**Cross-sectional associations between Angiotensin Converting Enzyme inhibitor use and cancer diagnosis in US adults**

**Lee Smith\*±1, Christopher Parris\*2, Nicola Veronese3, Ce Shang4, Guillermo F. López-Sánchez5, Louis Jacob6, Ai Koyanagi7, Alessia Nottegar8, Sarah E Jackson9, Tobias Raupach10, Igor Grabovac11, Scott Crichton12, Fiona Dempsey12, Lin Yang±13**

**\***Authors contributed equally

± Corresponding Authors

1. The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK. Lee.Smith@anglia.ac.uk

2. Biomedical Research Group, Faculty of Science and Engineering, Anglia Ruskin University, Cambridge, UK

3. Aging Branch, Neuroscience Institute, National Research Council, Padua, Italy

4. Stephenson Cancer Centre, University of Oklahoma Health Social Science Centre, USA

5. Faculty of Sport Sciences, University of Murcia, Murcia, Spain

6. Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux 78180, France

7. Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Sant Boide Llobregat, Barcelona, Spain

8. Department of Surgery, Section of Pathology, San Bortolo Hospital, Vicenza, Italy

9. Department of Behavioural Science and Health, University College London, London, United Kingdom

10. Department of Cardiology and pneumology, University Medical Centre GoEttingen, GoEttingen, Germany

11. Department of Social and Preventive Medicine, Center for Public Health, Medical University of Vienna, Vienna, Austria

12. MedAnnex Ltd, 1 Summerhall Place, Techcube 3.5, Edinburgh EH9 1PL

13. Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Holy Cross Centre, Calgary, Alberta, Canada; Departments of Oncology and Community Health Sciences, University of Calgary, Calgary, Canada. lin.yang@ahs.ca

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**ABSTRACT**

**Purpose**: The objective of the present study was to investigate the association between Angiotensin converting enzyme (ACE) inhibitor use and cancer incidence (overall, and breast, prostate, and colorectal cancers specifically) in a large representative sample of US adults. **Methods:** Cross-sectional data on cancer diagnosis, timing of cancer diagnosis, ACE inhibitor use, and other characteristics were extracted from 49 512 adults aged ≥ 20 years participating in the National Health and Nutrition Examination Survey (1999-2016). Multivariable-logistic and propensity score matching (PSM) regressions examined the relationship between pre-diagnosis use of ACE inhibitors and diagnosis of all cancers, and breast, prostate, and colorectal cancers specifically. **Results:** Overall, we observed an increased likelihood of cancer diagnosis [odds ratio (OR)=1.269, 95% confidence interval (CI): 1.088 to 1.480] among those who used ACE inhibitors compared to non-ACE inhibitor use, and for prostate cancer diagnosis (OR=1.438, 95% CI: 1.090 to 1.897), after adjusting for age, sex, body mass index, race/ethnicity, educational attainment, physical activity, alcohol drinking status, smoking status, and high blood pressure. PSM regression retrieved more conservative estimates such that the increased likelihood of cancer diagnosis was only observed when comparing ACE inhibitor users with non-drug users (OR=1.022, 95% CI: 1.016 to 1.027). **Conclusion:** Compared with non-ACE inhibitor use, ACE inhibitor use was associated with an increased risk of prostate cancer. In conclusion, in this large representative sample of US adults, it was found that ACE inhibitor use may have a marginal influence on some cancers.

**Key Words:** Angiotensin converting enzyme inhibitors; Cancer; Epidemiology; NHANES; Observational

**INTRODUCTION**

Angiotensin converting enzyme (ACE) inhibitors are drugs often used for heart failure management [1] and in the treatment of hypertension with positive clinical outcomes, such as the lowering of high blood pressure and then maintenance, as demonstrated through systematic reviews [2]. Importantly, this group of drugs is typically used over a long period of time and their influence on cancer either as a risk factor or a preventive agent is of considerable debate. Observational studies surrounding ACE inhibitor use and cancer have produced mixed findings. For example, one meta-analysis found a non-significant association between the use of ACE inhibitors and overall risk of cancer [3]. Other observational studies have reported associations with reduced [4] and increased cancer risk [5].

These mixed findings may be owing to limitations in the studies such as the use of an inappropriate comparator group, introducing potential confounding by indication and the inclusion of prevalent users of antihypertensives [5]. Many of these studies did not control for important behavioural covariates such as smoking, alcohol intake, or physical activity, and thus results may be subject to confounding bias. Moreover, data have typically been analysed using regression models that do not entirely account for differences between groups (i.e., users vs. non-users of ACE inhibitors). This selection bias can be reduced by using ‘matching procedures’ that aim to equate (or balance) the distribution of covariates in the exposed and unexposed groups. One such technique is propensity score matching (PSM), which pairs participants in the exposed group (ACE inhibitor users) with those with similar propensity scores in the unexposed group (non-ACE inhibitor users) based on propensity scores that express the likelihood of participants selecting the treatment condition given observed covariates [6].

Another key limitation of the current literature in this area is that most studies have investigated the association between ACE inhibitor use and cancer per se, as opposed to specific cancers which may be more informative for frontline practitioners. Excluding non-melanoma skin cancer, breast and prostate cancers are the most common types of malignancy in US women [7] and men [8] respectively, with colorectal cancer ranking as the third most common in both genders [9]. Despite the high prevalence of these cancers, few studies have investigated their association with ACE inhibitor use, and those that have have produced conflicting findings [3].

The aim of the present study was therefore to investigate the association between ACE inhibitor use and cancer per se, and breast, prostate, and colorectal cancers specifically, using PSM in a large representative sample of US adults, controlling for a range of sociodemographic and behavioural covariates.

**METHODS**

Study population

The National Health and Nutrition Examination Survey (NHANES) was designed to provide cross-sectional estimates on the prevalence of health, nutrition, and potential risk factors among the civilian non-institutionalized U.S. population up to 85 years of age [10]. In brief, NHANES surveys a nationally representative complex, stratified, multistage, probability clustered sample of approximately 5,000 participants each year in 15 counties across the country. Survey participants were asked to attend physical examination in a mobile examination centre (MEC). The NHANES obtained approval from the National Centre for Health Statistics Research Ethics Review Board and participants provided written consent.

We extracted and aggregated data on ACE inhibitor use, time and site of cancer diagnosis, and other characteristics from NHANES in 1999-2000 to 2015-2016. We excluded those who started using ACE inhibitors after a cancer diagnosis.

Cancer diagnosis

Cancer diagnosis was defined as anyone who has been diagnosed with cancer. Cancer survivors were identified if participants answered “yes” to the question “Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?” We excluded participants who had non-melanoma skin cancer. Specific cancer types that were considered were breast, prostate, and colorectal cancers because these cancers are highly prevalent in the general population and had a sufficient sample size to allow statistical models to converge. The age at cancer diagnosis was used to establish whether the diagnosis was prior to or after initiation of ACE inhibitor use.

ACE inhibitor use

Participants reported the names of all prescribed drugs, duration of taking each drug, and showed the interviewer the medication container for recording the name of each drug. Use of ACE inhibitors was defined as use of trandolapril, fosinopril, quinapril, captopril, enalapril, cilazapril, ramipril, lisinopril, benzazepril, moexipril, or perindopril; alone, or in a combination with other agents (e.g. amlodipine, verapamil).

Based on the prescribed drug use reported by participants, we created three binary variables to indicate the use of ACE inhibitors: 1) ACE inhibitor users vs. ACE inhibitor non-users (including those who reported not using any prescribed drugs and those who reported using prescribed drugs other than ACE inhibitors); 2) ACE inhibitor users vs. non-drug users (those who reported not using any prescribed drugs); and 3) non-ACE inhibitor drug users (who reported using prescribed drugs other than ACE inhibitor) vs. non-drug users.

Socio-demographic characteristics

Data on age, sex, body mass index (BMI), race/ethnicity, educational attainment, physical activity, alcohol drinking status, smoking status [11], and high blood pressure were extracted. Height and weight were measured at the time of physical examination following standard procedures. BMI was calculated as weight in kg/(height in meters)2 and categorized into standard BMI categories: underweight (<18.5kg/m2), normal weight (18.5 to <25 kg/m2), overweight (25 to <30 kg/m2), and obese (≥30.0 kg/m2). For analytic purposes, we excluded underweight due to potential underlying health conditions. Based on self-reported race and ethnicity, participants were classified into one of the three racial/ethnic groups: Non-Hispanic White, Non-Hispanic Black, and Hispanic. Participants’ educational attainment was classified into three groups: less than high school, high school, and more than high school. Using two questions asking if participants engaged in sports or recreational activities for at least 10 minutes continuously over the past 30 days, at vigorous and moderate levels, leisure time physical activity was defined by a binary variable, with “no” responses to both questions classified as inactive, and “yes” to any or both questions classified as active. Alcohol drinking was classified into three groups: never drinker (did not drink at least 12 alcohol drinks in lifetime), past drinker (ever drunk at least 12 alcohol drinks in lifetime, but not 12 alcohol drinks in the past year), and current drinker (had at least 12 alcohol drinks in the past year). Similarly, smoking status was defined as: never smokers (did not smoke 100 cigarettes in life and do not smoke now), former smokers (smoked 100 cigarettes in life and do not smoke now), and current smokers (smoked 100 cigarettes in life and smoke now). High blood pressure was defined according to participants’ self-reports of having been told by a physician or health professional to have this condition.

Statistical analysis

Participants with complete data for the present analyses were included. Sample exclusions were reported using unweighted (crude) proportions. Descriptive characteristics were normally distributed and were summarized using means and standard deviation for continuous variables and proportions for categorical variables, with *P-*values reported for comparisons by cancer diagnosis status. The most frequently diagnosed cancer sites were reported using both unweighted (crude) and weighted (weighted to the national representative sample) proportions.

Logistic regressions were first carried out to quantify associations of three indicators of ACE inhibitor use with cancer diagnosis status. The multivariable logistic regression models were adjusted for age, sex, race/ethnicity, BMI, education attainment, physical activity, alcohol drinking, smoking status, and hypertension. We further explored three sub-types of cancer (cancer, prostate, colorectal) wherever sample sizes allowed. As a sensitivity analysis, we restricted our study to those aged 40 years and older to exclude paediatric, adolescent and young adult cancer diagnoses due to their potentially different aetiology.

Finally, propensity scores were calculated using a logistic regression model, regressing the treatment indicator on the baseline covariates. For each treated subject, untreated matches were chosen at 1:4 nearest neighbour matching on propensity scores (for instance, ACE inhibitor users vs. ACE inhibitor non-users) [6]. This method better accounts for significant differences between two groups in observational studies, particularly when medications are used as exposure [6].

Although the present analyses is exploratory for hypothesis generation, multiple testing adjustment was applied to allow for generation of conservative values. In both logistic regression and propensity score matched analysis, Bonferroni adjustment were used to correct P-values for multiple testing. P-values as well as P-values multiplied by number of tests (n=8) were reported and compared with significant level of 0.05. All statistical analyses were performed using Stata version 14.0 (STATA Corp., College Station, Texas, USA).

Data availability

The data that support the findings of this study are available from the corresponding authors, upon reasonable request.

**RESULTS**

A total of 49 512 participants reported data on cancer diagnosis and prescribed drug use from 1999 to 2016. Of these, we excluded 2 219 (5%) participants who reported initiating use of ACE inhibitors after their cancer diagnosis. We further excluded 4 812 (10.1%) participants who did not provide information on other characteristics. Our analysed sample consisted of 36 837 individuals 20 years or older, including 974 (unweighted proportion: 2.6%; weighted proportion: 2.2%) with a cancer diagnosis. Overall, 4 726 (unweighted proportion: 23.0%; weighted proportion: 19.8%) participants reported using ACE inhibitors (initiated before a cancer diagnosis). Of 32 111 participants who reported not using ACE inhibitors, 16 246 (unweighted proportion: 49.4%; weighted proportion: 48.0%) reported using other prescribed drugs, while 15 865 (unweighted proportion: 50.6%; weighted proportion: 52.0%) reported not using any prescribed drugs. Among 974 cancer diagnoses, the most common sites were prostate (n=242; unweighted proportion: 24.8%, weighted proportion: 18.1%) breast (n=186; unweighted proportion: 19.1%, weighted proportion: 20.7%), and colorectal cancer (n=101; unweighted proportion: 10.4%; weighted proportion: 7.7%). Those who reported a cancer diagnosis were significantly older, leaner, more likely to be male, non-Hispanic White, and living with high blood pressure. In addition, those who had received a cancer diagnosis were less likely to be a current drinker, current smoker or physically active (Table 1).

Associations of ACE inhibitor use with cancer diagnosis/incidence

Table 2 summarizes the adjusted associations of ACE inhibitor use and cancer diagnosis. Overall, we observed an increased likelihood of cancer diagnosis [odds ratio (OR)=1.269, 95% confidence interval (CI): 1.088 to 1.480, Bonferroni corrected P-value=0.020] among those who used ACE inhibitors compared with non-users of ACE inhibitors (those who reported not using ACE inhibitors and those not using any other prescribed drugs among adults 20 years and older). This association was stronger (OR=8.035, 95% CI: 4.864 to 13.271, Bonferroni corrected P-value<.001) when comparing ACE inhibitor users to those not using any prescribed drugs. Although those who used prescribed drugs other than ACE inhibitors also appeared to be more likely to have a cancer diagnosis (OR=8.796, 95% CI:5.944 to 13.015, Bonferroni corrected P-value<.001). Considering cancer sub-types, the highest likelihood of cancer diagnosis associated with ACE inhibitor use compared to ACE inhibitor non-users was observed for prostate cancer (OR=1.438, 95% CI: 1.090 to 1.897, Bonferroni corrected P-value=0.081), but was not significant for breast or colorectal cancers. Similar results were observed when the sample was restricted to adults 40 years and older.

PSM regression retrieved more conservative estimates (Table 3). A very small increase in the odds of cancer diagnosis was observed when comparing ACE inhibitor users with non-drug users (OR=1.022, 95% CI: 1.016 to 1.027, Bonferroni corrected P-value<.001) and when comparing non-ACE inhibitor drug users with non-drug users (OR=1.024, 95% CI: 1.021 to 1.026, Bonferroni corrected P-value<.001). There was no association of ACE inhibitor users vs. ACE inhibitor non-users with the likelihood of a cancer diagnosis among all cancer types, but ACE inhibitor use appeared to be associated with a significant, but small reduction in the odds of breast cancer diagnosis (OR=0.998, 95% CI: 0.997 to 0.999, Bonferroni corrected P-value=0.044), but a small increase in the odds of prostate cancer diagnosis (OR=1.004, 95% CI: 1.000 to 1.007, Bonferroni corrected P-value=0.201). Analyses restricting the sample to adults 40 years and older returned similar results.

**DISCUSSION**

In this large representative sample of US adults, it was found that those using ACE inhibitors have an overall increased risk of cancer diagnosis. Within cancer subtypes an increased risk of prostate cancer diagnosis, but not cancers of the breast or colorectum was observed. Taken together, data from regression analyses suggest that ACE inhibitor use increases the risk of cancer diagnosis after adjusting for several important sociodemographic and behavioural covariates. However, PSM analyses, which better accounts for selection bias, showed that there was no association between ACE inhibitor users and ACE inhibitor non-users with the likelihood of a cancer diagnosis among all cancer types. Interestingly, ACE inhibitor use appeared to have a small but significant effect with a higher likelihood of a prostate cancer diagnosis.

Findings from the present study support that of previous literature that has yielded mixed findings [3-5] and adds to it by demonstrating that these mixed results may be explained through the use of varying statistical techniques to model the data for example regression analyses versus PSM.

Our findings that ACE inhibitor use may influence the risk of cancer developing in different tissues are certainly of interest and highlight that cancer is not an organ-specific disease, but it is first of all a genetic and general disease that can affect a specific organ [12]. Notably, cancer is also strongly associated with variations in metabolism, mitochondrial status and energy cell disturbances [13-15]. It is possible that ACE inhibitor function may also influence cell metabolism, causing a higher cancer risk. The intimate correlations involving metabolism variations and the biological reponses to hormones in hormone-sensitive tissues [16-18] may explain the differences between prostate cancer, in which the ACE inhibitor-associated cancer risk was the highest observed compared to breast and colorectal cancer. Another important aspect which has been demonstrated to be very important in influencing the risk of cancer developing in certain tissues is obesity [19,20]. This is strongly associated with several tumour types, and is very high, among others, for prostate cancer [21]. Data from this study showed that ACE inhibitors were significantly associated with the risk of cancer development also after adjusting for BMI, further corroborating the reliability of our results.

Strengths of the present study include the large representative sample, adjustment for a broad range of sociodemographic and behavioural variables, and the conduct of PSM. However, findings from the present study must be interpreted in light of its limitations. First, NHANES is cross-sectional in design; it is therefore not possible to determine the direction of the association, although we utilised data on whether ACE inhibitor use was commenced before or after cancer diagnosis. Next, there are several types of ACE inhibitor and the present analyses collapsed them into a single variable. It is possible that each ACE inhibitor type has a different influence on cancer per se and site-specific cancers. Future research should aim to investigate such associations. Moreover, the present study only investigated the association between ACE inhibitor use and breast, prostate, and colorectal cancer, owing to these cancers having a sufficient sample size for analyses. Future studies investigating the association between ACE inhibitor use and other cancers are warranted. Finally, data were self-reported and thus subject to self-report bias. There can also be recall bias in terms of when ACE inhibitor therapy was started, and cancer was diagnosed.

In conclusion, it was found that ACE inhibitor use may have a marginal influence on some cancers, specifically increasing the risk of prostate cancer within a large representative sample of US adults. The present findings suggest that the existing mixed literature may be a result of statistical models employed and the influence of confounding bias. Future research examining such associations longitudinally using robust statistical techniques are required next.

**Conflict of interest:** The authors declare that they have no conflict of interest.

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| Table 1. Sample characteristics in the NHANES adult population 1999-2016 (n=36837) |
|  | Non-cancer | Cancer | P -value |
| n | 35 863 | 974 |   |
| Age (mean, sd) | 48.6 (17.8) | 68.6 (12.6) | <.001 |
| BMI (mean, sd) | 29.1 (6.8) | 28.7 (6.1) | 0.045 |
| Gender |  |  | 0.003 |
| Male | 48.9 | 53.8 |  |
| Female | 51.1 | 46.2 |  |
| Race and Ethnicity |  |  | <.001 |
| Non-Hispanic White | 48.7 | 67.2 |  |
| Non-Hispanic Black | 22.4 | 20.3 |  |
| Hispanic | 28.9 | 12.5 |  |
| Education attainment |  |  | 0.380 |
| Less than high school | 28.2 | 26.2 |  |
| High school | 23.8 | 24.5 |  |
| Higher than high school | 48 | 49.3 |  |
| Alcohol drinking |  |  | 0.050 |
| Never drinker | 14 | 15.1 |  |
| Past drinker | 14.6 | 16.9 |  |
| Current drinker | 71.4 | 68 |  |
| Smoking status |  |  | <.001 |
| Never smoker | 53.2 | 41.3 |  |
| Past smoker | 24.9 | 46.2 |  |
| Current smoker | 21.9 | 12.5 |  |
| Physical activity |  |  | <.001 |
| Inactive | 48.5 | 58.3 |  |
| Active | 51.5 | 41.7 |  |
| High blood pressure |  |  | <.001 |
| Yes | 33.6 | 65.7 |  |
| No | 66.4 | 34.3 |   |

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| Table 2. Logistic Regression on the Association of ACE inhibitor Use with Cancer in the NHANES Studya |  |
|   | Cases | Odds ratio (95%) |   | *P-*value | *Bonferroni correction*b |
|  | ACE users | ACE non-users |  |  |  |  |  |  |  |  |  |
| All Cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 296 | 678 | 1.269 | ( | 1.088 | to | 1.480 | ) |  | 0.002 | 0.020 |
| >=40 years  | 293 | 643 | 1.264 | ( | 1.083 | to | 1.477 | ) |  | 0.003 | 0.024 |
| Breast cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 52 | 149 | 1.091 | ( | 0.773 | to | 1.540 | ) |  | 0.618 | >.999 |
| >=40 years  | 52 | 148 | 1.085 | ( | 0.769 | to | 1.530 | ) |  | 0.642 | >.999 |
| Prostate cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 96 | 165 | 1.438 | ( | 1.090 | to | 1.897 | ) |  | 0.010 | 0.081 |
| >=40 years  | 96 | 165 | 1.430 | ( | 1.084 | to | 1.885 | ) |  | 0.011 | 0.090 |
| Colorectal cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 35 | 76 | 1.086 | ( | 0.713 | to | 1.656 | ) |  | 0.700 | >.999 |
| >=40 years  | 35 | 75 | 1.086 | ( | 0.712 | to | 1.656 | ) |   | 0.701 | >.999 |
|  | ACE users | Non-drug users |  |  | Odds ratio (95%) |  |  | *P-*value | *Bonferroni correction* |
| All Cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 296 | 28 | 8.035 | ( | 4.864 | to | 13.271 | ) |  | <.001 | <.001 |
| >=40 years  | 293 | 20 | 8.696 | ( | 5.073 | to | 14.904 | ) |  | <.001 | <.001 |
| Breast cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 52 | 1 | 11.686 | ( | 1.281 | to | 106.569 | ) |   | 0.029 | 0.234 |
| >=40 years  | 52 | 1 | 10.159 | ( | 1.163 | to | 88.761 | ) |   | 0.036 | 0.288 |
| Prostate cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 96 | 8 | 8.016 | ( | 3.417 | to | 18.807 | ) |   | <.001 | <.001 |
| >=40 years  | 96 | 8 | 7.677 | ( | 3.308 | to | 17.812 | ) |   | <.001 | <.001 |
| Colorectal cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 35 | 3 | 2.984 | ( | 0.717 | to | 12.411 | ) |   | 0.133 | >.999 |
| >=40 years  | 35 | 3 | 2.872 | ( | 0.703 | to | 11.737 | ) |   | 0.142 | >.999 |
|  | Non-ACE drug users | Non-drug users |  |  | Odds ratio (95%) |  |  | *P-*value | *Bonferroni correction* |
| All Cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 650 | 28 | 8.796 | ( | 5.944 | to | 13.015 | ) |  | <.001 | <.001 |
| >=40 years  | 623 | 20 | 9.778 | ( | 6.197 | to | 15.427 | ) |  | <.001 | <.001 |
| Breast cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 148 | 1 | 36.427 | ( | 5.048 | to | 262.853 | ) |   | <.001 | 0.003 |
| >=40 years  | 147 | 1 | 33.737 | ( | 4.681 | to | 243.139 | ) |   | <.001 | 0.004 |
| Prostate cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 157 | 8 | 6.035 | ( | 2.878 | to | 12.653 | ) |   | <.001 | <.001 |
| >=40 years  | 157 | 8 | 5.887 | ( | 2.816 | to | 12.305 | ) |   | <.001 | <.001 |
| Colorectal cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 73 | 3 | 5.682 | ( | 1.723 | to | 18.736 | ) |   | 0.004 | 0.035 |
| >=40 years  | 72 | 3 | 5.682 | ( | 1.723 | to | 18.736 | ) |   | 0.004 | 0.035 |
| aAll models adjusted for age, gender (for all cancer and colorectal cancer), BMI, race and ethnicity, education attainment, alcohol drinking, smoking, physical activity, and high blood pressurebBonferroni adjustment were used to correct P-values for multiple testing. Bonferroni correction were calculated as P-values multiplied by number of tests (n=8). |  |

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| Table 3. Propensitiy Score-Matched Analysis on the Association of ACE inhibitor Use with Cancer in the NHANES Studya |  |
|   | Cases  | Odds ratio (95%) |   | *P-*value | *Bonferroni correction*a |
|  | ACE users | ACE non-users |  |  |  |  |  |  |  |  |  |
| All Cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 296 | 678 | 1.004 | ( | 0.998 | to | 1.010 | ) |  | 0.188 | >.999 |
| >=40 years  | 293 | 643 | 1.005 | ( | 0.997 | to | 1.012 | ) |  | 0.202 | >.999 |
| Breast cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 52 | 149 | 0.998 | ( | 0.997 | to | 0.999 | ) |  | 0.005 | 0.044 |
| >=40 years  | 52 | 148 | 0.998 | ( | 0.995 | to | 1.000 | ) |  | 0.036 | 0.284 |
| Prostate cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 96 | 165 | 1.004 | ( | 1.000 | to | 1.007 | ) |  | 0.025 | 0.201 |
| >=40 years  | 96 | 165 | 1.005 | ( | 1.000 | to | 1.010 | ) |  | 0.053 | 0.420 |
| Colorectal cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 35 | 76 | 1.000 | ( | 0.998 | to | 1.001 | ) |  | 0.513 | >.999 |
| >=40 years  | 35 | 75 | 0.999 | ( | 0.998 | to | 1.001 | ) |   | 0.562 | >.999 |
|  | ACE users | Non-drug users |  |  | Odds ratio (95%) |  | *P-*value | *Bonferroni correction* |
| All Cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 296 | 28 | 1.022 | ( | 1.016 | to | 1.027 | ) |  | <.001 | <.001 |
| >=40 years  | 293 | 20 | 1.037 | ( | 1.028 | to | 1.045 | ) |  | <.001 | <.001 |
| Breast cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 52 | 1 | 1.003 | ( | 1.002 | to | 1.004 | ) |   | <.001 | <.001 |
| >=40 years  | 52 | 1 | 1.005 | ( | 1.004 | to | 1.006 | ) |   | <.001 | <.001 |
| Prostate cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 96 | 8 | 1.007 | ( | 1.004 | to | 1.010 | ) |   | <.001 | <.001 |
| >=40 years  | 96 | 8 | 1.013 | ( | 1.009 | to | 1.018 | ) |   | <.001 | <.001 |
| Colorectal cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 35 | 3 | 1.002 | ( | 1.001 | to | 1.002 | ) |   | <.001 | <.001 |
| >=40 years  | 35 | 3 | 1.003 | ( | 1.001 | to | 1.005 | ) |   | 0.002 | 0.015 |
|  | Non-ACE drug users | Non-drug users |  |  | Odds ratio (95%) |  | *P-*value | *Bonferroni correction* |
| All Cancer |  |  |  |  |  |  |  |  |  |  |  |
| >=20 years | 650 | 28 | 1.024 | ( | 1.021 | to | 1.026 | ) |  | <.001 | <.001 |
| >=40 years  | 623 | 20 | 1.037 | ( | 1.033 | to | 1.041 | ) |  | <.001 | <.001 |
| Breast cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 148 | 1 | 1.005 | ( | 1.004 | to | 1.006 | ) |   | <.001 | <.001 |
| >=40 years  | 147 | 1 | 1.009 | ( | 1.007 | to | 1.010 | ) |   | <.001 | <.001 |
| Prostate cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 157 | 8 | 1.005 | ( | 1.004 | to | 1.007 | ) |   | <.001 | <.001 |
| >=40 years  | 157 | 8 | 1.008 | ( | 1.006 | to | 1.011 | ) |   | <.001 | <.001 |
| Colorectal cancer |   |   |   |   |   |   |   |   |   |   |  |
| >=20 years | 73 | 3 | 1.003 | ( | 1.002 | to | 1.003 | ) |   | <.001 | <.001 |
| >=40 years  | 72 | 3 | 1.004 | ( | 1.003 | to | 1.005 | ) |   | <.001 | <.001 |
| aAll models adjusted for age, gender (for all cancer and colorectal cancer), BMI, race and ethnicity, education attainment, alcohol drinking, smoking, physical activity, and high blood pressurebBonferroni adjustment were used to correct P-values for multiple testing. Bonferroni correction were calculated as P values multiplied by number of tests (n=8). |  |