## **Supplemental Online Content**

Bommareddy K, Hamade H, Lopez-Olivo MA, Wehner M, Tosh T, Barbieri JS. Association of spironolactone use with risk of cancer: a systematic review and meta-analysis. *JAMA Dermatol*. Published online February 9, 2022. doi:10.1001/jamadermatol.2021.5866

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This supplemental material has been provided by the authors to give readers additional information about their work.

### eAppendix. Search Strategy

#### PubMed Search Syntax:

1. (spironolactone OR aldactone OR spiractin OR verospiron OR Aldactone-A OR Berlactone, CaroSpir OR Espironolactona OR Espironolactona Genfar OR Novo-Spiroton, OR Spiridon OR Spirix OR Spiroctan OR Spiroderm OR Spirogamma OR Spirohexal OR Spirolon OR Spirolone OR Spiron OR Spironolactone Actavis OR Spironolactone Orion OR Spironolactone Teva OR Spirotone OR Uractone OR Uractonum OR Vivitar)

2. (cancer OR neoplasms OR adenoma OR malignancy OR tumor) 3. #1 AND #2

In addition, to ensure potentially relevant articles were not excluded, PubMed was searched using appropriate medical subject heading (MeSH) terms listed in the table. These terms were identified by reviewing the MeSH terms associated with the most relevant articles identified by the initial search. A similar search was performed in Cochrane library. Initial search strategy AND MeSH term were used in the search.

MeSH Terms
Spironolactone
Aldactone
Young Adult
Breast Neoplasms
Breast Adenoma
Breast Cancer
Ovarian Cancer
Cohort Studies
Case-Control Studies
Incidence
Retrospective Studies

# eFigure. Forest Plot Including All Individual Studies

				Risk Ratio		Risk Ratio	
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
1.1.1 Bladder							
Chuang 2017 females	-0.206	0.0589	34.1%	0.81 [0.73, 0.91]		-	
Chuang 2017 males	0.026	0.0411	36.9%	1.03 [0.95, 1.11]		+	
Mackenzie 2017	-0.2113	0.0871	29.0%	0.81 [0.68, 0.96]		-	
Subtotal (95% CI)			100.0%	0.89 [0.74, 1.06]		•	
Heterogeneity: Tau <sup>2</sup> = 0.0	02; Chi² = 13.42, d	f= 2 (P =	0.001); P	²= 85%			
Test for overall effect: Z =	: 1.36 (P = 0.17)						
4420-							
1.1.2 Breast						_	
Biggar 2013	0.174	0.0309	40.9%	1.19 [1.12, 1.26]			
Mackenzie 2017	0.0794	0.0534	37.1%	1.08 [0.98, 1.20]			
Subtotal (05% CI)	-0.2876	0.1311	100.0%	0.75 [0.58, 0.97]			
Hotorogonoity: Tou <sup>2</sup> – 0.0	12. Chiz - 12.06 d	f = 2 /P =	0.0043-8	= 0500		Ť	
Teet for overall effect: 7 -	0 43 (P = 0.67)	n – 2 (r –	0.001),1	- 00 %			
Testion overall ellect. Z -	0.45 (1 = 0.07)						
1.1.3 Gastric							
Busby 2017	0.1638	0.3175	12.3%	1.18 [0.63, 2.19]			
Mackenzie 2017	0.1000	0.1189	87.7%	1.00 [0.79, 1.26]			
Subtotal (95% CI)			100.0%	1.02 [0.82, 1.27]			
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> = 0.23, df	= 1 (P = (	0.63); I <sup>z</sup> =	0%			
Test for overall effect: Z =	0.18 (P = 0.86)						
1.1.4 Kidney							
Chuang 2017 females	-0.0712	0.057	48.6%	0.93 [0.83, 1.04]		-	
Chuang 2017 males	-0.0712	0.0631	43.2%	0.93 [0.82, 1.05]		-	
Mackenzie 2017	0.2412	0.1801	8.2%	1.27 [0.89, 1.81]		<b></b>	
Subtotal (95% CI)			100.0%	0.96 [0.86, 1.06]		•	
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi² = 2.85, df	= 2 (P = (	0.24); I <sup>z</sup> =	30%			
Test for overall effect: Z =	: 0.85 (P = 0.39)						
445 Ocean basis							
1.1.5 Oesophagical			~~~~				
Busby 2017 Maskannia 2017	0.236	0.2085	20.0%	1.27 [0.84, 1.91]			
Mackenzie 2017 Subtotal (95% CI)	0.0541	0.1044	100.0%	1.06 [0.86, 1.30]		<b>—</b>	
Hotorogonoity: Tou <sup>2</sup> = 0.0	00: Chiz = 0.61 df	- 1 /D - (	1441-12-	00			
Tect for overall effect: 7 =	0, CIII = 0.01, UI	- 1 (F - 0	J.44), I -	0.0			
Testion overall effect. Z -	0.37 (1 = 0.33)						
1.1.6 Ovary							
Biggar 2013	0.7514	0.0668	55.4%	2.12 [1.86, 2.42]		-	
Mackenzie 2017	0.239	0.1814	44.6%	1.27 [0.89, 1.81]		- <b>-</b>	
Subtotal (95% CI)			100.0%	1.69 [1.02, 2.78]			
Heterogeneity: Tau <sup>2</sup> = 0.1	11; Chi <sup>2</sup> = 7.03, df	= 1 (P = (	0.008); I <sup>2</sup> :	= 86%			
Test for overall effect: Z =	: 2.05 (P = 0.04)						
1.1.7 Prostate							
Beckmann 2019	-0.2824	0.0419	31.9%	0.75 [0.69, 0.82]		•	
Chuang 2017 males	-0.1236	0.035	33.8%	0.88 [0.83, 0.95]			
Hiebert 2020	-0.462	0.2069	5.9%	0.63 [0.42, 0.95]			
Mackenzie 2017	-0.2601	0.0537	28.4%	0.77 [0.69, 0.86]		<b>.</b>	
Subtotal (95% CI)		0. 0.000	100.0%	0.79 [0.71, 0.88]		•	
Heterogeneity: Tau <sup>2</sup> = 0.0	J1; Chi <sup>2</sup> = 11.41, d	f=3(P=	0.010); P	*= 74%			
i est for overall effect: Z =	: 4.29 (P < 0.0001)	)					
					0.1 0.2	0.5 1 2 5	10

### eTable 1. Sensitivity Analyses

Cancer	# estimates	Converted RRs	DATA AS REPORTED IN THE ORIGINAL PUBLICATION**					
		[95% CI]*	# estimates	Reported OR [95% CI]	# estimates	Reported IRRs [95% Cl]	# estimates	Reported HRs [95% CI]
Bladder	3 (Chuang 2017 females, Chuang 2017 males, Mackenkie 2017)	0.89 [0.71, 1.07]	2 (Chuang 2017 females, Chuang 2017 males)	0.92 [0.72, 1.16]	1 (Mackenzie 2017)	0.81 [0.68, 0.96]	-	
Breast	3 (Biggar 2013, Mackenzie 2017, Sabatier 2019)	1.04 [0.86, 1.22]	1 (Sabatier 2019)	0.75 [0.58, 0.97]	2 (Biggar 2013, Mackenzie 2017)	1.15 [1.05, 1.26]	-	
Gastric	2 (Busby 2017, Mackenzie 2017)	1.02 [0.80, 1.24]	1 (Busby 2017)	1.18 [0.63, 2.21]	1 (Mackenzie 2017)	1.00 [0.79, 1.26]	-	
Kidney	(Chuang 2017 females, Chuang 2017 males, Mackenkie 2017)	0.96 [0.85, 1.07]	2 (Chuang 2017 females, Chuang 2017 males)	0.93 [0.86, 1.01]	1 (Mackenzie 2017)	1.27 [0.89, 1.81]	-	
Esophageal	2 (Busby 2017, Mackenzie 2017)	1.09 [0.91, 1.27]	1 (Busby 2017)	1.27 [0.84, 1.92]	1 (Mackenzie 2017)	1.06 [0.86, 1.30]	-	
Ovary	2 (Biggar 2013, Mackenzie 2017)	1.52 [0.84, 2.20]	-	-	1 (Biggar 2013)	2.12 [1.86, 2.42]	1 (Mackenzie 2017)	1.28 [0.90, 1.82]
Prostate	4 (Beckmann 2019, Chuang 2017 males, Hiebert 2020, Mackenzie 2017)	0.79 [0.68, 0.90]	2 (Beckmann 2019, Chuang 2017 males)	0.81 [0.70, 0.95]	2 (Hiebert 2020, Mackenzie 2017)	0.71 [0.55, 0.91]	2 (Hiebert 2020, Mackenzie 2017)	0.77 [0.53, 1.13]

Boldtype font indicates statistical significance p≤0.05.

\*Converted RRs refers to the use of previously published formulas to convert ORs or HRs into RRs.<sup>17-19</sup> [RR = OR / (1 - p + (p \* OR); and RR=(1- $e^{HR \ln(1-r)})/r$ ]

\*\*Data reported in the original publication without any imputations.

Cancer	Determinant (#	RR [95% CI]	P-value	
	studies)			
Bladder	Female (1)	0.81 [0.73, 0.91]	0.001	
	Male (1)	1.03 [0.95, 1.11]		
Prostate	Heart failure (1)	0.63 [0.42, 0.95]	0.04	
	Hypertension (1)	0.88 [0.83, 0.95]	7	
	Any (2)	0.76 [0.71, 0.81]	7	

## eTable 2. Subgroup Analysis to Explore Heterogeneity (only analyses with I2>50%)