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ORIGINAL RESEARCH

N-nitrosodimethylamine-Contaminated Valsartan and Risk of Cancer: A Nationwide Study of 1.4 Million Valsartan Users

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BACKGROUND: Since July 2018, numerous lots of valsartan have been found to be contaminated with *N*-nitrosodimethylamine (NDMA). We aimed to assess the association between exposure to valsartan products contaminated with NDMA and the risk of cancer.

METHODS AND RESULTS: This study was based on data from the Système National des Données de Santé, which is a national database that includes all French residents' health-related expenses. The target population was consumers of valsartan between January 1, 2013 and December 31, 2017, aged between 40 and 80 years old. The association of exposure to contaminated valsartan with the occurrence of any malignancy and cancer by location was evaluated by fitting Cox proportional hazards models weighted by the inverse probability of treatment. A total of 1.4 million subjects without any history of cancer were included. A total of 986 126 and 670 388 patients were exposed to NDMA-contaminated and uncontaminated valsartan, respectively. The use of the NDMA-contaminated valsartan did not increase the overall risk of cancer (adjusted hazard ratio [aHR], 0.99 [95% CI, 0.98–1.0]). However, exposed patients had a higher risk of liver cancer (aHR, 1.12 [95% CI, 1.04–1.22]) and melanoma (aHR, 1.10 [95% CI, 1.03–1.18]). We estimated a mean of 3.7 and 5.8 extra cases per year per 100 000 person-years of liver cancer and melanoma, respectively.

CONCLUSIONS: Our study was the largest to date to examine cancer risks associated with exposure to NDMA-contaminated valsartan. Our findings suggest a slight increased risk of liver cancer and melanoma in patients exposed to NDMA in regularly taken medications.

Key Words: health claims data ■ liver cancer ■ melanoma ■ *N*-nitrosodimethylamine (NDMA) ■ valsartan

Valsartan is an angiotensin II receptor blocker (ARBs) widely prescribed to treat heart failure and hypertension.[1] In the middle of 2018, numerous lots of generic valsartan were found to be contaminated with nitrosamine agents, notably *N*-nitrosodimethylamine (NDMA), through the synthesis of the active substance. Although the initial investigations focused on valsartan, they were expanded to include 4 other ARBs featuring a similar structure, namely irbesartan, candesartan, losartan, and olmesartan.[2–4]

NDMA exposure can occur through endogenous production, water, processed foods, alcoholic beverages, and tobacco smoke.[5,6] It is classified as a powerful animal carcinogen and probable human carcinogen, associated with malignant tumors of the gastrointestinal tract, liver, kidneys, lungs, and nasal cavity.[7–9] The carcinogenicity of NDMA has been established in rats after chronic-duration exposure by inhalation and has mainly been associated with liver tumors.[10] NDMA was also linked to hepatic adverse outcomes in humans after several poisoning incidents[11–13] and was associated with higher excess mortality from nonalcoholic-related chronic liver disease after occupational exposure.[14]

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CLINICAL PERSPECTIVE

What Is New?

- In the middle of 2018, numerous lots of generic valsartan were found to be contaminated with nitrosamine agents, notably *N*-nitrosodimethylamine, through the synthesis of the active substance.
- Only 2 studies have examined the potential impact of these impurities among patients who have been taking *N*-nitrosodimethylamine-contaminated valsartan.
- Our study included 1.4 million users and found exposure to contaminated valsartan to be associated with a slightly increased risk of liver cancer and melanoma. Risks for liver cancer were higher in the most socially deprived patients, male subjects, and long term-users.

What Are the Clinical Implications?

- Carcinogenic nitrosamine contaminants detected in valsartan products constitute a public health concern, given the extensive and widespread use of this medication.
- Our study raises concerns regarding the risks of liver cancer and melanoma in patients exposed to *N*-nitrosodimethylamine in regularly taken medications.
- More pharmacoepidemiologic studies are needed to evaluate cancer risks from the use of such drugs and to establish clinically relevant causality.

Nonstandard Abbreviations and Acronyms

IPTW	inverse probability of treatment weighting
NDMA	*N*-nitrosodimethylamine

The unexpected contaminations of valsartan products have triggered a series of recalls for a number of lots of valsartan by various worldwide regulatory agencies since the summer of 2018.[15,16] Investigations showed that the nitrosamine contaminants appeared around July 2012 following changes introduced in the manufacturing process.[17] Hence, owing to lack of oversight and failure to detect these impurities sooner within the finished drug products, many patients have been unknowingly exposed and potentially affected for several years.

Only 2 studies have examined the potential impact of these impurities among patients who have been taking NDMA-contaminated valsartan. A German health care database of almost one-third of the population of Germany found only a higher risk of liver cancer and no association with the risk of cancer overall among patients exposed to NDMA-contaminated valsartan.[18] Also, a registry-based Danish cohort study found no increase in overall cancer risk among exposed users, although the risk of liver cancer was not evaluated in that study because of lack of statistical power and the limited number of patients included.[4]

We aimed to assess the association between exposure to valsartan products contaminated with NDMA and the risk of cancer, using the French National Health Data System (SNDS) (French acronym: Système National des Données de Santé).

METHODS

According to data protection and French regulation, the authors cannot publicly release data from the SNDS. However, any individual or organization, public or private, for profit or nonprofit, can access SNDS data on authorization from the French Data Protection Authority to perform a study, research, or an evaluation of public interest (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://www.indsante.fr/).

Data Sources

This study was based on data from the SNDS, which is a national database that includes all French residents' health-related expenses and covers around 99% of the French population.[19] In the SNDS database, an encrypted and unique personal identifier links information from different data sources: the national hospital and discharge database PMSI (hospital Medical Information System) and DCIR (the French Healthcare Reimbursement Database).

The PMSI database contains details of all private and public hospital admissions and discharges for both inpatient stays and ambulatory care. Data on diagnoses, treatments, and surgical procedures provided during hospital stays are also accessible. The DCIR database includes individual information on sociodemographic characteristics, outpatient medical care, laboratory tests, and dispensed drugs. Further details on these databases are described elsewhere.[20]

All data requests were made by duly authorized people. In accordance with the permanent regulatory access granted to EPI-PHARE, this work did not require the approval from the French Data Protection Authority. The study was registered on the study register of EPI-PHARE concerning studies from SNDS data under the reference T-2020-02-242.

Study Population

The target population of our research was consumers of valsartan between January 1, 2013 and December 31, 2017, aged between 40 and 80 years

old and residing in France excluding overseas regions (Figure 1). A prevalent user was defined as a patient who was reimbursed at least twice for valsartan in monthly packaging in a semester or for 1 dispensing in quarterly packaging; an incident user of valsartan was defined as a subject who received a first delivery without any prior deliveries over the preceding 12 months.

Exposure Assessment

A prescription of valsartan was defined as having the following Anatomical Therapeutic Chemical codes: C09CA03, C09DA03, C09DB01, C09DB08, C10BX10, C09DX01, C09DX02, C09DX04, and C09DX05.

All subsequent valsartan products supplied by manufacturers who disclosed that their active pharmaceutical ingredient contained NDMA impurities were classified as contaminated with NDMA between January 1, 2013 and December, 31, 2017. Uncontaminated products were those supplied by manufacturers who declared their valsartan products to be free of NDMA impurities (Table S1). The official lists of suppliers were obtained from the French National Agency for Medicines and Health Products.[2,21] Additionally, because the NDMA impurities were related to the synthesis of the active substance, we estimated that the concentration of NDMA would be correlated with the dose of valsartan. Thus, dose–response analysis was conducted based on the cumulative dose and the standard daily dose delivered. Cumulative dose of valsartan was calculated between first the date of the valsartan claim and June 30, 2018, and stratified by quartile.

Daily dose was defined as valsartan dose delivered per time unit (mg/day) and was calculated after dividing the cumulative dose by the days of therapy. The dose was then stratified according to the standard daily dose as follows: 80 or less, 81 to 160, and >160 mg/day. A separate dose–response analysis was conducted among long-term valsartan users, defined as those who filled valsartan prescriptions during at least 3 consecutive years of the study period.

Outcomes

Incident cancers were defined by using a validated algorithm that combined information about patients covered with a long-term disease scheme and hospital discharge diagnosis coded according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*) (Table S2). The algorithm's positive and negative predictive values were 90.5% and 97.5%, respectively.[22–24] Patients identified by the cancer algorithm were those (1) hospitalized with a cancer diagnosis and those (2) covered with a long-term disease scheme for cancer.[25]

The outcomes were the occurrence of any type of active malignancy and cancer by location: breast, prostate, colon, rectal, lung, liver, uterine cancer, or malignant melanoma.

Study Design

Patients who had cancer (except non-melanoma skin cancer) 7 years before or within 1 year of valsartan initiation were excluded in order to exclude malignancies most probably unrelated to NDMA exposure (Figure 2). Patients who died or discontinued health care during the first year of treatment initiation were also excluded (Figure 2).

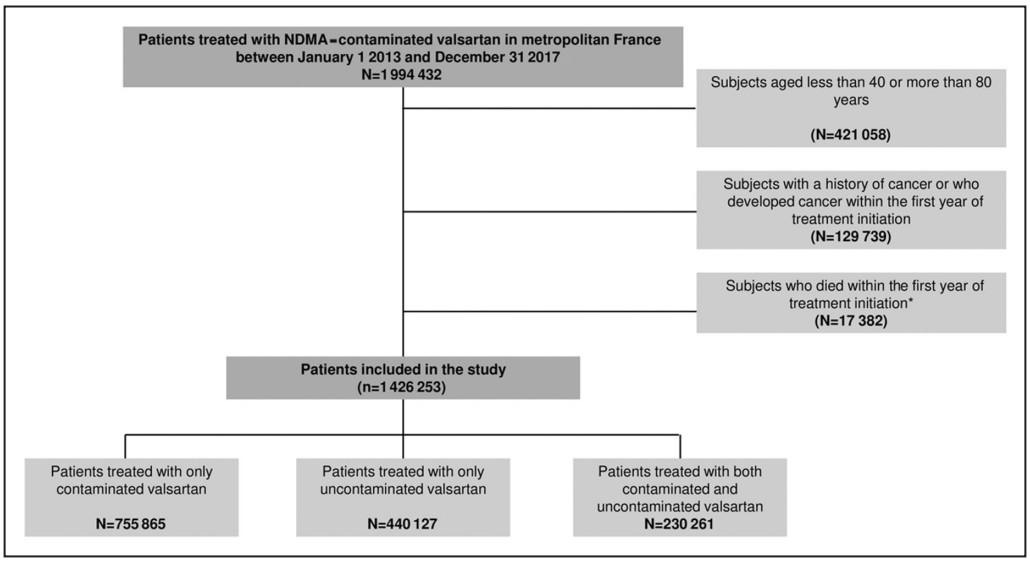

Figure 1. Study population flow chart.
*No patients discontinued health care during the first year post treatment initiation. NDMA indicates *N*-nitrosodimethylamine.

Follow-up began 1 year after the first valsartan claim and continued until the patient's death, occurrence of cancer, health care discontinuation, or the end of the study (December 31, 2020), whichever came first. In case of health care discontinuation, the end of follow-up was the last known contact date, defined as the last claim in the database.

Clinical Characteristics

Sociodemographic covariates used were: sex, age at initiation of treatment, the deprivation index of the patient's municipality of residence, and the region of residency.

Comorbidities included cardiovascular disease (heart failure, valvular disease, coronary disease, dysrhythmia, lower extremity arterial disease, other cardiac disease, and stroke), diabetes, chronic respiratory disease, pulmonary embolism, advanced chronic kidney disease, hepatic cirrhosis or fibrosis or liver failure, chronic inflammatory bowel disease, dementia, and lifestyle risk factors (alcohol abuse, smoking, and obesity) (Table S3). Smoking proxy was based on reimbursements for nicotine replacement therapy and hospital discharge diagnoses related to tobacco use, alcohol abuse was based on hospital discharge diagnosis and medications related to alcohol abuse, and obesity was based on both hospital discharge diagnosis related to morbid obesity and medical procedures related to bariatric surgery (Table S3).

Concomitant medications were based on at least 2 claims in the year before treatment initiation and included statins, low doses of aspirin, nonsteroidal anti-inflammatory drugs excluding low-dose aspirin, and medications that may affect the risk of cancer: spironolactone, oral corticosteroids, selective serotonin reuptake inhibitor antidepressants, 5α-reductase inhibitors, and hormone replacement therapy (Table S4). Use of other antihypertensive drugs at baseline (Table S4) was also accounted for by stratifying patients into 3 groups: those treated with only valsartan (monotherapy), with valsartan and another antihypertensive drug (association of 2 drugs), and with valsartan and at least 2 other antihypertensive medications (association of 3 drugs or more).

Statistical Analysis

Patients' characteristics at baseline were summarized with standard descriptive statistics.

Crude incidence ratios were calculated as the number of observed cancer cases divided by the number of person-years (PY). Absolute excess risks were computed as the difference between cancer rates in the exposed and unexposed cohorts per 100 000 and may be interpreted as the mean excess number of incident neoplasms observed per 100 000 subjects per year.

Because recalls applied only to some generic valsartan products, the probability of receiving contaminated versus uncontaminated valsartan cannot be assumed to be random. Hence, a multivariable logistic regression model was used to calculate propensity scores,[26] with the aim of predicting the individual probability of receiving contaminated rather than uncontaminated valsartan, conditional on the following baseline covariates: sex, age at treatment initiation (continuous), social deprivation index, region of residence, prevalent users (yes/no), year of treatment initiation, specialty of first prescriber, polymedication at treatment initiation, comedications, and comorbidities (Figure S2).

Next, from each patient's specific propensity score value, the inverse probability of treatment weighting (IPTW) values were derived as 1/propensity score for patients who received NDMA-contaminated valsartan

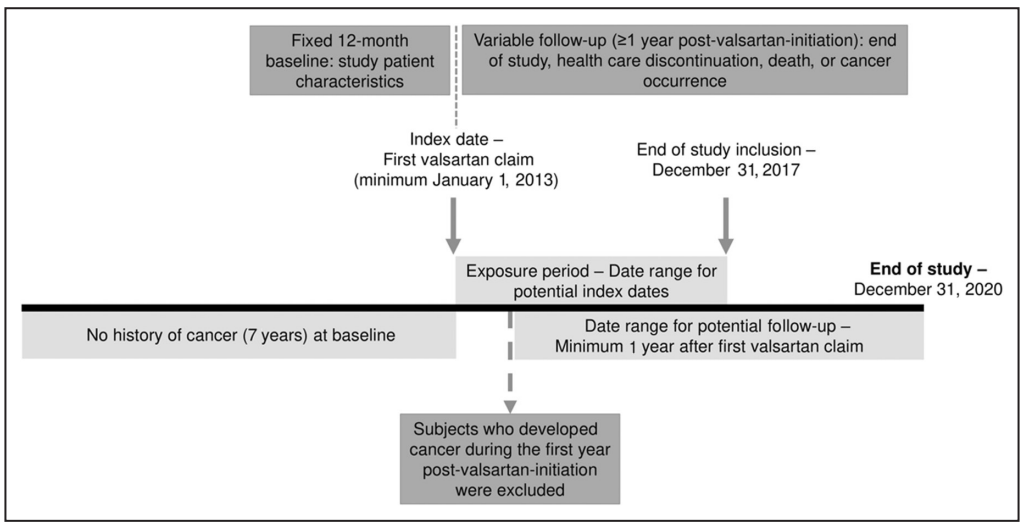

Figure 2. Study design.

and 1/(1–propensity score) for patients who did not. To reduce the variability in the inverse probability of treatment–weighted models, we used stabilized weights.[27]

The covariate imbalance between the 2 groups was assessed by evaluating standardized differences for each covariate separately in the unadjusted and the IPTW-adjusted cohorts (Data S1). A difference of 10% or less was considered to indicate a well-balanced result. Acceptable standardized differences for all covariates were achieved (Figure S2).

The association of receiving NDMA-contaminated valsartan with the occurrence of any malignancy and cancer by location was evaluated by fitting weighted Cox proportional-hazards models.[28] Proportional hazard assumption was tested using Schoenfeld and scaled Schoenfeld residuals.

To avoid many biases such as selection, immortal time, and measurement biases, patients treated with both NDMA-contaminated and uncontaminated valsartan contributed to the follow-up in both groups and were censored after a lag of 1 year post-treatment change.

We also conducted subgroup by sex, age, prevalent or incident users, deprivation index quintiles, and the standard daily dose of valsartan. Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup.

Finally, we accounted for multiple hypothesis testing by using the Benjamini-Hochberg false discovery rate method.[29,30] Using this approach, the expected number of type I errors was kept below 5%, and the adopted *P* values are denoted as false discovery rate–adjusted *P*.

All analyses were performed with Statistical Analysis System Guide version 9.4 (Saint-Denis, France).

Sensitivity Analyses

We conducted several sensitivity analyses. First, we varied the lag period for patients treated with both NDMA-contaminated and uncontaminated valsartan from 1 to 2 years, then we excluded those patients from the analysis. A second analysis was also conducted excluding patients with less than 2 years of follow-up. We then estimated the risks of liver cancer in separate models adjusted for hepatotoxic drugs.

Because detection biases may occur if there are differences in screening and care-seeking behavior between exposed and unexposed patients, we estimated the risks of cancer after adjusting on health care consumption at baseline (Data S2). Furthermore, in a separate analysis, we adjusted on exposure to metformin and ranitidine that may potentially be contaminated with NDMA.[31,32] Further analysis taking into account death as competing event was conducted using Cox cause-specific hazard method.[33]

Finally, we conducted an additional analysis, setting the index date at the median of valsartan use duration and on January 1, 2015, to more thoroughly examine the question of cumulative exposure risk.

RESULTS

The SNDS database included around 2 million users of valsartan between January 1, 2013 and December 31, 2017 (Figure 1). In 2017, 5.7 million prescriptions of NDMA-contaminated valsartan were issued (Figure S1). Of the 1.4 million subjects eligible for this study, 986 126 and 670 388 patients received NDMA-contaminated and uncontaminated valsartan, respectively, including 230 261 who received both during the follow-up (Table 1).

The exposed cohort was followed up for a total of 4 253 623 PY, with a median follow-up of 4.0 (interquartile range [IQR] 2.7–6.8) years. The unexposed cohort was followed up for a total of 2 565 339 PY, with a median of 3.5 (IQR 2.0–6.7) years. A total of 22 926 (2.3%) and 12 673 (1.9%) discontinued all health care services in the contaminated and uncontaminated cohorts, respectively.

Characteristics of Study Participants and Success of IPTW Weighting

Table 1 summarizes the baseline characteristics of subjects stratified by exposure. The median age at treatment initiation was 64.8 years (IQR 57.3–71.7) and 64.6 years (IQR 57.2–71.4) in exposed and unexposed patients, respectively.

Exposed individuals were more likely to be women, prevalent users, and materially deprived (Table 1). They were also less likely to have received their first valsartan prescription from a cardiologist (5.3%) compared with unexposed subjects (8.6%) (Table 2). All baseline covariates were well balanced after IPTW, with all the standardized differences less than 10%, the highest being 0.4% (Table 1).

The proportion of monotreated subjects receiving only valsartan was higher in those exposed to NDMA (38.7%) than in unexposed subjects (31.1%), who were more likely to be polymedicated (Table 1). The daily delivered dose of valsartan was similar in both groups; exposed subjects received a median dose of 78.1 mg/day (IQR 41.3–132.1), and unexposed patients received 71.7 mg/day (IQR 27–130) (Table 2). The numbers of valsartan claims during follow-up were also similar in both cohorts, with a median of 12 claims (IQR 5–22) and 11 (IQR 4–21) in exposed and unexposed subjects, respectively. Exposed patients were treated for longer, with a median of 2.0 years (IQR 0.5–4.3) compared with 1.6 years (IQR 0.4–4.3) among the unexposed (Table 2).

Table 1. Patients' Baseline Characteristics Stratified by Exposure

Characteristics	Unexposed patients N=670 388		Exposed patients N=986 126		ASD before IPTW	ASD after IPTW*
	N	(%)	N	(%)		
Sex					0.041	0
Female	314 009	(46.8)	502 107	(50.9)		
Male	356 379	(53.2)	484 019	(49.1)		
Age at treatment initiation, y, median (IQR)	64.6	(57.2–71.4)	64.8	(57.3–71.7)	0.166	−0.031
<50	62 368	(9.3)	90 558	(9.2)		
50–59	162 258	(24.2)	234 888	(23.8)		
60–69	246 862	(36.8)	360 470	(36.6)		
70–79	198 900	(29.7)	300 210	(30.4)		
Prevalent users, yes	212 077	(31.6)	461 177	(46.8)	−0.151	−0.002
Social deprivation index						
Quintile 1 (richest 20%)	124 133	(18.5)	160 009	(16.2)	0.022	0
Quintile 2	124 327	(18.5)	180 341	(18.3)	0.003	0
Quintile 3	128 206	(19.1)	192 334	(19.5)	−0.004	0
Quintile 4	132 235	(19.7)	208 606	(21.2)	−0.014	0
Quintile 5 (poorest 20%)	140 300	(20.9)	214 807	(21.8)	−0.009	0
Missing	21 187	(3.2)	30 029	(3)	0.001	0
Polymedication (at index date)						
Monotherapy	208 822	(31.1)	381 795	(38.7)	−0.075	−0.004
Association of 2 drugs	389 327	(58.1)	500 118	(50.7)	0.07342	0.002
Association of 3 drugs or more	72 239	(10.8)	104 213	(10.6)	0.002	0.003
Comedications						
Statins, yes	247 579	(36.9)	370 645	(37.6)	−0.007	−0.001
Aspirin, low dose, yes	93 454	(13.9)	134 433	(13.6)	0	0
Spironolactone, yes	13 088	(2)	18 417	(1.9)	0	0
NSAIDs excl. aspirin, yes	177 039	(26.4)	260 608	(26.4)	0	−0.001
Glucocorticoids, yes	63 283	(9.4)	92 868	(9.4)	0	0
SSRI antidepressants, yes	28 201	(4.2)	46 627	(4.7)	−0.005	0
Dihydrotestosterone blockers, yes	9311	(1.4)	12 910	(1.3)	−0.004	0
Hormone replacement therapy, yes	26 003	(3.9)	42 479	(4.3)	0	0
Metabolic comorbidities						
Heart failure, yes	16 782	(2.5)	25 497	(2.6)	0	0
Valvular disease, yes	9935	(1.5)	14 788	(1.5)	0	0
Coronary disease, yes	33 013	(4.9)	45 793	(4.6)	0.003	0
Dysrhythmia, yes	33 499	(5)	51 614	(5.2)	−0.002	0
Lower extremity arterial disease, yes	18 535	(2.8)	24 621	(2.5)	0.003	0
Other cardiac disease, yes	62 499	(9.3)	93 378	(9.5)	0.003	0
Stroke, yes	14 154	(2.1)	19 840	(2)	0	0
Diabetes, yes	135 495	(20.2)	189 892	(19.3)	0.009	0
Other comorbidities						
Chronic respiratory disease, yes	38 028	(5.7)	57 557	(5.8)	−0.002	0
Pulmonary embolism, yes	2864	(0.4)	4704	(0.5)	0	0
Advanced chronic kidney disease, yes	9230	(1.4)	11 752	(1.2)	0	0
Hepatic cirrhosis or fibrosis or liver failure, yes	9301	(1.4)	14 078	(1.4)	0.002	0
Chronic inflammatory bowel disease, yes	2252	(0.3)	3439	(0.3)	0	0

(*Continued*)

Table 1. Continued

Characteristics	Unexposed patients N=670 388		Exposed patients N=986 126		ASD before IPTW	ASD after IPTW*
	N	(%)	N	(%)		
Dementia, yes	1516	(0.2)	3308	(0.3)	−0.001	0
Lifestyle-related risk factors†						
Alcohol abuse, yes	14 227	(2.1)	25 221	(2.6)	0	0
Smoking, yes	32 025	(4.8)	48 716	(4.9)	−0.002	0
Obesity, yes	4790	(0.7)	7327	(0.7)	−0.004	0

Age was treated as continuous variables in the propensity score model. ASD indicates absolute standardized difference; CKD, chronic kidney disease, IPTW, inverse probability of treatment weighting; IQR, interquartile range; N, number of patients; NSAID, nonsteroidal anti-inflammatory drug; and SSRI, selective serotonin reuptake inhibitor.

*Absolute weighted standardized differences were used to compare baseline characteristics between patients treated with NDMA-contaminated and -uncontaminated valsartan before and after IPTW.

†Smoking proxy was based on reimbursements for nicotine replacement therapy and hospital discharge diagnoses related to tobacco use, alcohol abuse was based on hospital discharge diagnosis related to alcohol abuse, obesity was based on both hospital discharge diagnosis related to morbid obesity and medical procedures related to bariatric surgery.

The Association of NDMA Exposure With the Risk of Cancer

During follow-up, 55 690 cancers were observed in the exposed cohort with crude event rates of 1309.2 per 100 000 person-years, and included a total of 8085 breast, 10 358 prostate, 4866 colon, 1303 rectal, 1473 liver, and 2410 melanoma cases. In the unexposed cohort, a total of 33 174 cancers occurred and the crude event rates were 1293.2 per 100 000 person-years, yielding a total of 4376 breast, 6734 prostate, 2815 colon, 758 rectal, 789 liver, and 1297 melanoma cancers. The full breakdown of individual incident cancer types as defined by *ICD-10* codes was detailed in Table S2 and is available in Table 3.

Table 2. Characteristics of Valsartan Prescriptions Among Exposed and Unexposed Patients

	Unexposed patients N=670 388		Exposed patients N=986 126	
	N	(%)	N	(%)
Year of valsartan treatment				
2013	353 627	(52.6)	530 990	(53.7)
2014	62 507	(9.3)	799 45	(8.1)
2015	55 059	(8.2)	85 755	(8.7)
2016	90 485	(13.4)	131 655	(13.3)
2017	110 812	(16.5)	160 299	(16.2)
First prescriber's specialty				
General practitioner	557 228	(82.9)	856 744	(86.7)
Private cardiologist	57 820	(8.6)	52 865	(5.3)
Hospital practitioner	45 756	(6.8)	65 183	(6.6)
Other specialties	11 686	(1.7)	13 852	(1.4)
Duration of valsartan use, y median (IQR)	1.6	(0.4–4.3)	2.0	(0.5–4.3)
Number of valsartan claims, median (IQR)	11	(4–21)	12	(5–22)
Valsartan dose, mg/day, median (IQR)	71.7	(27–130)	78.1	(41.3–132.1)

Daily dose was calculated as the cumulative dispensed valsartan during episode divided by the number of episode days covered by drug supply.

The use of NDMA-contaminated valsartan did not increase the overall risk of cancer (adjusted hazard ratio [aHR], 0.99 [95% CI, 0.98–1.0]). Nevertheless, exposed subjects had a 12% higher risk of liver cancer (aHR, 1.12; [95% CI, 1.04–1.22]) (false discovery rate adjusted P=0.04) (Figure 3A) compared with unexposed subjects. The crude incidence rates of liver cancer were 29.9 and 33.6 per 100 000 PY in unexposed and exposed cohorts, respectively (Table 3), yielding an absolute excess risk of 3.7 per 100 000 PY.

The risks of melanoma were also 1.10 times higher in exposed subjects compared with unexposed subjects (aHR, 1.10 [95% CI, 1.03–1.18]) (false discovery rate adjusted P=0.01) (Figure 3B). The crude incidence of malignant melanoma was 49.2 and 55 per 100 000 PY in unexposed and exposed cohorts, respectively (Table 3), yielding a total of 5.8 extra cases per 100 000 PY.

No statistically significant increased risks of any other type of malignancies were observed (Table 3), and the other aHRs were between 0.95 and 1.01.

Subgroup Analysis

Risks of liver cancer were higher in exposed male subjects (HR, 1.21-fold [95% CI, 1.10–1.33]) compared with unexposed male subjects (Figure 3A).

Similarly, most materially deprived patients in the exposed cohort were at higher risk of both liver cancer and melanoma compared with materially deprived subjects in the unexposed cohort (aHR, 1.35-fold [95% CI, 12–1.63] for liver cancer and 1.20-fold [95% CI, 1.03–1.40] for melanoma) (Figure 3B).

Table 3. Comparison of Outcomes Between Patients Exposed and Unexposed to NDMA-Contaminated Valsartan

Outcome	Number of patients with cancer	Median follow-up in years (IQR)	PYR	Crude incidence/100 000 PYR	Multivariable (IPTW)		P	FDR-adjusted P
					aHR (95% CI)			
Any malignancy							0.28	0.27
Unexposed	33 174	3.5 (2.0–6.7)	2 565 339.2	1293.2	Reference			
Exposed	55 690	4.0 (2.7–6.8)	4 253 623	1309.2	0.99	(0.98–1.0)		
Breast cancer							0.49	0.42
Unexposed	4376	3.6 (2–6.8)	2 629 160.7	166.4	Reference			
Exposed	8085	4 (2.8–6.8)	4 363 445.3	185.3	0.99	(0.95–1.02)		
Prostate cancer							0.10	0.16
Unexposed	6734	3.6 (2–6.8)	2 623 599.5	256.7	Reference			
Exposed	10 358	4 (2.8–6.8)	4 358 175.6	237.7	0.97	(0.95–1.0)		
Colon cancer							0.74	0.57
Unexposed	2815	3.6 (2–6.8)	2 631 084.8	107	Reference			
Exposed	4866	4 (2.8–6.8)	4 368 570	111.4	1.01	(0.96–1.05)		
Rectal cancer							0.97	0.61
Unexposed	758	3.6 (2–6.8)	2 639 317.4	28.7	Reference			
Exposed	1303	4.1 (2.8–6.8)	4 382 762.9	29.7	1.0	(0.92–1.09)		
Lung cancer							0.05	0.05
Unexposed	3235	3.6 (2–6.8)	2 636 051	122.7	Reference			
Exposed	5104	4.1 (2.8–6.8)	4 377 623.9	116.6	0.95	(0.91–1.0)		
Liver cancer							0.03	0.04
Unexposed	789	3.6 (2–6.8)	2 639 969	29.9	Reference			
Exposed	1473	4.1 (2.8–6.8)	4 383 838	33.6	1.12	(1.04–1.22)		
Bladder cancer							0.30	0.28
Unexposed	2110	3.6 (2–6.8)	2 636 070.2	80.0	Reference			
Exposed	3343	4.1 (2.8–6.8)	4 377 780.1	76.4	0.96	(0.91–1.02)		
Uterine cancer							0.82	0.56
Unexposed	693	3.6 (2–6.8)	2 639 496.5	26.3	Reference			
Exposed	1291	4.1 (2.8–6.8)	4 382 787.6	29.5	1.01	(0.92–1.10)		
Malignant melanoma							0.003	0.01
Unexposed	1297	3.6 (2–6.8)	2 638 131.7	49.2	Reference			
Exposed	2410	4.1 (2.8–6.8)	4 380 290.2	55.0	1.10	(1.03–1.18)		

All hazard ratios were derived from IPTW multivariable Cox models that were fit using follow-up as the time scale and a lag period of 1 year. aHR indicates adjusted hazard ratio; FDR, false discovery rate; IPTW, inverse probability of treatment weighting; IQR, interquartile range; and PYR. person-year.

Dose–Response Analyses

We found no evidence of a dose–response relationship between the daily dose of valsartan and the risk of any cancer by location. For liver cancer, aHRs were 1.14 (95% CI, 1.02–1.27) in patients treated with 80 mg/day or less and 0.99 (95% CI, 0.71–1.37) in those who received the highest dosage (more than 160 mg/day) (Figure 3A).

For melanoma, aHRs were 1.14 (95% CI, 1.02–1.27) in patients treated with 80 mg/day or less, 1.07 (95% CI, 0.99–1.31) among those treated with 80 to 160 mg/day, and 1.01 (95% CI, 0.71–1.37) in those who received more than 160 mg/day. Results remained similar when using the cumulative dose of valsartan (Figure 3B).

Sensitivity Analyses

None of the sensitivity analyses produced meaningfully different results to those observed in the main analysis (Table S8, Table S9, and Table S13). When varying the lag period to 2 years, the risks of liver cancer decreased slightly (aHR, 1.10 [95% CI, 1.01–1.20]), and the risks of melanoma remained similar to the primary analysis (aHR, 1.10 [95% CI, 1.03–1.17]) (Table S8, Appendix S9). We then excluded subjects who received both contaminated and uncontaminated valsartan from the analysis (n=230 261). Our results remained overall consistent (Table S10, Appendix S11). However, the risks for overall cancer were statistically significant but very low (in fact negligible) (aHR, 1.03 [95% CI, 1.01–1.04]) (Table S10). The risks for liver cancer were 1.15-fold higher (95% CI, 1.05–1.26) and 1.15-fold higher for melanoma (95%CI, 1.06–1.23). Male patients treated with NDMA-contaminated valsartan were also at a significantly higher risk of liver cancer (aHR, 1.23 [95% CI, 1.10–1.37]) (Table S11). Risks remained higher among most socially deprived patients exposed to NDMA-contaminated valsartan compared with those unexposed (aHR, 1.38 [95% CI, 1.12–1.69] for liver cancer and aHR, 1.23 [95% CI, 1.03–1.46] for melanoma) (Table S11).

When restricting the analysis to those with at least 2 years of follow-up, risks increased to 1.13-fold (95% CI, 1.02–1.24) for liver cancer and to 1.14 (95% CI, 1.05–1.25) for melanoma (Table S12, Table S13).

A further adjustment for hepatotoxic medications as detailed in Table S14 did not change the risks of liver cancer (aHR, 1.12 [95% CI, 1.03–1.22]) (Table S15).

Health care consumption at baseline in both exposed and unexposed cohorts was described in Table S16. The risks of both liver cancer and melanoma remained similar after adjusting for health consumption (aHR, 1.12 [95% CI, 1.03–1.22] for liver cancer and aHR, 1.10 [95% CI, 1.03–1.18] for melanoma) (Table S17). Also, after further adjusting on exposure to other potentially NDMA-contaminated drugs (metformin and ranitidine), results remained consistent (Table S18). When taking into account death as a competing event, results also remained consistent (Table S19).

Results from dose–response analyses also remained unchanged after setting the index date at the median valsartan use duration and at January 1, 2015 to more thoroughly examine the question of cumulative exposure risk (Table S20 and S21).

Finally, a total of 218 060 and 412 218 treated with uncontaminated and contaminated valsartan were considered long-term users. Among these users, the risks of liver cancer were higher (aHR, 1.22 [95% CI, 1.08–1.38]). However, there was also no evidence of a linear dose response relationship (Table S22).

DISCUSSION

In this large, real-world, observational cohort study, we evaluated the risk of cancer associated with exposure to NDMA-contaminated valsartan in France. Our study features the longest follow-up reported so far, and the largest number of patients to date, with more than 1.4 million users. There was no increased risk of overall cancer among exposed patients. However, for individual cancer outcomes we found a slightly increased risk of liver cancer (12%) and melanoma (10%) in those exposed to NDMA-contaminated valsartan compared with unexposed subjects. Risks for liver cancer were higher in the most socially deprived patients, male subjects, and long term-users. We also estimated the number of 3.7 extra cases of liver cancer and 5.8 extra cases of malignant melanoma per year per 100 000 person-years. The European Medicines Agency has estimated a total of 20 extra cases of cancer for every 100 000 patients exposed to contaminated valsartan at the highest dose, which is about double our overall estimation.[34] Only 2 studies have investigated the risk of cancer in patients treated with NDMA-contaminated valsartan. The first study, which used the Danish health claims database with only 5150 subjects, did not find any significant short-term risk of cancer. However, liver cancer was not included in the main outcomes, and the study was also limited by the low number of events and lack of statistical power.[4] Another study based on a German health insurance database found an increased risk of liver cancer, 1.16-fold higher, which was very close to our findings.[18] Conversely, neither study reported a significant risk of melanoma, although malignant melanoma related to valsartan has been reported in few case reports.[35,36]

NDMA is characterized as a potent hepatotoxin, carcinogen, and mutagen[37–39] and primarily targets the liver, which contains the necessary enzymes for its metabolic activation.[40] Rats exposed to NDMA developed predominantly liver tumors, including hepatocellular

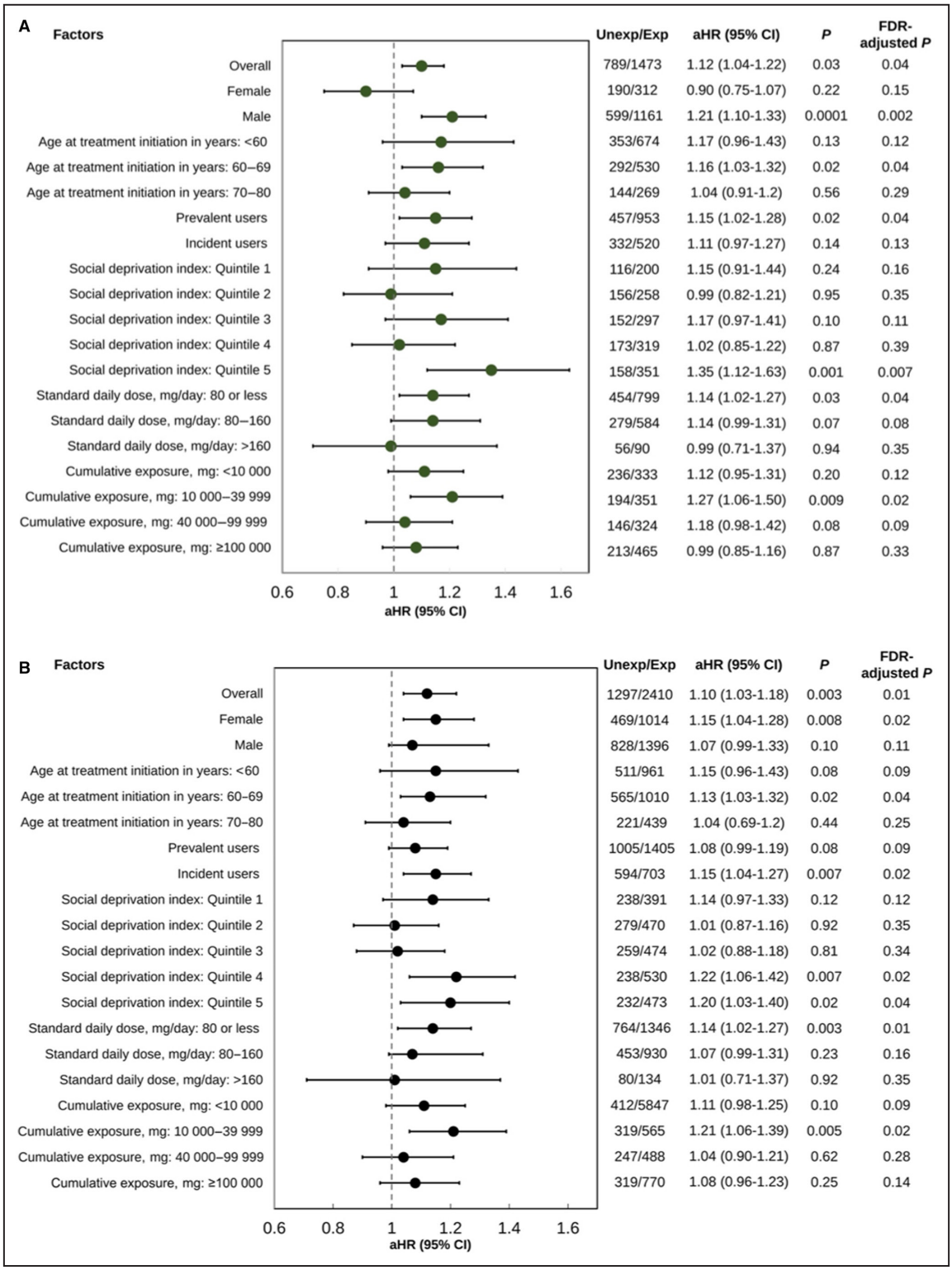

Figure 3. Subgroup analysis of the association between NDMA-contaminated valsartan exposure and the risk of liver cancer and melanoma.

A, Subgroup analysis of the association between NDMA-contaminated valsartan exposure and the risk of liver cancer. **B**, Subgroup analysis of the association between NDMA-contaminated valsartan exposure and the risk of melanoma. Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup, and hazard ratios were estimated using the inverse probability of treatment weighted Cox proportional hazards model. Reference category was unexposed subjects in each subgroup. aHR indicates adjusted hazard ratio; Exp, number of patients with cancer in the exposed cohort; FDR, false discovery rate; and Unexp, number of patients with cancer in the unexposed cohort.

carcinomas, bile ducts, blood vessels, and Kupffer cells.[41,42] The hepatocarcinogenic efficacy of NDMA can be related to the induction of DNA replication in addition to the accumulation of DNA damage.[9] The hepatocarcinogenicity of NDMA was also noted even at low doses and increased sharply at doses higher than 1 part per million (ppm).[41,42] Other previous studies on the genotoxicity of NDMA also found that exposure to NDMA in rodents can alter the natural defense mechanisms against melanoma, especially in women,[38] and that mutagenic and clastogenic mechanisms may also be involved in NDMA-induced melanoma.

The Food and Drug Administration has indicated that exposure levels of NDMA up to 0.1 μg/day are considered safe, which is equivalent to 0.3 ppm in a valsartan tablet.[43,44] However, the European Medicines Agency reported that levels of NDMA impurities were way above this threshold in some valsartan batches, reaching up to 240.1 ppm.[43] Based on the mean NDMA contamination of 60.13 ppm detected in valsartan batches, NDMA concentration would reach 19.24 μg/day in a 320 mg valsartan tablet,[40] which does not exceed the carcinogenicity threshold set by rat models at 10 μg/kg/day.[41] Although DNA damage mechanisms documented in animal studies might be relevant in humans, estimates of the carcinogenicity of NDMA in humans based on levels established for rodents can be inaccurate.

In our study, we estimated a dose–response relationship between the prescribed and cumulative dose of valsartan, which may be correlated with the dose of NDMA and the risk of cancer, and found no significant linear dose–response relationship. Risk assessments of NDMA to date have been based on only a classical linear modeling approach based on cancer potency data.[45] These large studies were unable to conclude upon a linear dose–response relationship, especially for exposure to lower doses.

Nevertheless, exposure to NDMA in medicines constitutes a highly complex issue because it is a known environmental contaminant found routinely in processed meat, tobacco, and alcohol, which may result in increased exposure and hence may affect the accuracy of the dose–response relationship.[7] In addition, other *N*-nitrosamines (*N*-nitrosodiethylamine) have been detected in different valsartan products, resulting in possible additive exposure. Manufacturers have provided only limited data on these *N*-nitrosodiethylamine impurities owing to the unavailability of validated analytical methods.[40]

Strengths and Weaknesses

The primary strength of this study was the population size, selected from a high-quality comprehensive nationwide and population-based database that covers around 99% of the French population. Furthermore, we used IPTW to balance differences between the 2 cohorts and to adjust for potential bias. We also tested the robustness of our findings in several sensitivity analyses, which were consistent with the main findings.

In our study, those unexposed to NMDA were more often new users compared with exposed patients (68.4% and 53.2%, respectively), an outcome that was also found in the 2 other studies mentioned previously. Although this covariate was incorporated as a dichotomous variable in the propensity weighting, residual confounding could remain, as the dichotomization sacrifices information on the total duration of past use. Furthermore, we excluded patients older than 80 years because they may be specific in terms of health outcomes, and thus our results cannot be generalized to this population.

We also used proxies to measure smoking behaviors, alcohol abuse, and morbid obesity in our study population. Although, the distributions of these risk factors were strongly similar in both cohorts, residual confounding may still be present.

We were also unable to adjust for differences in ultraviolet light radiation exposure. Ultraviolet light radiation through unprotected sun exposure is a major risk factor leading to melanoma development through carcinogenesis via direct and indirect DNA damage.[46] The slight increase in risk of melanoma skin cancer associated with exposure to NDMA-contaminated valsartan in our study may therefore be explained by residual confounding by sunlight exposure or other unmeasured confounding.

Lastly, we were unable to obtain information regarding the number of valsartan packages sold containing impurities to evaluate the extent of nitrosamine contamination. The official authorities released the number of contaminated batches recalled from the market only in the summer of 2018, and the batches delivered to patients were not available in our database.

Implications for Clinicians and Policymakers

Carcinogenic nitrosamine contaminants detected in valsartan products constitute a public health concern, given the extensive and widespread use of this medication. In 2017 alone, 10 million prescriptions of valsartan were dispensed in France. Our results provide additional evidence of a slight increased risk of liver cancer and new data on the increased risk of melanoma related to NDMA impurities in valsartan products. Further studies are necessary to confirm the association between malignant melanoma and exposure to NDMA in valsartan products. A close monitoring of the potential long-term carcinogenic effects of NDMA in regularly taken medication seems also necessary.

Additionally, clinicians faced major prescribing difficulties, in many cases switching patients from valsartan to another ARB that was recalled later (irbesartan or losartan), which may have prompted some patients to discontinue their treatments.[47] At present, it is still unclear whether switching to other ARBs or treatment cessation in some cases could have increased the risks of strokes and transient ischemic attacks.[47,48]

CONCLUSIONS

Only a few epidemiological studies have evaluated cancer risk from the use of NDMA contaminated valsartan. Our study had the longest follow-up so far, provides a much-needed insight into the risk of cancer following exposure to these products, and reveals a slightly increased risk of liver cancer and melanoma. More research is needed to gain further evidence and to understand more deeply the relationship between NDMA exposure and the risks of liver cancer and melanoma.

After the recalls of several ARBs, including valsartan, NDMA impurities were also detected in several other drugs (ranitidine, metformin). Our study raises concerns regarding the risks of cancer in patients exposed to NDMA in regularly taken medications. Pharmacoepidemiologic studies are needed to evaluate cancer risks from the use of such drugs and to establish clinically relevant causality.

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None.

Supplemental Material

Appendix S1

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SUPPLEMENTAL MATERIAL

Supplemental Methods

DATA S1:

Standardized difference was used to compare the mean of continuous and binary variables between both treatment groups.
For continuous covariates, the standardized difference was expressed as follows:

$$SD = \frac{\bar{X}_{exposed} - \bar{X}_{unexposed}}{\sqrt{(S^2_{exposed} - S^2_{unexposed})/2}}$$

Where $\bar{X}$ and S^2 denote the mean and variance of the covariates respectively in exposed and unexposed cohorts.
For categorical variables, the standardized difference was defined as:

$$\boldsymbol{SD = \frac{\hat{P}_{exposed} - \hat{P}_{unexposed}}{\sqrt{\left[\left(\hat{P}_{exposed}(1 - \hat{P}_{exposed})\right) + \left(\hat{P}_{unexposed}(1 - \hat{P}_{unexposed})\right)\right]/2}}}$$

Where $\hat{P}$ denote the prevalence of a covariate or a category of covariate in exposed and unexposed cohorts. For covariates with more than two categories, the standardized difference for each level of the categorical variable was calculated.

DATA S2:

Healthcare utilization at baseline

The proportion of exposed subjects who had one hospital stay ≥24h at baseline was higher (10.1%) compared to the unexposed cohort (8.7%). The number of patients who had at least two hospital stays ≥24h were similar in both cohorts (7.5% and 7.7% in exposed and unexposed subjects respectively).
Unexposed subjects had a higher number of medical procedures performed at baseline (median 22, IQR, 9-46) and a higher number of visitations with a health professional (median 21, IQR 10-38) compared to unexposed subjects (median number of medical procedures=19, IQR, 8-41 and median number of visitations with a health professional=19 IQR, 10-34) (Supplementary Table 16)

TABLE S1. Manufactures of NDMA contaminated and uncontaminated Valsartan

Contaminated Valsartan	*Uncontaminated Valsartan*
Arrow Generiques	Accord Healthcare
Biogran	ALTER
Cristers	IPSEN Pharma
Evolupharm	KRKA
Mylan	Novartis
Ranbaxy pharmacie generiques	PHR LAB
Sandoz	
Zentiva	
Zydus	

Contaminated Valsartan was fabricated by manufactures who recalled all unexpired valsartan from the market between 06/07/2018 and 20/12/2018 and uncontaminated valsartan was manufactured by those unaffected by the recalls.
The official lists of suppliers was obtained from the French National Agency for Medicines and Health Products [2, 21].

TABLE S2. ICD-10 codes used to identify cancer overall and by location using hospital diagnoses and long-term disease coded in ICD-10

Outcomes ≥ 1 year after treatment initiation	***Hospitalisation diagnoses and/or LTD coded in ICD-10****
Any active malignancy	C00-D09 excluding non-melanoma skin cancer (C44) T860, T860, Z08, Z510, Z511
Breast cancer	C50
Prostate cancer	C61
Lung cancer	C34
Colon cancer	C18, C19
Rectal cancer	C20
Liver cancer	C22
Bladder cancer	C67
Uterine cancer	C54, C55
Malignant melanoma	C43

*Patients with a history of cancer and those who developed cancer during the first-year post-treatment-initiation were excluded

TABLE S3. Diagnosis (ICD-10), specific drug reimbursement (ATC) codes and medical procedures used to identify comorbidities considered for adjustment

Comorbidities ≤7 years before index date	*Identification algorithm*		
	*Hospitalisation diagnoses and/or LTD coded in ICD-10**	*Medication*	*Medical procedures*
Any malignancy	C00-D09 excluding non-melanoma skin cancer (C44) D37-D48, D630, E883, G533, G550, G631, G732, G941, J700, J701, K520, K627, L412, L580, L581, L598, L599, M360, M361, M906, M962, M965, N304, O356, T860, Z08, Z510, Z511, Z85, Z948		
Breast cancer	C50		
Prostate cancer	C61		
Lung cancer	C34		
Colon cancer	C18, C19		
Rectal cancer	C20		
Liver cancer	C22		
Bladder cancer	C67		
Uterine cancer	C54, C55		
Malignant melanoma	C43		
Baseline covariates			
Heart failure	I50 or I110, I130, I132, I1,9, K761, J81		
Valvular disease	I05-I08, I34-I39		
Coronary heart disease	I20-I25		
Dysrhythmia	I44-I49		

Lower extremities arterial disease	I70-I73	
Other cardiac disease	I01, I09, I27, I28, I30-I32, I33,I40-I43,I51, I52, I65, I66, I71, I72, I77-I79, I80-I83, I87, I95, I99, P29, Q20-Q28, K55, R00, T82, Z95	
Stroke	I60-I69	
Diabetes	E10-E14	Positive if the individual has at least three reimbursements of an antidiabetic drug in a given year ATC: A10 —except Benfluorex)
Chronic respiratory disease	J40-J47, J96, J98	
Pulmonary embolism	I26	
Advanced chronic kidney disease	N18, I12, I131, I132, Z940	
Hepatic cirrhosis or fibrosis or liver failure	R18, I85, K70, K71, K72, K74	
Chronic inflammatory bowel disease	K50, K51, M074, M075	
Dementia	F00-F03, G30, F051	
Alcohol abuse	E244, E512, G312, G621, G721, I426, K292, K70, K860, R780, T51, Y15, Y90, Y91, Y573, Z502, Z714, Z721, F10, Z714, E244, G312, Y15, X45, X65, Z864	Positive if the individual has at least one reimbursement for drugs used in alcohol dependence ATC: N07BB

Smoking	F17	Positive if individual has at least one reimbursement for drugs used in nicotine dependence or to support smoking cessation ATC: N06AX12, N07BA, R03AC18, R03AC19, R03BB04, R03BB05 R03BB06, R03BB07, R03AL04, R03AL05, R03AK04	
Obesity	E66		Positive if individual as any reimbursement for medical procedures related to Bariatric surgery: HFCA001, HFCC003, HFFA001, HFFA011, HFFC004, HFFC018, HFFC018 , HFGC900, HFKA001,HFKA002, HFKC001, HFMA009, HFMA010, HFMA011, HFMC006, HFMC007, HFMC008, HGCA009, HGCC027

Abbreviations: LTD: long term disease, ICD-10: international classification of disease 10th version, ATC: Anatomical Therapeutic Chemical
Medical procedures are coded according to the French medical classification for clinical procedures (CCAM Classification Commune des Actes Médicaux)

TABLE S4. ATC codes used to identify medications considered for adjustment

Medications	*ATC codes*
Comedication ≤1 year before index date	
Aspirin	B01AC06, B01AC08, B01AC30, N02BA01, N02BA51, C10BX02)
Non aspirin NSAIDs	M01A
Statins	C10AA, C10BA, C10BX
Spironolactone	C03DA01
Dihydrotestosterone blockers	G04CB01, G04CB02, G04CA51, G04CA52
Hormone replacement therapy	G03C, G03D, G03F
Glucocorticoids	H02AB
SSRIs	N06AB
Polytreatment for hypertension ≤1 year before index date	
ACE inhibitors	ACE inhibitors (ATC: C09A), ACE inhibitors in combinations with diuretics (ATC: C09BA), ACE in combination with calcium channel blockers (ATC: C09BB) and ARB with other combinations (ATC: C09BX)
Alpha-adrenoreceptor antagonists	C02CA
Angiotensin II antagonists	ARB (ATC: C09C), ARB in combinations with diuretics (ATC: C09DA), ARB in combination with calcium channel blockers (ATC: C09DB) and ARB with other combinations (ATC: C09DX)
Beta-adrenoceptor blockers	Beta-blockers (ATC: C07A), beta-blockers in combinations with thiazides (ATC: C07F)
Calcium channel blockers	Calcium channel blockers (ATC: C08C, C08D)
Diuretics	Thiazide diuretics (ATC: C03A), potassium-sparing diuretics (ATC: C03D), combinations of thiazide and potassium-sparing diuretics (ATC: C03E).
Renin-inhibitors	Remikiren (ATC: C09XA01, Aliskiren (ATC: C09XA02), Aliskiren and hydrochlorothiazide (ATC: C09XA52), Aliskiren and amlodipine (ATC: C09XA53) and Aliskiren, Amlodipine and hydrochlorothiazide(ATCC: C09XA54).
Other hypertensive drugs	Antiadrenergic agents, centrally acting (ATC: C02A), Arteriolar smooth muscle agents (ATC: C02D) and Antihypertensives and diuretics in combination (ATC: C02L)

ATC; Anatomical Therapeutic Chemical, NSAID: Nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitor

TABLE S5. Subgroup analysis of the association between NDMA contaminated valsartan exposure and the risk of any active malignancy, breast and prostate cancer (main analysis)

Subgroup	*Any active cancer*			*Breast cancer*			*Prostate cancer*		
	Unexposed	**Exposed**		**Unexposed**	**Exposed**		**Unexposed**	**Exposed**	
	Number of cancer patients	*Number of cancer patients*	**aHR (95% CI)***	*Number of cancer patients*	*Number of cancer patients*	**aHR (95% CI)***	*Number of cancer patients*	*Number of cancer patients*	**aHR (95% CI)***
Sex									
Females	12317	22851	0.98 (0.95- 1.0)	4376	8085	0.97 (0.94- 1.01)	0	0	*
Males	20857	32839	1.0 (0.99- 1.02)	0	0	*	6734	10358	0.98 (0.95- 1.01)
Age at treatment initiation									
<60	6987	11367	0.98 (0.95- 1.01)	1158	2097	0.96 (0.89- 1.03)	1161	1591	0.92 (0.85- 0.99)
60-69	14130	23780	1.0 (0.98- 1.02)	1772	3315	0.99 (0.94- 1.05)	3341	5287	1.0 (0.96- 1.05)
70-80	12057	20543	0.97 (0.95- 0.99)	1446	2673	1.0 (0.94- 1.07)	2232	3480	0.93 (0.88- 0.98)
Prevalent Users	21941	33749	0.97 (0.95- 0.99)	2418	4796	0.9 (0.86- 0.95)	3725	6295	0.99 (0.95- 1.03)
Incident Users	14565	18609	1.06 (1.04- 1.08)	1958	3289	1.09 (1.03- 1.15)	3009	4063	1.0 (0.95- 1.04)
Social deprivation index									
Quintile 1 (richest 20%)	5990	8671	0.99 (0.96- 1.03)	836	1340	1.0 (0.92- 1.09)	1308	1728	0.98 (0.91- 1.05)
Quintile 2	6254	10286	0.99 (0.96- 1.02)	782	1492	1.03 (0.95- 1.12)	1267	1950	1.0 (0.93- 1.07)
Quintile 3	6452	10893	0.97 (0.94- 1.0)	841	1560	0.96 (0.88- 1.04)	1289	2079	0.98 (0.91- 1.05)
Quintile 4	6648	11965	0.98 (0.95- 1.01)	885	1703	0.96 (0.89- 1.04)	1302	2120	0.95 (0.89- 1.02)
Quintile 5 (poorest 20%)	6731	12125	1.01 (0.99- 1.04)	943	1785	0.96 (0.89- 1.04)	1286	2102	0.99 (0.93- 1.06)
DDD of Valsartan, mg/day									
80 or less	19419	30148	0.99 (0.97- 1.01)	2602	4389	0.97 (0.92- 1.02)	3926	5620	0.98 (0.94- 1.02)
81-160	11503	22077	1.01 (0.99- 1.04)	1489	3197	1.02 (0.96- 1.08)	2399	4094	0.97 (0.92- 1.02)
>160	2252	3465	0.95 (0.90- 1.0)	285	499	0.98 (0.85- 1.13)	409	644	1.04 (0.92- 1.18)

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose

*Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup, and HRs were estimated using the inverse probability of treatment weighted Cox proportional hazards model

Reference category was unexposed subjects in each subgroup

TABLE S6. Subgroup analysis of the association between NDMA contaminated valsartan exposure and the risk of colon and rectal cancer (main analysis)

Subgroup	*Colon cancer*					*Rectal cancer*				
	Unexposed	**Exposed**				**Unexposed**	**Exposed**			
	Number of cancer patients	*Number of cancer patients*	**aHR (95% CI)***			*Number of cancer patients*	*Number of cancer patients*	**aHR (95% CI)***		
Sex										
Females	1036	1951	0.97	(0.91-	1.05)	237	456	1	(0.86-	1.17)
Males	1779	2915	0.96	(0.9-	1.02)	521	847	1	(0.90-	1.11)
Age at treatment initiation										
<60	467	753	0.97	(0.87-	1.09)	160	218	0.82	(0.67-	1.0)
60-69	1149	2041	1.06	(0.99-	1.14)	322	569	1.05	(0.92-	1.20)
70-80	1199	2072	0.96	(0.89-	1.03)	276	516	1.03	(0.9-	1.19)
Prevalent Users	1675	3023	0.96	(0.9-	1.02)	446	848	1	(0.89-	1.12)
Incident Users	1140	1843	1.14	(1.06-	1.23)	312	455	1.02	(0.88-	1.17)
Social deprivation index										
Quintile 1 (richest 20%)	474	720	1.04	(0.93-	1.16)	136	184	0.91	(0.73-	1.13)
Quintile 2	525	905	1.02	(0.92-	1.13)	129	233	1.12	(0.91-	1.39)
Quintile 3	590	934	0.9	(0.82-	1.0)	139	251	1.03	(0.85-	1.26)
Quintile 4	565	1075	1.02	(0.93-	1.13)	160	277	0.93	(0.77-	1.12)
Quintile 5 (poorest 20%)	564	1090	1.08	(0.98-	1.20)	171	313	1.02	(0.85-	1.22)
DDD of Valsartan, mg/day										
80 or less	1637	2601	1.0	(0.94-	1.06)	458	686	0.93	(0.83-	1.04)
81-160	985	1974	1.04	(0.97-	1.12)	242	525	1.17	(0.99-	1.40)
>160	193	291	0.91	(0.76-	1.09)	58	92	0.93	(0.67-	1.28)

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose

*Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup, and HRs were estimated using the inverse probability of treatment weighted Cox proportional hazards model

Reference category was unexposed subjects in each subgroup

TABLE S7. Subgroup analysis of the association between NDMA contaminated valsartan exposure and the risk of lung, bladder and uterine cancer (main analysis)

Subgroup	*Lung cancer*			*Bladder cancer*			*Uterine cancer*		
	Unexposed	**Exposed**	**aHR (95% CI)***	**Unexposed**	**Exposed**	**aHR (95% CI)***	**Unexposed**	**Exposed**	**aHR (95% CI)***
	Number of cancer patients	*Number of cancer patients*		*Number of cancer patients*	*Number of cancer patients*		*Number of cancer patients*	*Number of cancer patients*	
Sex									
Females	887	1504	0.89 (0.82- 0.97)	287	567	1.01 (0.88- 1.16)	693	1291	1.0 (0.91- 1.09)
Males	2348	3600	0.95 (0.9- 1.01)	1823	2776	0.96 (0.91- 1.02)	0	0	*
Age at treatment initiation									
<60	749	1218	0.99 (0.9- 1.08)	314	471	0.96 (0.83- 1.1)	139	273	1.02 (0.84- 1.24)
60-69	1457	2241	0.93 (0.87- 0.99)	888	1389	0.96 (0.88- 1.04)	297	543	1.0 (0.87- 1.14)
70-80	1029	1645	0.94 (0.87- 1.02)	908	1483	0.97 (0.89- 1.05)	257	475	1.04 (0.89- 1.20)
Prevalent Users	1772	3089	0.95 (0.9- 1.01)	1220	2085	0.95 (0.89- 1.02)	383	814	1.0 (0.86- 1.09)
Incident Users	1463	2015	0.99 (0.92- 1.06)	890	1258	1.06 (0.97- 1.16)	310	477	1.02 (0.87- 1.18)
Social deprivation index									
Quintile 1 (richest 20%)	545	786	1.0 (0.9- 1.11)	382	525	0.99 (0.87- 1.12)	117	190	0.97 (0.77- 1.21)
Quintile 2	615	981	0.98 (0.89- 1.08)	396	621	0.99 (0.87- 1.12)	117	203	1.02 (0.82- 1.27)
Quintile 3	606	1009	0.98 (0.89- 1.08)	432	647	0.93 (0.82- 1.04)	147	236	0.86 (0.71- 1.05)
Quintile 4	679	1082	0.9 (0.82- 0.99)	418	752	1.02 (0.91- 1.15)	150	295	0.99 (0.82- 1.20)
Quintile 5 (poorest 20%)	672	1080	0.91 (0.83- 1.0)	396	680	0.97 (0.86- 1.09)	149	338	1.17 (0.97- 1.40)
DDD Valsartan, mg/day									
80 or less	1865	2739	0.94 (0.89- 1.0)	1264	1799	0.93 (0.87- 1.0)	406	675	0.97 (0.86 1.09)
81-160	1146	2031	0.97 (0.90- 1.04)	704	1338	1.06 (0.97- 1.16)	230	532	1.11 (0.96 1.29)
>160	224	334	0.96 (0.82- 1.14)	142	206	0.95 (0.77- 1.17)	57	84	0.86 (0.62 1.20)

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose

*Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup, and HRs were estimated using the inverse probability of treatment weighted Cox proportional hazards model

Reference category was unexposed subjects in each subgroup

TABLE S8. Risks of overall cancer and cancer by location in patients exposed to NDMA contaminated valsartan compared to unexposed subjects after setting the lag period to two years (sensitivity analysis 1)

Outcome	*Number of cancer patients*	*Median follow-up, years (IQR)*	*PYR*	*Crude incidence /100 000 Pyr*	*Multivariable (IPTW)* aHR (95% CI)	*P*	*FDR-adjusted P*
Any malignancy							
Unexposed	36 092	3.7 (2.3-6.7)	2 565 339.2	1406.9	Reference	0.16	0.14
Exposed	58 569	4.4 (2.8-6.8)	4 253 622.9	1376.9	0.99 (0.98- 1.0)		
Breast cancer							
Unexposed	4 805	3.9 (2.5-6.8)	2 629 160.7	182.8	Reference	0.32	0.20
Exposed	8 519	4.7 (2.9-6.8)	4 363 445.3	195.2	0.98 (0.95- 1.02)		
Prostate cancer							
Unexposed	7 317	3.9 (2.5-6.8)	2 623 599.5	278.9	Reference	0.13	0.12
Exposed	10 916	4.7 (2.9-6.8)	4 358 175.6	250.5	0.98 (0.95- 1.01)		
Colon cancer							
Unexposed	2 815	3.9 (2.6-6.8)	2 631 084.8	107	Reference	0.73	0.32
Exposed	4 866	4.8 (2.9-6.8)	4 368 570	111.4	1.02 (0.97- 1.06)		
Rectal cancer							
Unexposed	758	3.9 (2.6-6.8)	2 639 317.4	28.7	Reference	0.96	0.35
Exposed	1 303	4.8 (2.9-6.8)	4 382 762.9	29.7	1.01 (0.93- 1.10)		
Lung cancer							
Unexposed	3 501	3.9 (2.5-6.8)	2 636 051	122.7	Reference	0.06	0.07
Exposed	5 359	4.8 (2.9-6.8)	4 377 623.9	116.6	0.95 (0.92- 1.0)		
Liver cancer							
Unexposed	859	3.9 (2.6-6.8)	2 639 969	32.5	Reference	0.02	0.03
Exposed	1 527	4.8 (2.9-6.8)	4 383 838	34.8	1.10 (1.01- 1.20)		
Bladder cancer							
Unexposed	2 287	3.9 (2.5-6.8)	2 636 070.2	86.8	Reference	0.21	0.15
Exposed	3 498	4.8 (2.9-6.8)	4 377 780.1	79.9	0.97 (0.92- 1.02)		
Uterine cancer							
Unexposed	774	3.9 (2.6-6.8)	2 639 496.5	29.3	Reference	0.93	0.36
Exposed	1 374	4.8 (2.9-6.8)	4 382 787.6	31.3	1 (0.92- 1.09)		
Malignant melanoma							
Unexposed	1 410	3.9 (2.6-6.8)	2 638 131.7	53.4	Reference	0.005	0.02
Exposed	2 536	4.8 (2.9-6.8)	4 380 290.2	57.9	1.10 (1.03- 1.17)		

Abbreviations: IQR interquartile range, PYR person year, IPTW inverse probability of treatment weighting, aHR adjusted Hazard Ratio, CI confidence interval, FDR false discovery rate

All hazard ratios were derived from IPTW multivariable Cox models which were fit using follow-up as the time scale and a lag period of two years

TABLE S9. Subgroup analysis of the association between NDMA contaminated valsartan exposure and the risk of liver cancer and melanoma after setting the lag period to two years (sensitivity analysis 1)

Subgroup	*Liver cancer*							*Melanoma*						
	Unexposed	**Exposed**	**HR (95% CI)***			**P**	**FDR-adjusted P**	**Unexposed**	**Exposed**	**HR (95% CI)***			***P***	***FDR-adjusted P***
	Number of cancer patients	*Number of cancer patients*						*Number of cancer patients*	*Number of cancer patients*					
Sex														
Females	210	331	0.9	(0.75-	1.07)	0.22	0.15	518	1070	1.15	(1.04-	1.28)	0.02	0.04
Males	649	1 196	1.21	(1.10-	1.33)	0.0001	0.002	892	1466	1.07	(0.99-	1.17)	0.12	0.12
Age at treatment initiation														
<60	161	273	1.17	(0.96-	1.43)	0.13	0.12	243	466	1.15	(0.98-	1.35)	0.12	0.12
60-69	382	697	1.16	(1.03-	1.32)	0.02	0.04	557	1008	1.13	(1.02-	1.25)	0.03	0.05
70-80	316	557	1.04	(0.91-	1.20)	0.23	0.29	610	1062	1.04	(0.94-	1.15)	0.40	0.23
Prevalent Users	467	983	1.15	(1.02-	1.28)	0.02	0.04	716	1469	1.08	(0.99-	1.19)	0.003	0.01
Incident Users	392	544	1.11	(0.97-	1.27)	0.14	0.13	694	1067	1.15	(1.04-	1.27)	0.14	0.13
Social deprivation index														
Quintile 1 (richest 20%)	127	209	1.15	(0.91-	1.44)	0.24	0.16	259	414	1.14	(0.97-	1.33)	0.12	0.12
Quintile 2	168	264	0.99	(0.82-	1.21)	0.95	0.35	306	499	1.01	(0.87-	1.16)	0.90	0.35
Quintile 3	165	310	1.17	(0.97-	1.41)	0.10	0.11	276	494	1.02	(0.88-	1.18)	0.85	0.34
Quintile 4	193	332	1.02	(0.85-	1.22)	0.87	0.35	261	555	1.22	(1.06-	1.42)	0.01	0.03
Quintile 5 (poorest 20%)	172	362	1.35	(1.12-	1.63)	0.001	0.007	255	499	1.20	(1.03-	1.40)	0.03	0.05
DDD of Valsartan, mg/day														
80 or less	487	833	1.14	(1.02-	1.27)	0.03	0.04	823	1411	1.14	(1.05-	1.25)	0.004	0.02
81-160	309	601	1.14	(0.99-	1.31)	0.07	0.08	497	983	1.07	(0.96-	1.19)	0.25	0.17
>160	63	93	0.99	(0.71-	1.37)	0.94	0.35	90	142	1.01	(0.77-	1.33)	0.96	0.35

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate

Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup, and HRs were estimated using the inverse probability of treatment weighted Cox proportional hazards model

Reference category was unexposed subjects in each subgroup

TABLE S10. Risks of overall cancer and cancer by location in patients exposed to NDMA contaminated valsartan compared to unexposed subjects after excluding patients who received both NDMA contaminated and uncontaminated valsartan (sensitivity analysis 2)

Outcome	*Number of cancer patients*	*Median follow-up in years (IQR)*	*PYR*	*Crude incidence /100 000 Pyr*	*Multivariable (IPTW) aHR (95% CI)*	*P*	*FDR-adjusted P*
Any malignancy							
Unexposed	27 882	5.3 (3.1-6.9)	2 179 870.2	1 279.1	Reference	0.0004	0.003
Exposed	49 501	5.4 (3.2-6.9)	3 783 635.1	1 308.3	1.03 (1.01- 1.04)		
Breast cancer							
Unexposed	3 594	5.6 (3.3-6.9)	2 2385 02.6	160.6	Reference	0.44	0.25
Exposed	7 098	5.7 (3.4-6.9)	3 886 703.3	182.6	0.98 (0.95- 1.02)		
Prosate cancer							
Unexposed	5 768	5.6 (3.3-6.9)	2 233 191.8	258.3	Reference	0.18	0.15
Exposed	9 219	5.7 (3.4-6.9)	3 881 544.2	237.5	1.02 (0.99- 1.06)		
Colon cancer							
Unexposed	2 336	5.7 (3.3-6.9)	2 240 662.9	104.3	Reference	0.06	0.08
Exposed	4 294	5.8 (3.4-6.9)	3891825.5	110.3	1.05 (0.99- 1.10)		
Rectal cancer							
Unexposed	631	5.7 (3.3-6.9)	2247784	28.1	Reference	0.15	0.14
Exposed	1 170	5.8 (3.4-6.9)	3904628.7	30	1.07 (0.97- 1.18)		
Lung cancer							
Unexposed	2 718	5.7 (3.3-6.9)	2 244 827.7	121.1	Reference	0.48	0.26
Exposed	4 563	5.8 (3.4-6.9)	3 899 844.8	117	0.98 (0.94- 1.03)		
Liver cancer							
Unexposed	686	5.7 (3.3-6.9)	2 248 373	30.5	Reference	0.003	0.01
Exposed	1 333	5.8 (3.4-6.9)	3 905 659.6	34.1	1.15 (1.05- 1.26)		
Bladder cancer							
Unexposed	1 789	5.7 (3.3-6.9)	2 244 769.6	79.7	Reference	0.97	0.36
Exposed	2 936	5.8 (3.4-6.9)	3 900 025.1	75.3	1.0 (0.94- 1.06)		
Uterine cancer							
Unexposed	551	5.7 (3.3-6.9)	2 247 999.3	24.5	Reference	0.83	0.34
Exposed	1 109	5.8 (3.4-6.9)	3 904 743.9	28.4	1.01 (0.91- 1.12)		
Malignant melanoma							
Unexposed	1 092	5.7 (3.3-6.9)	2 246 703.2	48.6	Reference	0.0003	0.003
Exposed	2 161	5.8 (3.4-6.9)	3 902 322.3	55.4	1.15 (1.06- 1.23)		

Abbreviations: IQR interquartile range, PYR person year, IPTW inverse probability of treatment weighting, aHR adjusted Hazard Ratio, CI confidence interval, FDR false discovery rate

All hazard ratios were derived from IPTW multivariable Cox models which were fit using follow-up as the time scale and a lag period of one year

TABLE S11. Subgroup analysis of the association between NDMA contaminated valsartan exposure and the risk of liver cancer and melanoma subjects after excluding patients who received both NDMA contaminated and uncontaminated valsartan (sensitivity analysis 2)

Subgroup	*Liver cancer*							*Melanoma*						
	Unexposed *Number of cancer patients*	**Exposed** *Number of cancer patients*	**aHR (95% CI)***			***P***	***FDR-adjusted P***	**Unexposed** *Number of cancer patients*	**Exposed** *Number of cancer patients*	**aHR (95% CI)***			***P***	***FDR-adjusted P***
Sex														
Females	155	279	0.90	(0.75-	1.09)	0.30	0.19	381	914	1.18	(1.05-	1.32)	0.004	0.02
Males	531	1 054	1.23	(1.10-	1.37)	0.0001	0.002	711	1247	1.12	(1.02-	1.23)	0.02	0.04
Age at treatment initiation														
<60	133	245	1.16	(0.94-	1.44)	0.17	0.15	189	401	1.24	(1.05-	1.48)	0.01	0.03
60-69	308	614	1.18	(1.03	1.36)	0.02	0.04	437	853	1.15	(1.03-	1.30)	0.02	0.04
70-80	245	474	1.11	(0.95-	1.30)	0.20	0.15	466	907	1.09	(0.98-	1.22)	0.12	0.12
Prevalent Users	424	861	1.23	(1.09-	1.38)	0.001	0.004	438	892	1.14	(1.04-	1.25)	0.007	0.02
Incident Users	262	472	1.04	(0.89-	1.20)	0.65	0.30	654	1 269	1.16	(1.03-	1.30)	0.01	0.03
Social deprivation index														
Quintile 1 (richest 20%)	182	182	1.21	(0.95-	1.55)	0.12	0.12	47	339	1.19	(0.99-	1.42)	0.05	0.07
Quintile 2	231	231	1.02	(0.83-	1.26)	0.84	0.34	199	414	1.03	(0.88-	1.21)	0.70	0.31
Quintile 3	264	264	1.17	(0.95-	1.44)	0.15	0.14	239	436	1.09	(0.93-	1.29)	0.27	0.18
Quintile 4	294	294	1.06	(0.87-	1.29)	0.58	0.230	218	480	1.28	(1.08-	1.51)	0.004	0.01
Quintile 5 (poorest 20%)	317	317	1.38	(1.12-	1.69)	0.002	0.01	201	424	1.23	(1.03-	1.46)	0.02	0.04
DDD of Valsartan, mg/day														
80 or less	404	684	1.09	(0.96-	1.23)	0.19	0.15	647	1179	1.14	(1.04-	1.25)	0.008	0.02
81-160	239	566	1.24	(1.06-	1.44)	0.007	0.021	380	834	1.12	(0.99-	1.27)	0.07	0.08
>160	43	83	1.17	(0.81-	1.69)	0.40	0.23	65	148	1.40	(1.04-	1.87)	0.03	0.04

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate

*Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup, and HRs were estimated using the inverse probability of treatment weighted Cox proportional hazards model

Reference category was unexposed subjects in each subgroup

TABLE S12. Risks of overall cancer and cancer by location in patients exposed to NDMA contaminated valsartan compared to unexposed subjects after excluding patients with less than two years of follow-up (sensitivity analysis 3)

Outcome	*Number of cancer patients*	*Median follow-up, years (IQR)*	*PYR*	*Crude incidence*	*Multivariable (IPTW)*			*P*	*FDR-adjusted P*
				/100 000 Pyr	**aHR (95% CI)**				
Any malignancy									
Unexposed	25075	5.0 (3.9-7.8)	2 472 585.1	1 014.1	Reference			0.21	0.19
Exposed	43714	5.6 (4.0-7.9)	4 172 838.5	1 047.6	1.01	(0.99-	1.02)		
Breast cancer									
Unexposed	3244	5.1 (4.0-7.9)	2 516 410.3	128.9	Reference			0.90	0.36
Exposed	6206	5.9 (4.0-8.0)	4 250 172.8	146	1.0	(0.96-	1.04)		
Prosate cancer									
Unexposed	5070	5.2 (4.0-7.9)	2 512 593.3	201.8	Reference			0.74	0.32
Exposed	8148	5.8 (4.0-7.9)	4 245 911	191.9	0.99	(0.96-	1.03)		
Colon cancer									
Unexposed	2153	5.2 (4.0-7.9)	2 516 482.6	85.6	Reference			0.40	0.23
Exposed	3845	5.9 (4.0-8.0)	4251418.9	90.4	1.02	(0.97-	1.08)		
Rectal cancer									
Unexposed	542	5.2 (4.0-7.9)	2 523 225.7	21.5	Reference			0.12	0.12
Exposed	1029	5.9 (4.0-8.0)	4 263 013.5	24.1	1.09	(0.98-	1.21)		
Lung cancer									
Unexposed	2378	5.2 (4.0-7.9)	2 520 961.5	94.3	Reference			0.57	0.30
Exposed	3958	5.9 (4.0-7.9)	4 259 350.1	92.9	0.99	(0.93-	1.04)		
Liver cancer									
Unexposed	625	5.2 (4.0-7.9)	2 523 521.2	24.8	Reference			0.02	0.04
Exposed	1190	5.9 (4.0-7.9)	4 263 721.9	27.9	1.13	(1.02-	1.24)		
Bladder cancer									
Unexposed	1601	5.2 (4.0-7.9)	2 520 941.3	63.5	Reference			0.29	0.19
Exposed	2584	5.9 (4.0-7.9)	4 259 660.7	60.7	0.96	(0.91-	1.02)		
Uterine cancer									
Unexposed	526	5.2 (4.0-7.9)	2 523 261.1	20.8	Reference			0.75	0.33
Exposed	1011	5.9 (4.0-8.0)	4 263 096.1	23.7	1.02	(0.91-	1.13)		
Malignant melanoma									
Unexposed	989	5.2 (4.0-7.9)	2 522 287.6	39.2	Reference			0.001	0.007
Exposed	1927	5.9 (4.0-7.9)	4 261 250.8	45.2	1.14	(1.05-	1.23)		

Abbreviations: IQR interquartile range, PYR person year, IPTW inverse probability of treatment weighting, aHR adjusted Hazard Ratio, CI confidence interval, FDR false discovery rate
All hazard ratios were derived from IPTW multivariable Cox models which were fit using follow-up as the time scale and a lag period of one year

TABLE S13. Subgroup analysis of the association between NDMA contaminated valsartan exposure and the risk of liver cancer and melanoma after excluding patients with less than two years of follow-up (sensitivity analysis 3)

Subgroup	Liver cancer							Melanoma						
	Unexposed	Exposed	aHR (95% CI)*			P	FDR-adjusted P	Unexposed	Exposed	aHR (95% CI)*			P	FDR-adjusted P
	Number of cancer patients	Number of cancer patients						Number of cancer patients	Number of cancer patients					
Sex														
Females	150	260	0.91	(0.74-	1.11)	0.34	0.2	362	816	1.16	(1.03-	1.32)	0.01	0.03
Males	475	930	1.21	(1.09-	1.35)	0.0004	0.004	627	1111	1.13	(1.02-	1.24)	0.02	0.04
Age at treatment initiation														
<60	285	548	1.09	(0.88-	1.36)	0.42	0.24	404	755	1.1	(0.91-	1.31)	0.32	0.20
60-69	218	420	1.17	(1.01-	1.35)	0.03	0.05	416	843	1.10	(0.99-	1.24)	0.13	0.12
70-80	122	222	1.09	(0.92-	1.28)	0.32	0.20	169	329	1.18	(1.05-	1.33)	0.005	0.02
Prevalent Users	389	813	1.19	(1.06-	1.35)	0.004	0.02	577	1194	1.14	(1.03-	1.26)	0.009	0.02
Incident Users	236	377	1.06	(0.90-	1.24)	0.51	0.28	412	733	1.14	(1.01-	1.29)	0.04	0.06
Social deprivation index														
Quintile 1 (richest 20%)	96	160	1.07	(0.83-	1.38)	0.60	0.31	184	306	1.17	(0.97-	1.40)	0.10	0.11
Quintile 2	123	209	0.98	(0.78-	1.22)	0.83	0.34	211	374	1.04	(0.88-	1.23)	0.62	0.30
Quintile 3	119	240	1.18	(0.95-	1.47)	0.13	0.12	195	378	1.06	(0.90-	1.26)	0.47	0.26
Quintile 4	143	255	1.0	(0.81-	1.22)	0.97	0.36	181	418	1.23	(1.04-	1.47)	0.02	0.04
Quintile 5 (poorest 20%)	117	287	1.47	(1.18-	1.82)	0.001	0.004	178	393	1.28	(1.07-	1.53)	0.006	0.02
DDD of Valsartan, mg/day														
80 or less	351	638	1.15	(1.01-	1.31)	0.03	0.05	578	1078	1.19	(1.08-	1.31)	0.001	0.004
81-160	227	477	1.12	(0.95-	1.31)	0.18	0.15	352	742	1.09	(0.95-	1.23)	0.21	0.16
>160	47	75	0.97	(0.68-	1.39)	0.87	0.35	59	107	1.03	(0.76-	1.41)	0.83	0.34

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate

*Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup, and HRs were estimated using the inverse probability of treatment weighted Cox proportional hazards model

Reference category was unexposed subjects in each subgroup

TABLE S14. ATC codes used to identify hepatotoxic medications used for sensitivity analysis 4

ATC CODE	*DENOMINATION*
ANTI-INFECTIVE FOR SYSTEMIC USE	
Tetracyclines	
J01AA07	minocycline
Antimycobacterials	
J04AB02	rifampicin
J04AC01	isoniazid
J04AC51	isoniazid, COMBINATIONS
J04AK01	pyrazinamide
Penicillins	
J01CF04	oxacillin
J01CR02	amoxicillin+clavulaniC ACID
Macrolides	
J01FA01	erythromycin
J01FA10	azithromicin
Fluoroquinolones	
J01MA01	ofloxacin
J01MA02	ciprofloxacin
J01MA12	lEvofloxacin
Others	
J01EE01	sulfamEthoxazole + trimEthoprim
J01XE01	nitrofurantoIN
ANTI-INFLAMMATORY AND ANTIRHEUMATIC DRUGS	
M01AB02	sunlindac
M01AB05	DiclofEnac
M01AE01	IbuprofEn
M01AE51	IBUPROFEN, COMBINATIONS
M01AX17	nimesulide
ANTIEPILEPTIC DRUGS	
N03AA02	phEnobarbital
N03AB02	phEnytoIN
N03AF01	carbamazEpine
N03AG01	valproIC ACID
ANTIFUNGALS FOR SYSTEMIC USE	
D01BA02	terbinafine
J02AB02	kEtoconazole
ANTIPSYCHOTIC DRUGS	
N05AA01	CHLORPROMAZINE
ANTIARRHYTHMIC DRUGS	
C01BA01	quinidine
C01BD01	amiodarone
ANTITHROMBOTIC AGENTS	
B01AB	HEPARIN GROUP
B01AC05	TICLOPIDINE
IMMUNOMODULATING AGENTS	
Immunosuppressant drugs	
L04AB02	infliximab
L04AX01	azathioprine
L04AX03	methotrexate
Immunostimulant drugs	
L03AB04	INTERFERON ALFA-2A
L03AB05	INTERFERON ALFA-2B
L03AB07	INTERFERON BETA-1A
L03AB08	INTERFERON BETA-1B
L03AB10	PEGINTERFERON ALFA-2B
L03AB11	PEGINTERFERON ALFA-2A
L03AB13	PEGINTERFERON BETA-1A

OTHER HEPATOTOXIC DRUGS

H03BA02	propylthiouracil
M03CA01	dantrolEne
M04AA01	allopurinol

TABLE S15. The risk of liver cancer in patients exposed to NDMA contaminated valsartan compared to uncontaminated valsartan after adjusting on hepatotoxic medication (sensitivity analysis 4)

Subgroup	*Liver cancer*						
	Unexposed *Number of cancer patients*	***Exposed*** *Number of cancer patients*	***aHR (95% CI)****			***P***	***FDR-adjusted P***
Overall : Exposed vs unexposed	789	1473	1.12	(1.03-	1.22)	0.007	0.021
Sex							
Females	190	312	0.9	(0.75-	1.07)	0.26	0.173
Males	599	1161	1.21	(1.10-	1.33)	0.0001	0.002
Age at treatment initiation							
<60	353	674	1.18	(0.96-	1.44)	0.06	0.07
60-69	292	530	1.16	(1.03-	1.32)	0.02	0.04
70-80	144	269	1.04	(0.91-	1.2)	0.63	0.30
Prevalent Users	457	953	1.15	(1.02-	1.28)	0.02	0.04
Incident Users	332	520	1.11	(0.97-	1.27)	0.12	0.14
Social deprivation index							
Quintile 1 (richest 20%)	116	200	1.15	(0.91-	1.44)	0.23	0.16
Quintile 2	156	258	0.99	(0.82-	1.21)	0.98	0.36
Quintile 3	152	297	1.17	(0.97-	1.41)	0.09	0.10
Quintile 4	173	319	1.02	(0.85-	1.22)	0.96	0.35
Quintile 5 (poorest 20%)	158	351	1.35	(1.12-	1.62)	0.001	0.004
DDD Valsartan, mg/day							
80 or less	454	799	1.15	(1.03-	1.29)	0.01	0.03
81-160	279	584	1.11	(0.97-	1.28)	0.14	0.13
>160	56	90	1.0	(0.72-	1.38)	0.99	0.36

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate
Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup
*All hazard ratios were derived from IPTW multivariable Cox models which were fit using follow-up as the time scale and a lag period of one year
Reference category was unexposed subjects in each subgroup

TABLE S16. Healthcare consumption at baseline among patients exposed and unexposed to NDMA contaminated valsartan (sensitivity analysis 5)

	Unexposed patients		Exposed patients	
	N=670 388		*N=986 126*	
	N	*(%)*	*N*	*(%)*
Number of hospital stays (<24h)				
0	584 613	(87.2)	861 939	(87.4)
1	50 966	(7.6)	78 688	(8.0)
2 or more	34 809	(5.2)	45 499	(4.6)
Number of hospital stay ≥24h				
0	560 733	(83.6)	812 616	(82.4)
1	58 283	(8.7)	99 311	(10.1)
2 or more	51 372	(7.7)	74 199	(7.5)
Days spent in hospital				
0	501 624	(74.8)	728 942	(73.9)
1-10	162 765	(24.3)	249 120	(25.3)
11-31	4263	(0.6)	5 830	(0.6)
>31	1736	(0.3)	2 234	(0.2)
Number of reimbursed laboraory tests				
Median (IQR)	22 (9-46)		19 (8-41)	
0	125 938	(18.8)	189 838	(19.2)
1-10	61 378	(9.2)	111 081	(11.3)
>10	483 072	(72.1)	685 207	(69.5)
Number of reimbursements of medical procedures				
Median (IQR)	4 (1-10)		4 (1-9)	
0	162 261	(24.2)	205 187	(20.8)
1-10	155 832	(23.2)	234 563	(23.8)
>10	352 295	(52.6)	546 376	(55.4)
Number of visits to a healthcare professional				
Median (IQR)	21 (10-38)		19 (10-34)	
0	41 334	(6.2)	189 838	(19.2)
1-10	127 898	(19.0)	111 081	(11.3)
>10	501 156	(74.8)	685 207	(69.5)

TABLE S17. The risk of any malignancy, liver cancer and melanoma in patients exposed to NDMA contaminated valsartan compared to uncontaminated valsartan after adjusting on healthcare consumption at baseline (sensitivity analysis 5)

	Any active cancer					*liver cancer*					*melanoma*				
	Unexposed	**Exposed**	**aHR (95% CI)***			**Unexposed**	**Exposed**	**aHR (95% CI)***			**Unexposed**	**Exposed**	**aHR (95% CI)***		
Subgroup	*Number of cancer patients*	*Number of cancer patients*				*Number of cancer patients*	*Number of cancer patients*				*Number of cancer patients*	*Number of cancer patients*			
Overall	33174	55690	0.99	(0.98-	1.00)	789	1473	1.12	(1.03-	1.22)	1297	2410	1.10	(1.03-	1.18)
Sex															
Females	12317	22851	0.97	(0.95-	0.99)	190	312	0.88	(0.74	1.05)	469	1014	1.16	(1.04-	1.29)
Males	20857	32839	1.01	(0.99-	1.03	599	1161	1.21	(1.10-	1.34)	828	1396	1.08	(0.99-	1.17)
Age at treatment initiation															
<60	6987	11367	0.98	(0.95-	1.0)	353	674	1.16	(0.95-	1.41)	511	961	1.16	(1.0-	1.36)
60-69	14130	23780	1	(0.98-	1.02)	292	530	1.16	(1.02-	1.32)	565	1010	1.13	(1.01-	1.25)
70-80	12057	20543	0.98	(0.96-	1.0)	144	269	1.04	(0.91-	1.20)	221	439	1.05	(0.95-	1.16)
Prevalent Users	21941	33749	0.97	(0.95-	0.98)	457	953	1.14	(1.02-	1.28)	1005	1405	1.08	(0.99-	1.19)
Incident Users	14565	18609	1.06	(1.04-	1.08)	332	520	1.1	(0.96-	1.26)	594	703	1.15	(1.04-	1.27)
Social deprivation index															
Quintile 1 (richest 20%)	5990	8671	0.99	(0.96-	1.03)	116	200	1.15	(0.92-	1.45)	238	391	1.14	(0.97-	1.34)
Quintile 2	6254	10286	0.99	(0.96-	1.02)	156	258	0.97	(0.80-	1.18)	279	470	1	(0.87-	1.16)
Quintile 3	6452	10893	0.97	(0.94-	1.0)	152	297	1.16	(0.96-	1.41)	259	474	1.02	(0.88-	1.18)
Quintile 4	6648	11965	0.98	(0.95-	1.01)	173	319	1.01	(0.85-	1.22)	238	530	1.23	(1.06-	1.43)
Quintile 5 (poorest 20%)	6731	12125	1.01	(0.98-	1.04)	158	351	1.34	(1.12-	1.62)	232	473	1.2	(1.03-	1.40)
DDD of Valsartan, mg/day															
80 or less	19419	30148	0.99	(0.97-	1.01)	622	453	1.13	(1.01-	1.27)	1003	854	1.14	(1.05-	1.25)
81-160	11503	22077	1.01	(0.99-	1.04)	123	736	1.14	(0.99-	1.31)	215	1193	1.07	(0.96-	1.20)
>160	2252	3465	0.95	(0.89-	1.0)	44	284	0.98	(0.67-	1.43)	79	363	1.0	(0.73-	1.38)

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate
Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup
*All hazard ratios were derived from IPTW multivariable Cox models which were fit using follow-up as the time scale and a lag period of one year
Reference category was unexposed subjects in each subgroup

TABLE S18. The risk any malignancy, liver cancer and melanoma in patients exposed to NDMA contaminated valsartan compared to uncontaminated valsartan after adjusting on other drugs potentially contaminated with NDMA (metformin and ranitidine) (sensitivity analysis 6)

Subgroup	Any active cancer			Liver cancer			Melanoma		
	Unexposed *Number of cancer patients*	**Exposed** *Number of cancer patients*	**aHR (95% CI)***	**Unexposed** *Number of cancer patients*	**Exposed** *Number of cancer patients*	**aHR (95% CI)***	**Unexposed** *Number of cancer patients*	**Exposed** *Number of cancer patients*	**aHR (95% CI)***
Overall	33174	55690	0.99 (0.98- 1.01)	789	1473	1.12 (1.03- 1.22)	1297	2410	1.10 (1.03- 1.18)
Sex									
Females	12317	22851	0.98 (0.95- 1.0)	190	312	0.9 (0.75- 1.07)	469	1014	1.15 (1.04- 1.28)
Males	20857	32839	1.01 (0.99- 1.03)	599	1161	1.22 (1.10- 1.34)	828	1396	1.08 (0.99- 1.17)
Age at treatment initiation									
<60	6987	11367	0.98 (0.95- 1.0)	353	674	1.15 (0.94- 1.40)	511	961	1.16 (0.99- 1.35)
60-69	14130	23780	1.0 (0.98- 1.02)	292	530	1.16 (1.03- 1.32)	565	1010	1.13 (1.02- 1.25)
70-80	12057	20543	0.98 (0.96- 1.01)	144	269	1.06 (0.92- 1.22)	221	439	1.05 (0.95- 1.16)
Prevalent Users	21941	33749	0.97 (0.95- 0.99)	457	953	1.14 (1.02- 1.28)	1005	1405	1.08 (0.99- 1.19)
Incident Users	14565	18609	1.06 (1.04- 1.08)	332	520	1.11 (0.97- 1.27)	594	703	1.15 (1.04- 1.27)
Social deprivation index									
Quintile 1 (richest 20%)	5990	8671	0.99 (0.96- 1.03)	116	200	1.15 (0.91- 1.44)	238	391	1.14 (0.97- 1.33)
Quintile 2	6254	10286	0.99 (0.96- 1.02)	156	258	0.99 (0.82- 1.20)	279	470	1.01 (0.87- 1.16)
Quintile 3	6452	10893	0.97 (0.94- 1.0)	152	297	1.17 (0.97- 1.41)	259	474	1.02 (0.88- 1.18)
Quintile 4	6648	11965	0.98 (0.95- 1.01)	173	319	1.01 (0.85- 1.22)	238	530	1.22 (1.05- 1.42)
Quintile 5 (poorest 20%)	6731	12125	1.01 (0.99- 1.04)	158	351	1.35 (1.12- 1.62)	232	473	1.20 (1.03- 1.40)
DDD of Valsartan, mg/day									
80 or less	19419	30148	0.99 (0.97- 1.01)	622	453	1.14 (1.01- 1.27)	1003	854	1.14 (1.05- 1.24)
81-160	11503	22077	1.01 (0.99- 1.04)	123	736	1.14 (0.99- 1.31)	215	1193	1.07 (0.96- 1.19)
>160	2252	3465	0.95 (0.89- 1.01)	44	284	0.99 (0.68- 1.44)	79	363	1.02 (0.74- 1.39)

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate

*Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup

All hazard ratios were derived from IPTW multivariable Cox models which were fit using follow-up as the time scale and a lag period of one year

Exposure to possibly NDMA contaminated ranitidine and metformin were included in multivariable models as time-dependent variables

Reference category was unexposed subjects in each subgroup

TABLE S19. The risk of any malignancy, liver cancer and melanoma in patients exposed to NDMA contaminated valsartan compared to uncontaminated valsartan taking into account competing events using cause-specific hazard method (sensitivity analysis 7)

Subgroup	*Any active cancer*					*Liver cancer*					*Melanoma*				
	Unexposed	**Exposed**	**aHR (95% CI)***			**Unexposed**	**Exposed**	**aHR (95% CI)***			**Unexposed**	**Exposed**	**aHR (95% CI)***		
	Number of cancer patients	*Number of cancer patients*				*Number of cancer patients*	*Number of cancer patients*				*Number of cancer patients*	*Number of cancer patients*			
Overall	33174	55690	0.99	(0.98-	1.01)	789	1473	1.12	(1.03-	1.22)	1297	2410	1.10	(1.03-	1.18)
Sex															
Females	12317	22851	0.98	(0.95-	1.0)	190	312	0.90	(0.75-	1.07)	469	1014	1.15	(1.04-	1.28)
Males	20857	32839	1.01	(0.99-	1.03)	599	1161	1.22	(1.11-	1.34)	828	1396	1.08	(0.99-	1.17)
Age at treatment initiation															
<60	6987	11367	0.98	(0.95-	1.0)	353	674	1.15	(0.94-	1.40)	511	961	1.16	(0.99-	1.35)
60-69	14130	23780	1.0	(0.98-	1.02)	292	530	1.16	(1.03-	1.32)	565	1010	1.13	(1.02-	1.25)
70-80	12057	20543	0.98	(0.96-	1.01)	144	269	1.06	(0.92-	1.22)	221	439	1.05	(0.95-	1.16)
Prevalent Users	21941	33749	0.97	(0.95-	0.99)	457	953	1.15	(1.02-	1.28)	1005	1405	1.08	(0.99-	1.19)
Incident Users	14565	18609	1.06	(1.04-	1.08)	332	520	1.11	(0.97-	1.27)	594	703	1.15	(1.04-	1.27)
Social deprivation index															
Quintile 1 (richest 20%)	5990	8671	0.99	(0.96-	1.03)	116	200	1.15	(0.91-	1.44)	238	391	1.14	(0.97-	1.33)
Quintile 2	6254	10286	0.99	(0.96-	1.02)	156	258	0.99	0.82-	1.21)	279	470	1.01	(0.87-	1.16)
Quintile 3	6452	10893	0.97	(0.94-	1.0)	152	297	1.17	(0.97-	1.41)	259	474	1.02	(0.88-	1.18)
Quintile 4	6648	11965	0.98	(0.95-	1.01)	173	319	1.02	(0.85-	1.22)	238	530	1.22	(1.06-	1.42)
Quintile 5 (poorest 20%)	6731	12125	1.01	(0.99-	1.04)	158	351	1.35	(1.12-	1.63)	232	473	1.2	(1.03-	1.40)
DDD of Valsartan. mg/day															
80 or less	19419	30148	0.99	(0.97-	1.01)	622	453	1.14	(1.02-	1.27)	1003	854	1.14	(1.05	1.25)
81-160	11503	22077	1.01	(0.99-	1.04)	123	736	1.14	(0.99-	1.31)	215	1193	1.07	(0.96	1.19)
>160	2252	3465	0.95	(0.89-	1.01)	44	284	0.99	(0.68-	1.44)	79	363	1.01	(0.74-	1.39)

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate
Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup
*All hazard ratios were derived from IPTW multivariable cause-specific hazard models taking into account death as a competing event
Follow-up as the time scale with a lag period of one year
Reference category was unexposed subjects in each subgroup

TABLE S20. Dose-response analysis after setting the index date at the median of valsartan use duration (sensitivity analysis 8)

	Liver cancer					***Melanoma***				
	Unexposed	**Exposed**	**aHR (95% CI)***			**Unexposed**	**Exposed**	**aHR (95% CI)***		
	Number of cancer patients	*Number of cancer patients*				*Number of cancer patients*	*Number of cancer patients*			
Overall	614	1111	1.13	(1.02-	1.24)	1009	1868	1.14	(1.06-	1.23)
DDD of Valsartan, mg/day										
80 or less	357	594	1.13	(0.99-	1.28)	609	1049	1.18	(1.07	1.30)
81-160	211	444	1.17	(0.99-	1.37)	340	715	1.11	(0.98-	1.26)
>160	46	73	0.98	(0.68-	1.41)	60	104	1.03	(0.76-	1.40)
Cumulative exposure, (mg)										
<10 000	201	274	1.11	(0.93-	1.32)	336	487	1.19	(1.04-	1.36)
10 000-39 999	150	263	1.30	(1.07-	1.58)	264	432	1.15	(0.99-	1.33)
40 000 -99 999	107	247	1.20	(0.96-	1.49)	179	370	1.06	(0.89-	1.26)
≥100 000	156	327	1.02	(0.99-	1.05)	230	579	1.14	(0.98-	1.32)

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate

*Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup

TABLE S21. Dose-response analysis after setting the index date at January, 1, 2015 (sensitivity analysis 9)

	Liver cancer					*Melanoma*				
	Unexposed	**Exposed**	**aHR (95% CI)***			**Unexposed**	**Exposed**	**aHR (95% CI)***		
	Number of cancer patients	*Number of cancer patients*				*Number of cancer patients*	*Number of cancer patients*			
Overall	623	1158	1.12	(1.02-	1.23)	1041	1974	1.12	(1.04-	1.20)
Prevalent users	322	690	1.23	(1.08-	1.4	510	1042	1.12	(1.01-	1.24)
Incident Users	301	468	1.04	(0.90-	1.20)	531	932	1.13	(1.01-	1.26)
DDD of Valsartan, mg/day										
80 or less	353	610	1.12	(0.98-	1.27)	614	1105	1.16	(1.05-	1.28)
81-160	222	470	1.16	(0.99-	1.36)	368	759	1.08	(0.95-	1.22)
>160	48	78	0.99	(0.69-	1.41)	59	110	1.1	(0.81-	1.51)
Cumulative exposure, (mg)										
<10 000	191	264	1.1	(0.91-	1.32)	324	475	1.14	(0.99-	1.31)
10 000-39 999	152	265	1.22	(1.0-	1.49)	263	461	1.19	(1.02-	1.38)
40 000 -99 999	112	261	1.22	(0.98-	1.52)	194	407	1.11	(0.94-	1.31)
≥100 000	168	368	1.0	(0.84-	1.20)	260	631	1.09	(0.95-	1.26)

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate

*Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup

All hazard ratios were derived from IPTW multivariable Cox models which were fit using follow-up as the time scale and a lag period of one year

TABLE S22. Risk of liver cancer and melanoma by valsartan dose category among long term users (sensitivity analysis 10)

	Liver cancer					*Melanoma*				
	Unexposed	**Exposed**	**aHR (95% CI)***			**Unexposed**	**Exposed**	**aHR (95% CI)***		
	Number of cancer patients	*Number of cancer patients*				*Number of cancer patients*	*Number of cancer patients*			
Overall	371	884	1.22	(1.08-	1.38)	613	1332	1.11	(1.0-	1.22)
DDD of Valsartan, mg/day										
80 or less	189	450	1.25	(1.06-	1.48)	324	735	1.22	(1.07-	1.39)
81-160	154	385	1.25	(1.04-	1.51)	245	530	1.03	(0.89-	1.20)
>160	28	49	0.98	(0.61-	1.57)	44	67	0.83	(0.57-	1.22)
Cumulative exposure, (mg)										
< 10 000	75	156	1.37	(1.04-	1.79)	135	232	1.09	(0.89-	1.34)
10 000-39 999	88	194	1.29	(1.0-	1.66	138	301	1.28	(1.04-	1.56)
40 000 -99 999	78	205	1.29	(0.99	1.67)	132	278	1.06	0.86-	1.30)
≥100 000	130	329	1.07	(0.86-	1.33)	208	278	1.05	(0.89-	1.25)

Abbreviations: aHR adjusted hazard ratio, CI confidence interval, DDD defined daily dose, FDR false discovery rate
*Separate propensity score models were fitted to predict the probability of the NDMA exposure for each subgroup
All hazard ratios were derived from IPTW multivariable Cox models which were fit using follow-up as the time scale and a lag period of one year
Long term valsartan users defined as those who filled valsartan prescriptions during least 3 consecutive years of the study period.

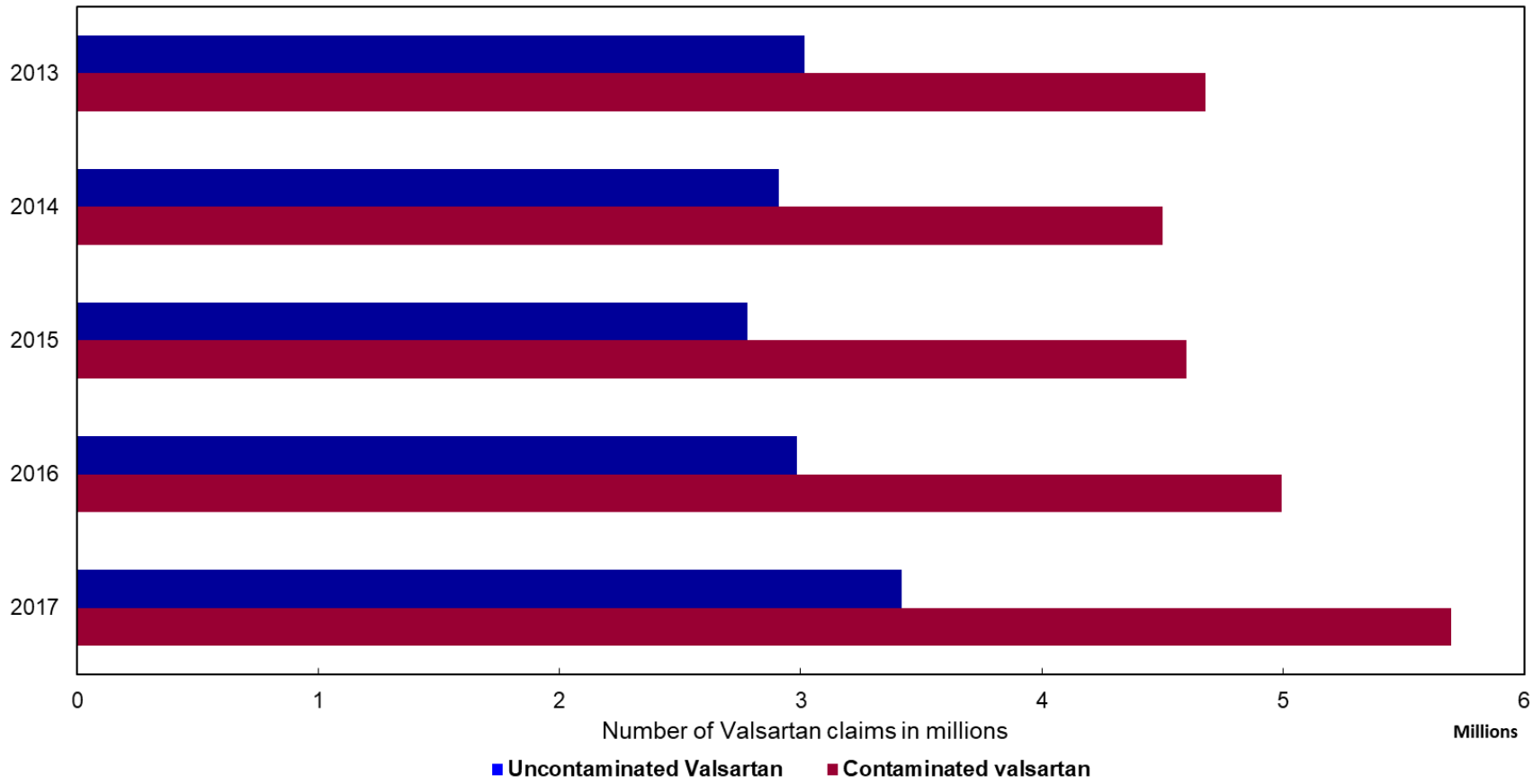

FIGURE S1. Number of NDMA contaminated and uncontaminated valsartan during the study period

Abbreviations: IPTW: Inverse Probability of Treatment Weighting, NSAID: Non-steroidal anti-inflammatory drugs, SSRI: Selective serotonin reuptake inhibitor, CKD: chronic kidney disease

FIGURE S2. Standardized mean difference before and after IPTW