|  |  |  |  |  |
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| **Supplementary Table 1. Estimates of lung cancer risk associated with metformin use in patient subgroups** | | | | |
|  |  |  | **Adjusted***a* | |
| **Metformin Use** | **No. of events** | **Person-Years** | **HR (95% CI)** | |
| **Among sulfonylurea users at baseline** | | |  |  |
| Never | 138 | 80,849.35 | 1.00 | (reference) |
| Ever | 91 | 58,754.86 | 0.96 | (0.70-1.31) |
|  |  |  |  |  |
| *Total duration, years* |  |  |  |  |
| <2.0 | 38 | 25,053.68 | 1.05 | (0.72-1.54) |
| 2.0 - 4.9 | 33 | 20,712.43 | 0.92 | (0.60-1.41) |
| ≥5.0 | 20 | 12,988.75 | 0.77 | (0.44-1.35) |
|  |  |  |  |  |
| *Recency of use* |  |  |  |  |
| Former | 9 | 4,064.32 | 1.19 | (0.58-2.44) |
| Recent | 16 | 6,483.90 | 1.50 | (0.87-2.59) |
| Current |  |  |  |  |
| <5.0 years | 48 | 37,174.87 | 0.86 | (0.60-1.23) |
| ≥5.0 years | 18 | 11,031.76 | 0.90 | (0.50-1.61) |
|  |  |  |  |  |
| *Cumulative dose (mg), quartiles* |  |  |  |  |
| ≤750,000 | 33 | 22,818.74 | 0.98 | (0.66-1.45) |
| 750,001 – 2,300,000 | 35 | 20,679.55 | 1.01 | (0.67-1.53) |
| 2,300,001 – 4,930,000 | 15 | 11,690.79 | 0.73 | (0.41-1.33) |
| >4,930,000 | 8 | 3,565.78 | 1.10 | (0.48-2.49) |
|  |  |  |  |  |
| **Among non-insulin users at baseline** | |  |  |  |
| Never | 161 | 91,863.33 | 1.00 | (reference) |
| Ever | 174 | 106,366.90 | 0.97 | (0.75-1.27) |
|  |  |  |  |  |
| *Total duration, years* |  |  |  |  |
| <2.0 | 56 | 34,788.49 | 1.04 | (0.75-1.43) |
| 2.0 - 4.9 | 53 | 35,366.61 | 0.88 | (0.62-1.25) |
| ≥5.0 | 65 | 36,211.80 | 1.00 | (0.68-1.46) |
|  |  |  |  |  |
| *Recency of use* |  |  |  |  |
| Former | 42 | 19,220.13 | 1.17 | (0.77-1.79) |
| Recent | 27 | 12,931.99 | 1.28 | (0.83-1.98) |
| Current |  |  |  |  |
| <5.0 years | 60 | 46,929.95 | 0.84 | (0.61-1.16) |
| ≥5.0 years | 45 | 27,284.84 | 1.02 | (0.67-1.54) |
|  |  |  |  |  |
| *Cumulative dose (mg), quartiles* |  |  |  |  |
| ≤750,000 | 49 | 31,443.67 | 0.98 | (0.70-1.37) |
| 750,001 – 2,300,000 | 52 | 32,294.09 | 0.97 | (0.68-1.37) |
| 2,300,001 – 4,930,000 | 39 | 26,616.55 | 0.87 | (0.58-1.31) |
| >4,930,000 | 34 | 16,012.60 | 1.26 | (0.78-2.02) |
|  |  |  |  |  |
| **With 2-year lag** |  |  |  |  |
| Never | 516 | 297,988.39 | 1.00 | (reference) |
| Ever | 231 | 130,569.08 | 1.12 | (0.92-1.37) |
|  |  |  |  |  |
| *Total duration, years* |  |  |  |  |
| <2.0 | 98 | 50,215.85 | 1.22 | (0.96-1.54) |
| 2.0 - 4.9 | 70 | 45,406.41 | 0.97 | (0.73-1.29) |
| ≥5.0 | 63 | 34,946.82 | 1.15 | (0.83-1.59) |

*a* Stratified on age and adjusted for gender, race/ethnicity, birth year, diabetes duration, BMI, alcohol use, Charlson comorbidity index, smoking history (status and pack-years), education, income level, creatinine level, HbA1c level, and use of other diabetes medications

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| **Supplementary Table 2. Estimates of lung cancer risk associated with metformin use, by gender** | | | | | | | | | |
|  | **Men** | | | |  | **Women** | | | |
|  |  |  | **Adjusted***a*  **HR (95% CI)** | |  |  |  | **Adjusted***a*  **HR (95% CI)** | |
| **Metformin Use** | **No. of events** | **Person-Years** |  | **No. of events** | **Person-Years** |
| Never | 274 | 138,498.73 | 1.00 | (reference) |  | 190 | 119,043.69 | 1.00 | (reference) |
| Ever | 170 | 87,479.88 | 1.10 | (0.87-1.38) |  | 113 | 83,535.17 | 0.94 | (0.71-1.25) |
|  |  |  |  |  |  |  |  |  |  |
| *Total duration, years* | |  |  |  |  |  |  |  |  |
| <2.0 | 66 | 30,996.49 | 1.21 | (0.91-1.61) |  | 34 | 30,050.51 | 0.81 | (0.55-1.19) |
| 2.0 - 4.9 | 51 | 29,293.08 | 0.97 | (0.70-1.36) |  | 42 | 27,130.25 | 1.05 | (0.72-1.53) |
| ≥5.0 | 53 | 27,190.31 | 1.05 | (0.72-1.51) |  | 37 | 26,354.41 | 1.06 | (0.68-1.64) |
|  |  |  |  |  |  |  |  |  |  |
| *Recency of use* |  |  |  |  |  |  |  |  |  |
| Former | 48 | 16,852.27 | 1.36 | (0.94-1.96) |  | 27 | 16,644.45 | 1.01 | (0.63-1.60) |
| Recent | 21 | 10,567.45 | 1.11 | (0.70-1.77) |  | 16 | 10,916.92 | 1.07 | (0.62-1.82) |
| Current |  |  |  |  |  |  |  |  |  |
| <5.0 years | 65 | 39,419.81 | 1.01 | (0.75-1.35) |  | 42 | 35,945.39 | 0.84 | (0.59-1.21) |
| ≥5.0 years | 36 | 20,640.34 | 1.04 | (0.69-1.57) |  | 28 | 20,028.42 | 1.08 | (0.67-1.73) |
|  |  |  |  |  |  |  |  |  |  |
| *Cumulative dose (mg), quartiles* | |  |  |  |  |  |  |  |  |
| ≤750,000 | 57 | 27,515.77 | 1.16 | (0.86-1.57) |  | 34 | 27,844.44 | 0.84 | (0.57-1.24) |
| 750,001 – 2,300,000 | 50 | 26,712.57 | 1.04 | (0.75-1.44) |  | 34 | 25,405.76 | 0.93 | (0.62-1.38) |
| 2,300,001 – 4,930,000 | 38 | 21,507.54 | 1.02 | (0.69-1.50) |  | 29 | 19,590.27 | 1.11 | (0.71-1.74) |
| >4,930,000 | 25 | 11,743.99 | 1.19 | (0.73-1.94) |  | 16 | 10,694.70 | 1.26 | (0.69-2.30) |

*a* Stratified on age and adjusted for race/ethnicity, birth year, diabetes duration, BMI, alcohol use, Charlson comorbidity index, smoking history (status and pack-years), education, income level, creatinine level, HbA1c level, and use of other diabetes medications

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| **Supplementary Table 3. Estimates of lung cancer risk associated with metformin use, by tumor stage** | | | | | | | | | | | |
|  | **Localized** | | |  | **Regional** | | |  | **Metastatic** | | |
|  |  | **Adjusted***a* | |  |  | **Adjusted***a* | |  |  | **Adjusted***a* | |
| **Metformin Use** | **No. of events** | **HR (95% CI)** | |  | **No. of events** | **HR (95% CI)** | |  | **No. of events** | **HR (95% CI)** | |
| Never | 56 | 1.00 | (reference) |  | 114 | 1.00 | (reference) |  | 281 | 1.00 | (reference) |
| Ever | 40 | 1.11 | (0.67-1.83) |  | 62 | 1.13 | (0.77-1.65) |  | 170 | 0.91 | (0.73-1.15) |
|  |  |  |  |  |  |  |  |  |  |  |  |
| *Total duration, years* |  |  |  |  |  |  |  |  |  |  |  |
| <2.0 | 10 | 0.88 | (0.43-1.79) |  | 17 | 0.81 | (0.47-1.38) |  | 66 | 1.03 | (0.77-1.36) |
| 2.0 - 4.9 | 12 | 1.03 | (0.51-2.07) |  | 27 | 1.57 | (0.97-2.57) |  | 51 | 0.80 | (0.58-1.11) |
| ≥5.0 | 18 | 1.71 | (0.85-3.45) |  | 18 | 1.24 | (0.66-2.35) |  | 53 | 0.87 | (0.61-1.25) |
|  |  |  |  |  |  |  |  |  |  |  |  |
| *Recency of use* |  |  |  |  |  |  |  |  |  |  |  |
| Former | 11 | 1.45 | (0.68-3.11) |  | 10 | 0.81 | (0.39-1.67) |  | 50 | 1.17 | (0.83-1.67) |
| Recent | 4 | 0.90 | (0.31-2.59) |  | 8 | 1.14 | (0.54-2.41) |  | 24 | 1.04 | (0.67-1.61) |
| Current |  |  |  |  |  |  |  |  |  |  |  |
| <5.0 years | 13 | 0.92 | (0.48-1.78) |  | 31 | 1.24 | (0.80-1.93) |  | 58 | 0.77 | (0.57-1.05) |
| ≥5.0 years | 12 | 1.45 | (0.68-3.12) |  | 13 | 1.08 | (0.54-2.14) |  | 38 | 0.92 | (0.62-1.36) |
|  |  |  |  |  |  |  |  |  |  |  |  |
| *Cumulative dose (mg), quartiles* | |  |  |  |  |  |  |  |  |  |  |
| ≤750,000 | 11 | 1.02 | (0.51-2.01) |  | 17 | 0.88 | (0.51-1.49) |  | 57 | 0.96 | (0.71-1.30) |
| 750,001 – 2,300,000 | 9 | 0.84 | (0.39-1.81) |  | 22 | 1.35 | (0.81-2.25) |  | 51 | 0.88 | (0.64-1.21) |
| 2,300,001 – 4,930,000 | 12 | 1.46 | (0.70-3.06) |  | 15 | 1.35 | (0.72-2.54) |  | 37 | 0.82 | (0.56-1.21) |
| >4,930,000 | 8 | 2.11 | (0.84-5.30) |  | 8 | 1.36 | (0.58-3.23) |  | 25 | 1.06 | (0.66-1.70) |

*a* Stratified on age and adjusted for gender, race/ethnicity, birth year, diabetes duration, BMI, alcohol use, Charlson comorbidity index, smoking history (status and pack-years), education, income level, creatinine level, HbA1c level, and use of other diabetes medication