Supplemental Digital Content

Figure e1. Flow diagram showing the study population for an analysis of fumigant, fungicide, and herbicide use and incident breast cancer in wives enrolled in the Agricultural Health Study.

Table e1. Associations of the relative extent of the wives’ use of individual fumigants, fungicides, and herbicides (reported at enrollment and/or the 5-year follow-up) with risk of breast cancer among farmers’ wives in the Agricultural Health Study.

Table e2. Associations between the wives’ ever use of individual fumigants, fungicides, and herbicides at enrollment and risk of breast cancer among farmers’ wives in the Agricultural Health Study, stratified by state of residence.

Table e3. Associations between the wives’ ever use of individual fumigants, fungicides, and herbicides at enrollment and risk of breast cancer among farmers’ wives in the Agricultural Health Study, stratified by tumor hormone receptor status.

Table e4. Associations between the wives’ ever use of individual fumigants, fungicides, and herbicides at enrollment and risk of breast cancer among farmers’ wives in the Agricultural Health Study, stratified by menopausal status at diagnosis.

Table e5. Associations between the husbands’ use of individual fumigants, fungicides, and herbicides and risk of breast cancer among farmers’ wives who never used pesticides in the Agricultural Health Study, stratified by state of residence.

Table e6. Associations between the husbands’ use of individual fumigants, fungicides, and herbicides and risk of breast cancer among farmers’ wives who never used pesticides in the Agricultural Health Study, stratified by tumor hormone receptor status.

Table e7. Associations between the husbands’ use of individual fumigants, fungicides, and herbicides and risk of breast cancer among farmers’ wives who never used pesticides in the Agricultural Health Study, stratified by menopausal status at diagnosis.

Figure e1. Flow diagram showing the study population for an analysis of fumigant, fungicide, and herbicide use and incident breast cancer in wives enrolled in the Agricultural Health Study. Boxes with solid lines represent individuals who remained in the analysis after each step while boxes with dashed lines represent individuals who were excluded after each step. Cancer and mortality follow-up was via registry linkage.

***Ncases=592***

***Ncases=1,081***

310 prevalent breast cancer cases

22,271 wives

**End of follow-up**

22,581 completed follow-up interview

30,594 wives

7,646 did not complete follow-up interview or moved out of state

367 deceased

Follow-up through 2010/2011

***Incident breast
cancer cases since…***

478 prevalent breast cancer cases

941 missing all data on pesticide use

113 residing out of state
at enrollment

19,578 completed reproductive health history questionnaire

32,126 wives

219 males

32,345 spouses completed enrollment questionnaire

52,394 private applicators enrolled

Enrollment (1993-1997)

First follow-up interview (1999-2003)

Table e1. Associations of the relative extent of the wives’ use of individual fumigants, fungicides, and herbicides (reported at enrollment and/or the 5-year follow-up) with risk of breast cancer among farmers’ wives in the Agricultural Health Study.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   |   | Exposed cases (n=906)a | Exposed noncases (n=29,688) | Covariate-adjusted | Coexposure-adjusted |
| Exposure | Level | HRb | 95% CI | HRc | 95% CI |
| 2,4-D | Never | 737 | 23926 | Ref |   | Ref |   |
|  | Enrollment only | 113 | 3333 | 0.9 | (0.7, 1.2) | 1.1 | (0.8, 1.4) |
|  | Follow-up only | 8 | 824 | 0.5 | (0.3, 1.1) | 0.6 | (0.3, 1.4) |
|   | Both | 26 | 860 | 1.4 | (0.9, 2.0) | 1.6 | (1.0, 2.5) |
|  |  |  |  |  |  |  |  |
| Atrazine | Never | 840 | 27438 | Ref |  | Ref |  |
|  | Enrollment only | 33 | 1200 | 0.7 | (0.5, 1.1) | 0.8 | (0.5, 1.5) |
|  | Follow-up only | <5 | 122 | ─ | ─ | ─ | ─ |
|   | Both | <5 | 89 | ─ | ─ | ─ | ─ |
|  |  |  |  |  |  |  |  |
| Dicamba | Never | 834 | 27282 | Ref |   | Ref |   |
|  | Enrollment only | 39 | 1015 | 1.1 | (0.7, 1.7) | 1.4 | (0.8, 2.2) |
|  | Follow-up only | <5 | 400 | ─ | ─ | ─ | ─ |
|   | Both | <5 | 109 | ─ | ─ | ─ | ─ |
|  |  |  |  |  |  |  |  |
| Glyphosate | Never | 575 | 17736 | Ref |   | Ref |   |
|  | Enrollment only | 210 | 6832 | 0.9 | (0.7, 1.1) | 1 | (0.8, 1.2) |
|  | Follow-up only | 33 | 1703 | 1 | (0.7, 1.4) | 1 | (0.7, 1.4) |
|  | Both | 72 | 3011 | 1.2 | (0.9, 1.5) | 1.2 | (0.9, 1.6) |
|  |  |  |  |  |  |  |  |
| Trifluralin | Never | 816 | 26694 | Ref |  | Ref |  |
|  | Enrollment only | 42 | 1326 | 0.9 | (0.6, 1.3) | 1.2 | (0.8, 2.0) |
|  | Follow-up only | 16 | 603 | 1.5 | (0.9, 2.4) | 1.7 | (1.0, 2.8) |
|   | Both | <5 | 158 | ─ | ─ | ─ | ─ |

a Numbers of exposed and unexposed may not sum to 100% for some pesticides due to missing data.

b Time scale is attained age, with left truncation at cohort enrollment. Adjusted for time-varying menopausal status, race (White, other), and combined parity/age at first birth (nulliparous or all births after age 30 years; 1 birth, by age 30 years;

≥ 2 births, first of which was by age 30 years).

c Adjusted as in (b) and additionally adjusted for use of dicamba, cyfluthrin, Bacillus thuringiensis, and mecoprop-p, except for “Any herbicide” which was additionally adjusted for use of cyfluthrin, Bacillus thuringiensis, and mecoprop-p only.

Table e2. Associations between the wives’ ever use of individual fumigants, fungicides, and herbicides at enrollment and risk of breast cancer among farmers’ wives in the Agricultural Health Study, stratified by state of residence.

|  |  |  |
| --- | --- | --- |
|   | Iowa | North Carolina |
|  | Exposed cases (n=703) | Exposed noncases (n=20,812) |  | Exposed cases (n=378) | Exposed noncases (n=9,331) |  |
| Exposure | HRa | 95% CI | HRa | 95% CI |
| **Any fumigant** | 8 | 186 | 0.9 | (0.4, 2.1) | 15 | 322 | 0.8 | (0.4, 1.6) |
| Carbon Tetrachloride/Carbon Disulfide | 6 | 129 | 0.9 | (0.3, 2.4) | <5 | 26 | ─ | ─ |
| Methyl bromide | <5 | 44 | ─ | ─ | 15 | 299 | 0.9 | (0.5, 1.7) |
| **Any fungicide** | 18 | 629 | 0.8 | (0.5, 1.3) | 33 | 755 | 0.9 | (0.6, 1.4) |
| Benomyl | <5 | 63 | ─ | ─ | 14 | 178 | 1.7 | (0.9, 3.1) |
| Captan | 15 | 405 | 1.1 | (0.6, 1.9) | 10 | 212 | 1.0 | (0.5, 2.0) |
| Chlorothalonil | <5 | 118 | ─ | ─ | 5 | 149 | 0.5 | (0.1, 1.6) |
| Maneb | 5 | 121 | 0.7 | (0.2, 2.3) | 14 | 314 | 0.8 | (0.4, 1.5) |
| Metalaxyl | <5 | 75 | ─ | ─ | 13 | 364 | 0.6 | (0.3, 1.3) |
| **Any herbicideb** | 264 | 8184 | 0.9 | (0.7, 1.0) | 101 | 2646 | 0.9 | (0.7, 1.2) |
| 2,4-D | 124 | 3673 | 0.9 | (0.7, 1.1) | 30 | 505 | 1.4 | (0.9, 2.1) |
| 2,4,5-T | 10 | 176 | 1.5 | (0.7, 3.2) | <5 | 26 | ─ | ─ |
| 2,4,5-TP | <5 | 82 | ─ | ─ | <5 | 16 | ─ | ─ |
| Alachlorb | 34 | 1016 | 0.9 | (0.6, 1.4) | 6 | 180 | 0.9 | (0.3, 2.2) |
| Atrazine | 34 | 1124 | 0.8 | (0.5, 1.3) | 7 | 160 | 1.1 | (0.5, 2.7) |
| Butylate | 6 | 351 | 0.5 | (0.2, 1.2) | <5 | 51 | ─ | ─ |
| Chlorimuron ethyl | 14 | 428 | 1.2 | (0.7, 2.2) | 2 | 63 | 1.3 | (0.3, 5.8) |
| Cyanazine | 23 | 765 | 0.9 | (0.5, 1.5) | <5 | 49 | ─ | ─ |
| Dicamba | 39 | 1060 | 1.1 | (0.8, 1.7) | 7 | 58 | 2.8 | (1.2, 6.4) |
| EPTC | 10 | 367 | 0.9 | (0.4, 2.1) | <5 | 23 | ─ | ─ |
| Glyphosateb | 229 | 7265 | 0.9 | (0.8, 1.1) | 93 | 2538 | 0.9 | (0.7, 1.2) |
| Imazethapyr | 26 | 844 | 1.1 | (0.7, 1.8) | <5 | 18 | ─ | ─ |
| Metolachlor | 32 | 846 | 1.2 | (0.8, 1.9) | <5 | 93 | ─ | ─ |
| Metribuzin | 11 | 464 | 0.7 | (0.4, 1.5) | <5 | 37 | ─ | ─ |
| Paraquatb | <5 | 134 | ─ | ─ | 13 | 206 | 1.5 | (0.8, 2.8) |
| Pendimethalin | 18 | 538 | 1.2 | (0.7, 2.1) | 7 | 140 | 0.9 | (0.3, 2.5) |
| Petroleum oil | 33 | 835 | 1.2 | (0.8, 1.9) | <5 | 165 | ─ | ─ |
| Trifluralin | 48 | 1398 | 1.1 | (0.7, 1.5) | <5 | 80 | ─ | ─ |

a Reference category is never exposed for all analyses. Time scale is attained age, with left truncation at cohort enrollment. Adjusted for time-varying menopausal status, race, and combined parity/age at first birth. Additionally adjusted for use of benomyl, metribuzin, butylate, and toxaphene, except for “Any fungicide” which was additionally adjusted for use of metribuzin, butylate, and toxaphene only, and “Any herbicide” which was additionally adjusted for use of benomyl and toxaphene only.

b Evidence of nonproportional hazards: any herbicide (Iowa, p=0.01; North Carolina, p=0.02), alachlor (Iowa, p=0.02), glyphosate (Iowa, p=0.01; North Carolina, p=0.01), paraquat (North Carolina, p=0.01).

Table e3. Associations between the wives’ ever use of individual fumigants, fungicides, and herbicides at enrollment and risk of breast cancer among farmers’ wives in the Agricultural Health Study, stratified by tumor hormone receptor status.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | ER positive |   | ER negative |   |
| Exposure | Exposed cases(n=712) | Exposed noncases(n=29,513) | HRa | 95% CI |  | Exposed cases(n=190) | Exposed noncases(n=29,513) | HRa | 95% CI | Interaction p-value |
| **Any fumigant** | 17 | 510 | 1 | (0.5, 1.9) |  | <5 | 525 | ─ | ─ | ─ |
| Carbon Tetrachloride/ Carbon Disulfide | 6 | 156 | 0.8 | (0.2, 2.3) |  | <5 | 161 | ─ | ─ | ─ |
| Methyl bromide | 12 | 344 | 1.2 | (0.6, 2.5) |  | <5 | 355 | ─ | ─ | ─ |
| **Any fungicide** | 32 | 1388 | 0.8 | (0.6, 1.2) |  | 4 | 1416 | 0.5 | (0.2, 1.4) | 0.39 |
| Benomyl | 8 | 243 | 1.3 | (0.6, 2.9) |  | <5 | 249 | ─ | ─ | ─ |
| Captan | 16 | 618 | 1.0 | (0.5, 1.7) |  | <5 | 633 | ─ | ─ | ─ |
| Chlorothalonil | 7 | 267 | 0.5 | (0.2, 1.7) |  | <5 | 274 | ─ | ─ | ─ |
| Maneb | 13 | 435 | 0.9 | (0.5, 1.8) |  | <5 | 448 | ─ | ─ | ─ |
| Metalaxyl | 9 | 441 | 0.5 | (0.2, 1.4) |  | <5 | 448 | ─ | ─ | ─ |
| **Any herbicide** | 248 | 10897 | 0.9 | (0.7, 1.0) |  | 67 | 11078 | 0.9 | (0.6, 1.2) | 0.98 |
| 2,4-D | 104 | 4205 | 0.9 | (0.7, 1.2) |  | 27 | 4282 | 0.9 | (0.6, 1.4) | 0.91 |
| 2,4,5-T | 7 | 205 | 1.2 | (0.5, 2.8) |  | <5 | 209 | ─ | ─ | ─ |
| 2,4,5-TP | <5 | 99 | ─ | ─ |  | <5 | 101 | ─ | ─ | ─ |
| Alachlorb | 28 | 1203 | 1.0 | (0.6, 1.5) |  | 7 | 1224 | 0.6 | (0.2, 1.8) | 0.46 |
| Atrazine | 27 | 1291 | 0.8 | (0.5, 1.3) |  | 7 | 1311 | 0.6 | (0.2, 1.6) | 0.59 |
| Butylate | <5 | 404 | ─ | ─ |  | <5 | 405 | ─ | ─ | ─ |
| Chlorimuron ethyl | 7 | 498 | 0.9 | (0.4, 1.9) |   | 7 | 498 | 2.3 | (0.9, 5.7) | 0.10 |
| Cyanazine | 16 | 821 | 0.8 | (0.4, 1.5) |  | 7 | 830 | 1.3 | (0.5, 3.2) | 0.42 |
| Dicamba | 31 | 1127 | 1.1 | (0.7, 1.7) |  | 9 | 1149 | 1.4 | (0.7, 3.0) | 0.56 |
| EPTC | 8 | 392 | 0.9 | (0.3, 2.3) |  | <5 | 398 | ─ | ─ | ─ |
| Glyphosate | 217 | 9865 | 0.9 | (0.8, 1.1) |  | 62 | 10020 | 0.9 | (0.7, 1.3) | 0.94 |
| Imazethapyr | 18 | 869 | 1.1 | (0.6, 1.9) |  | 7 | 880 | 1.3 | (0.5, 3.2) | 0.72 |
| Metolachlor | 25 | 947 | 1.2 | (0.7, 1.9) |  | 8 | 964 | 1.4 | (0.6, 3.2) | 0.77 |
| Metribuzin | 9 | 503 | 0.9 | (0.4, 1.8) |  | <5 | 510 | ─ | ─ | ─ |
| Paraquat | 9 | 342 | 1.2 | (0.6, 2.5) |  | <5 | 349 | ─ | ─ | ─ |
| Pendimethalin | 15 | 686 | 1.0 | (0.5, 1.9) |  | 8 | 693 | 1.7 | (0.7, 4.1) | 0.36 |
| Petroleum oil | 24 | 1006 | 1.1 | (0.7, 1.7) |  | 6 | 1024 | 0.6 | (0.2, 1.9) | 0.34 |
| Trifluralin | 35 | 1490 | 1.0 | (0.7, 1.5) |   | 12 | 1513 | 1.2 | (0.6, 2.4) | 0.65 |

1 Reference category is never exposed for all analyses. Time scale is attained age, with left truncation at cohort enrollment. Adjusted for race, state, and combined parity/age at first birth. Additionally adjusted for use of benomyl, metribuzin, butylate, and toxaphene, except for “Any fungicide” which was additionally adjusted for use of metribuzin, butylate, and toxaphene only, and “Any herbicide” which was additionally adjusted for use of benomyl and toxaphene only.

b Evidence of nonproportional hazards (p=0.01)

Table e4. Associations between the wives’ ever use of individual fumigants, fungicides, and herbicides at enrollment and risk of breast cancer among farmers’ wives in the Agricultural Health Study, stratified by menopausal status at diagnosis.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Premenopausal |  | Postmenopausal |  |
| Exposure | Exposed cases(n=145) | HRa | 95% CI |  | Exposed cases(n=936) | HRa | 95% CI | Interaction p-value |
| **Any fumigant** | <5 | ─ | ─ |  | 20 | 0.8 | (0.4, 1.4) |  |
| Carbon Tetrachloride/Carbon Disulfide | <5 | ─ | ─ |  | 7 | 0.8 | (0.3, 2.0) |  |
| Methyl bromideb | <5 | ─ | ─ |  | 14 | 0.8 | (0.4, 1.6) |  |
| **Any fungicide** | <5 | ─ | ─ |  | 48 | 0.9 | (0.6, 1.2) |  |
| Benomyl | <5 | ─ | ─ |   | 15 | 1.6 | (0.9, 2.9) |  |
| Captan | <5 | ─ | ─ |  | 23 | 1.1 | (0.7, 1.7) |  |
| Chlorothalonil | <5 | ─ | ─ |  | 7 | 0.3 | (0.1, 1.1) |  |
| Maneb | <5 | ─ | ─ |  | 18 | 0.8 | (0.4, 1.4) |  |
| Metalaxyl | <5 | ─ | ─ |  | 14 | 0.7 | (0.4, 1.4) |  |
| **Any herbicide** | 53 | 1.0 | (0.7, 1.4) |  | 312 | 0.9 | (0.7, 1.0) | 0.34 |
| 2,4-D | 24 | 1.2 | (0.8, 1.9) |  | 130 | 0.9 | (0.8, 1.2) | 0.32 |
| 2,4,5-T | <5 | ─ | ─ |  | 12 | 1.4 | (0.7, 2.8) |  |
| 2,4,5-TP | <5 | ─ | ─ |  | 5 | 1.2 | (0.4, 3.9) |  |
| Alachlor | 12 | 2.2 | (1.2, 4.3) |   | 28 | 0.7 | (0.4, 1.1) | 0.003 |
| Atrazine | 8 | 1.5 | (0.7, 3.2) |  | 33 | 0.7 | (0.5, 1.2) | 0.11 |
| Butylate | <5 | ─ | ─ |  | 5 | 0.3 | (0.1, 1.0) |  |
| Chlorimuron ethyl | <5 | ─ | ─ |  | 14 | 1.2 | (0.7, 2.2) |  |
| Cyanazineb | 5 | 1.0 | (0.3, 3.1) |  | 18 | 0.8 | (0.4, 1.4) | 0.73 |
| Dicamba | 6 | 1.4 | (0.6, 3.2) |  | 40 | 1.2 | (0.8, 1.8) | 0.79 |
| EPTC | <5 | ─ | ─ |  | 10 | 1 | (0.4, 2.3) |  |
| Glyphosate | 48 | 1 | (0.7, 1.4) |  | 274 | 0.9 | (0.8, 1.0) | 0.46 |
| Imazethapyr | <5 | ─ | ─ |  | 24 | 1.2 | (0.7, 2.0) |  |
| Metolachlor | <5 | ─ | ─ |  | 29 | 1.1 | (0.7, 1.8) |  |
| Metribuzin | <5 | ─ | ─ |  | 11 | 0.8 | (0.4, 1.5) |  |
| Paraquat | <5 | ─ | ─ |  | 16 | 1.2 | (0.7, 2.2) |  |
| Pendimethalin | <5 | ─ | ─ |  | 24 | 1.2 | (0.7, 1.9) |  |
| Petroleum oil | 8 | 2.1 | (1.0, 4.3) |   | 29 | 0.9 | (0.6, 1.4) | 0.05 |
| Trifluralin | 5 | 1.1 | (0.5, 2.5) |   | 47 | 1.1 | (0.7, 1.5) | 0.93 |

a Reference category is never exposed for all analyses. Time scale is attained age, with left truncation at cohort enrollment. Adjusted for race, state, and combined parity/age at first birth. Additionally adjusted for use of benomyl, metribuzin, butylate, and toxaphene, except for “Any fungicide” which was additionally adjusted for use of metribuzin, butylate, and toxaphene only, and “Any herbicide” which was additionally adjusted for use of benomyl and toxaphene only.

b Evidence of nonproportional hazards: cyanazine (p=0.03), methyl bromide (p=0.02)

Table e5. Associations between the husbands’ use of individual fumigants, fungicides, and herbicides and risk of breast cancer among farmers’ wives who never used pesticides in the Agricultural Health Study, stratified by state of residence.

|  |  | Iowa |  | North Carolina |
| --- | --- | --- | --- | --- |
|   |   | Exposed cases (n=224)a | Exposed noncases (n=8,121) |   |  | Exposed cases (n=152)a | Exposed noncases (n=13,124) |   |
| Exposure | Level | HRb | 95% CI |  | HRb | 95% CI |
| **Fumigants** |  |  |  |  |  |  |  |  |  |  |
| Aluminum Phosphide | Never | 210 | 7541 | Ref |  |  | 129 | 4165 | Ref |  |
|  | Ever | 5 | 112 | 1.2 | (0.4, 3.8) |  | <5 | 98 | ─ | ─ |
| Carbon Tetrachloride/ Carbon Disulfide | Never | 191 | 7415 | Ref |  |  | 130 | 4165 | Ref |  |
| Ever | 10 | 172 | 1.4 | (0.7, 2.9) |  | <5 | 58 | ─ | ─ |
| Methyl Bromide | Never | 220 | 7902 | Ref |  |  | 93 | 3086 | Ref |  |
|  | Ever | <5 | 98 | ─ | ─ |  | 38 | 1316 | 0.9 | (0.5, 1.5) |
| **Fungicides** |  |  |  |  |  |  |  |  |  |  |
| Benomyl | Never | 212 | 7725 | Ref |  |  | 98 | 3283 | Ref |  |
|  | Ever | <5 | 68 | ─ | ─ |  | 16 | 374 | 1.5 | (0.8, 2.9) |
| Captan | Never | 180 | 6813 | Ref |  |  | 100 | 3629 | Ref |  |
|  | Ever | 23 | 843 | 1.1 | (0.6, 1.9) |  | 12 | 362 | 0.9 | (0.4, 2.3) |
| Chlorothalonil | Never | 220 | 7900 | Ref |  |  | 111 | 3699 | Ref |  |
|  | Ever | <5 | 109 | ─ | ─ |  | 27 | 853 | 1.5 | (0.7, 3.0) |
| Maneb | Never | 211 | 7772 | Ref |  |  | 99 | 3308 | Ref |  |
|  | Ever | <5 | 42 | ─ | ─ |  | 17 | 418 | 1.0 | (0.5, 1.9) |
| Metalaxyl | Never | 209 | 7206 | Ref |  |  | 72 | 2289 | Ref |  |
|  | Ever | <5 | 263 | ─ | ─ |  | 27 | 945 | 1.0 | (0.6, 1.8) |
| **Herbicides** |  |  |  |  |  |  |  |  |  |  |
| 2,4-D | None | 30 | 1202 | Ref |  |  | 62 | 2105 | Ref |  |
|  | Any | 191 | 6840 | 0.8 | (0.5, 1.3) |  | 71 | 2350 | 0.8 | (0.5, 1.3) |
|  | 1 | 37 | 1763 | 0.7 | (0.4, 1.3) |  | 33 | 940 | 0.9 | (0.5, 1.6) |
|  | 2 | 65 | 2152 | 0.9 | (0.6, 1.5) |  | 17 | 602 | 0.9 | (0.4, 1.9) |
|  | 3 | 54 | 2121 | 0.8 | (0.5, 1.4) |  | 13 | 566 | 0.5 | (0.2, 1.4) |
|  |  |  |  | p trend=0.86 |  |  |  | p trend=0.26 |
| 2,4,5-T | Never | 136 | 6070 | Ref |  |  | 103 | 3572 | Ref |  |
|  | Ever | 45 | 828 | 1.2 | (0.8, 1.9) |  | 13 | 297 | 1.1 | (0.4, 2.6) |
| 2,4,5-TP | Never | 183 | 7179 | Ref |  |  | 115 | 3998 | Ref |   |
|  | Ever | 13 | 214 | 1.3 | (0.7, 2.6) |  | 7 | 96 | 2.6 | (0.9, 7.7) |
| Alachlor | None | 82 | 3682 | Ref |  |  | 70 | 2551 | Ref |  |
|  | Any | 128 | 4026 | 1.1 | (0.8, 1.5) |  | 38 | 1303 | 1.0 | (0.6, 1.8) |
|  | ≤ Median | 64 | 2153 | 1.0 | (0.7, 1.6) |  | 18 | 498 | 1.5 | (0.8, 2.9) |
|  | > Median | 62 | 1775 | 1.3 | (0.9, 1.9) |  | 15 | 641 | 0.7 | (0.3, 1.6) |
|  |  |  |  | p trend=0.33 |  |  |  | p trend=0.99 |
| Atrazine | None | 43 | 1493 | Ref |  |  | 69 | 2309 | Ref |  |
|  | Any | 178 | 6545 | 0.9 | (0.6, 1.3) |  | 60 | 2158 | 0.8 | (0.5, 1.4) |
|  | 1 | 44 | 1784 | 0.9 | (0.5, 1.4) |  | 25 | 753 | 1.0 | (0.5, 1.9) |
|  | 2 | 45 | 2081 | 0.8 | (0.5, 1.2) |  | 14 | 580 | 0.8 | (0.4, 1.7) |
|  | 3 | 55 | 1953 | 1.0 | (0.6, 1.6) |  | 13 | 555 | 0.6 | (0.2, 1.6) |
|  |  |  |  | p trend=0.63 |  |  |  | p trend=0.43 |
| Butylate | Never | 135 | 5191 | Ref |  |  | 114 | 3530 | Ref |  |
|  | Ever | 46 | 1189 | 1.2 | (0.8, 1.8) |  | 6 | 207 | 1.4 | (0.6, 3.3) |
| Chlorimuron ethyl | Never | 145 | 4642 | Ref |  |  | 103 | 3043 | Ref |  |
|  | Ever | 35 | 1446 | 0.8 | (0.5, 1.3) |  | 11 | 543 | 0.7 | (0.3, 1.5) |
| Cyanazine | Never | 99 | 3880 | Ref |  |  | 105 | 3598 | Ref |  |
|  | Ever | 108 | 3847 | 0.9 | (0.6, 1.2) |  | 8 | 339 | 1.1 | (0.4, 3.1) |
| Dicamba | Never | 65 | 2441 | Ref |  |  | 100 | 3459 | Ref |  |
|  | Ever | 143 | 5344 | 1.0 | (0.7, 1.4) |  | 12 | 475 | 0.5 | (0.2, 1.4) |
| EPTC | Never | 153 | 5919 | Ref |  |  | 110 | 3821 | Ref |  |
|  | Ever | 49 | 1728 | 1.0 | (0.7, 1.5) |  | <5 | 106 | ─ | ─ |
| Glyphosate | None | 49 | 1742 | Ref |  |  | 23 | 905 | Ref |  |
|  | Any | 174 | 6320 | 0.9 | (0.6, 1.3) |  | 123 | 3831 | 1.2 | (0.7, 2.1) |
|  | 1 | 48 | 1727 | 0.8 | (0.5, 1.2) |  | 50 | 1119 | 1.2 | (0.7, 2.2) |
|  | 2 | 46 | 1818 | 1.1 | (0.7, 1.6) |  | 33 | 1091 | 1.2 | (0.6, 2.3) |
|  | 3 | 32 | 1822 | 0.9 | (0.6, 1.5) |  | 19 | 1010 | 0.6 | (0.3, 1.5) |
|  |  |  |  | p trend=0.71 |  |  |  | p trend=0.91 |
| Imazethapyr | Never | 95 | 3201 | Ref |  |  | 102 | 3711 | Ref |  |
|  | Ever | 115 | 4563 | 1.0 | (0.7, 1.4) |  | 8 | 215 | 1.6 | (0.6, 4.6) |
| Metolachlorc | None | 97 | 3488 | Ref |  |  | 89 | 2816 | Ref |  |
|  | Any | 112 | 4290 | 1.1 | (0.8, 1.5) |  | 20 | 1184 | 0.4 | (0.2, 1.0) |
|  | ≤ Median | 52 | 1975 | 1.0 | (0.7, 1.5) |  | 7 | 459 | 0.6 | (0.2, 1.5) |
|  | > Median | 44 | 1929 | 1.1 | (0.7, 1.7) |  | 7 | 517 | 0.3 | (0.1, 1.1) |
|  |  |  |  | p trend=0.52 |  |  |  | p trend=0.04 |
| Metribuzin | Never | 96 | 3679 | Ref |  |  | 108 | 3420 | Ref |  |
|  | Ever | 61 | 1887 | 1.3 | (0.8, 1.9) |  | 8 | 252 | 1.4 | (0.6, 3.2) |
| Paraquat | Never | 193 | 6900 | Ref |  |  | 83 | 2553 | Ref |  |
|  | Ever | 10 | 271 | 0.8 | (0.4, 1.8) |  | 20 | 685 | 1.0 | (0.5, 1.7) |
| Pendimethalin | Never | 128 | 4161 | Ref |  |  | 79 | 2431 | Ref |  |
|  | Ever | 50 | 1871 | 0.9 | (0.6, 1.3) |  | 21 | 854 | 0.9 | (0.4, 1.6) |
| Petroleum oil | Never | 102 | 3829 | Ref |  |  | 88 | 2833 | Ref |  |
|  | Ever | 28 | 1041 | 0.8 | (0.5, 1.4) |  | 12 | 335 | 0.9 | (0.4, 1.8) |
| Trifluralin | Never | 94 | 3088 | Ref |  |  | 91 | 2961 | Ref |  |
|   | Ever | 118 | 4742 | 0.7 | (0.5, 1.0) |   | 16 | 863 | 0.6 | (0.3, 1.1) |

a Numbers of exposed and unexposed may not sum to 100% for some insecticides due to missing data.

b Reference category is never exposed for all analyses. Other categories are defined among only the exposed. Time scale is attained age, with left truncation at cohort enrollment. Adjusted for race, state, and combined parity/age at first birth. Additionally adjusted for use of 2,4,5-T, 2,4,5-TP, trifluralin, aldicarb, and dieldrin.

c Evidence of non-proportional hazards (p=0.02)

Table e6. Associations between the husbands’ use of individual fumigants, fungicides, and herbicides and risk of breast cancer among farmers’ wives who never used pesticides in the Agricultural Health Study, stratified by tumor hormone receptor status.

|  |  | ER-positive |  | ER-negative |  |
| --- | --- | --- | --- | --- | --- |
| Exposure | Level | Exposed cases (n=243)a | HRb | 95% CI |   | Exposed cases (n=64)a | HRb | 95% CI | Interaction p-value |
| **Fumigants** |  |  |  |  |  |  |  |  |  |
| Aluminum Phosphide | Never | 221 | Ref |  |  | 58 | Ref |  |  |
|  | Ever | 5 | 1.7 | (0.6, 4.6) |  | <5 | ─ | ─ | ─ |
| Carbon Tetrachloride/  | Never | 210 | Ref |   |   | 52 | Ref |   |  |
| Carbon Disulfide | Ever | 6 | 1.2 | (0.5, 2.7) |   | 5 | 3.0 | (1.0, 9.4) | 0.17 |
| Methyl Bromide | Never | 212 | Ref |  |  | 55 | Ref |  |  |
|  | Ever | 16 | 0.6 | (0.2, 1.2) |  | 6 | 1.2 | (0.4, 3.4) | 0.26 |
| **Fungicides** |  |  |  |  |  |  |  |  |  |
| Benomyl | Never | 205 | Ref |   |   | 55 | Ref |   |  |
|   | Ever | 11 | 1.5 | (0.7, 3.1) |   | <5 | ─ | ─ | ─ |
| Captan | Never | 183 | Ref |  |  | 46 | Ref |  |  |
|  | Ever | 25 | 1.3 | (0.8, 2.2) |  | 5 | 0.3 | (0.0, 1.9) | 0.12 |
| Chlorothalonil | Never | 220 | Ref |  |  | 58 | Ref |  |  |
|  | Ever | 15 | 1.4 | (0.7, 3.2) |  | <5 | ─ | ─ | ─ |
| Maneb | Never | 204 | Ref |  |  | 57 | Ref |  |  |
|  | Ever | 12 | 1.0 | (0.4, 2.2) |  | <5 | ─ | ─ | ─ |
| Metalaxyl | Never | 194 | Ref |  |  | 50 | Ref |  |  |
|  | Ever | 13 | 0.7 | (0.3, 1.3) |  | 6 | 1.5 | (0.6, 3.7) | 0.14 |
| **Herbicides** |  |  |  |  |  |  |  |  |  |
| 2,4-D | Never | 55 | Ref |   |   | 13 | Ref |   |  |
|  | Ever | 177 | 0.8 | (0.5, 1.1) |  | 45 | 0.8 | (0.4, 1.5) | 1.00 |
| 2,4,5-T | Never | 151 | Ref |  |  | 45 | Ref |  |  |
|  | Ever | 38 | 1.2 | (0.7, 1.9) |  | 11 | 1.3 | (0.6, 3.1) | 0.77 |
| 2,4,5-TP | Never | 191 | Ref |  |  | 55 | Ref |  |  |
|  | Ever | 12 | 1.4 | (0.7, 2.9) |  | <5 | ─ | ─ | ─ |
| Alachlor | Never | 96 | Ref |  |  | 30 | Ref |  |  |
|  | Ever | 118 | 1.2 | (0.8, 1.7) |  | 24 | 0.8 | (0.4, 1.4) | 0.20 |
| Atrazine | Never | 66 | Ref |  |  | 18 | Ref |  |  |
|  | Ever | 166 | 1.0 | (0.7, 1.6) |  | 43 | 0.6 | (0.3, 1.2) | 0.16 |
| Butylate | Never | 152 | Ref |  |  | 44 | Ref |  |  |
|  | Ever | 37 | 1.2 | (0.8, 1.9) |  | 10 | 1.2 | (0.5, 2.6) | 0.92 |
| Chlorimuron ethyl | Never | 158 | Ref |  |  | 43 | Ref |  |  |
|  | Ever | 32 | 0.8 | (0.5, 1.2) |  | 8 | 0.8 | (0.3, 1.8) | 0.96 |
| Cyanazine | Never | 121 | Ref |  |  | 39 | Ref |  |  |
|  | Ever | 90 | 1.0 | (0.7, 1.5) |  | 17 | 0.6 | (0.3, 1.1) | 0.11 |
| Dicamba | Never | 96 | Ref |  |  | 29 | Ref |  |  |
|  | Ever | 117 | 0.9 | (0.6, 1.4) |  | 25 | 0.6 | (0.3, 1.2) | 0.23 |
| EPTC | Never | 172 | Ref |  |  | 43 | Ref |  |  |
|  | Ever | 39 | 1.1 | (0.7, 1.7) |  | 9 | 0.7 | (0.3, 1.8) | 0.41 |
| Glyphosate | Never | 46 | Ref |  |  | 15 | Ref |  |  |
|  | Ever | 194 | 1.0 | (0.7, 1.5) |  | 46 | 0.7 | (0.3, 1.3) | 0.26 |
| Imazethapyr | Never | 124 | Ref |  |  | 30 | Ref |  |  |
|  | Ever | 92 | 1.0 | (0.7, 1.5) |  | 23 | 1.0 | (0.6, 2.0) | 0.97 |
| Metolachlor | Never | 115 | Ref |  |  | 33 | Ref |  |  |
|  | Ever | 96 | 1.0 | (0.7, 1.5) |  | 20 | 0.7 | (0.4, 1.3) | 0.29 |
| Metribuzin | Never | 115 | Ref |   |   | 37 | Ref |   |  |
|   | Ever | 56 | 1.6 | (1.1, 2.5) |   | 9 | 0.8 | (0.3, 1.8) | 0.10 |
| Paraquat | Never | 190 | Ref |  |  | 42 | Ref |  |  |
|  | Ever | 15 | 0.8 | (0.4, 1.5) |  | 7 | 1.5 | (0.6, 4.0) | 0.24 |
| Pendimethalin | Never | 126 | Ref |  |  | 41 | Ref |  |  |
|  | Ever | 51 | 1.0 | (0.6, 1.5) |  | 11 | 0.6 | (0.3, 1.4) | 0.35 |
| Petroleum oil | Never | 111 | Ref |  |  | 39 | Ref |  |  |
|  | Ever | 26 | 0.9 | (0.5, 1.5) |  | 9 | 0.8 | (0.3, 1.9) | 0.88 |
| Trifluralin | Never | 110 | Ref |  |  | 32 | Ref |  |  |
|   | Ever | 103 | 0.8 | (0.6, 1.1) |   | 22 | 0.5 | (0.3, 1.0) | 0.24 |

a Numbers of exposed and unexposed may not sum to 100% for some insecticides due to missing data.

b Reference category is never exposed for all analyses. Other categories are defined among only the exposed. Time scale is attained age, with left truncation at cohort enrollment. Adjusted for race, state, and combined parity/age at first birth. Additionally adjusted for use of 2,4,5-T, 2,4,5-TP, trifluralin, aldicarb, and dieldrin.

Table e7. Associations between the husbands’ use of individual fumigants, fungicides, and herbicides and risk of breast cancer among farmers’ wives who never used pesticides in the Agricultural Health Study, stratified by menopausal status at diagnosis.

|  |  | Premenopausal |  | Postmenopausal |  |
| --- | --- | --- | --- | --- | --- |
| Exposure | Level | Exposed cases (n=54)a | HRb | 95% CI |   | Exposed cases (n=322)a | HRb | 95% CI | Interaction p-value |
| **Fumigants** |  |  |  |  |  |  |  |  |  |
| Aluminum Phosphide | Never | 49 | Ref |  |  | 290 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 5 | 0.9 | (0.3, 3.1) | ─ |
| Carbon Tetrachloride/ Carbon Disulfide | Never | 51 | Ref |  |  | 270 | Ref |  |  |
| Ever | <5 | ─ | ─ |  | 12 | 1.4 | (0.7, 2.6) | ─ |
| Methyl Bromide | Never | 50 | Ref |  |  | 263 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 37 | 0.7 | (0.4, 1.3) | ─ |
| **Fungicides** |  |  |  |  |  |  |  |  |  |
| Benomyl | Never | 49 | Ref |  |  | 261 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 18 | 1.2 | (0.7, 2.3) | ─ |
| Captan | Never | 47 | Ref |  |  | 233 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 33 | 1.3 | (0.8, 2.1) | ─ |
| Chlorothalonil | Never | 51 | Ref |  |  | 280 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 26 | 1.3 | (0.7, 2.4) | ─ |
| Maneb | Never | 48 | Ref |  |  | 262 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 19 | 1.0 | (0.5, 1.8) | ─ |
| Metalaxyl | Never | 43 | Ref |  |  | 238 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 29 | 0.9 | (0.6, 1.5) | ─ |
| **Herbicides** |  |  |  |  |  |  |  |  |  |
| 2,4-D | Never | 13 | Ref |   |   | 79 | Ref |   |   |
|  | Ever | 38 | 0.6 | (0.3, 1.2) |  | 224 | 0.9 | (0.6, 1.2) | 0.38 |
| 2,4,5-T | Never | 45 | Ref |   |   | 194 | Ref |   |   |
|   | Ever | <5 | ─ | ─ |   | 56 | 1.4 | (0.9, 2.1) | ─ |
| 2,4,5-TP | Never | 46 | Ref |   |   | 252 | Ref |   |   |
|   | Ever | <5 | ─ | ─ |   | 19 | 1.7 | (0.9, 3.0) | ─ |
| Alachlor | Never | 26 | Ref |  |  | 126 | Ref |  |  |
|  | Ever | 22 | 1.3 | (0.7, 2.2) |  | 144 | 1.0 | (0.7, 1.4) | 0.48 |
| Atrazine | Never | 17 | Ref |  |  | 95 | Ref |  |  |
|  | Ever | 34 | 0.7 | (0.4, 1.3) |  | 204 | 0.9 | (0.6, 1.3) | 0.48 |
| Butylate | Never | 41 | Ref |   |   | 208 | Ref |   |   |
|   | Ever | <5 | ─ | ─ |   | 51 | 1.5 | (1.0, 2.2) | ─ |
| Chlorimuron ethyl | Never | 36 | Ref |  |  | 212 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 43 | 0.8 | (0.5, 1.3) | ─ |
| Cyanazine | Never | 34 | Ref |  |  | 170 | Ref |  |  |
|  | Ever | 16 | 0.8 | (0.4, 1.4) |  | 100 | 0.9 | (0.7, 1.4) | 0.56 |
| Dicamba | Never | 24 | Ref |  |  | 141 | Ref |  |  |
|  | Ever | 26 | 0.7 | (0.4, 1.2) |  | 129 | 1.0 | (0.7, 1.4) | 0.20 |
| EPTC | Never | 41 | Ref |  |  | 222 | Ref |  |  |
|  | Ever | 8 | 0.8 | (0.4, 1.8) |  | 44 | 1.1 | (0.7, 1.8) | 0.51 |
| Glyphosate | Never | 7 | Ref |  |  | 65 | Ref |  |  |
|  | Ever | 46 | 0.8 | (0.5, 1.5) |  | 251 | 1.0 | (0.7, 1.5) | 0.56 |
| Imazethapyr | Never | 31 | Ref |  |  | 166 | Ref |  |  |
|  | Ever | 19 | 0.9 | (0.5, 1.6) |  | 104 | 1.1 | (0.8, 1.6) | 0.53 |
| Metolachlor | Never | 31 | Ref |  |  | 155 | Ref |  |  |
|  | Ever | 17 | 0.6 | (0.3, 1.1) |  | 115 | 1.1 | (0.8, 1.5) | 0.09 |
| Metribuzin | Never | 31 | Ref |   |   | 173 | Ref |   |   |
|   | Ever | 5 | 0.8 | (0.4, 1.7) |   | 64 | 1.5 | (1.0, 2.2) | 0.12 |
| Paraquat | Never | 42 | Ref |  |  | 234 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 29 | 1.0 | (0.6, 1.6) | ─ |
| Pendimethalin | Never | 33 | Ref |  |  | 174 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 67 | 1.0 | (0.7, 1.5) | ─ |
| Petroleum oil | Never | 26 | Ref |  |  | 164 | Ref |  |  |
|  | Ever | <5 | ─ | ─ |  | 36 | 0.8 | (0.5, 1.3) | ─ |
| Trifluralin | Never | 32 | Ref |  |  | 153 | Ref |  |  |
|   |   | 17 | 0.6 | (0.4, 1.1) |   | 117 | 0.7 | (0.5, 1.0) | 0.80 |

a Numbers of exposed and unexposed may not sum to 100% for some insecticides due to missing data.

b Reference category is never exposed for all analyses. Other categories are defined among only the exposed. Time scale is attained age, with left truncation at cohort enrollment. Adjusted for race, state, and combined parity/age at first birth. Additionally adjusted for use of 2,4,5-T, 2,4,5-TP, trifluralin, aldicarb, and dieldrin.