Adrenergic blockers and the risk of common solid cancers: a case-control study

Adrenergic blockers and common cancers risk[3]

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Abstract

Introduction

Laboratory studies suggest adrenergic blockers may inhibit the proliferation and migration of cancer cells, but epidemiological evidence of their effect on cancer incidence has proved inconsistent. We therefore conducted a case-control study using the Clinical Practice Research Datalink to assess the effect of adrenergic blockers upon incidence of prostate, lung, bowel and breast cancer.

Methods

Amongst patients aged 18 years or older contributing at least 2 years of prospectively gathered data between 01/01/1987 – 31/12/2012, we selected incident cases of relevant cancers and controls, frequency matched 10:1 by age. Logistic regression was used to adjust effect estimates for age, sex, smoking, alcohol use, and a number of potentially confounding co-morbidities and co-prescriptions.

Results

18968 colorectal, 19082 lung, 21608 prostate and 29109 breast cancers were identified. We found no evidence of a protective effect of adrenergic blockade in lung and prostate cancer and found a slightly increased risk of colorectal and breast cancers in users. This was largely explained by the effects of confounding in a multivariate analyses with final OR estimates of lung, colorectal, breast and prostate cancer of 0.99, 95% CI [0.96-1.04]1.14, [1.09 – 1.18]1.10, [1.06 – 1.14]1.01, [0.98-1.05] respectively for beta blocker exposure and 1.03, [0.97 – 1.09]1.13, [1.07 – 1.20]1.08, [1.00 – 1.17] for alpha blocker exposure.

Conclusion

We found no evidence to suggest that adrenergic blocker use prevents common cancers. Indeed, we found a slight increased risk of colorectal and breast cancer which may reflect residual confounding.

Keywords: adrenergic blockers; Clinical Practice Research Datalink; prostate cancer; lung cancer; colorectal cancer; breast cancer

Introduction

Progress in developing treatments for cancer remains slow thus alternative strategies for drug development such as repurposing previously approved drugs are being considered (Pasquier, Ciccolini et al. 2011). This strategy may reduce risks, costs and time required in drug development (Pasquier, Ciccolini et al. 2011). A specific example of this is the potential anti-neoplastic effects of aspirin with a near 50% reduction in cancer specific mortality from colorectal cancer recently shown in those starting aspirin after diagnosis (Chan, Ogino et al. 2009), which has already led to a randomised controlled trial (Ali, Toh et al. 2011).

Laboratory studies of both beta- and alpha-blockers have shown that by blocking adrenergic signalling they inhibit both stimulation of growth and migratory activity of tumour cells by these neurotransmitters (Masur, Niggemann et al. 2001; Benning and Kyprianou 2002; Drell IV, Joseph et al. 2003; Foster, Yono et al. 2004; Lang, Drell IV et al. 2004; Palm, Lang et al. 2006; Sood, Bhatty et al. 2006; Hui, Fernando et al. 2008; Al-Wadei, Al-Wadei et al. 2009; Sakamoto, Schwarze et al. 2011; Pasquier, Andre et al. 2013). Furthermore beta blockade is of proven efficacy in the treatment of infantile haemangiomas (Fuchsmann, Quintal et al. 2011; Xu, Lv et al. 2012).

These encouraging results have led to a number of epidemiological studies on β-blockers which have not shown a consistent beneficial effect in common cancers (González-Pérez, Ronquist et al. 2004; Perron, Bairati et al. 2004; Ronquist, Rodríguez et al. 2004; Algazi, Plu-Bureau et al. 2006; Rodriguez, Jacobs et al. 2009; Friedman, Udaltsova et al. 2011; Hallas, Christensen et al. 2012; Jansen, Below et al. 2012). Few epidemiological studies have been undertaken in alpha blockers but what evidence there is, is inconsistent. (Friedman, Udaltsova et al. 2011; Hallas, Christensen et al. 2012).

Limited sample sizes and inadequate adjustment for confounders in some studies have possibly contributed to the differences in the results observed. To address this problem,

we conducted a case-control study using data from the Clinical Practice Research Datalink (CPRD) database, a large population healthcare database to allow adjustment for relevant confounding variables. We investigated the 4 most common cancers in the UK; colorectal, lung, breast and prostate cancer (Statistics 2012) since laboratory studies have shown evidence of an anti-tumourigenic effects of adrenergic blockers upon them (Schuller and Cole 1989; Masur, Niggemann et al. 2001; Drell IV, Joseph et al. 2003) and CPRD provided adequate power to investigate each. Additionally, we have investigated the effect of differing doses and durations of adrenergic blocker use and the specificity of its effect by comparing results to those found with another class of agents sharing a number of its indications (calcium channel blockers).

Materials and Methods

Setting

The Clinical Practice Research Datalink (CPRD) contains anonymised computerised clinical information from over 600 general practices across the UK with the earliest records dating to 1987. These records include more than 11 million patients (Card, Siffledeen et al. 2014) making it the largest source of anonymised longitudinal data from primary care in the world (Khan, Harrison et al. 2010). Individual records include demographic information, clinical diagnoses, prescription and treatment details.

Study Population

We conducted a frequency matched case-control study of subjects during the period in which they contributed prospectively gathered data to CPRD from the period 01/01/1987 – 31/12/2012 and occurring after the age of 18 and at least 2 years after they entered the dataset. Cases were defined by a first recorded medical diagnosis of lung, bowel, prostate or breast cancer in females. Controls were selected from contributing subjects with no recorded medical diagnosis of prostate, lung, bowel or breast cancer in their clinical record prior to a random date allocated (henceforth referred to as their pseudo-diagnosis date) and frequency matched by 10 year age bands in a ratio of 10:1 for each malignancy separately. In addition we limited control selection for breast cancer to females and for prostate cancer to males.

Exposure and covariates

Subjects with two or more prescriptions for alpha or beta blocker use within the 2 year window prior to diagnosis or pseudo-diagnosis were considered exposed. We then considered dose by determining the mean dose across all exposed days for each subject, and then dividing by the maximum recommended daily dose (of the individual adrenergic blocker used as determined by the BNF). We used the median of the

standardised doses across a combination of the cancers under study to split subjects into high dose, low dose and unexposed categories.

Age and sex were considered *a priori* confounders. Other potential confounders considered include smoking, alcohol use, co-morbidity (using the Charlson comorbidity Index as a composite measure (Charlson, Pompei et al. 1987), prophylactic medications (NSAID, statin and aspirin use), hormone replacement therapy and potential indications for use of the medications studied including ischaemic heart disease (IHD), heart failure (HF), hypertension, history of diabetes and benign prostatic hyperplasia and/or prostatism. Medication use was defined as two or more prescriptions for the specific medication within the 2 year window prior to diagnosis or pseudo-diagnosis. Co-morbidity and indication for use of the drug were assessed as any recordings of the variable prior to the date of diagnosis or pseudo-diagnosis. Charlson Index was a composite score of comorbidities categorised into none, 1 and 2. Age was calculated at diagnosis or pseudo-diagnosis date while BMI, smoking and alcohol were measured as the most recent recording of the variable prior to the diagnosis or pseudo-diagnosis date. Smoking status was categorised as non-smoker, current smoker, ex-smoker, missing; alcohol status as non-drinker, current drinker, problem-drinker and missing and BMI into 5 categories including missing. We created a missing category for all variables with missing data.

Data Analysis

We analysed data using logistic regression with univariable and subsequently multivariable analyses for each cancer under study with the resulting odds ratios and 95% confidence intervals presented. Amongst the variables we extracted data for based on the plausibility of their confounding the relationship being studies, we determined potential confounders based on their association with the exposure and outcome and corroborated by similar studies conducted in this area. We built the multivariable model by first including all possible confounders in the model and progressively removed

confounders one at a time from the model in increasing importance that do not change the estimate of the effect of the primary exposure by at least 10%. We did this until none of the variables retained in the model could be removed without altering the effect estimate of the model significantly. At the end of each step of fitting the model, we repeated this process but instead progressively added the confounders one at a time to the model in decreasing importance to determine if included confounders remain significant in the model and removed confounders become significant in the model. We did this until we had only significant confounders present in the model.

Sensitivity Analysis

We assessed the effect of duration of adrenergic blocker use within a 10 year window prior to diagnosis or pseudo-diagnosis in a subset of subjects with 10 years of prospectively gathered data. We assessed the number of years of exposure of a subject starting with their diagnosis or pseudo-diagnosis date and looking at prior exposure back in time until their earliest exposure within this 10 year window. Subjects were considered exposed for those years in which they had at least one relevant prescription, and continuous exposure was considered to occur for the number of consecutive years in which subjects were exposed counting backwards from the diagnosis or pseudo-diagnosis date.

Further Analysis

Finally we repeated all analyses substituting calcium channel blockers as the exposure. All analyses were conducted in Stata 12 [College Station, TX, USA.]

Results

We identified 18968 cases of colorectal cancer (46% women), 19082 cases of lung cancer (42% women), 21608 cases of prostate cancer and 29109 cases of breast cancer. Supplementary table 1 shows the age distribution of cases and their age-matched controls.

Cancer cases were more likely to be current drinkers and had more comorbidities and hypertension than their respective controls (Table 1). In addition, Lung cancer cases had more current and ex-smokers and a higher level of aspirin and statin use than their controls. There were also a smaller proportion of missing data for smoking, alcohol and BMI cases compared to their respective controls for all cancers (Table 1). All other variables were similarly distributed in cases and controls.

Cancer cases had more adrenergic blocker use than controls (Table 2). Univariable analysis showed a significant positive association between both alpha and beta blocker exposure and all cancers. (Table 2) After adjustment for confounders we observed no effect of betablocker use on the risk of prostate cancer (OR: 1.01, 95% CI [0.98 – 1.05]) and lung cancer 0.99 [0.96 – 1.04]) and similarly no effect of alphablocker use on the risk of breast cancer 1.08 [1.00 – 1.17] and lung cancer 1.03 [0.97 – 1.09] compared to non-use. A weak positive association remained between betablocker use and colorectal cancer 1.14 [1.09 – 1.18] breast cancer 1.10 [1.06 – 1.14] and similarly between alphablocker use and colorectal cancer 1.13 [1.07 – 1.20]. (Table 2)

For calcium channel blockers similar patterns of effect to betablockers were observed in colorectal, breast and lung cancer in the multivariable analysis, though in prostate cancer

1.14 [1.10 – 1.18] a slight increased risk was observed with calcium blocker exposure. (Supplementary table 2)

Analysis by dose

We found no clear evidence of differences in cancer risk with variations in dose. Though point estimates did vary by dose, changes were small and confidence intervals overlapped. Further details of adrenergic blocker use by dose are shown below (Table 3)

Analysis of duration in those with prolonged data

We found no significant effects on cancer risk from regular long-term adrenergic blocker use in the subset of subjects with more prolonged data availability (Table 4).

Discussion

In this large case-control study we found no effect of betablocker exposure in the 2 year period prior to cancer diagnosis on the risk of lung or prostate cancer and a slight increase on the risk of colorectal and breast cancer. Alphablocker exposure showed no effect on the risk of breast and prostate cancer and a slight increase in the risk of colorectal cancer. Analysis by dose and long term exposure showed no clear dose or temporal effect for adrenergic blocker use on cancer risk.

Study strengths and limitations

This study is from a large primary care database representative of the UK population (Herrett, Thomas et al. 2010) and as data collection within the CPRD is prospective, information bias due to recall will be minimised. In addition, we were able to adjust for a number of important confounders including alcohol status, smoking status, BMI, medication use and comorbidities.

A major limitation is our inability to individually validate cancer diagnoses and a potential therefore for misclassification. However, given the previously demonstrated high levels of specificity for diagnoses in these data i.e 99% of neoplasms (Dregan, Moller et al. 2012) we do not believe this will have greatly influenced our study.

Our analyses confirm the presence of appreciable confounding in the relationships we have studied, but as we lack data on some potential confounders such as family history, diet and exercise it is likely that residual confounding will remain.

Another potential limitation is missing data for confounding factors both by over the counter medication use (primarily NSAIDS and aspirin) and by lifestyle factors with a smaller proportion of missing data observed for smoking, alcohol and BMI cases compared to their respective control. It is likely that these data will not be missing at random, and instead due to variations in medical records consequent upon variation in

comorbidities or the frequency of physician visits. We have attempted to minimise this potential information bias by including missing as a separate category in the analysis for alcohol use, smoking and BMI. The potential for some information bias and likelihood of residual confounding remains however.

Another potential bias is the possibility that those who are prescribed anti-hypertensives, due to their increased contact with health services, are more likely to have an early cancer diagnosed. This bias cannot be entirely overcome, but since the same mechanism might be expected to increase prescription of other drugs used for similar indications we analysed calcium channel blockers. The results of the effect of calcium blockers were similar to those of betablockers and as these have different mechanisms of action it is unlikely the results seen in betablocker use reflect the effect of the drug but instead suggests bias by healthcare seeking behaviour.

Our primary analysis restricted the assessment of adrenergic blocker use to the presence of 2 prescriptions within 2 years. It is possible that these criteria did not adequately reflect exposure as we have no data on adherence to treatment and results could instead represent low dose of adrenergic drug use. We therefore analysed the dose of adrenergic blocker use. Since minimal effects were seen with varying dose, we do not think that these issues are likely to invalidate our primary analysis.

Furthermore, it is possible that the time window of 2 years represents insufficiently prolonged exposure to see a therapeutic effect on the occurrence of cancer, and a longer exposure period may be required. We therefore examined the effect of a longer duration of exposure in a subset of subjects that had up to 10 years of data prior to diagnosis or pseudo diagnosis date. These results did not alter our effect estimates and as a result we believe that a longer duration of adrenergic blocker exposure does not have a greater effect on the risk of cancer.

Comparison with other studies

Previous studies have examined betablocker use and the incidence of colorectal (Friedman, Udaltsova et al. 2011; Jansen, Below et al. 2012) prostate (Perron, Bairati et al. 2004; Ronquist, Rodríguez et al. 2004; Rodriguez, Jacobs et al. 2009; Friedman, Udaltsova et al. 2011) breast (González-Pérez, Ronquist et al. 2004; Fryzek, Poulsen et al. 2006; Friedman, Udaltsova et al. 2011) lung (Friedman, Udaltsova et al. 2011) and all cancers (Algazi, Plu-Bureau et al. 2006; Friedman, Udaltsova et al. 2011; Hallas, Christensen et al. 2012).

Some studies such as the matched case-control studies by Perron et al, utilised large clinical databases (Perron, Bairati et al. 2004) showing a reduced incidence of prostate cancer on betablocker exposure 0.86 [0.77-0.96] but only adjusted for the confounding factors of age, sex, aspirin use and recent medical contacts which differed from the results of our study.

Other studies considered betablocker use and cancer risk in sub-group analyses only and it is likely that these studies were underpowered to detect significant effects (González-Pérez, Ronquist et al. 2004; Fryzek, Poulsen et al. 2006; Rodriguez, Jacobs et al. 2009). For instance, a nested case-control study by Gonazalez-Perez et al on antihypertensive use and breast cancer risk (González-Pérez, Ronquist et al. 2004) started with 3708 cases and 20000 controls but to examine adrenergic blocker use, duration of use was split into current use, past and no use and this resulted in a population of cases and controls with very small numbers for some levels of drug exposure. Results showed no statistically significant difference in breast cancer incidence for those patients on beta and alpha blocker use and differ from the results of our study on betablocker use (González-Pérez, Ronquist et al. 2004).

The most convincing evidence from large population based studies was a case-control study by Ronquist et al in 2004 (Ronquist, Rodríguez et al. 2004), conducted using the CPRD database. This examined 1013 cases of prostate cancer and 10000 controls with adjustments for important confounders including smoking status, BMI and alcohol use.

Results showed no statistically significant difference between beta blocker users and non-users with an odds ratio of 0.8 [0.6-1.0] for current use and 1.1 [0.9-1.4] for past use compared to non-use and for alpha blocker use an odds ratio of 3.6 [2.8-4.6] for current use and 1.1 [0.8-1.7] for past use compared to non-use. As we have used the same data source, though a larger and more recent version of it than in this study, it is reassuring that we find similar results. We have however expanded upon this study by including cancers of the breast, bowel and lung and within this investigated the dose and duration of use as well as the indication of use and can therefore provide more extensive information on the effect of adrenergic blocker exposure on the risk of cancer.

Interpretation

In this study we find no effect in some cancers or a weakly positive association of adrenergic blockade in others, contrary to what might be expected based on evidence from laboratory studies. It is possible that a higher concentration of adrenergic blockers than that prescribed for cardiovascular indications are needed to reproduce the pro-apoptotic effects observed in these laboratory models. Also, several preclinical studies propose that downstream beta adrenergic effects are mediated mainly by the β2 or β3 adrenergic receptors (E, M et al. 2006; Thaker, Han et al. 2006). As β1-selective beta blockers are more commonly prescribed for cardiovascular therapy, we were unable to look at the non-selective beta blocker subgroup for a beneficial effect. However, results are not strongly significant in any cancer under study and it is possible that the slight increase in cancer risk observed in some cancers and the associated small effect sizes represent residual confounding due to the limited or lack of data on potential confounders such as family history, diet and exercise.

Conclusion

To our knowledge, this is the most comprehensive study to date of the effect of alpha and beta blocker use on the incidence of common cancers in the UK. We found no significant association between adrenergic blocker use and a reduced incidence of cancer and our finding of no consistent dose-response, temporal relationship or specificity of effect (compared to calcium channel blockers) mean we believe it more than likely that the slight increased risk observed in some cancers is as a result of residual confounding. However, an effect in specific beta blocker subgroups cannot be ruled out and further epidemiological research will require even larger epidemiological studies or pooled data to produce statistically robust results. This study using a large population database does not provide support for the hypothesis that adrenergic blocker use is associated with a reduced incidence of cancer.

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Table 1: Lifestyle factors and Indications for use of adrenergic blockers for cases and controls

	Colorectalcancer			Lungcancer			Prostatecancer			Breastcancer		
	Cases N=18968	Controls N=189667		Cases N=19082	Controls N=190816		Cases N=21608	Controls N=215959		Cases N=29109	Controls N=291142	
Exposure	%	%	*P*-value	%	%	*P*-value	%	%	*P*-value	%	%	*P*-value
Male	54.4	44.6	<0.001	57.9	45.0	<0.001						
Female	45.6	55.4		42.1	55.0							
Smoking status												
Non-smoker	48.7	43.6		15.0	43.7		45.3	34.8		58.3	50.1	
Current smoker	14.4	13.9	<0.0001	40.7	13.8	<0.0001	12.8	15.0	<0.0001	16.3	15.7	<0.0001
Ex-smoker	32.0	22.4		41.1	22.7		37.9	30.3		20.2	16.0	
missing	4.9	20.1		3.2	19.8		4.0	19.9		5.2	18.2	
Alcohol status												
Non-drinker	14.6	14.2		15.6	14.4		10.0	9.2		17.3	17.7	
Current drinker	68.7	56.1	<0.0001	66.3	56.4	<0.0001	75.6	60.8	<0.0001	68.0	59.1	<0.0001
Problem-drinker	2.8	1.9		5.3	1.9		2.7	2.9		1.4	0.2	
missing	13.9	27.8		12.8	27.3		11.7	27.1		13.3	23.0	
BMI												
19-24	31.5	26.1		36.6	26.0		30.1	24.2		34.5	30.1	
25-29	33.6	27.5		29.3	28.2		41.4	32.1		28.9	23.9	
30-34	13.2	11.0	<0.0001	10.3	11.1	<0.0001	12.6	11.2	<0.0001	13.8	11.1	<0.0001
>35	4.8	4.4		3.6	4.5		2.7	3.0		7.3	6.4	
<19	2.9	2.4		6.4	2.2		1.2	1.3		2.4	2.6	
missing	14.0	28.6		13.8	28.0		12.0	28.2		13.1	25.9	
Hypertension												
Yes	41.5	32.1	<0.001	38.7	33.0	<0.001	41.9	32.0	<0.001	31.9	24.9	<0.001
IHD												
Yes	16.4	13.4	<0.001	21.9	13.5	<0.001	19.1	18.0	<0.001	7.5	6.7	<0.001
Aspirin use												
Yes	26.8	21.4	<0.001	33.1	21.7	<0.001	30.2	25.7	<0.001	14.2	11.9	<0.001
Statin use												
Yes	27.7	20.1	<0.001	31.5	21.0	<0.001	31.0	24.5	<0.001	16.4	13.1	<0.001
Charlson Index												
0	42.2	57.8		27.1	57.3		46.3	54.5		59.8	68.8	
1	18.8	18.6	<0.0001	22.6	18.5	<0.0001	20.8	19.5	<0.0001	17.1	16.8	<0.0001
2	39.0	23.6		50.3	24.2		32.9	26.0		23.1	14.4	
BPH Yes	7.9	4.8	<0.001	7.8	4.9	<0.001	30.6	11.3	<0.001			

Abbreviations: BMI=body mass index; IHD=ischaemic heart disease; BPH=benign prostatic hyperplasia

Table 2: Association of alpha and betablockers with cancer

						Univariate Analysis			Multivariable Analysis		
Cancer type	**Exposure status**	**Cases**		**Controls**		**Odds ratio**	**95% CI**		**Odds ratio**	**95% CI**	
Betablocker use											
		n	%	n	%		Lower	Upper		Lower	Upper
Colorectal Cancer[a]	Unexposed	15,080	79.5	160,137	84.4	1			1		
	Exposed	3,888	20.5	29,530	15.6	1.398	1.347	1.451	1.137	1.094	1.181
Lung Cancer[a]	Unexposed	15,551	81.5	160,076	83.9	1			1		
	Exposed	3,531	18.5	30,740	16.1	1.182	1.138	1.229	0.994	0.955	1.035
Prostate Cancer[b]	Unexposed	17,237	79.8	179,690	83.2	1			1		
	Exposed	4,371	20.2	36,269	16.8	1.256	1.213	1.301	1.013	0.978	1.050
Breast Cancer[b]	Unexposed	24,895	85.5	257,365	88.4	1			1		
	Exposed	4,214	14.5	33,777	11.6	1.290	1.246	1.335	1.097	1.059	1.137
Alphablocker use											
Colorectal Cancer[a]	Unexposed	17,438	91.9	179,364	94.6	1			1		
	Exposed	1,530	8.1	10,303	5.4	1.527	1.444	1.615	1.129	1.067	1.196
Lung Cancer[c]	Unexposed	17,460	91.5	180,155	94.4	1			1		
	Exposed	1,622	8.5	10,661	5.6	1.570	1.487	1.658	1.028	0.970	1.090
Breast Cancer[d]	Unexposed	28,333	97.3	285,293	98.0	1			1		
	Exposed	776	2.7	5,849	2.0	1.336	1.238	1.441	1.080	0.999	1.167

Abbreviations: CI=confidence interval

[a] Adjusted for gender, age and smoking

[b] Adjusted for age and smoking

[c] Adjusted for gender, age, smoking and Charlson's score

[d] Adjusted for age and hypertension

Table 3: Dose of alpha and betablocker exposure[a]

		Multivariable Analysis				Multivariable Analysis			
Cancer type		**β use**	**OR**	**95% CI**		**α use**	**OR**	**95% CI**	
Betablocker use						*Alphablocker use*			
Colorectal Cancer[b]									
	Unexposed	175217	1			196802	1		
	Low	23248	1.14	1.09	1.19	6186	1.07	0.99	1.16
	High	10084	1.15	1.08	1.22	5643	1.19	1.10	1.28
Lung Cancer[b]									
	Unexposed	175627	1			197615	1		
	Low	23896	0.99	0.95	1.04	6516	0.96	0.88	1.04
	High	10282	1.01	0.94	1.08	5763	1.10	1.02	1.19
Breast Cancer[c]									
	Unexposed	282260	1			313626	1		
	Low	25816	1.08	1.03	1.13	5333	1.06	0.97	1.16
	High	12062	1.14	1.08	1.21	1291	1.16	0.98	1.37
Prostate Cancer[c]									
	Unexposed	196927	1						
	Low	28756	1.02	0.98	1.06				
	High	11798	1.00	0.94	1.06				

[a] Dose was missing for 0.04% of betablocker use for all cancers
Dose was missing for 0.002% of alphablocker use in colorectal and lung cancer and 0.0003% in breast cancer

[b] Adjusted for gender, age and smoking

[c] Adjusted for age and smoking

Table 4: Long-term betablocker and alphablocker exposure

				Multivariable Analysis		
Betablocker use						
Cancer type	Exposure	Cases	Controls	Multivariable	95% CI	
Breast Cancer	Unexposed	7,904	63,988	1		
	≥10yr	536	3,512	1.101	1.000	1.211
Colorectal Cancer	Unexposed	5,211	41,318	1		
	≥10yr	516	3,290	1.071	0.971	1.182
Lung Cancer	Unexposed	5,283	41,659	1		
	≥10yr	449	3,456	0.860	0.771	0.959
Prostate Cancer	Unexposed	6,148	48,739	1		
	≥10yr	602	3,955	1.011	0.924	1.107
Alphablocker use						
Breast Cancer	Unexposed	10,310	80,906	1		
	≥10yr	44	218	1.390	1.003	1.925
Colorectal Cancer	Unexposed	6,617	51,888	1		
	≥10yr	55	326	0.953	0.712	1.275
Lung Cancer	Unexposed	6,636	52,505	1		
	≥10yr	65	342	1.100	0.829	1.461

Supplementary Tables

Supplementary Table 1: Demographic characteristics of cancer cases and controls

	Cases		Controls	
Cancer	n	%	n	%
Colorectal				
Total	18968		189667	
Age				
18-39	217	1.2	2,190	1.2
40-49	756	4.0	7,571	4.0
50-59	2,323	12.2	23,217	12.2
60-69	4,722	24.9	47,190	24.9
70-79	6,317	33.3	63,167	33.3
80 and above	4,633	24.4	46,332	24.4
Lung				
Total	19082		190816	
Age				
18-39	111	0.6	1,110	0.6
40-49	483	2.5	4,842	2.5
50-59	2,189	11.5	21,885	11.5
60-69	5,093	26.7	50,959	26.7
70-79	7,008	36.7	70,061	36.7
80 and above	4,198	22.0	41,959	22.0
Prostate				
Total	21608		215959	
Age				
18-39	19	0.1	190	0.1
40-49	159	0.7	1,589	0.7
50-59	2,022	9.4	20,225	9.4
60-69	6,589	30.5	65,883	30.5
70-79	8,246	38.2	82,328	38.1
80 and above	4,573	21.1	45,744	21.2
Breast*				
Total	29109		291142	
Age				
18-39	1,267	4.3	12,669	4.4
40-49	4,305	14.8	43,069	14.8
50-59	7,385	25.4	73,912	25.4
60-69	7,262	24.9	72,598	24.9
70-79	4,876	16.8	48,779	16.8
80 and above	4,014	13.8	40,115	13.8

*restricted to women

Supplementary Table 2: Association of calcium channel blockers with cancer

					Univariate Analysis			Multivariable Analysis		
Cancer type	**Cases**		**Controls**		**Odds ratio**	**95% CI**		**Odds ratio**	**95% CI**	
Calcium blocker use										
	n	%	n	%		Lower	Upper		Lower	Upper
Colorectal Cancer[a]	15,230	80	161,169	85	1			1		
	3,738	20	28,498	15	1.388	1.336	1.442	1.107	1.065	1.151
Lung Cancer[b]	14,842	78	161,184	85	1			1		
	4,240	22	29,632	15	1.554	1.499	1.611	1.037	0.997	1.079
Prostate Cancer[c]	16,824	78	179,779	83	1			1		
	4,784	22	36,180	17	1.413	1.366	1.462	1.141	1.102	1.181
Breast Cancer[d]	25,423	87	261,863	90	1			1		
	3,686	13	29,279	10	1.297	1.25	1.345	1.073	1.03	1.118

[a] Adjusted for gender, age and smoking

[b] Adjusted for gender, age, smoking and charlsonscore

[c] Adjusted for age and smoking

[d] Adjusted for age and hypertension