less likely to consume alcoholic beverages compared with the general population, while commercial applicators were more likely. Mean BMI was comparable in AHS and the general population.

Cancer incidence in the cohort was lower than in the general population ($SIR_{\text{private}}=0.91$, CI 0.89–0.93, $SIR_{\text{commercial}}=0.83$, CI 0.76–0.92, $SIR_{\text{spouse}}=0.89$, CI 0.86–0.92), adjusting for age, year, race, and sex (Table 2). This was largely driven by lower rates of respiratory cancers including all lung subtypes and larynx cancer, other smoking-related cancers such as bladder, and digestive system cancers including esophagus, colon, rectum, liver, and pancreas. Among private applicators, the SIRs for lip cancer ($SIR=2.22$, CI 1.71–2.84), prostate cancer ($SIR=1.15$, CI 1.11–1.19), B-cell lymphomas overall ($SIR=1.12$, CI 1.03–1.21), chronic lymphocytic leukemia (CLL; $SIR=1.17$, CI 1.00–1.36), and acute myeloid leukemia (AML; $SIR=1.29$, CI 1.03–1.59) were significantly elevated. Among spouses of private applicators, SIRs for peritoneal cancer ($SIR=1.80$, CI 1.11–2.75), melanoma ($SIR=1.21$, CI 1.04–1.40), uterine cancer ($SIR=1.13$, CI 1.01–1.27), papillary thyroid cancer ($SIR=1.30$, CI 1.07–1.57), and follicular lymphoma (FL; $SIR=1.33$, CI 1.00–1.74) were significantly elevated. No SIRs were significantly elevated for commercial applicators.

In addition to the elevated SIRs previously reported among private applicators, RSIRs, the site-specific SIR relative to all other cancer sites, were elevated for several sites (Table 3). These included melanoma ($RSIR=1.12$, CI 1.01–1.24), serous ovarian cancer ($RSIR=2.53$, CI 1.20–5.30, $n=7$, not shown), testicular cancer ($RSIR=1.45$, CI 1.08–1.94), papillary thyroid cancer ($RSIR=1.32$, CI 1.03–1.68), CLL ($RSIR=1.30$, CI 1.11–1.51), diffuse large B-cell lymphoma (DLBCL; $RSIR=1.29$, CI 1.10–1.52), FL ($RSIR=1.27$, CI 1.02–1.58), and multiple myeloma ($RSIR=1.30$, CI 1.11–1.54). Among commercial applicators, RSIRs were significantly elevated for prostate ($RSIR=1.33$, CI 1.09–1.62) and thyroid cancer ($RSIR=1.88$, CI 1.03–3.42). In addition to the elevated SIRs previously reported among spouses, RSIRs were elevated for breast cancer ($RSIR=1.28$, CI 1.20–1.37), DLBCL ($RSIR=1.39$, CI 1.09–1.76), MZL ($RSIR=1.64$, CI 1.11–2.44), and FL ($RSIR=1.50$, CI 1.15–1.96).

We noted an overall deficit of lung cancers in the cohort (Table 2) for private applicators ($SIR=0.51$, CI 0.48–0.55), commercial applicators ($SIR=0.67$, CI 0.50–0.88), and spouses ($SIR=0.41$, CI 0.36–0.46). Historically, lower incidence of lung cancer in agricultural

Table 1 Descriptive characteristics of the Agricultural Health Study cohort at enrollment (unless otherwise specified)

	Applicators			Spouses	
	Private		Commercial		
	Iowa	North Carolina	Iowa	Iowa	North Carolina
	<i>n</i> = 31,033	<i>n</i> = 20,132	<i>n</i> = 4,708	<i>n</i> = 20,977	<i>n</i> = 10,344
Total person-years contributed	564,494	335,966	86,729	379,526	176,948
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Attained age					
<55	5,933 (19.1)	3,846 (19.1)	1,901 (40.4)	4,349 (20.7)	1,838 (17.8)
55–64	10,698 (34.5)	5,373 (26.7)	1,654 (35.1)	7,049 (33.6)	2,758 (26.7)
65–74	8,053 (25.9)	5,500 (27.3)	801 (17.0)	5,279 (25.2)	2,833 (27.4)
75+	6,349 (20.5)	5,413 (26.9)	352 (7.5)	4,300 (20.5)	2,915 (28.2)
Gender					
Male	30,602 (98.6)	19,227 (95.5)	4,513 (95.9)	65 (0.3)	147 (1.4)
Female	431 (1.4)	905 (4.5)	195 (4.1)	20,912 (99.7)	10,197 (98.6)
Race					
White	30,692 (98.9)	17,949 (89.2)	4,656 (98.9)	20,611 (98.3)	9,351 (90.4)
Black/Other	49 (0.2)	1,439 (7.1)	22 (0.5)	50 (0.2)	489 (4.7)
Missing	292 (0.9)	744 (3.7)	30 (0.6)	316 (1.5)	504 (4.9)
Education					
<High school	1,619 (5.2)	3,408 (16.9)	142 (3.0)	525 (2.5)	998 (9.6)
High school or equivalent	15,304 (49.3)	8,190 (40.7)	1,962 (41.7)	7,250 (34.6)	3,679 (35.6)
Vocational/some college	8,180 (26.4)	3,701 (18.4)	1,358 (28.8)	5,976 (28.5)	2,305 (22.3)
College graduate	4,441 (14.3)	2,529 (12.6)	943 (20)	3,394 (16.2)	1,416 (13.7)
Graduate school	698 (2.2)	758 (3.8)	155 (3.3)	1,113 (5.3)	574 (5.5)
Something else	55 (0.2)	59 (0.3)	11 (0.2)	2,153 (10.3)	625 (6.0)
Missing	736 (2.4)	1,487 (7.4)	137 (2.9)	566 (2.7)	747 (7.2)
Smoking status					
Never	18,492 (59.6)	7,885 (39.2)	2,216 (47.1)	15,637 (74.5)	6,604 (63.8)
Former	8,590 (27.7)	6,857 (34.1)	1,192 (25.3)	3,413 (16.3)	1,876 (18.1)
Current	3,619 (11.7)	4,474 (22.2)	1,228 (26.1)	1,678 (8.0)	1,505 (14.5)
Missing	332 (1.1)	916 (4.5)	72 (1.5)	249 (1.2)	359 (3.5)
Alcohol use (last year)					
Less than once/month	11,609 (37.4)	12,070 (60.0)	1,205 (25.6)	13,197 (62.9)	8,431 (81.5)
At least once/month	18,475 (59.5)	5,508 (27.4)	3,416 (72.6)	7,216 (34.4)	1,170 (11.3)
Missing	949 (3.1)	2,554 (12.7)	87 (1.8)	564 (2.7)	743 (7.2)
Farm exposures					
Herbicides ^a	30,069 (96.9)	17,945 (89.1)	3,960 (84.1)	8,384 (40.0)	2,827 (27.3)
Insecticides ^a	28,549 (92.0)	16,598 (82.4)	3,543 (75.3)	8,370 (39.9)	3,479 (33.6)
Fungicides ^a	5,658 (18.2)	12,005 (59.6)	1,014 (21.5)	643 (3.1)	846 (8.2)
Fumigants ^a	2,851 (9.2)	8,430 (41.9)	808 (17.2)	197 (0.9)	381 (3.7)
Endotoxin ^b	29,346 (94.6)	10,981 (54.5)	2,325 (49.4)	12,674 (60.4)	3,216 (31.1)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Person-years follow-up ^c	18.2 (4.92)	16.7 (5.47)	18.4 (5.65)	18.1 (4.36)	17.1 (4.41)
Body mass index	27.6 (3.90)	27.5 (4.24)	27.4 (4.44)	26 (4.87)	26 (4.97)
Pack-years (among former smokers)	12.8 (17.41)	19.8 (23.63)	14 (17.28)	7.9 (12.11)	10.2 (14.24)
Pack-years (among current smokers)	20.7 (18.55)	26.6 (23.16)	19.6 (17.04)	16.1 (15.38)	18.6 (15.79)

^aReport lifetime ever use of at least one of the 50 pesticides (18 herbicides, 22 insecticides, 6 fungicides, 4 fumigants) queried at enrollment

^bApplicators: raise farm animals or exposed to grain dust; Spouses: direct contact with farm animals at least once/year or occupationally exposed to grain dust

^cIowa participants have one additional year of cancer and mortality follow-up (through 2015) compared to North Carolina participants (through 2014)

Table 2 Standardized Incidence Ratios (SIRs) and 95% confidence intervals (CI) adjusted for age, year, race, and sex

	Private applicators			Commercial applicators			Spouses		
	N	SIR	CI	N	SIR	CI	N	SIR	CI
All sites	8,256	0.91	(0.89, 0.93)	444	0.83	(0.76, 0.92)	3,720	0.89	(0.86, 0.92)
Oral cavity and pharynx	198	0.69	(0.60, 0.80)	10	0.50	(0.24, 0.92)	44	0.72	(0.52, 0.96)
Lip	63	2.22	(1.71, 2.84)	4	–	–	7	1.76	(0.71, 3.63)
Tongue	35	0.46	(0.32, 0.64)	2	–	–	15	0.89	(0.50, 1.47)
Tonsil	27	0.47	(0.31, 0.68)	1	–	–	3	–	–
Digestive system	1,407	0.87	(0.82, 0.91)	84	0.83	(0.66, 1.03)	540	0.81	(0.74, 0.88)
Esophagus	102	0.71	(0.58, 0.86)	13	1.29	(0.69, 2.21)	9	0.51	(0.23, 0.97)
Stomach	114	0.91	(0.75, 1.10)	2	–	–	28	0.78	(0.52, 1.12)
Small intestine	44	1.13	(0.82, 1.52)	4	–	–	11	0.61	(0.30, 1.09)
Colon and rectum	842	0.95	(0.89, 1.02)	49	0.89	(0.66, 1.18)	346	0.87	(0.78, 0.96)
Proximal colon	310	0.94	(0.84, 1.05)	17	0.89	(0.52, 1.42)	169	0.93	(0.80, 1.09)
Distal colon	226	0.99	(0.87, 1.13)	13	0.93	(0.49, 1.58)	84	0.91	(0.73, 1.13)
Rectum and rectosigmoid junction	260	0.95	(0.84, 1.08)	17	0.89	(0.52, 1.42)	74	0.75	(0.59, 0.94)
Anus, anal canal and anorectum	8	0.44	(0.19, 0.87)	1	–	–	6	0.30	(0.11, 0.66)
Liver and intrahepatic bile duct	78	0.56	(0.45, 0.70)	4	–	–	21	0.71	(0.44, 1.08)
Pancreas	183	0.83	(0.72, 0.96)	10	0.76	(0.37, 1.41)	71	0.69	(0.54, 0.87)
Peritoneum, omentum and mesentery	1	—	–	0	–	–	21	1.80	(1.11, 2.75)
Respiratory system	881	0.51	(0.47, 0.54)	56	0.65	(0.49, 0.85)	259	0.40	(0.36, 0.46)
Larynx	66	0.48	(0.37, 0.62)	4	–	–	5	0.26	(0.09, 0.62)
Lung and bronchus	807	0.51	(0.48, 0.55)	51	0.67	(0.50, 0.88)	252	0.41	(0.36, 0.46)
Small-cell carcinoma	138	0.58	(0.48, 0.68)	10	0.81	(0.39, 1.49)	39	0.34	(0.24, 0.46)
Non-small cell carcinoma	633	0.51	(0.47, 0.55)	40	0.67	(0.48, 0.91)	199	0.44	(0.38, 0.50)
Squamous cell carcinoma	209	0.51	(0.45, 0.59)	15	0.81	(0.45, 1.34)	42	0.39	(0.28, 0.53)
Adenocarcinoma	238	0.54	(0.47, 0.61)	16	0.62	(0.35, 1.01)	106	0.51	(0.42, 0.61)
Large-cell carcinoma	68	0.39	(0.30, 0.50)	3	–	–	9	0.17	(0.08, 0.31)
Melanoma of the skin	393	1.01	(0.91, 1.12)	26	1.03	(0.67, 1.51)	177	1.21	(1.04, 1.40)
Breast	63	0.86	(0.66, 1.10)	2	–	–	1,389	1.05	(0.99, 1.11)
Female genital system	21	0.95	(0.59, 1.45)	2	–	–	498	0.97	(0.88, 1.05)
Cervix uteri	3	—	–	0	–	—	29	0.50	(0.34, 0.72)
Corpus and uterus	6	0.49	(0.18, 1.08)	1	–	–	323	1.13	(1.01, 1.27)
Ovary and fallopian tube	11	1.80	(0.90, 3.22)	0	–	–	122	0.87	(0.72, 1.04)
Male genital system	3,228	1.15	(1.11, 1.19)	157	1.03	(0.87, 1.20)	11	0.89	(0.44, 1.59)
Prostate	3,169	1.15	(1.11, 1.19)	149	1.02	(0.86, 1.19)	11	0.90	(0.45, 1.61)
Testis	45	1.31	(0.96, 1.75)	7	1.28	(0.51, 2.65)	0	–	–
Urinary system	740	0.80	(0.74, 0.85)	39	0.72	(0.51, 0.98)	154	0.76	(0.64, 0.88)
Urinary bladder	411	0.70	(0.63, 0.77)	26	0.83	(0.54, 1.22)	60	0.64	(0.49, 0.82)
Kidney and renal pelvis	314	0.96	(0.86, 1.07)	12	0.53	(0.28, 0.93)	92	0.88	(0.71, 1.07)
Brain	87	0.79	(0.63, 0.97)	6	0.72	(0.26, 1.57)	49	1.00	(0.74, 1.32)
Endocrine system	92	1.17	(0.95, 1.44)	12	1.58	(0.82, 2.76)	123	1.20	(1.00, 1.44)
Thyroid	82	1.15	(0.92, 1.43)	11	1.55	(0.77, 2.77)	118	1.20	(0.99, 1.44)
Papillary carcinoma	66	1.19	(0.92, 1.52)	8	1.37	(0.59, 2.70)	110	1.30	(1.07, 1.57)
All lymphohematopoietic	830	1.07	(0.99, 1.14)	40	0.76	(0.54, 1.04)	330	1.00	(0.89, 1.11)
Lymphoid malignancies	700	1.08	(1.00, 1.16)	36	0.82	(0.57, 1.13)	290	1.04	(0.92, 1.16)
Hodgkin lymphoma	27	0.99	(0.65, 1.44)	2	–	–	10	0.87	(0.42, 1.60)
B-cell lymphoma	624	1.12	(1.03, 1.21)	32	0.85	(0.58, 1.20)	265	1.09	(0.96, 1.23)
Chronic lymphocytic leukemia	166	1.17	(1.00, 1.36)	9	0.93	(0.42, 1.76)	43	0.88	(0.63, 1.18)
Diffuse large B-cell lymphoma	145	1.16	(0.98, 1.37)	5	0.56	(0.18, 1.32)	70	1.23	(0.96, 1.55)
Marginal zone lymphoma	16	0.61	(0.35, 0.99)	2	–	–	25	1.46	(0.95, 2.16)

Table 2 (continued)

	Private applicators			Commercial applicators			Spouses		
	N	SIR	CI	N	SIR	CI	N	SIR	CI
Follicular lymphoma	81	1.14	(0.91, 1.42)	7	1.25	(0.50, 2.58)	54	1.33	(1.00, 1.74)
Multiple myeloma	146	1.18	(0.99, 1.38)	5	0.71	(0.23, 1.67)	57	1.04	(0.79, 1.35)
T-Cell lymphoma	27	0.89	(0.58, 1.29)	1	–	–	8	0.69	(0.30, 1.36)
Leukemia	145	1.10	(0.93, 1.30)	7	0.82	(0.33, 1.7)	45	0.88	(0.65, 1.18)
Lymphocytic leukemia	14	0.77	(0.42, 1.30)	2	–	–	5	0.81	(0.26, 1.88)
Myeloid and monocytic leukemia	115	1.12	(0.92, 1.34)	4	–	–	38	0.94	(0.66, 1.29)
Acute myeloid/monocytic leukemia	86	1.29	(1.03, 1.59)	3	–	–	33	1.21	(0.83, 1.69)
Chronic myeloid leukemia	25	0.76	(0.49, 1.13)	1	–	–	5	0.41	(0.13, 0.95)
Mesothelioma	21	0.85	(0.53, 1.30)	0	–	–	4	–	–
Myelodysplastic/myeloproliferative neoplasm ^a	87	0.81	(0.65, 1.00)	0	–	–	38	0.78	(0.55, 1.07)
Myelodysplastic syndrome	48	0.84	(0.62, 1.12)	0	–	–	19	0.95	(0.57, 1.48)
Myeloproliferative neoplasm	36	0.75	(0.53, 1.04)	0	–	–	16	0.59	(0.34, 0.95)

^aAnalyses restricted to 2001-on when these tumors became reportable to central cancer registries

populations has been attributed to lower rates of smoking, although the literature has also shown that endotoxin exposure is inversely associated with lung cancer risk [29]. To evaluate this, we stratified by smoking and computed lung cancer SIRs for private applicators and spouses compared to the general population, which includes smokers and never smokers (Fig. 1). For private applicators, SIRs were lower than expected among both ever smokers (SIR = 0.84, CI 0.78–0.91) and never smokers (SIR = 0.10, CI 0.08–0.13). We further stratified by endotoxin exposure. Among smokers, SIRs were elevated for smokers who did not report endotoxin-related tasks (SIR = 1.15, CI 1.01–1.30), while they were lower than expected for smokers reporting endotoxin-related activity (SIR = 0.74, CI 0.67–0.81). Similar patterns for endotoxin were observed for spouses, though we did not observe a significant deficit of lung cancers among smokers overall. We also evaluated SIRs stratified by endotoxin separately for former and current smokers. Similarly, SIRs for potentially endotoxin-exposed current and former smokers were significantly lower compared to those who did not report endotoxin-related tasks ($p < 0.001$, not shown).

SIRs for private applicators and spouses stratified by state of residence are reported in Supplemental Table 2. There were few sites where the SIRs differed substantially by state. Pancreatic cancer incidence was lower than expected in IA for applicators (SIR = 0.72, CI 0.58–0.88) and spouses (SIR = 0.61, CI 0.44–0.82). Lung cancer SIRs were lower for IA (SIR_{private} = 0.34, CI 0.30–0.38) compared to NC (SIR_{private} = 0.78, CI 0.71–0.85). Among applicators, SIRs for colorectal cancer were lower than expected in IA (SIR = 0.83, CI 0.76–0.91) but not NC (SIR = 1.07, CI 0.96–1.18), while DLBCL was elevated in NC (SIR = 1.38, CI 1.06–1.77) but not IA (SIR = 0.96, 96% CI 0.76–1.19).

Melanoma, thyroid cancer, and MZL SIRs were elevated in IA spouses only.

Discussion

The lower rate of cancer overall in the AHS cohort is consistent with previous reports [4, 7]. Despite this deficit, we found some elevations, including elevated SIRs for prostate and lip cancers, multiple myeloma, DLBCL, and CLL among AHS private applicators, and melanoma, breast cancer, uterine cancer, DLBCL, and MZL among spouses of pesticide applicators that are consistent with previous reports from this cohort. Some elevated SIRs that were previously only observed in RSIR analyses are now apparent in SIR analyses (e.g., uterine cancer among spouses). The previously reported significant excess of ovarian cancer among pesticide applicators was no longer statistically significant, with ten years of additional follow-up and only one additional case [7]. We did observe a significant RSIR specifically for the serous subtype. Several sites demonstrated excesses (lip, melanoma, thyroid, FL, AML) or deficits (oral cavity, pancreas, larynx, lung, bladder, kidney) across AHS private applicators, commercial applicators, and spouses.

Contributing to the overall deficit were many cancers associated with known preventable or modifiable risk factors including smoking (e.g., lung, larynx, bladder), HPV (e.g., cervix, oral cavity, anus), obesity (e.g., colorectal [spouses], esophagus, pancreas), and alcohol (e.g., liver, esophagus). Koutros et al. discussed in detail the potential farm-related exposures that may be influencing these findings including pesticides, viral and bacterial exposures related to livestock and poultry, growing up on a farm, sun exposure, and endotoxin [7]. Compared to the general population [28], AHS

Table 3 Relative standardized Incidence Ratios (RSIRs)^a and 95% confidence intervals (CI) adjusted for age, year, race, and sex

	Private applicators			Commercial applicators			Spouses		
	N	RSIR	CI	N	RSIR	CI	N	RSIR	CI
Oral cavity and pharynx	198	0.76	(0.66, 0.88)	10	0.59	(0.31, 1.10)	44	0.80	(0.59, 1.08)
Lip	63	2.46	(1.92, 3.16)	4	–	–	7	1.98	(0.94, 4.16)
Tongue	35	0.50	(0.36, 0.70)	2	–	–	15	1.00	(0.60, 1.66)
Tonsil	27	0.52	(0.35, 0.75)	1	–	–	3	–	–
Digestive system	1,407	0.95	(0.90, 1.01)	84	1.00	(0.79, 1.27)	540	0.90	(0.82, 0.98)
Esophagus	102	0.78	(0.64, 0.95)	13	1.57	(0.90, 2.73)	9	0.57	(0.30, 1.10)
Stomach	114	1.01	(0.84, 1.21)	2	–	–	28	0.87	(0.60, 1.26)
Small intestine	44	1.25	(0.93, 1.69)	4	–	–	11	0.68	(0.38, 1.23)
Colon and rectum	842	1.06	(0.98, 1.13)	49	1.08	(0.80, 1.45)	346	0.97	(0.87, 1.08)
Proximal colon	310	1.04	(0.93, 1.17)	17	1.07	(0.66, 1.73)	169	1.05	(0.90, 1.22)
Distal colon	226	1.10	(0.96, 1.25)	13	1.11	(0.64, 1.93)	84	1.02	(0.82, 1.27)
Rectum and rectosigmoid junction	260	1.05	(0.93, 1.19)	17	1.07	(0.66, 1.73)	74	0.84	(0.67, 1.06)
Anus, anal canal, and anorectum	8	0.49	(0.24, 0.97)	1	–	–	6	0.34	(0.15, 0.76)
Liver and intrahepatic bile duct	78	0.62	(0.50, 0.77)	4	–	–	21	0.79	(0.52, 1.22)
Pancreas	183	0.92	(0.79, 1.06)	10	0.92	(0.49, 1.71)	71	0.77	(0.61, 0.97)
Peritoneum, omentum and mesentery	1	–	–	0	–	–	21	2.02	(1.32, 3.10)
Respiratory system	881	0.51	(0.47, 0.54)	56	0.75	(0.57, 0.99)	259	0.41	(0.36, 0.47)
Larynx	66	0.53	(0.42, 0.68)	4	–	–	5	0.30	(0.12, 0.71)
Lung and bronchus	807	0.52	(0.48, 0.55)	51	0.78	(0.58, 1.04)	252	0.42	(0.37, 0.48)
Small-cell carcinoma	138	0.63	(0.53, 0.75)	10	0.97	(0.52, 1.82)	39	0.37	(0.27, 0.51)
Non-small cell carcinoma	633	0.53	(0.49, 0.58)	40	0.78	(0.56, 1.08)	199	0.46	(0.40, 0.53)
Squamous cell carcinoma	209	0.55	(0.48, 0.64)	15	0.97	(0.58, 1.62)	42	0.44	(0.32, 0.59)
Adenocarcinoma	238	0.58	(0.51, 0.66)	16	0.74	(0.45, 1.21)	106	0.56	(0.46, 0.67)
Large-cell carcinoma	68	0.43	(0.34, 0.54)	3	–	–	9	0.18	(0.10, 0.35)
Melanoma of the skin	393	1.12	(1.01, 1.24)	26	1.25	(0.84, 1.86)	177	1.37	(1.18, 1.60)
Breast	63	0.95	(0.74, 1.22)	2	–	–	1389	1.28	(1.20, 1.37)
Female genital system	21	1.05	(0.68, 1.61)	2	–	–	498	1.10	(1.00, 1.21)
Cervix uteri	3	–	–	0	–	–	29	0.56	(0.39, 0.81)
Corpus and uterus	6	0.54	(0.24, 1.21)	1	–	–	323	1.30	(1.16, 1.46)
Ovary and fallopian tube	11	1.99	(1.10, 3.59)	0	–	–	122	0.97	(0.81, 1.16)
Male genital system	3,228	1.44	(1.38, 1.51)	157	1.36	(1.12, 1.65)	11	1.00	(0.55, 1.80)
Prostate	3,169	1.44	(1.38, 1.50)	149	1.33	(1.09, 1.62)	11	1.01	(0.56, 1.83)
Testis	45	1.45	(1.08, 1.94)	7	1.55	(0.73, 3.27)	0	–	–
Urinary system	740	0.87	(0.80, 0.93)	39	0.84	(0.61, 1.17)	154	0.84	(0.72, 0.99)
Urinary bladder	411	0.76	(0.69, 0.84)	26	1.00	(0.67, 1.49)	60	0.71	(0.55, 0.92)
Kidney and renal pelvis	314	1.06	(0.95, 1.19)	12	0.63	(0.36, 1.12)	92	0.98	(0.80, 1.21)
Brain	87	0.87	(0.70, 1.07)	6	0.86	(0.39, 1.93)	49	1.12	(0.85, 1.49)
Endocrine system	92	1.30	(1.06, 1.60)	12	1.92	(1.08, 3.41)	123	1.36	(1.14, 1.63)
Thyroid	82	1.28	(1.03, 1.59)	11	1.88	(1.03, 3.42)	118	1.36	(1.13, 1.63)
Papillary carcinoma	66	1.32	(1.03, 1.68)	8	1.65	(0.82, 3.33)	110	1.48	(1.22, 1.79)
All lymphohematopoietic	830	1.20	(1.11, 1.29)	40	0.90	(0.65, 1.25)	330	1.13	(1.01, 1.27)
Lymphoid malignancies	700	1.21	(1.12, 1.31)	36	0.98	(0.70, 1.38)	290	1.18	(1.04, 1.33)
Hodgkin lymphoma	27	1.09	(0.75, 1.60)	2	–	–	10	0.98	(0.53, 1.82)
B-Cell Lymphoma	624	1.26	(1.16, 1.36)	32	1.02	(0.71, 1.46)	265	1.24	(1.09, 1.41)
Chronic lymphocytic leukemia	166	1.30	(1.11, 1.51)	9	1.11	(0.58, 2.16)	43	0.98	(0.73, 1.33)
Diffuse large B-cell lymphoma	145	1.29	(1.10, 1.52)	5	0.67	(0.28, 1.63)	70	1.39	(1.09, 1.76)
Marginal zone lymphoma	16	0.67	(0.41, 1.10)	2	–	–	25	1.64	(1.11, 2.44)
Follicular lymphoma	81	1.27	(1.02, 1.58)	7	1.51	(0.72, 3.18)	54	1.50	(1.15, 1.96)

Table 3 (continued)

	Private applicators			Commercial applicators			Spouses		
	N	RSIR	CI	N	RSIR	CI	N	RSIR	CI
Multiple myeloma	146	1.30	(1.11, 1.54)	5	0.86	(0.35, 2.06)	57	1.17	(0.90, 1.52)
T-Cell lymphoma	27	0.98	(0.67, 1.43)	1	–	–	8	0.77	(0.39, 1.55)
Leukemia	145	1.22	(1.04, 1.44)	7	0.99	(0.47, 2.08)	45	0.99	(0.74, 1.33)
Lymphocytic leukemia	14	0.85	(0.50, 1.44)	2	–	–	5	0.90	(0.38, 2.17)
Myeloid and monocytic leukemia	115	1.24	(1.03, 1.49)	4	–	–	38	1.05	(0.76, 1.45)
Acute myeloid/monocytic leukemia	86	1.42	(1.15, 1.76)	3	–	–	33	1.36	(0.96, 1.91)
Chronic myeloid leukemia	25	0.84	(0.57, 1.25)	1	–	–	5	0.46	(0.19, 1.10)
Mesothelioma	21	0.94	(0.61, 1.44)	0	–	–	4	–	–
Myelodysplastic/myeloproliferative neoplasm ^b	87	0.89	(0.72, 1.10)	0	–	–	38	0.87	(0.63, 1.20)
Myelodysplastic syndrome	48	0.93	(0.70, 1.24)	0	–	–	19	1.06	(0.68, 1.67)
Myeloproliferative neoplasm	36	0.83	(0.60, 1.15)	0	–	–	16	0.66	(0.40, 1.07)

^aRatio of the SIR for the cancer site of interest to the SIR for all cancers except the cause of interest

^bAnalyses restricted to 2001-on when these tumors became reportable to central cancer registries

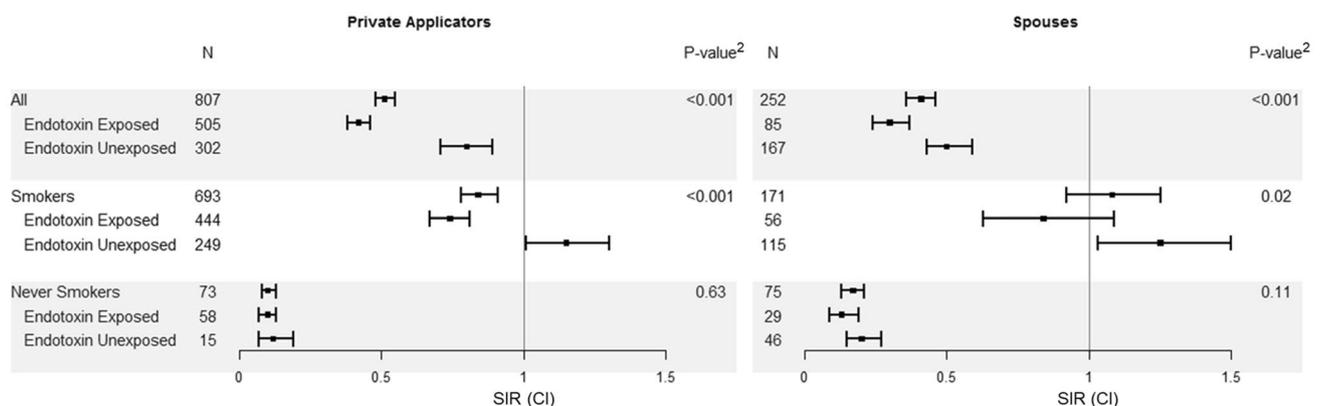


Fig. 1 Lung cancer standardized incidence ratios (SIRs) and 95% confidence intervals (CI) adjusted for age, year, race, and sex among current and former smoking private applicators and spouses in the AHS cohort, stratified by endotoxin exposure activities at study

private applicators and spouses report less current smoking (though similar number of cigarettes/day among current smokers), lower alcohol consumption (frequency, number of drinks), and slightly higher BMI, possibly due to greater muscle mass resulting from farming activity. Commercial applicators were similar to the general population in terms of tobacco and alcohol consumption.

Cancer excesses

This updated analysis also provided the opportunity to evaluate additional cancers with insufficient numbers in previous analyses. We observed elevated SIRs for thyroid cancer, testicular cancer, peritoneal cancer, and AML. Many pesticides have been shown to have thyroid hormone disrupting properties *in vivo* and/or *in vitro* [30], suggesting that

enrollment¹. ¹Private Applicators: raise farm animals or exposed to grain dust. Spouses: direct contact with farm animals at least once/year or occupationally exposed to grain dust ²Wald test comparing endotoxin exposed and unexposed within categories of smoking

pesticide exposure may be associated with risk of thyroid cancer. Smoking has been consistently inversely associated with thyroid cancer risk, particularly the most common papillary subtype [31]. When results for papillary thyroid cancer in our analysis were stratified by smoking (and compared to the general population including smokers and non-smokers), we noted an elevated SIR among never smoking private applicators (SIR = 1.48, 95%CI 1.09–1.99) and no association among current or former smokers (SIR = 0.85, 95%CI 0.52–1.30). Thus, it is possible that the elevated SIRs for thyroid cancer in the cohort are largely due to the lower rates of smoking in the AHS compared to the general population, though other occupational risk factors, such as certain pesticides, cannot be completely ruled out. Within the AHS cohort, endocrine-disrupting pesticides atrazine (herbicide) and malathion (insecticide) have been associated

with thyroid cancer risk in applicators and spouses, respectively [32, 33]. A number of pesticide ingredients have also been linked to incident self-reported thyroid disease in AHS applicators [34] and spouses [35, 36]. Furthermore, aldrin (insecticide) and pendimethalin (herbicide) have been associated with thyroid hormone dysfunction in AHS male pesticide applicators [37].

Increased incidence of testicular cancer has been suggested in some pesticide-exposed occupational cohorts [38, 39]. However, studies examining the effect of specific pesticide exposures on testicular cancer etiology have produced inconsistent findings [40]. The evidence is strongest for certain organochlorine insecticides, particularly DDT and its major metabolite, *p,p'*-DDE, which are thought to have endocrine-disrupting properties [40]. *In vitro*, *p,p'*-DDE has been shown to completely inhibit binding of [³H]5 α -dihydrotestosterone to the androgen receptor [41]. The AHS cohort is not an ideal setting to study testicular cancer; the average age of applicators at study enrollment was 45, while the peak incidence occurs at 25–29 for the non-seminomatous germ cell tumors subtype and 35–39 for the seminomatous subtype [40]. Despite this, with the most recent update, we do observe a statistically significantly elevated RSIR among private applicators with mean age at diagnosis in the AHS of 45 (median = 43) for seminomas ($n = 33$) and 42 (median = 40) for non-seminomas ($n = 12$).

Peritoneal tumors are rare and often diagnosed at late stage due to a lack of clinical symptoms [42]. Among spouses of pesticide applicators, we observed an excess of peritoneal cancers, with 21 incident cases, the majority ($n = 18$) of which were serous peritoneal carcinomas. Recent evidence suggests that most extrauterine high-grade serous carcinomas may be etiologically similar in that they originate from the fimbriated end of fallopian tubes [43]. When we evaluated high- and low-grade serous cancers of the ovary, fallopian tube, and peritoneum combined, we did not observe significantly elevated incidence ($RSIR_{\text{high-grade}} = 1.19$, CI 0.89–1.58, $RSIR_{\text{low-grade}} = 1.17$, CI 0.68–2.02). Nearly all peritoneal tumors in AHS spouses were diagnosed in IA ($n = 18$), while incidence for ovarian and fallopian tube tumors was similar for IA and NC, perhaps indicating true regional differences in disease risk or regional variation in pathology practices. While we observe an excess of peritoneal cancers in our analysis, evidence for an etiologic relationship between farm exposures and serous extrauterine tumors based on our findings is relatively weak and requires further examination.

We observed a significantly elevated SIR and RSIR for AML among private applicators, and a non-significantly elevated SIR among spouses. In the previous analysis of cancer incidence in the cohort, Koutros et al. reported elevated AML in RSIR analyses for spouses and applicators, though these elevations did not reach statistical significance [7]. A

number of occupational risk factors have been associated with AML, such as benzene [44], ionizing radiation [45], and formaldehyde [46, 47], which are unlikely to explain the excess in this cohort. A meta-analysis found that workers exposed to pesticides were at elevated risk of AML, summarizing data from five cohort studies [48]. In recent AHS analyses, two herbicides, glyphosate and alachlor, were associated with non-significantly increased risk of AML and myeloid leukemia, respectively [49, 50].

Koutros et al. previously reported an elevated RSIR among private applicators for lip cancer, along with an overall decreased SIR/RSIR for cancers of the oral cavity and pharynx [7]. This increase was attributed to potential risk factors such as tobacco use (cigarettes as well as smokeless tobacco) and UV exposure. In our update, we calculated SIRs for several specific types of oral cavity cancer, including tongue, tonsil, gum, and pharynx, which all had SIRs less than one, and salivary gland for which we saw no association. We continued to see strong evidence for an excess of lip cancer among private applicators, as well as non-significantly elevated RSIRs for spouses ($RSIR = 1.98$) and commercial applicators ($RSIR = 1.83$, not shown). Compared with the general population, AHS participants were less likely to be ever smokers, but more likely to have used smokeless tobacco products including chewing tobacco, snus, and snuff [51]. However, because tobacco is a risk factor for all these cancers, it seems unlikely that differences in tobacco use are alone in explaining the lip cancer excess. Cancers of the external lip (ICD-O-3: C00.0-C00.2) appear to be driving the excess of lip cancers among private applicators ($SIR = 2.36$, CI 1.77–3.08, $n = 53$, not shown), lending support to the hypothesis that UV exposure may, in part, explain the elevated SIR for lip cancer. Additionally, HPV is a known or suspected risk factor for many of the cancers where we see a deficit, including tonsil and base of the tongue, but not for lip [52]. We do not have information on HPV status of participants in the cohort, but we suspect HPV prevalence is low based on known risk factors for HPV infection and sociodemographic characteristics of the AHS [53, 54].

Lung cancer deficit

The deficit of lung cancer is striking, with SIRs for private applicators ranging from 0.39 for large-cell lung cancer to 0.58 for small-cell lung cancer. The magnitude of the deficit of lung cancer seemed lower than could be explained solely by differences in smoking. This deficit is seen consistently in farming populations [29], and is similar to that recently reported in a French agricultural cohort [12]. We evaluated incident lung cancer in the cohort among smokers (current and former) compared to the general population, hypothesizing that AHS smokers

would have an excess of lung cancers compared to the general population comprised of both smokers and non-smokers. Yet even among pesticide applicators who were former or current smokers, there remained significantly lower lung cancer incidence compared to the general population. Therefore, we further explored whether endotoxin exposure may explain this deficit.

Endotoxin has been inversely associated with lung cancer among various occupationally exposed groups, such as agricultural and textile workers [29]. Certain farm activities confer greater probability of endotoxin exposure, for example, handling stored grain or working in proximity to farm animals [20]. Prior studies in the AHS reported that increasing number of livestock was associated with decreased risk of lung cancer [19], and that endotoxin exposure activities modify the association between diesel exhaust and lung cancer risk [16]. Similarly, results from a French agricultural cohort demonstrated that increasing years of farm animal exposure was associated with decreased lung cancer risk in smokers and non-smokers [55]. In our analysis, we used information collected at baseline regarding handling of stored grain and proximity to farm animals to assign probable exposure to higher levels of endotoxin [16]. Among smokers, those who did not report these high-probability endotoxin exposure activities had elevated lung cancer incidence compared to the general population, which is in line with expectation when comparing a group of smokers to a population which combines smokers and non-smokers. This SIR was small, perhaps reflecting fewer years of smoking or greater time since quitting (among former smokers) compared to the general population. Smoking is a well-established risk factor for lung cancer, with smokers having more than 15 times greater risk of lung cancer diagnosis compared to non-smokers [56]; yet, smokers with endotoxin exposure had lower lung cancer risk than expected, even compared to a population comprised of smokers and non-smokers. We did not observe a reduction in lung cancer associated with potential endotoxin exposure among non-smokers. This may be due to very low lung cancer risk in non-smokers [57], or reflect an interaction between endotoxin and tobacco, as has been observed with endotoxin and diesel exhaust in the AHS [16]. While these results seem to support the hypothesis that the AHS lung cancer deficit may be tied to both lower rates of smoking and potential endotoxin exposure, some caution is warranted in interpreting these findings. SIRs do not directly evaluate the relationship between endotoxin, smoking, and lung cancer. Due to a limited sample size, we did not evaluate SIRs more finely stratified by smoking intensity or duration. Endotoxin-exposed smokers report fewer pack-years compared to unexposed; however, restricting our study population to highly exposed

(> 30 pack-year) smokers, we still observed significantly lower SIRs among endotoxin-exposed farmers compared to unexposed (SIR 1.77 vs. 2.22, respectively, results not shown).

Strengths and limitations

This updated assessment of cancer incidence in the AHS provided us with the unique ability to evaluate the impact of farm lifestyle and exposures on cancer risk. Since the last cancer incidence evaluation, we have nearly doubled the number of cancer cases in the cohort, allowing for examination of more cancer sites (e.g., testis and thyroid) and finer subtypes of previously evaluated cancer sites (e.g., lung and NHL). The larger number of cases also allowed us to evaluate additional hypotheses, such as whether endotoxin, along with lower rates of smoking, may contribute to the low lung cancer incidence in this agricultural population. However, there are some important, well-known, limitations to the SIR approach. The general population of IA and NC may not represent the cancer experience of AHS participants had they not been living and working on farms. Furthermore, while we were able to standardize the study population according to some important characteristics (i.e., age, sex, race, time period), we were not able to control for other relevant factors such as tobacco use and BMI. We did compare these characteristics in the AHS to data from BRFSS to try to understand important demographic and behavioral differences. The differences in age, lifestyle, and agricultural exposures among private applicators, spouses, and commercial applicators provide opportunities for hypothesis development for targeted etiologic studies in the future. An important limitation for our lung cancer analysis is classification of smoking status at study enrollment. Prevalence of current smoking in the cohort decreased over time among those who completed enrollment questionnaire and subsequent follow-up interviews, which has implications for lung cancer risk. However, smoking prevalence in the general population also decreased by a similar magnitude during this time [58], and therefore we assume the effect on the SIRs is small. Our evaluation of endotoxin used a classification developed for a prior analysis in the cohort and is based on self-reported activities known to be associated with high levels of endotoxin exposure at study enrollment [16]; this self-reported metric is relatively crude and may result in misclassification of endotoxin exposure.

Conclusions

As previously observed, overall cancer incidence in the AHS remains lower than expected compared to the general population. We confirmed excesses of cancers observed in prior

analyses, notably prostate cancer, lip cancer, breast cancer, uterine cancer, melanoma, and certain B-cell lymphomas. New in this analysis, we observed elevated SIRs for thyroid cancer, testicular cancer, peritoneal cancer, and AML, as well as differences in lung cancer incidence among smokers that may be due to endotoxin exposure. The observed SIRs are likely due to a range of exposures from behavioral and lifestyle factors to unique occupational and environmental exposures that arise from living and/or working on a farm. These findings will inform future etiologic analyses and focus efforts to better understand the relationship between agricultural exposures and cancer risk.

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References

- Blair A, Zahm SH, Pearce NE, Heineman EF, Fraumeni JF Jr (1992) Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health* 18:209–215
- Acquavella J, Olsen G, Cole P et al (1998) Cancer among farmers: a meta-analysis. *Ann Epidemiol* 8:64–74
- Kirkeleit J, Riise T, Bjorge T, Christiani DC (2013) The healthy worker effect in cancer incidence studies. *Am J Epidemiol* 177:1218–1224
- Alavanja MC, Sandler DP, Lynch CF et al (2005) Cancer incidence in the agricultural health study. *Scand J Work Environ Health*. 31 Suppl 1: 39–45; discussion 5–7
- Eriksson M, Hardell L, Carlberg M, Akerman M (2008) Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *Int J Cancer* 123:1657–1663
- Fortes C, Mastroeni S, Melchi F et al (2007) The association between residential pesticide use and cutaneous melanoma. *Eur J Cancer* 43:1066–1075
- Koutros S, Alavanja MC, Lubin JH et al (2010) An update of cancer incidence in the Agricultural Health Study. *J Occup Environ Med* 52:1098–1105
- Merhi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, Gamet-Payrastra L (2007) Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies. *Cancer Causes Control* 18:1209–1226
- Samanic CM, De Roos AJ, Stewart PA, Rajaraman P, Waters MA, Inskip PD (2008) Occupational exposure to pesticides and risk of adult brain tumors. *Am J Epidemiol* 167:976–985
- Van Maele-Fabry G, Libotte V, Willems J, Lison D (2006) Review and meta-analysis of risk estimates for prostate cancer in pesticide manufacturing workers. *Cancer Causes Control* 17:353–373
- Nordby KC, Andersen A, Kristensen P (2004) Incidence of lip cancer in the male Norwegian agricultural population. *Cancer Causes Control* 15:619–626
- Lemarchand C, Tual S, Leveque-Morlais N et al (2017) Cancer incidence in the AGRICAN cohort study (2005–2011). *Cancer epidemiology*. 49: 175–185
- Blair A, Zahm SH (1995) Agricultural exposures and cancer. *Environ Health Perspect* 103(Suppl 8):205–208
- Ramirez CC, Federman DG, Kirsner RS (2005) Skin cancer as an occupational disease: the effect of ultraviolet and other forms of radiation. *Int J Dermatol* 44:95–100
- Merchant J (1987) Agricultural exposures to organic dusts. *Occupational medicine (Philadelphia, Pa.)*. 2: 409–425
- Tual S, Silverman DT, Koutros S et al (2016) Use of dieselized farm equipment and incident lung cancer: findings from the agricultural health study cohort. *Environ Health Perspect* 124:611–618
- Koutros S, Beane Freeman LE, Lubin JH et al (2013) Risk of total and aggressive prostate cancer and pesticide use in the agricultural health study. *Am J Epidemiol* 177:59–74
- Alavanja MC, Hofmann JN, Lynch CF et al (2014) Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. *PLoS ONE* 9:e109332
- Freeman LEB, DeRoos AJ, Koutros S et al (2012) Poultry and livestock exposure and cancer risk among farmers in the agricultural health study. *Cancer Cause Control* 23:663–670
- Basinas I, Sigsgaard T, Kromhout H, Heederik D, Wouters IM, Schlunssen V (2015) A comprehensive review of levels and determinants of personal exposure to dust and endotoxin in livestock farming. *J Exposure Sci Environ Epidemiol* 25:123–137
- Alavanja MC, Sandler DP, McMaster SB et al (1996) The Agricultural Health Study. *Environ Health Perspect* 104:362–369
- Fritz AG (2000) International Classification of Diseases for Oncology: ICD-O: World Health Organization
- Morton LM, Turner JJ, Cerhan JR et al (2007) Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). *Blood* 110:695–708
- NAACCR (2016) SEER*Stat Database: NAACCR Incidence Data - CiNA Analytic File, 1995–2014, Public Use (which includes data from CDC's National Program of Cancer Registries (NPCR), CCCR's Provincial and Territorial Registries, and the NCI's Surveillance, Epidemiology and End Results (SEER) Registries), certified by the North American Association of Central Cancer Registries (NAACCR) as meeting high-quality incidence data standards for the specified time periods, submitted December 2016.: NAACCR
- Breslow NE, Lubin JH, Marek P, Langholz B (1983) Multiplicative models and cohort analysis. *J Am Stat Assoc* 78:1–12
- Breslow NE, Day N (1987) Statistical methods in cancer research Vol II-The design and analysis of cohort studies
- Pierce DA, Preston DL (1993) Joint analysis of site-specific cancer risks for the atomic-bomb survivors. *Radiat Res* 134:134–142
- CDC (1995) Behavioral risk factor surveillance system survey data. Centers for Disease Control and Prevention (CDC), Atlanta
- Lenters V, Basinas I, Beane-Freeman L et al (2010) Endotoxin exposure and lung cancer risk: a systematic review and meta-analysis of the published literature on agriculture and cotton textile workers. *Cancer Causes Control* 21:523–555
- Brucker-Davis F (1998) Effects of environmental synthetic chemicals on thyroid function. *Thyroid* 8:827–856
- Kitahara CM, Linet MS, Beane Freeman LE et al (2012) Cigarette smoking, alcohol intake, and thyroid cancer risk: a pooled analysis of five prospective studies in the United States. *Cancer Causes Control* 23:1615–1624
- Freeman LEB, Rusiecki JA, Hoppin JA et al (2011) Atrazine and cancer incidence among pesticide applicators in the agricultural health study (1994–2007). *Environ Health Perspect* 119:1253–1259
- Lerro CC, Koutros S, Andreotti G et al (2015) Organophosphate insecticide use and cancer incidence among spouses of pesticide

- applicators in the Agricultural Health Study. *Occupational and environmental medicine*. 72: 736–744
34. Goldner WS, Sandler DP, Yu F et al (2013) Hypothyroidism and pesticide use among male private pesticide applicators in the agricultural health study. *J Occup Environ Med* 55:1171–1178
 35. Goldner WS, Sandler DP, Yu F, Hoppin JA, Kamel F, Levan TD (2010) Pesticide use and thyroid disease among women in the Agricultural Health Study. *Am J Epidemiol* 171:455–464
 36. Shrestha S, Parks CG, Goldner WS et al (2018) Incident thyroid disease in female spouses of private pesticide applicators. *Environ Int* 118:282–292
 37. Lerro CC, Beane Freeman LE, Della Valle CT et al (2018) Occupational pesticide exposure and subclinical hypothyroidism among male pesticide applicators. *Occup Environ Med*. 75: 79–89
 38. Fleming LE, Bean JA, Rudolph M, Hamilton K (1999) Cancer incidence in a cohort of licensed pesticide applicators in Florida. *J Occup Environ Med* 41:279–288
 39. Frost G, Brown T, Harding AH (2011) Mortality and cancer incidence among British agricultural pesticide users. *Occupational medicine (Oxford, England)*. 61: 303–310
 40. McGlynn KA, Trabert B (2012) Adolescent and adult risk factors for testicular cancer. *Nat Rev Urol* 9:339–349
 41. Danzo BJ (1997) Environmental xenobiotics may disrupt normal endocrine function by interfering with the binding of physiological ligands to steroid receptors and binding proteins. *Environ Health Perspect* 105:294–301
 42. Liu Q, Lin JX, Shi QL, Wu B, Ma HH, Sun GQ (2011) Primary peritoneal serous papillary carcinoma: a clinical and pathological study. *Pathol Oncol Res* 17:713–719
 43. Liao CI, Chow S, Chen LM, Kapp DS, Mann A, Chan JK (2018) Trends in the incidence of serous fallopian tube, ovarian, and peritoneal cancer in the US. *Gynecol Oncol*. 149: 318–323
 44. Loomis D, Guyton KZ, Grosse Y et al (2017) Carcinogenicity of benzene. *Lancet Oncol* 18:1574–1575
 45. Greaves MF (1997) Aetiology of acute leukaemia. *Lancet* 349:344–349
 46. Beane Freeman LE, Blair A, Lubin JH et al (2009) Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. *J Natl Cancer Inst* 101:751–761
 47. Hauptmann M, Stewart PA, Lubin JH et al (2009) Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *J Natl Cancer Inst* 101:1696–1708
 48. Van Maele-Fabry G, Duhayon S, Lison D (2007) A systematic review of myeloid leukemias and occupational pesticide exposure. *Cancer Cause Control* 18:457–478
 49. Andreotti G, Koutros S, Hofmann JN et al (2017) Glyphosate use and cancer incidence in the agricultural health study. *J Natl Cancer Inst* 110:509–516
 50. Lerro CC, Andreotti G, Koutros S et al (2018) Alachlor use and cancer incidence in the agricultural health study: an updated analysis. *J Natl Cancer Inst*
 51. Andreotti G, Freedman ND, Silverman DT et al (2017) Tobacco use and cancer risk in the agricultural health study. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 26: 769–778
 52. Blomberg M, Nielsen A, Munk C, Kjaer SK (2011) Trends in head and neck cancer incidence in Denmark, 1978–2007: focus on human papillomavirus associated sites. *Int J Cancer* 129:733–741
 53. Dunne EF, Unger ER, Sternberg M et al (2007) Prevalence of HPV infection among females in the United States. *JAMA* 297:813–819
 54. Han JJ, Beltran TH, Song JW, Klaric J, Choi YS (2017) Prevalence of genital human papillomavirus infection and human papillomavirus vaccination rates among us adult men: National Health and Nutrition Examination Survey (NHANES) 2013–2014. *JAMA Oncol* 3:810–816
 55. Tual S, Lemarchand C, Boulanger M et al (2017) Exposure to farm animals and risk of lung cancer in the AGRICAN cohort. *Am J Epidemiol* 186:463–472
 56. Baron JA, Rohan TE (1996) Tobacco. In: Schottenfeld D, Fraumeni JF Jr (eds) *Cancer epidemiology and prevention*, 2nd edn. Oxford University Press, New York, pp 269–289
 57. Wakelee HA, Chang ET, Gomez SL et al (2007) Lung cancer incidence in never smokers. *J Clin Oncol* 25:472–478
 58. CDC (2009) Cigarette smoking among adults and trends in smoking cessation - United States, 2008. *MMWR. Morbidity and mortality weekly report*. 2009/11/17 ed: Centers for Disease Control and Prevention (CDC). pp. 1227–1232

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