



Appendix

**This appendix was part of the submitted manuscript and has been peer reviewed.
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Appendix to: Ng HS, Koczwara B, Roder DM, et al. Comorbidities in Australian women with hormone-dependent breast cancer: a population-based analysis. *Med J Aust* 2018; 208: 24-28. doi: 10.5694/mja17.00006.

Table 1 Rx-Risk-V medicine groups included in our study

Rx-Risk-V class	Medication classes/ medications	ATC codes/ PBS codes
Alcohol dependence	Disulfiram, naltrexone	N07BB03-N07BB04, V03AA01, N07BB01
Anticoagulation	Anticoagulants	B01AA03-B01AB06, B01AB09, B01AE06, B01AE07, B01AF01, B01AF02, B01AX05
Antiplatelet agents	Antiplatelet	B01AC04-B01AC30
Anxiety and tension	Anxiolytics	N05BA01-N05BA12, N05BE01
Arrhythmias	Antiarrhythmics, digoxin	C01AA05, C01BA01-C01BD01, C07AA07
Bipolar disorders	Lithium	N05AN01
Heart failure (CHF)-hypertension	Loop diuretics AND, Angiotensin converting enzyme (ACE) inhibitors or Angiotensin receptor blockers (ARB); Beta blockers selective for heart failure; Aldosterone antagonists specific for heart failure	C03CA01-C03CC01, C09AA01-C09AX99, C09CA01-C09CX99, C03DA04, C07AB07, C07AG02, C07AB12, C01EB17
Dementia	Anticholinesterases or other dementia medicines	N06DA02-N06DA04, N06DX01
Depression	Antidepressants	N06AA01-N06AG02, N06AX03-N06AX11, N06AX13-N06AX18, N06AX21-N06AX23 (excluding amitriptyline)
Diabetes	Insulins, oral hypoglycaemics	A10AA01-A10BH05, A10BX04, A10BX09, A10BX12, A10BH51
End stage renal disease	Erythropoietin, calciferol, calcitriol, sevelamer, sucroferric oxyhydroxide	B03XA01-B03XA03, A11CC01-A11CC04, V03AE02, V03AE03, V03AE05
Epilepsy	Anticonvulsants	N03AA01-N03AX15, N03AX18, N03AX22
Gastric acid disorder	H2-antagonist, proton pump inhibitors	A02BA01-A02BX05
Glaucoma	Topical anti-glaucoma agents	S01EA01-S01EB03, S01EC03-S01EX99
Gout	Antigout agents	M04AA01-M04AC01
Hepatitis B	Anti-virals for hepatitis B	J05AF08, J05AF10, J05AF11
Hepatitis C	Interferon/ribavirin combinations, protease inhibitors for hepatitis	J05AB54, J05AE11-J05AE12, L03AB10, L03AB11, L03AB60, L03AB61, J05AE14, J05AX14-J04AX15, J05AX65, J05AB04
HIV	Anti-retrovirals	J05AG05, J05AX12, J05AE01-J05AE10, J05AF01-J05AG04, J05AR01-J05AR99, J05AX07-J05AX09 (excluding ATC codes for hepatitis B)
Hyperkalaemia	Sodium polystyrene sulfonate	V03AE01
Hyperlipidaemia	Anti-lipaemic agents	C10AA01-C10BX09
Hypertension	Thiazides, potassium-sparing agents, combination anti-hypertensives, other antihypertensives	C03AA01-C03BA11, C03DB01-C03DB99, C03EA01, C09BA02-C09BA09, C09DA02-C09DA08, C02AB01-C02AC05, C02DB02-C02KX02, C02KX04, C02CA01
Hyperthyroidism/ hypothyroidism	Thyroid replacements	H03AA01-H03AA02, H03BA02, H03BB01
Ischaemic heart disease (IHD)-Angina	Nitrates	C01DA02-C01DA14, C01DX16, C08EX02

IHD-Hypertension	Beta-blockers, calcium channel blockers	C07AA01-C07AA06, C07AA8-C07AB01, C07AG01, C08CA01-C08DB01, C09DB01-C09DB04, C09DX01, C09BB02-C09BB10, C10BX03, C07AB03, C09DX03 Metoprolol requires testing according to PBS item code for indication
Inflammatory bowel syndrome (IBS)	IBS specific drugs, rectal anti-inflammatories	A07EC01-A07EC04, A07EA01-A07EA02, A07EA06, L04AA33
Malignancies	Antineoplastics agents (excluding topical)	L01AA01-L01XX41
Malnutrition	Enteral nutritional supplements	B05BA01-B05BA10
Migraine	Antimigraine medications	N02CA01-N02CX01
Osteoporosis/ Paget's	Bisphosphonates, selected drugs affecting bones	M05BA01-M05BB05, M05BX03, M05BX04, G03XC01, H05AA02 (excluding PBS item code for hypercalcemia/ multiple myeloma)
Pain	Opiate containing medications	N02AA01-N02AX02, N02AX06, N02AX52, N02BE51
Pain-inflammation	Nonsteroidal anti-inflammatory drugs (NSAIDS)	M01AB01-M01AH06
Pancreatic insufficiency	Pancreatic exocrine enzyme replacement	A09AA02
Parkinson's disease	Antiparkinson agents	N04AA01-N04BX02
Psoriasis	Systemic and topical antipsoriatics	D05AA01-D05AA99, D05BB01-D05BB02, D05AX02, D05AC01-D05AC51, D05AX52
Psychotic illness	Antipsychotics	N05AA1-N05AB02, N05AB06-N05AL07, N05AX07-N05AX13
Reactive airways diseases	Inhaled bronchodilators	R03AC02-R03DC03, R03DX05
Smoking cessation	Nicotine, bupropion, varenicline	N07BA01-N07BA03, N06AX12
Steroid-responsive conditions	Glucocorticoids	H02AB01-H02AB10
Transplant	Immune suppressants	L04AA06, L04AA10, L04AA18, L04AD01, L04AD02
Tuberculosis	Anti-tubercular agents	J04AC01-J04AC51, J04AM01-J04AM99

Table 2 Baseline characteristics for women with hormone-dependent breast cancer and without cancer for each type of comorbidity under evaluation

Characteristics	Cancer group	Control group (age- and sex- matched at 1:10 ratio)
(1) Cardiovascular		
Age at index date†		
<35 years	28 (2%)	280 (2%)
35–44 years	112 (7%)	1120 (7%)
45–54 years	237 (16%)	2370 (16%)
55–64 years	419 (28%)	4190 (28%)
≥ 65 years	726 (48%)	7260 (48%)
Subtotal	1522	15220
Number of baseline comorbidities‡		
None	290 (19%)	2543 (17%)
1–2	720 (47%)	7805 (51%)
3–4	382 (25%)	3659 (24%)
5–7	120 (8%)	1151 (8%)
≥8	10 (1%)	62 (<1%)
Subtotal	1522	15220
Median follow up (Q1, Q3)	3.4 (1.5, 5.6)	4.0 (2.2, 6.0)
(2) Depression		
Age at index date†		
<35 years	25 (1%)	250 (1%)
35–44 years	92 (3%)	920 (3%)
45–54 years	235 (7%)	2350 (7%)
55–64 years	712 (21%)	7120 (21%)
≥ 65 years	2280 (68%)	22800 (68%)
Subtotal	3344	33440
Number of baseline comorbidities‡		
None	290 (9%)	2519 (8%)
1–2	1003 (30%)	10919 (33%)
3–4	958 (29%)	10174 (30%)
5–7	858 (26%)	7843 (23%)
≥8	235 (7%)	1985 (6%)
Subtotal	3344	33440
Median follow up (Q1, Q3)	4.3 (2.4, 6.8)	5.0 (3.0, 7.0)
(3) Diabetes		
Age at index date†		
<35 years	30 (1%)	300 (1%)
35–44 years	120 (3%)	1200 (3%)
45–54 years	328 (9%)	3280 (9%)
55–64 years	828 (22%)	8280 (22%)
≥ 65 years	2493 (66%)	24930 (66%)
Subtotal	3799	37990
Number of baseline comorbidities‡		
None	290 (8%)	2552 (7%)
1–2	1082 (28%)	12100 (32%)
3–4	1107 (29%)	11558 (30%)
5–7	1005 (26%)	9152 (24%)
≥8	315 (8%)	2628 (7%)
Subtotal	3799	37990
Median follow up (Q1, Q3)	5.1 (3.3, 7.3)	5.3 (3.6, 8.0)
(4) Gastric acid disorders		
Age at index date†		
<35 years	24 (1%)	240 (1%)
35–44 years	100 (4%)	1000 (4%)
45–54 years	244 (10%)	2440 (10%)
55–64 years	560 (22%)	5600 (22%)
≥ 65 years	1615 (63%)	16150 (63%)

Subtotal	2543	25430
Number of baseline comorbidities‡		
None	290 (11%)	2358 (9%)
1–2	895 (35%)	9598 (38%)
3–4	726 (29%)	7852 (31%)
5–7	535 (21%)	4832 (19%)
≥8	97 (4%)	790 (3%)
Subtotal	2543	25430
Median follow up (Q1, Q3)	3.8 (1.9, 6.3)	4.0 (2.4, 6.5)
(5) Hyperlipidaemia		
Age at index date†		
<35 years	31 (1%)	310 (1%)
35–44 years	124 (4%)	1240 (4%)
45–54 years	304 (11%)	3040 (11%)
55–64 years	627 (23%)	6270 (23%)
≥ 65 years	1671 (61%)	16710 (61%)
Subtotal	2757	27570
Number of baseline comorbidities‡		
None	290 (11%)	2767 (10%)
1–2	957 (35%)	10974 (40%)
3–4	819 (30%)	8043 (29%)
5–7	553 (20%)	4832 (18%)
≥8	138 (5%)	954 (3%)
Subtotal	2757	27570
Median follow up (Q1, Q3)	4.3 (2.5, 6.6)	4.4 (2.9, 7.0)
(6) Osteoporosis		
Age at index date†		
<35 years	32 (1%)	320 (1%)
35–44 years	125 (3%)	1250 (3%)
45–54 years	347 (9%)	3470 (9%)
55–64 years	870 (23%)	8700 (23%)
≥ 65 years	2491 (64%)	24910 (64%)
Subtotal	3865	38650
Number of baseline comorbidities‡		
None	290 (8%)	2612 (7%)
1–2	1056 (27%)	11904 (31%)
3–4	1113 (29%)	11536 (30%)
5–7	1047 (27%)	9650 (25%)
≥8	359 (9%)	2948 (8%)
Subtotal	3865	38650
Median follow up (Q1, Q3)	4.7 (3.1, 7.2)	5.0 (3.1, 7.4)
(7) Reactive airway diseases		
Age at index date†		
<35 years	31 (1%)	310 (1%)
35–44 years	111 (3%)	1110 (3%)
45–54 years	301 (9%)	3010 (9%)
55–64 years	732 (21%)	7320 (21%)
≥ 65 years	2286 (66%)	22860 (66%)
Subtotal	3461	34610
Number of baseline comorbidities‡		
None	290 (8%)	2703 (8%)
1–2	1024 (30%)	11179 (32%)
3–4	1007 (29%)	10638 (31%)
5–7	889 (26%)	8129 (23%)
≥8	251 (7%)	1961 (6%)
Subtotal	3461	34610
Median follow up (Q1, Q3)	4.3 (2.4, 6.6)	4.8 (3.0, 7.0)
(8) Pain/ pain-inflammation		
Age at index date†		
<35 years	20 (1%)	200 (1%)

35–44 years	54 (3%)	540 (3%)
45–54 years	169 (8%)	1690 (8%)
55–64 years	443 (21%)	4430 (21%)
≥ 65 years	1399 (67%)	13990 (67%)
Subtotal	2085	20850
Number of baseline comorbidities‡		
None	290 (14%)	2166 (10%)
1–2	759 (36%)	7550 (36%)
3–4	560 (27%)	6242 (30%)
5–7	399 (19%)	4139 (20%)
≥8	77 (4%)	753 (4%)
Subtotal	2085	20850
Median follow up (Q1, Q3)	2.4 (0.9, 4.4)	3.0 (1.3, 5.0)

†The year of age where first endocrine therapy was initiated for the cancer cohort; the year of age where index date was assigned to the control group matching with the year of endocrine therapy initiation of the corresponding case; ‡Number of baseline comorbidities up to one year prior to the index date, excluding cancer in the count; both cancer and control group without the individual comorbidity of interest up to one year prior to the assigned index date.

Table 3 Incidence rates for each type of comorbidities in women with hormone-dependent breast cancer and women without cancer

	Cancer group	Control group
Cardiovascular		
No. of cases	768	7033
Person-years	5821	64611
IR	13.19 (12.29–14.16)	10.89 (10.63–11.14)
Depression		
No. of cases	863	7013
Person-years	15534	170898
IR	5.56 (5.20–5.94)	4.10 (4.01–4.20)
Diabetes		
No. of cases	296	2485
Person-years	20241	212924
IR	1.46 (1.30–1.64)	1.17 (1.12–1.21)
Gastric acid disorders		
No. of cases	1157	10093
Person-years	10765	113897
IR	10.75 (10.15–11.39)	8.86 (8.69–9.04)
Hyperlipidaemia		
No. of cases	662	7318
Person-years	12893	132070
IR	5.13 (4.76–5.54)	5.54 (5.42–5.67)
Osteoporosis		
No. of cases	589	5029
Person-years	19412	208560
IR	3.03 (2.80–3.29)	2.41 (2.35–2.48)
Reactive airway diseases		
No. of cases	936	9176
Person-years	15915	169108
IR	5.88 (5.52–6.27)	5.43 (5.32–5.54)
Pain/ pain-inflammation		
No. of cases	1466	12901
Person-years	6336	71925
IR	23.14 (21.98–24.35)	17.94 (17.63–18.25)

IR= Incidence rates, per 100-person years (95% Confidence Interval)