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Body Mass Index, Agricultural Pesticide Use, and Cancer Incidence in the Agricultural Health Study Cohort

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Abstract

Obesity is associated with increased risks of several cancers including, colon, lower esophagus, kidney, female breast, and endometrium. Some studies have associated pesticides with higher risks of cancer in agricultural populations. The interaction between obesity and pesticide use on cancer risk has not been well studied. Using data from the Agricultural Health Study we examined the association between body mass index (BMI) and the risk of cancer at 17 sites, and the interaction between BMI and pesticide use. Pesticide applicators (primarily farmers), and their spouses residing in Iowa and North Carolina were enrolled between 1993 and 1997 and followed through 2005. This analysis included 39,628 men and 28,319 women who provided information on pesticide use, height and weight data, and were cancer-free at enrollment. Of all subjects, 64% were overweight or obese, and 4,432 incident cancers were diagnosed during the follow-up period. We found positive associations between BMI (continuous) and colon cancer among men (Hazard Ratio (HR) 1.05, 95% confidence interval (CI) 1.02–1.09) and breast cancer among postmenopausal women (HR 1.03, 95% CI 1.01–1.06), as well as an inverse association with lung cancer among men who were ever smokers (HR 0.92, 95% CI 0.88–0.96). Men who ever used carbofuran (HR=1.10, 95% CI 1.04–1.17), metolachlor (HR=1.09, 95% CI 1.04–1.15), and alachlor (HR=1.08, 95% CI 1.03–1.13) had significant positive associations between BMI and colon cancer, but non-users did not. Men who ever smoked and used carbofuran had a positive, although not significant, association between BMI and lung cancer, while users of carbofuran had a significant inverse association. These findings, which suggest that certain pesticides may modify the association between BMI and colon and lung cancer risk, should be further evaluated in other populations.

Keywords

obesity; body mass index; pesticides; cancer; agriculture

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Introduction

The prevalence of obesity in the U.S. has doubled since the 1980's. Currently, one-third of U.S. adults are obese and another third are overweight (Ogden, 2007). Obesity has been associated with higher risks of several cancers, including colon, lower esophagus, kidney, gallbladder, female breast, and endometrium (Calle, 2004; Semanic, 2004; Hjartaker, 2008;). The association between obesity and cancer is likely linked to several related factors including diabetes, hypertension, hyperlipidemia, low physical activity, and a high-fat diet (Hjartaker, 2008), and involve several possible biological mechanisms such as increased availability of growth and sex hormones, increased insulin, inflammation, altered immunity, cell proliferation, and angiogenesis (Calle, 2004; Hjartaker, 2008; Bianchini, 2002).

Excess cancer rates, particularly prostate, lymphohematopoietic, brain, stomach and soft-tissue tumors have been reported among agricultural workers and pesticide applicators and manufacturers around the world (Blair 1992; Keller-Byrne, 1997; Khuder, 1997; Khuder, 1999; Alavanja, 2007). Also, several epidemiological studies, have reported associations between specific pesticides and increased cancer risks (Alavanja, 2004; Alavanja Bonner 2005). It has been suggested that lipophilic pesticides, such as organochlorines, may increase cancer risk via their persistent accumulation in adipose tissue, slow release into the blood and peripheral tissues, and eventual impact on the endocrine system (IARC, 1991; Kelce, 1995; Soto, 1995). Because of the accumulation of lipophilic pesticides in adipose tissue, there is speculation that obese persons may have a greater capacity to accumulate and have a higher body burden of these contaminants (Schildkraut, 1999; Pelletier, 2002). Non-lipophilic pesticides have been linked to cancer via pathways closely related to obesity such as hormones and oxidative stress (Diamanti-Kandarakis, 2009; Slotkin, 2009). Furthermore, laboratory studies have reported that toxicants, including pesticides, may contribute to obesity (Baillie-Hamilton, 2002; Heindel, 2003; Irigaray, 2006). Together, these factors support the possibility of a joint effect of pesticides and obesity on cancer risk, but this has not been well studied in humans. In this analysis, we examine the association between body mass index (BMI) and the risk of cancer, as well as the interaction between BMI and pesticide use, in a population of U.S. farmers, pesticide applicators and spouses.

Materials and Methods

Study Subjects

Details of the AHS have been previously reported (Alavanja, 1996). Briefly, the AHS cohort is composed of over 89,000 participants, including licensed private pesticide applicators and their spouses residing in Iowa and North Carolina, and commercial applicators residing in Iowa. In total, 57,310, or 82%, of applicators seeking pesticide licensing in each state, were enrolled in the study between December 13, 1993 and December 31, 1997. In addition, spouses of enrolled private applicators were asked to participate, and a total of 32,346, or 75%, chose to participate. The study protocol was approved by all appropriate institutional review boards.

Data Ascertainment

At enrollment, applicators completed a self-administered questionnaire collecting information on demographics, lifestyle factors, medical histories, ever/never use of 50 pesticides, and detailed use information (number of days and years pesticides were applied, use of personal protective equipment, and application methods) on 22 of the 50 pesticides. A self-administered take-home questionnaire was given to all enrolled applicators to collect additional information, including weight, height, and detailed use on the other 28 pesticides. The take-home questionnaire was returned by 44% of the enrolled applicators. No meaningful differences were found between applicators who completed and did not complete the take-home questionnaire

(Tarone, 1997). For spouses, information on demographics, lifestyle factors, medical histories, and ever/never use of the same 50 pesticides was obtained from a self-administered questionnaire (81%) or telephone interview (19%), and height and weight data was only collected from the self-administered questionnaire. Of all participants, 43% were missing height and weight data. Thus, to supplement this missing data, two additional sources, the 5-year follow-up phone interview and driver's license data from 1985, were used. In Iowa, drivers' licenses contain height and weight information, while in North Carolina they contain only height. Approximately 70% of the cohort completed the 5-year follow-up phone interview and provided information on current height and weight. After using these additional sources, we had complete height and weight data on 67,947 participants (76% of total cohort). Of these subjects, 76% had height and weight from the take-home questionnaire, and the remaining 24% came from supplemental sources. Thus, it is possible that some cancers cases could have weight reported after their cancer diagnosis if they were diagnosed within the first 5 years after enrollment. Subjects with implausible BMI values were removed (<11 or >70 kg/m²). To have the most current menopause status of female participants, we used data from the 5-year follow-up phone interview. Questionnaires are available on the AHS website (www.aghealth.org/questionnaires.html).

Cancer Identification

Cancer cases were identified using population-based state cancer registries. Only incident cancer cases diagnosed between enrollment and December 31, 2005 (median follow-up of over 10 years) were included, and participants with any type of cancer diagnosed prior to enrollment were excluded from the analysis. Vital status was obtained from the state death registries and the National Death Index. Participants who moved out of North Carolina or Iowa (based on IRS record) were not followed for cancer occurrence after moving and follow-up times were censored at date of exit from the state.

Statistical Analysis

For this study, we included participants with weight and height data, which totaled 38,190 private applicators, 2,325 commercial applicators, and 27,432 spouses. BMI was calculated as weight (kg) divided by the square of height (m²), and grouped as follows: underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obese I (30.0–34.9 kg/m²) and obese II/III (≥ 35 kg/m²) (WHO, 1998). The chi-square test was used to assess statistically significant differences between BMI groups and selected characteristics.

Associations between BMI and cancer were evaluated separately by sex due to their differences in risk factors for cancer. There were a sufficient number of cases (at least 10 for each sex) to examine 17 cancer sites. Hazard rate ratios (HR) and 95% confidence intervals (95% CI) were calculated using a Cox Proportional-Hazard regression model using age at enrollment and age at exit (minimum of: cancer diagnosis, death, or end of follow-up (December 31, 2005)) as the start and end of follow-up, respectively. A backward elimination procedure was conducted in order to determine the most parsimonious model for each of the 17 cancers evaluated. Initially, models included the following potential confounding factors: race (white, other), state of residence (Iowa, North Carolina), education (high school or lower, greater than high school), smoking status (never, former, current), alcohol intake in past 12 months (no, yes), hypertension (no, yes), diabetes (no, yes), family history of cancer (no, yes), meat intake (≤ 3 per month, 1–2 per week, ≥ 3 per week), fruit intake (<1 per day, 1–2 per day, ≥ 3 per day), vegetable intake (<1 per day, 1–2 per day, ≥ 3 per day), vitamin supplement (no, yes-not regularly, yes-regularly), and leisure-time exercise (0, <1 , 1–2, 3–5, >5 hours per week), as well as menopause status (pre, post) and parity (0, 1, 2, 3, 4, >4) for women. Iteratively, the factor with the highest p-value above 0.05 was removed from the model until only those factors that contributed 10% or more change in the HR remained. BMI values were generally normally

distributed, thus we also examined associations between BMI and cancer using a linear test of trend with a continuous BMI variable.

For the interaction between BMI and pesticide use, we examined pesticides used by at least 10% of male participants (36 pesticides: 16 insecticides, 17 herbicides, 2 fungicides, 1 fumigant), and 10% of female participants (5 pesticides: 3 insecticides, 2 herbicides). We also examined use of any organochlorine insecticide (aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphene) and any organophosphate insecticide (chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, trichlorofon). The cancer sites examined were those with at least 100 cases per sex (bladder, colon, lung, melanoma, non-Hodgkin lymphoma, prostate, and rectal for men; and breast and colon for women). Tests of interaction between ever/never pesticide use and continuous BMI were conducted using a cross-product interaction term in the Cox regression model. We also calculated HRs and 95% CIs for cancer risk in relation to BMI (<25, 25–29.9, and ≥ 30 kg/m²) stratified by ever/never use of each pesticide using a Cox regression model with the appropriate adjustments for each cancer. Associations with less than 5 exposed subjects per BMI category were not evaluated. SAS version 9.1 (Cary, NC) and the AHS data release PIREL0612 were used to conduct all analyses.

Results

Of the 67,947 subjects, 0.8% were underweight, 34.8% were normal, 43% were overweight, 16.7% were moderately obese (obese I) and 4.7% were highly obese (obese II/III) (Table 1). Compared to normal weight subjects, underweight subjects were more likely to be women, young (<40 years) or old (≥ 70 years), current smokers, never alcohol drinkers, non-hypertensives, high fruit consumers (≥ 3 servings/day), and do no or little exercise. In contrast, compared to normal weight subjects, overweight or obese subjects were more likely to be men, middle-aged (40–69), lower educated (high school or less), former smokers, hypertensive, diabetic, low fruit and vegetable consumers, not take vitamin supplements, and do no or little exercise.

We found a statistically significant positive linear trend for BMI and colon cancer among men (HR 1.05, 95% CI 1.02–1.09; p-trend=0.005) adjusting for race, education, and family history of colon cancer (Table 2). Overweight men had a 1.26-fold (95% CI=0.86–1.86), obese I men a 1.88-fold (95% CI=1.23–2.91), and obese II/III men a 2.03-fold (95% CI=1.05–3.93) risk compared to normal weight men. For rectal cancer, obese II/III men had a 3.21-fold (95% CI=1.34–7.71) risk compared to normal weight men adjusting for meat consumption, but the test of trend was not statistically significant. We also observed increased, but not statistically significant, risks of stomach and bladder cancers with higher BMI. In contrast, the risks of lung and oral cancers decreased with higher BMI. Stratifying by smoking status, we found a statistically significant test of trend for lung cancer among ever smokers (HR=0.93, 95% CI=0.88–0.97, p-trend=0.001) adjusting for state, race, vegetable consumption, exercise, and pack-years of cigarette smoking. There were only 21 men with lung cancer who never smoked, thus we could not completely calculate risk estimates for this group or the test of interaction between smoking status and BMI. In order to rule out the possibility of weight loss due to preclinical disease, we restricted the cases of lung cancer among ever smokers to those diagnosed 2 or 5 years after enrollment and found that the inverse association with BMI remained (2 years: HR=0.94, 95% CI=0.89–0.99, p-trend=0.01; 5 years: HR=0.93; 95% CI=0.88–0.99, p-trend=0.02).

Among women, we found statistically significant positive linear trend for BMI and all cancer sites combined (HR=1.02, 95% CI=1.01–1.04; p-trend=0.001) adjusting for smoking status, hypertension, taking vitamin supplements, and parity; and specifically for postmenopausal

breast cancer (HR=1.03, 95% CI =1.01–1.06; p-trend=0.02) adjusting for diabetes, vitamin supplement, parity, and family history of breast cancer. For breast cancer, overweight postmenopausal women had a 1.22-fold (95% CI 0.93–1.60), obese I a 1.62-fold (95% CI 1.17–2.24), and obese II/III a 1.07-fold (95% CI 0.61–1.88) risk compared to normal weight postmenopausal women. To explore the null association for breast cancer in obese II/III women, we compared the frequency of the factors in Table 1 between the obese I and II postmenopausal women using the chi-square test, and found that only alcohol consumption was significantly different (p=0.02), with 50% of the obese II versus 26% of the obese I women ever drinking alcohol. Stratifying by alcohol consumption, the linear trend for BMI and breast cancer among postmenopausal women was statistically significant among those who never drank alcohol (HR=1.05, 95% CI=1.02–1.08, p-trend=0.003), but not among those who drank alcohol (HR=1.00, 95% CI=0.95–1.04, p-trend=0.85) (p-interaction=0.01). In addition to breast cancer, women with higher BMI had increased, but not statistically significant, risks of pancreatic and kidney cancers, and melanoma. BMI was not associated with colon cancer in women (HR=0.99, 95% CI 0.95–1.04). Also, the risk of lung cancer decreased with increasing BMI, but the test of trend was not statistically significant for all women, ever smokers, or those diagnosed 2 or 5 years after enrollment.

For the interaction between pesticide use and BMI on colon cancer risk in men, we evaluated 22 pesticides that were used by at least 10% of the male study population and for which there were at least 5 cancer cases in each BMI group, as well as any organochlorine or organophosphate insecticide (Table 3). Of these 22 pesticides, carbofuran, metolachlor and alachlor had statistically significant ($p \leq 0.05$) modifying effects. Specifically, BMI was significantly associated with colon cancer among male users of carbofuran (HR=1.10, 95% CI 1.04–1.17, p-trend=0.002), but not among non-users of carbofuran (HR=1.02, 95% CI 0.97–1.06, p-trend=0.52). Similarly, BMI was significantly associated with colon cancer among male users of metolachlor (HR=1.09, 95% CI 1.04–1.15, p-trend=0.001) and alachlor (HR=1.08, 95% CI 1.03–1.13, p-trend=0.002), but not among non-users of each of these herbicides (No metolachlor: HR=1.01, 95% CI 0.96–1.06, p-trend=0.70; No alachlor: HR=1.01, 95% CI 0.95–1.06, p-trend=0.87). To explore possible confounding by use of multiple pesticides, we examined the correlation between never/ever use of carbofuran, metolachlor and alachlor among male participants and found that they were not highly correlated (metolachlor and alachlor $r=0.31$, metolachlor and carbofuran=0.18, and alachlor and carbofuran=0.26). We also examined whether each of these pesticides still had statistically significant modifying effects when we further adjusted for use of the other two pesticides, and found that the test of interaction was still statistically significant (<0.05). In addition to these three pesticides, we also found that men who used DDT, fonofos, malathion, carbaryl, permethrin, atrazine, cyanazine, trifluralin, EPTC, imazethpyr, and glyphosate had significant associations between BMI and colon cancer, but non-users of these pesticides did not, and the tests of interaction were not statistically significant. Furthermore, we also observed that men who did not use terbufos, chlorpyrifos, metribuzin, pendimethalin, chlorimuron-ethyl, and methyl bromide had significant associations between BMI and colon cancer, but users of these pesticides did not, and tests of interaction were not statistically significant.

We evaluated the interaction between pesticide use and BMI on postmenopausal breast cancer for four pesticides used by at least 10% of the women in the study population and for which there were at least 5 cancer cases in each BMI group, as well as any organochlorine or organophosphate insecticide. There was no evidence of a significant interaction between pesticide use and BMI on breast cancer risk among postmenopausal women; however, women who did not use malathion, diazinon, carbaryl or any organochlorine insecticide or any organophosphate insecticide had significant associations between BMI and breast cancer, but users did not. The significant associations among non-users of these pesticides remained

statistically significant among women who did not drink alcohol, but not among women who drank alcohol.

We also examined the interactions between pesticide use and BMI on the risks of lung, bladder, prostate, and rectal cancers, and NHL and melanoma in men, as well as colon cancer in women. For lung cancer among male ever smokers, we found that the inverse effect of BMI was statistically significant among non-users of carbofuran (HR=0.87, 95% CI=0.82–0.92, p-trend=<0.0001), but not among users (HR=1.01, 95% CI=0.93–1.09; p-trend=0.77) (p-interaction=0.02). We did not find any other statistically significant modifying effects on any of the other associations examined.

Discussion

In our AHS population of U.S. farmers and their spouses and commercial pesticide applicators, 64% were overweight or obese, which is comparable to the frequency reported in the non-Hispanic white U.S. population, but our population had a higher frequency of overweight (43%) and lower frequency of obesity (21%) than the U.S. population, where 33% are overweight and 31% are obese (Ogeden, 2006). The frequency of overweight and obesity in our population was similar to the frequency reported in an Austrian farming population where 43% were overweight and 15% obese (Dorner, 2004). The mean BMI in our study population (27.6 kg/m²) is very close to the mean BMI reported in New York dairy farmers (26.9 kg/m²) (Jenkins, 2004).

Consistent with previous studies, we found a significant positive association between BMI and colon cancer among men (Samanic, 2006; Rapp, 2005; Samanic, 2004; Moore, 2004). This association was not significantly modified by diet (meat, fruit, vegetable consumption) or leisure-time exercise, which is also in agreement with a previous study of male health professionals that showed an association between BMI and colon cancer independent of physical activity (Giovanuucci, 1995). Obesity has been suggested to contribute to colon cancer via increased leptin that is linked to growth of colonic epithelial cells (Hardwick, 2001), and increased insulin-like growth factor (IGF) that promotes tumor growth (Calle, 2004). We found no association between BMI and colon cancer among women, which has also been previously observed and attributed to waist size being a stronger predictor of colon cancer than BMI in women (Rapp, 2005; Moore, 2004).

We found that men who used metolachlor, alachlor, and carbofuran had significant positive associations between BMI and colon cancer, but non-users did not, with statistically significant interactions. The modifying effects of each of these pesticides remained statistically significant when adjusting for reported use of the other two pesticides. These findings suggest that pesticides somehow modify the carcinogenic effect of obesity, although the current understanding of the effect of pesticides in humans is limited. Alachlor and metolachlor are chloroacetanilide herbicides that have a chlorinated amide chemical structure (Kidd). Carbofuran is a carbamate insecticide that inhibits cholinesterase and has been shown to generate reactive oxygen species and induce lipid peroxidation (Kamboj et al., 2006). Based on U.S. EPA guidelines, alachlor is classified as a likely human carcinogen at high doses, but a non-likely carcinogen at low doses, metolachlor is as possible carcinogen, and carbofuran a non-likely carcinogen (Kegly, 2009). None of these three pesticides have been linked to colon cancer in the AHS (Rusiecki, 2006; Lee 2004; Bonner, 2005) or reported in other populations. The effect of these pesticides on obesity has not been reported. We found that users of metolachlor, alachlor, and carbofuran had slightly higher and statistically significant mean BMIs than non-users, adjusting for age, sex, and education, providing some additional evidence that the metabolism of these pesticides may be linked to obesity-related factors.

We also observed that men who used 11 other pesticides [insecticides: carbaryl (carbamate), fonofos and malathion (organophosphates), DDT (organochlorine), permethrin (pyrethroid)]; herbicides: atrazine and cyanazine (triazine), trifluralin (dinitroaniline), EPTC (thiocarbamate), imazethypyr (imidazolinone), glyphosate (phosphinic)] had positive associations between BMI and colon cancer, but non-users did not, and the interaction tests were not statistically significant. Of these, atrazine, cyanazine, trifluralin, and imazethypyr have an aromatic amine chemical structure (Kidd). Previous studies in the AHS reported that use of two aromatic amine pesticides, imazethypyr (Koutros) and trifluralin (Kang) were linked to increased colon cancer risk. Aromatic amine compounds, mostly those formed from meats cooked at high temperatures, have been linked to colon cancer (Butler, 2003; Nowell, 2002). It is important to note that we also observed that non-users of six pesticides [insecticide: terbufos and chlorpyrifos (organophosphate); herbicides: metribuzin (triazinone), pendimethalin (dinitroaniline), chlormurion-ethyl (urea); fumigant: methyl bromide] had significant associations between BMI and colon cancer, but users did not (interaction tests were not statistically significant). Of these, pendimethalin and chlormurion-ethyl are also aromatic amine compounds (Kidd). The occurrence of significant associations among users and non-users of pesticides in the same chemical group may indicate that these are chance findings.

Our finding of an inverse association between BMI and lung cancer in men, particularly in ever smokers, is consistent with previous studies (Renehan, 2008). For example, a meta-analysis of five prospective studies of BMI and lung cancer reported a statistically significant summary risk ratio of 0.76 (95% CI 0.67–0.85) among smokers, but not among non-smokers (RR=0.91, 95% CI 0.76–1.10) (Renehan, 2008). This could be due to uncontrolled confounding from smoking because smokers have lower BMIs and a higher risk for lung cancer (Canoy, 2005). In the AHS, underweight subjects were more likely to be current smokers, while overweight/obese subjects were more likely to be former smokers compared to normal weight subjects. Also, current smoking was associated with a significant 4-fold risk of lung cancer among men in our study population. Leanness due to preclinical disease did not appear to be a confounding factor in our study or other previous studies (Kark, 1995; Olson, 2002; Kanashiki, 2005). Biological mechanisms explaining the relationship between leanness and lung cancer risk among smokers is not well understood, but it has been suggested that leanness may serve as a marker of vulnerability to the effects of smoking either through acquired or inherited factors (Sidney, 1987; Shields, 1991).

The slight positive association between BMI and lung cancer among male ever smokers who used carbofuran, but the statistically significant inverse association among non-users of carbofuran, suggests that carbofuran use may interact with obesity to increase the risk of lung cancer. This observation corroborates previous findings from the AHS that found elevated risks of lung cancer with reported use of carbofuran (Alavanja, 2004; Bonner, 2005).

The positive association between BMI and breast cancer among postmenopausal women is in agreement with previous studies (Carmichael 2004, Kuriyama 2005). The main source of estrogen in postmenopausal women is from androstenedione in adipocytes; therefore, heavier postmenopausal women tend to produce more estrogen, which is linked to higher cell proliferation and DNA damage (LaGuardia 2001). In pre-menopausal women, regular anovulatory cycle reduces exposure to estrogen and decreases their breast cancer risk (Carmichael 2004, Potischman, 1996). It is unclear why the positive association between BMI and breast cancer was apparent in those who did not drink, since alcohol consumption is considered a risk factor for postmenopausal breast cancer due to the decrease in the clearance of estradiol (Wayne, 2008; Duffy, 2008). In our population, ever alcohol drinking was associated with an excess risk of postmenopausal breast cancer in women with a BMI <25 kg/m² (HR=1.25, 95% CI=0.85–1.86), but not in women with a BMI ≥25 kg/m² (HR=0.87, 95% CI=0.63–1.19). The interaction between BMI and alcohol consumption was also found in a

case-control study that reported that one drink per day was associated with estrogen receptor positive tumors in women with a BMI < 25 kg/m², but not in women with a BMI ≥ 25 kg/m² (Terry, 2006). A few other studies have suggested that alcohol intake and BMI may only be risk factors for certain histologic types of breast cancer (Suzuki, 2008; Li 2006), which we were not able to evaluate in our study.

The positive associations between BMI and postmenopausal breast cancer were present among women who did not use malathion, diazinon, carbaryl or any organophosphate or organochlorine insecticide, but not in women who used these pesticides. Since this modifying effect was not specific to a particular pesticide, this finding appears to suggest some uncontrolled difference between women who applied and did not apply pesticides. A previous study of breast cancer in the AHS found that women who never applied pesticides, including organophosphates or organochlorines, had higher risks of breast cancer than women who applied pesticides (Engel, 2005). This previous finding together with our observations is suggestive of possible protective effect of working on the farm for breast cancer.

This study has several important strengths. Due to the prospective study design, pesticide use and other self-reported data was obtained prior to cancer diagnosis, thus any recall bias should be non-differential and unlikely to create false-positive associations. Self-reported pesticide use among farmers in the AHS has been shown to be reasonably reliable (Blair, 2002; Hoppin 2002). Detailed demographic, lifestyle, and medical history data allowed us to adjust for several important risk factors. Misclassification of cancer diagnoses is unlikely given the linkage to population-based state cancer registries.

There also are limitations to this study. Although BMI is a well-defined indicator of obesity, it has been shown to overestimate obesity in athletes (Ode, 2007). This potentially could have occurred in our population given the physical activity of farmers, but the total prevalence of overweight and obesity was in agreement with that reported in the U.S. population. Due to the use of additional data sources to supplement missing height and weight, it is possible that some cancer cases had weight reported after their cancer diagnosis if they were diagnosed within the first 5 years after enrollment. This potentially could have resulted in lower weight values due to the effects of disease in cancer cases; however for lung cancer risk, we excluded cases diagnosed within the first 2 and 5 years of enrollment, and found the associations were not altered. Since we examined the interactions of several pesticides, it is possible that some of our results could have occurred by chance alone. Also, it is not clear whether pesticide use resulted in obesity, or if heavier people used certain pesticides, since pesticide use was reported as ever use and BMI was recorded at or near enrollment. Furthermore, since the mechanisms by which pesticides may interact with BMI on cancer risk in humans are unclear, our findings should be considered hypothesis generating for future studies.

In conclusion, in this U.S. population of farmers, pesticide applicators and their spouses, we confirmed previous findings that BMI is positively associated with colon cancer in men and with breast cancer in postmenopausal women, as well as inversely associated with lung cancer among men who ever smoked. This is the first large prospective cohort study with the capacity to examine possible modifying effects of several pesticides on the association between BMI and several cancer sites. The findings from this analysis, which suggest that certain pesticides may modify the association between BMI and colon and lung cancer risk, should be further evaluated in other populations.

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Table 1

Distribution of Study Population by BMI categories and Selected Characteristics

Characteristics	Total		Underweight BMI <18.5 kg/m ²		Normal Weight BMI 18.5– 24.9 kg/m ²		Overweight BMI 25–29.9 kg/m ²		Obese I BMI 30–34.9 kg/ m ²		Obese II+III BMI ≥35 kg/ m ²	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
All Subjects	67,947	(100.0)	513	(0.8)	23,620	(34.8)	29,235	(43.0)	11,356	(16.7)	3,223	(4.7)
Sex												
Male	39,628	58.3	81	15.8	10,108	42.8	20,151	68.9	7,460	65.7	1,828	56.7
Female	28,319	41.7	432	84.2	13,512	57.2	9,084	31.1	3,896	34.3	1,395	43.3
<i>P-value[†]</i>						<.0001		<.0001		<.0001		<.0001
Age (years)												
<40	21,122	31.1	240	46.8	8,853	37.5	8,208	28.1	2,934	25.8	887	27.5
40–49	19,116	28.1	110	21.4	6,169	26.1	8,233	28.2	3,509	30.9	1,095	34.0
50–59	15,398	22.7	77	15.0	4,561	19.3	7,004	24.0	2,925	25.8	831	25.8
60–69	9,619	14.2	50	9.8	2,943	12.5	4,628	15.8	1,647	14.5	351	10.9
70+	2,692	4.0	36	7.0	1,094	4.6	1,162	4.0	341	3.0	59	1.8
<i>P-value[†]</i>						<.0001		<.0001		<.0001		<.0001
Race												
White	65,150	98.0	491	98.0	22,836	98.6	28,038	98.1	10,761	97.1	3,024	95.8
Other	1,338	2.0	10	2.0	319	1.4	554	1.9	322	2.9	133	4.2
<i>P-value[†]</i>						0.24		<.0001		<.0001		0.0003
Residence												
Iowa	45,158	66.5	281	54.8	15,708	66.5	19,569	66.9	7,508	66.1	2,092	64.9
North Carolina	22,789	33.5	232	45.2	7,912	33.5	9,666	33.1	3,848	33.9	1,131	36.4
<i>P-value[†]</i>						<.0001		0.29		0.11		0.20
Participant Type												
Private applicator	38,190	56.2	88	17.2	9,873	41.8	19,307	66.0	7,170	63.1	1,752	54.4
Commercial applicator	2,325	3.4	10	2.0	671	2.8	1,103	3.8	422	3.7	119	3.7
Spouse	27,432	40.4	415	80.9	13,076	55.4	8,825	30.2	3,764	33.2	1,352	41.9
<i>P-value[†]</i>						<.0001		<.0001		<.0001		<.0001
Education												

Characteristics	Total		Underweight BMI <18.5 kg/m ²	Normal Weight BMI 18.5– 24.9 kg/m ²	Overweight BMI 25–29.9 kg/m ²	Obese I BMI 30–34.9 kg/ m ²	Obese II+III BMI ≥35 kg/ m ²
High school or lower	32,722	51.9	201	10,077	14,846	5,904	1,694
Greater than high school	30,284	48.1	267	11,620	12,488	4,645	1,264
<i>P-value[†]</i>				0.13	<.0001	0.004	0.17
Smoking status							
Never	40,203	61.4	313	14,737	16,816	6,453	1,884
Former	16,661	25.4	61	4,598	7,871	3,239	892
Current	8,616	13.2	110	3,374	3,558	1,247	327
<i>P-value[†]</i>				<.0001	<.0001	0.0001	0.20
Smoking pack-years							
0	40,203	62.4	313	14,737	16,816	6,453	1,884
1–12	13,287	20.6	95	4,438	5,872	2,269	613
≥13	10,927	17.0	74	3,265	5,016	2,017	555
<i>P-value[†]</i>				0.88	<.0001	0.30	0.21
Number cigarettes per day							
0	40,203	61.8	313	14,737	16,816	6,453	1,884
≤10	7,953	12.2	59	2,810	3,442	1,300	342
11–20	10,010	15.4	81	3,327	4,553	1,645	404
21–40	5,859	9.0	29	1,558	2,709	1,217	346
>40	982	1.5	2	162	470	242	106
<i>P-value[†]</i>				0.64	<.0001	<.0001	0.0001
Alcohol drinking year prior enrollment							
No	24,681	38.3	230	8,691	10,292	4,183	1,285
Yes	39,813	61.7	253	13,856	17,384	6,551	1,769
<i>P-value[†]</i>				<.0001	0.01	0.001	0.002
Frequency of alcohol drinking year prior enrollment							
None	24,681	38.3	230	8,691	10,292	4,183	1,285
1–5	21,352	33.1	172	7,873	8,747	3,499	1,061
≥6	18,461	28.6	81	5,983	8,637	3,052	708
<i>P-value[†]</i>				<.0001	0.002	<.0001	<.0001
Ever diagnosed with hypertension							

Characteristics	Total	Underweight BMI <18.5 kg/m ²	Normal Weight BMI 18.5– 24.9 kg/m ²	Overweight BMI 25–29.9 kg/m ²	Obese I BMI 30–34.9 kg/ m ²	Obese II+III BMI ≥35 kg/ m ²						
No	42,669	84.5	443	94.5	17,432	91.3	17,178	83.7	6,026	74.7	1,590	67.3
Yes	7,849	15.5	26	5.5	1,660	8.7	3,346	16.3	2,045	25.3	772	32.7
<i>P-value</i> [†]						0.02		<.0001		<.0001		<.0001
Ever diagnosed with diabetes												
No	63,437	96.6	481	98.0	22,421	98.1	27,338	96.8	10,357	94.6	2,840	91.4
Yes	2,202	3.4	10	2.0	423	1.9	907	3.2	596	5.4	266	8.6
<i>P-value</i> [†]						0.76		<.0001		<.0001		<.0001
Family history of cancer												
No	38,429	56.6	317	61.8	13,278	56.2	16,651	57.0	6,368	56.1	1,815	56.3
Yes	29,518	43.4	196	38.2	10,342	43.8	12,584	43.0	4,988	43.9	1,408	43.7
<i>P-value</i> [†]						0.01		0.09		0.11		0.81
Frequency of meat consumption year prior enrollment												
≤3 times per month or less	3,032	6.6	46	10.4	1,309	7.8	1,179	6.2	410	5.5	88	4.1
1–2 times per week	23,055	50.1	228	51.7	8,899	52.7	9,518	49.9	3,439	46.0	971	45.1
≥3 times per week	19,931	43.3	167	37.9	6,676	39.5	8,364	43.9	3,628	48.5	1,096	50.9
<i>P-value</i> [†]						0.11		<.0001		<.0001		0.04
Fruit consumption year prior enrollment (servings/day)												
<1	37,401	62.1	270	59.3	11,796	57.8	16,952	64.5	6,609	64.8	1,774	62.1
1–2	20,323	33.8	150	33.0	7,559	37.0	8,433	32.1	3,222	31.6	959	33.6
≥3	2,488	4.1	35	7.7	1,064	5.2	898	3.4	366	3.6	125	4.4
<i>P-value</i> [†]						0.03		<.0001		0.50		0.01
Vegetable consumption year prior enrollment (servings/day)												
<1	26,255	43.7	187	41.1	8,264	40.6	11,985	45.7	4,612	45.3	1,207	42.3
1–2	28,693	47.8	212	46.6	10,136	49.8	12,238	46.7	4,733	46.5	1,374	48.1
≥3	5,129	8.5	56	12.3	1,974	9.7	1,997	7.6	829	8.2	273	9.6
<i>P-value</i> [†]						0.13		<.0001		0.20		0.02
Vitamin or mineral supplements year prior enrollment												
No	25,002	54.9	187	43.0	8,064	48.2	10,908	56.0	4,560	61.5	1,283	60.0
Yes, not regularly	8,270	18.2	85	19.5	3,275	19.6	3,290	17.5	1,258	17.0	362	16.9
Yes, at least once/week	12,248	26.9	163	37.5	5,379	32.2	4,622	24.5	1,590	21.5	494	23.1

Characteristics	Total		Underweight BMI <18.5 kg/m ²	Normal Weight BMI 18.5– 24.9 kg/m ²	Overweight BMI 25–29.9 kg/m ²	Obese I BMI 30–34.9 kg/ m ²	Obese II+III BMI ≥35 kg/ m ²				
<i>P-value</i> ¹				0.04	<.0001	<.0001	0.24				
Strenuous leisure exercise (hours/week) ²											
0	10,391	22.7	128	3,431	20.4	4,339	22.0	1,893	25.5	600	27.9
>0 and <1	7,988	17.5	66	2,684	16.0	3,405	18.0	1,367	18.4	466	21.7
1–2	8,270	18.1	81	3,106	18.5	3,429	18.1	1,299	17.5	355	16.5
3–5	10,241	22.4	80	4,214	25.1	4,030	21.3	1,533	20.6	384	17.9
> 5	8,842	19.3	82	3,370	20.1	3,701	19.6	1,346	18.1	343	16.0
<i>P-value</i> ¹				<.0001	<.0001	0.0004	<.0001				0.0001
Lifetime pesticide use (days) ³											
0	11,947	19.7	206	5,750	27.8	3,763	14.2	1,635	16.0	593	20.8
1–50	13,149	21.7	112	5,126	24.8	5,382	20.3	1,969	19.3	560	19.6
51–178	13,114	21.6	62	4,003	19.3	6,213	23.5	2,258	22.2	578	20.2
179–369	10,680	17.6	27	2,910	14.1	5,275	19.9	1,983	19.5	485	17.0
≥370	11,787	19.4	34	2,924	14.1	5,838	22.1	2,351	23.1	640	22.4
<i>P-value</i> ¹				<.0001	<.0001	<.0001	<.0001		<.0001		<.0001
Menopause Status ⁴											
Premenopausal	10,021	41.0	161	5,355	46.8	2,866	35.8	1,177	34.3	462	37.4
Postmenopausal	14,411	59.0	163	6,080	53.2	5,144	64.2	2,252	65.7	772	62.6
<i>P-value</i> ¹					0.31	<.0001	<.0001		0.14		0.05
Parity											
0	262	1.6	6	141	1.8	72	1.4	32	1.4	11	1.3
1	1,922	11.5	55	1,015	12.7	516	9.6	234	10.2	102	12.3
2	5,989	35.9	100	3,066	38.5	1,833	34.3	722	31.4	268	32.3
3	4,802	28.7	61	2,236	28.1	1,601	29.9	675	29.3	229	27.6
4	2,293	13.7	21	981	12.3	785	14.7	380	16.5	126	15.2
>4	1,438	8.6	11	529	6.6	544	10.2	259	11.3	95	11.4
<i>P-value</i> ¹					0.001	<.0001	<.0001		0.08		0.55

¹ Chi square P-value comparing distribution of underweight to normal weight, overweight to normal, moderate obese to overweight, and highly obese to moderate obese, respectively

² Summer and winter exercise combined

³ Includes any pesticide use

⁴ Menopause status based on Phase II questionnaire data

Table 2
Hazard Rate Ratio (HR) and 95% Confidence Intervals (CI) for cancers in relation to BMI at enrollment by sex

Cancer	Men				Women			
	N	HR ^I	95%CI ^I		N	HR ^I	95%CI ^I	
BMI (kg/m²)								
All Cancers²	2,955	-	-	-	1,477	-	-	-
<18.5	4	-	-		20	0.88	0.79-0.98	
18.5-24.9	724	1.00	Ref		608	1.00	Ref	
25-29.9	1,559	1.07	0.95-1.20		516	1.14	0.89-1.33	
30-34.9	556	1.05	0.91-1.21		240	1.28	1.05-1.56	
≥35	112	1.13	0.88-1.46		93	1.36	1.01-1.82	
<i>trend^I</i>		1.01	0.99-1.02	0.24		1.02	1.01-1.04	0.001
Oral, Larynx, Pharynx³	74	-	-	-	14	-	-	-
<18.5	0	-	-		0	-	-	
18.5-24.9	24	1.00	Ref		6	1.00	Ref	
25-29.9	61	1.30	0.79-2.13		7	1.12	0.34-3.69	
30-34.9	13	0.69	0.34-1.44		3	-	-	
≥35	2	-	-		0	-	-	
<i>trend^I</i>		0.97	0.92-1.02	0.25		1.00	0.89-1.11	0.93
Lung⁴	261	-	-	-	96	-	-	-
<18.5	2	-	-		2	-	-	
18.5-24.9	86	1.00	Ref		47	1.00	Ref	
25-29.9	127	0.85	0.60-1.20		33	0.99	0.63-1.55	
30-34.9	40	0.85	0.54-1.35		10	0.67	0.33-1.38	
≥35	6	0.47	0.15-1.49		4	-	-	
<i>trend^I</i>		0.97	0.93-1.01	0.12		0.99	0.95-1.05	0.63
Lung⁵ (Ever Smokers)	228				64			
<18.5	1	-	-		1	-	-	
18.5-24.9	78	1.00	Ref		30	1.00	Ref	
25-29.9	108	0.60	0.42-0.87		22	0.97	0.56-1.68	
30-34.9	35	0.56	0.35-0.91		8	0.77	0.35-1.70	

Cancer	Men			Women		
	N	HR ^I	95%CI ^I	N	HR ^I	95%CI ^I
BMI (kg/m ²)						
≥35	6	0.19	0.05–0.80	3	-	-
trend ^I		0.93	0.88–0.97	0.001	0.98	0.93–1.03
Lung ^J (Never Smokers)	21	-	-	30	-	-
<18.5	1	-	-	0	-	-
18.5–24.9	4	1.00	Ref	17	1.00	Ref
25–29.9	14	2.03	0.66–6.24	11	0.76	0.36–1.62
30–34.9	2	-	-	1	-	-
≥35	0	-	-	1	0.93	0.85–1.12
trend ^I		0.93	0.82–1.06	0.27	-	-
Thyroid ⁷	27	-	-	38	-	-
<18.5	0	-	-	0	-	-
18.5–24.9	8	1.00	Ref	13	1.00	Ref
25–29.9	15	0.91	0.38–2.20	18	1.71	0.82–3.57
30–34.9	4	-	-	6	1.08	0.38–3.09
≥35	0	-	-	1	-	-
trend ^I		0.94	0.85–1.05	0.29	1.04	0.98–1.11
Esophagus ⁸	39			1	-	-
<18.5	0	-	-	1	-	-
18.5–24.9	23	1.00	Ref	0	-	-
25–29.9	9	2.09	0.84–5.15	0	-	-
30–34.9	1	-	-	0	-	-
≥35	0	-	-			
trend ^I		1.01	0.94–1.10	0.73		
Stomach ⁹	41	-	-	13	-	-
<18.5	0	-	-	1	-	-
18.5–24.9	10	1.00	Ref	5	1.00	Ref
25–29.9	18	0.96	0.44–2.10	6	1.38	0.42–4.53
30–34.9	10	1.61	0.66–3.91	1	-	-

Cancer	Men			Women		
	N	HR ^I	95%CI ^I	N	HR ^I	95%CI ^I
BMI (kg/m ²)						
≥35	3	-	-	0	-	-
<i>trend^I</i>		1.07	0.99–1.14	0.14	0.95	0.83–1.07
						0.41
Pancreatic ^{I0}						
45	45	-	-	21	-	-
<18.5	1	-	-	0	-	-
18.5–24.9	11	1.00	Ref	6	1.00	Ref
25–29.9	24	1.11	0.54–2.27	7	1.30	0.43–3.90
30–34.9	8	1.06	0.42–2.65	6	2.48	0.79–7.83
≥35	1	-	-	2	-	-
<i>trend^I</i>		0.99	0.92–1.07	0.83	1.06	0.98–1.15
						0.15
Kidney ^{I1}						
78	78	-	-	28	-	-
<18.5	0	-	-	0	-	-
18.5–24.9	19	1.00	Ref	11	1.00	Ref
25–29.9	35	0.66	0.33–1.30	6	0.51	0.18–1.50
30–34.9	21	0.72	0.31–1.70	11	2.30	0.96–5.49
≥35	3	-	-	0	-	-
<i>trend^I</i>		1.00	0.93–1.08	0.91	1.02	0.95–1.10
						0.61
Bladder ^{I2}						
131	131	-	-	17	-	-
<18.5	0	-	-	1	-	-
18.5–24.9	34	1.00	Ref	7	1.00	Ref
25–29.9	66	1.16	0.75–1.81	6	0.97	0.32–2.89
30–34.9	28	1.41	0.82–2.41	2	-	-
≥35	3	-	-	1	-	-
<i>trend^I</i>		1.01	0.96–1.05	0.82	0.93	0.83–1.05
						0.23
Prostate ^{I3}						
1,274	1,274	-	-	-	-	-
<18.5	0	-	-	-	-	-
18.5–24.9	308	1.00	Ref	-	-	-
25–29.9	696	1.06	0.89–1.27	-	-	-
30–34.9	226	0.89	0.71–1.13	-	-	-

Cancer	Men			Women		
	N	HR ^I	95%CI ^I	N	HR ^I	95%CI ^I
BMI (kg/m ²)						
≥35	44	0.94	0.61–1.44	-	-	-
trend ^I		0.99	0.98–1.01	0.56		
Colon ^{I4}	230	-	-	113	-	-
<18.5	1	-	-	1	-	-
18.5–24.9	44	1.00	Ref	40	1.00	Ref
25–29.9	112	1.26	0.86–1.86	49	1.48	0.97–2.26
30–34.9	58	1.88	1.23–2.91	19	1.36	0.79–2.36
≥35	15	2.03	1.05–3.93	4	-	-
trend ^I		1.05	1.02–1.09	0.005	0.99	0.95–1.04
Rectal ^{I5}	102	-	-	34	-	-
<18.5	0	-	-	0	-	-
18.5–24.9	23	1.00	Ref	15	1.00	Ref
25–29.9	53	0.96	0.51–1.82	10	0.82	0.37–1.83
30–34.9	16	0.60	0.24–1.50	6	1.15	0.45–2.98
≥35	10	3.21	1.34–7.71	3	-	-
trend ^I		1.06	0.99–1.12	0.06	1.03	0.96–1.11
Leukemia ^{I6}	94	-	-	26	-	-
<18.5	0	-	-	0	-	-
18.5–24.9	23	1.00	Ref	13	1.00	Ref
25–29.9	52	1.21	0.64–2.30	10	0.93	0.39–2.20
30–34.9	17	1.38	0.64–2.97	2	-	-
≥35	2	-	-	1	-	-
trend ^I		1.00	0.94–1.07	0.99	0.93	0.84–1.02
Non Hodgkin Lymphoma ^{I7}	131	-	-	63	-	-
<18.5	0	-	-	2	-	-
18.5–24.9	31	1.00	Ref	27	1.00	Ref
25–29.9	73	1.24	0.69–2.21	25	1.04	0.60–1.80
30–34.9	25	1.27	0.63–2.60	6	0.62	0.26–1.50

Cancer	Men			Women		
	N	HR ^I	95%CI ^I	N	HR ^I	95%CI ^I
BMI (kg/m ²)						
≥35	2	-	-	3	-	-
<i>trend^I</i>		1.02	0.96–1.08	0.61	0.98	0.93–1.04
0.52						
Multiple Myeloma ¹⁸						
<18.5	47	-	-	21	-	-
18.5–24.9	10	1.00	Ref	9	1.00	Ref
25–29.9	24	1.82	0.48–2.89	9	1.17	0.43–3.12
30–34.9	9	1.35	0.45–4.06	2	-	-
≥35	4	-	-	1	-	-
<i>trend^I</i>		1.02	0.93–1.12	0.64	0.98	0.89–1.08
0.71						
Melanoma ¹⁹						
<18.5	125	-	-	79	-	-
18.5–24.9	34	1.00	Ref	38	1.00	Ref
25–29.9	60	0.65	0.39–1.09	21	0.88	0.51–1.52
30–34.9	28	0.97	0.53–1.76	13	1.20	0.62–2.32
≥35	3	-	-	7	2.07	0.92–4.67
<i>trend^I</i>		1.01	0.95–1.06	0.73	1.03	0.99–1.08
0.14						
Breast (Female) ²⁰						
<18.5	-	-	-	622	-	-
18.5–24.9	-	-	-	6	0.92	0.80–1.04
25–29.9	-	-	-	274	1.00	Ref
30–34.9	-	-	-	205	0.99	0.81–1.21
≥35	-	-	-	106	1.22	0.95–1.56
<i>trend^I</i>		-	-	31	0.79	0.50–1.25
0.71					1.00	0.99–1.02
Breast ²¹ (Post-menopausal Female)						
<18.5	-	-	-	464	-	-
18.5–24.9	-	-	-	5	-	-
25–29.9	-	-	-	186	1.00	Ref
30–34.9	-	-	-	156	1.22	0.93–1.60
	-	-	-	93	1.62	1.17–2.24

Cancer	Men			Women		
BMI (kg/m ²)	N	HR ^I	95%CI ^I	N	HR ^I	95%CI ^I
≥35	-	-	-	24	1.07	0.61–1.88
<i>trend^I</i>					1.03	1.01–1.06 0.02
Ovarian	-	-	-	48	-	-
<18.5	-	-	-	1	-	-
18.5–24.9	-	-	-	19	1.00	Ref
25–29.9	-	-	-	21	1.47	0.79–2.74
30–34.9	-	-	-	5	0.49	0.15–1.67
≥35	-	-	-	2	-	-
<i>trend^I</i>					0.93	0.66–1.32 0.69

^IBased on Cox regression using age as time-dependent variable; trend test calculated with continuous BMI; models adjusted for:

²Men: race, smoking status, vegetable consumption, exercise, family history of cancer; Women: smoking status, hypertension, vitamin supplements, parity;

³Men: smoking status, fruit consumption; Women: smoking status;

⁴Men: state, race, smoking status, vegetable consumption, exercise; Women: smoking status;

⁵Men: state, race, vegetable consumption, exercise, pack-years of cigarette smoking; Women: pack-years of cigarette smoking;

⁶Men: state; Women: state;

⁷Men: family history of cancer; Women: hypertension;

⁸Men: smoking status;

⁹Men: smoking status;

¹⁰Men: diabetes; Women: race;

¹¹Men: hypertension, family history of cancer; Women: hypertension;

¹²Men: smoking status, alcohol drinking; Women: exercise;

¹³race, smoking status, exercise, family history of prostate cancer;

¹⁴Men: race, education, family history colon cancer;

¹⁵Men: meat consumption;

- ¹⁶ Men: state, education, diabetes, exercise; Women: vitamin supplements;
- ¹⁷ Men: vitamin supplements, exercise;
- ¹⁸ Men: race, meat consumption;
- ¹⁹ Men: diabetes, wear sunscreen;
- ²⁰ diabetes, meat consumption, family history of breast cancer;
- ²¹ diabetes, vitamin supplement, parity, family history of breast cancer.

Hazard Rate Ratio (HR) and 95% Confidence Intervals (CI) for Colon Cancer in relation to BMI at enrollment by ever/never use of pesticides among men

Table 3

BMI (kg/m ²)	N	HR ¹	95%CI ¹	N	HR ¹	95%CI ¹	p-interaction ²
INSECTICIDES							
Organochlorines							
No Organochlorine				Organochlorine ³			
<25	9	1.00	Ref	11	1.00	Ref	
25–29.9	41	2.20	0.97–4.99	37	1.33	0.67–2.63	
>=30	20	2.39	0.98–5.85	26	2.11	1.02–4.38	
trend ¹		1.05	0.99–1.12	0.14	1.07	1.01–1.13	0.02
DDT ⁵							
<25	11	1.00	Ref	9	1.00	Ref	
25–29.9	52	2.09	1.02–4.31	24	1.12	0.52–2.44	
>=30	26	2.29	1.04–5.05	18	2.01	0.89–4.56	
trend ¹		1.05	0.99–1.10	0.11	1.08	1.01–1.15	0.02
0.50							
Organophosphates							
No Organophosphate				Organophosphate ⁴			
<25	17	1.00	Ref	28	1.00	Ref	
25–29.9	33	1.24	0.61–2.52	79	1.29	0.81–2.06	
>=30	20	1.79	0.82–3.87	53	2.02	1.23–3.32	
trend ¹		1.03	0.97–1.10	0.37	1.06	1.02–1.10	0.004
0.47							
No Terbofos				Terbofos			
<25	29	1.00	Ref	7	1.00	Ref	
25–29.9	61	1.20	0.74–1.96	33	1.77	0.78–4.02	
>=30	40	1.85	1.09–3.14	21	2.32	0.97–5.55	
trend ¹		1.05	1.00–1.09	0.04	1.05	0.99–1.12	0.13
0.94							
No Fonofs				Fonofs			
<25	31	1.00	Ref	9	1.00	Ref	
25–29.9	69	1.22	0.76–1.94	26	1.23	0.54–2.78	
>=30	42	1.60	0.96–2.67	21	2.36	1.02–5.46	

BMI (kg/m ²)	N	HR ^I	95%CI ^I	N	HR ^I	95%CI ^I	p-interaction ²
<i>trend^I</i>		1.04	0.99–1.08	0.10	1.07	1.00–1.14	0.59
No Chlorpyrifos							
<25	27	1.00	Ref	17	1.00	Ref	
25–29.9	74	1.64	0.98–2.73	32	0.86	0.46–1.63	
>=30	40	1.97	1.12–3.46	30	1.86	0.98–3.54	
<i>trend^I</i>		1.05	1.01–1.10	0.01	1.04	0.98–1.11	0.61
No Malathion							
<25	9	1.00	Ref	11	1.00	Ref	
25–29.9	33	1.70	0.74–3.92	43	1.52	0.78–2.99	
>=30	20	2.22	0.90–5.46	25	2.07	0.99–4.29	
<i>trend^I</i>		1.06	0.99–1.13	0.09	1.06	1.00–1.12	0.88
No Dichlorvos							
<25	30	1.00	Ref	8	1.00	Ref	
25–29.9	82	1.33	0.86–2.06	10	0.69	0.24–1.98	
>=30	50	1.72	1.06–2.78	11	2.03	0.72–5.73	
<i>trend^I</i>		1.03	0.99–1.08	0.11	1.09	0.99–1.20	0.47
Carbamate							
No Carbofuran							
<25	31	1.00	Ref	7	1.00	Ref	
25–29.9	66	1.13	0.71–1.78	28	1.79	0.73–4.43	
>=30	38	1.38	0.82–2.30	24	3.68	1.46–9.26	
<i>trend^I</i>		1.02	0.97–1.06	0.52	1.10	1.04–1.17	0.04
No Carbaryl							
<25	11	1.00	Ref	9	1.00	Ref	
25–29.9	45	1.60	0.80–3.23	31	1.61	0.73–3.55	
>=30	23	1.87	0.87–4.03	22	2.49	1.08–5.78	
<i>trend^I</i>		1.04	0.99–1.11	0.14	1.08	1.01–1.14	0.43
Pyrethroid							
No Permethrin							
Permethrin (crops or animal)							

BMI (kg/m ²)	N	HR ^I	95%CI ^I	N	HR ^I	95%CI ^I	p-interaction ²
<25	33	1.00	Ref	7	1.00	Ref	
25–29.9	78	1.22	0.79–1.89	21	1.34	0.53–3.37	
>=30	47	1.63	1.01–2.64	19	2.70	1.05–6.96	
trend ^I		1.04	0.99–1.08	0.09	1.08	1.01–1.15	0.21

HERBICIDES

Triazine							
No Atrazine				Atrazine			
<25	20	1.00	Ref	24	1.00	Ref	
25–29.9	35	1.11	0.59–2.09	69	1.38	0.83–2.29	
>=30	14	1.05	0.48–2.28	58	2.61	1.55–4.40	
trend ^I		1.02	0.95–1.08	0.64	1.07	1.03–1.12	0.33
Cyanazine							
<25	27	1.00	Ref	14	1.00	Ref	
25–29.9	58	1.06	0.65–1.73	37	1.34	0.68–2.65	
>=30	33	1.34	0.78–2.32	31	2.54	1.26–5.11	
trend ^I		1.03	0.99–1.08	0.16	1.05	1.00–1.11	0.70
Metribuzin ⁵							
<25	13	1.00	Ref	6	1.00	Ref	
25–29.9	55	1.99	1.03–3.86	23	1.34	0.54–3.33	
>=30	32	2.70	1.33–5.47	12	1.41	0.50–3.96	
trend ^I		1.08	1.03–1.13	0.002	1.00	0.91–1.09	0.12

Chloroacetanilide

No Metolachlor				Metolachlor			
<25	28	1.00	Ref	12	1.00	Ref	
25–29.9	57	1.09	0.67–1.77	36	1.39	0.68–2.83	
>=30	31	1.29	0.74–2.25	35	2.91	1.42–5.96	
trend ^I		1.01	0.96–1.06	0.70	1.09	1.04–1.15	0.02
Alachlor							
<25	24	1.00	Ref	14	1.00	Ref	

BMI (kg/m ²)	N	HR ^I	95%CI ^I	N	HR ^I	95%CI ^I	p-interaction ²
25-29.9	40	0.87	0.51-1.48	53	1.92	1.00-3.68	
>=30	25	1.14	0.62-2.11	41	3.12	1.59-6.12	
trend ^I		1.01	0.95-1.06	0.87	1.08	1.03-1.13	0.05
Dinotroaniline							
No Pendimethalin				Pendimethalin ⁵			
<25	12	1.00	Ref	7	1.00	Ref	
25-29.9	57	2.28	1.15-4.51	20	0.97	0.40-2.36	
>=30	29	2.88	1.38-5.99	15	1.32	0.50-3.49	
trend ^I		1.06	1.01-1.11	0.02	1.06	0.98-1.14	0.95
No Trifluralin				Trifluralin			
<25	21	1.00	Ref	16	1.00	Ref	
25-29.9	46	1.34	0.75-2.39	49	1.37	0.75-2.49	
>=30	23	1.36	0.69-2.66	43	2.59	1.40-4.80	
trend ^I		1.03	0.98-1.09	0.30	1.07	1.02-1.12	0.38
Thiocarbamate							
No EPTC				EPTC			
<25	32	1.00	Ref	6	1.00	Ref	
25-29.9	73	1.21	0.77-1.89	19	1.25	0.49-3.22	
>=30	47	1.64	1.00-2.67	16	2.67	1.01-7.07	
trend ^I		1.03	0.99-1.08	0.14	1.09	1.01-1.17	0.38
Imidazolinone							
No Imazethpyr				Imazethpyr			
<25	28	1.00	Ref	11	1.00	Ref	
25-29.9	56	1.15	0.71-1.86	37	1.40	0.67-2.93	
>=30	38	1.66	0.97-2.84	28	2.25	1.05-4.81	
trend ^I		1.04	0.99-1.09	0.09	1.06	1.00-1.12	0.59
Phosphinic							
No Glyphosate				Glyphosate			

BMI (kg/m ²)	N	HR ¹	95%CI ¹	N	HR ¹	95%CI ¹	p-interaction ²
<25	11	1.00	Ref	34	1.00	Ref	
25–29.9	26	1.03	0.49–2.19	81	1.35	0.85–2.13	
≥30	18	1.46	0.64–3.31	53	2.07	1.27–3.37	
trend ¹		1.00	0.93–1.07	0.92	1.07	1.03–1.11	0.13

Urea							
No Chlorimuron-ethyl				Chlorimuron-ethyl ⁵			
<25	14	1.00	Ref	5	1.00	Ref	
25–29.9	54	1.74	0.92–3.29	24	1.74	0.65–4.64	
≥30	26	1.88	0.92–3.82	18	2.79	1.01–7.75	
trend ¹		1.06	1.01–1.12	0.03	1.05	0.98–1.13	0.89

Benzoic							
No Dicamba				Dicamba			
<25	22	1.00	Ref	17	1.00	Ref	
25–29.9	45	1.26	0.72–2.19	49	1.14	0.63–2.06	
≥30	35	1.92	1.05–3.49	30	1.73	0.92–3.24	
trend ¹		1.04	0.99–1.09	0.11	1.05	0.99–1.10	0.92

Fumigant							
No Methyl Bromide				Methyl Bromide			
<25	34	1.00	Ref	10	1.00	Ref	
25–29.9	88	1.38	0.88–2.14	17	0.79	0.33–1.91	
≥30	57	1.98	1.23–3.19	14	1.72	0.69–4.21	
trend ¹		1.05	1.01–1.09	0.02	1.06	0.98–1.14	0.85

¹Based on Cox regression using age as time-dependent variable; test of trend calculated using continuous BMI; models adjusted for race, education, family history colon cancer

²Interaction calculated using never/ever pesticide use and continuous BMI

³Used at least one of the following: Lidane, Aldrin, Chlordane, Dieldrin, DDT, Heptachlor, Toxaphene

⁴Used at least one of the following: Terbufos, Fonofos, Trichlorofon, Chlorpyrifos, Malthion, Parathion, Diazinon, Phorate, Coumaphos, Dichlorvos

⁵Data available from take-home questionnaire only

Hazard Rate Ratio (HR) and 95% Confidence Intervals (CI) for Breast Cancer in relation to BMI at enrollment by ever/never use of pesticides among postmenopausal women

Table 4

BMI (kg/m ²)	N	HR ^I	95%CI ^I	N	HR ^I	95%CI ^I	p-interaction ²
INSECTICIDES							
Organochlorines ²							
No Organochlorines				Organochlorines ³			
<25	161	1.00	Ref	21	1.00	Ref	
25–29.9	133	1.27	0.95–1.71	13	0.76	0.34–1.69	
>=30	99	1.52	1.09–2.12	12	1.23	0.55–2.76	
trend ^I		1.04	1.01–1.07	0.01	1.02	0.96–1.09	0.74
Organophosphates ³							
No Organophosphates				Organophosphates ⁴			
<25	127	1.00	Ref	64	1.00	Ref	
25–29.9	106	1.25	0.89–1.75	50	1.17	0.74–1.85	
>=30	93	1.76	1.22–2.53	24	1.00	0.56–1.76	
trend ^I		1.04	1.01–1.08	0.01	1.00	0.96–1.04	0.15
No Malathion				Malathion			
<25	130	1.00	Ref	52	1.00	Ref	
25–29.9	111	1.25	0.90–1.73	38	1.15	0.69–1.89	
>=30	92	1.69	1.18–2.41	19	1.00	0.53–1.85	
trend ^I		1.04	1.01–1.07	0.01	1.02	0.97–1.07	0.22
No Diazion				Diazion			
<25	158	1.00	Ref	21	1.00	Ref	
25–29.9	124	1.14	0.85–1.54	22	1.85	0.86–3.97	
>=30	99	1.49	1.07–2.07	11	1.60	0.65–3.91	
trend ^I		1.03	1.01–1.06	0.02	1.03	0.96–1.11	0.56
Carbamate							
No Carbaryl				Carbaryl			

BMI (kg/m ²)	N	HR ¹	95%CI ¹	N	HR ¹	95%CI ¹	p-interaction ²
<25	123	1.00	Ref	58	1.00	Ref	
25–29.9	96	1.04	0.74–1.46	53	1.65	1.02–2.67	
≥30	81	1.50	1.04–2.15	29	1.42	0.79–2.53	
trend ¹		1.04	1.00–1.07	0.04	1.03	0.99–1.08	0.73

HERBICIDES							
Phosphinic							
No Glyphosate				Glyphosate			
<25	130	1.00	Ref	54	1.00	Ref	
25–29.9	105	1.21	0.87–1.67	44	1.30	0.76–2.21	
≥30	85	1.40	0.97–2.01	28	1.70	0.95–3.06	
trend ¹		1.03	0.99–1.06	0.08	1.05	0.99–1.10	0.62

¹Based on Cox regression using age as time-dependent variable; test of trend calculated using continuous BMI; models adjusted for diabetes, vitamin supplement, parity, family history of breast cancer.

²Interaction calculated using never/ever pesticide use and continuous BMI

³Used at least one of the following: Lidane, Aldrin, Chlordane, Dieldrin, DDT, Heptachlor, Toxaphene

⁴Used at least one of the following: Terbufos, Fonofos, Trichlorofon, Chlorpyrifos, Malthion, Parathion, Diazinon, Phorate, Coumaphos, Dichlorvos