

Supplemental Materials

Supplemental Table 1. Read codes used to identify biliary tract cancers in CPRD

Cancer site	medcode	readcode	readterm
Gallbladder cancer			
	16105	B160.00	Malignant neoplasm of gallbladder
	31393	B160.11	Carcinoma gallbladder
	46594	B808300	Carcinoma in situ of gall bladder
Cholangiocarcinoma			
	8711	BB5D100	[M]Cholangiocarcinoma
	40438	BB5D111	[M]Bile duct carcinoma
	41313	BB5D300	[M]Bile duct cystadenocarcinoma
	110775	B151100	Malignant neoplasm of interlobular biliary canals
	89593	B151200	Malignant neoplasm of intrahepatic biliary passages
	16915	B151.00	Malignant neoplasm of intrahepatic bile ducts
	61643	B151z00	Malignant neoplasm of intrahepatic bile ducts NOS
	99580	B808100	Carcinoma in situ of intrahepatic bile ducts
	58088	B151400	Malignant neoplasm of intrahepatic gall duct
	65124	B151000	Malignant neoplasm of interlobular bile ducts
	23433	B161.00	Malignant neoplasm of extrahepatic bile ducts
	74896	B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
	36495	B161211	Carcinoma common bile duct
	7982	B161200	Malignant neoplasm of common bile duct
	52537	B161100	Malignant neoplasm of hepatic duct
	37501	B808200	Carcinoma in situ of hepatic duct
	64089	B808500	Carcinoma in situ of common bile duct
	72445	B161000	Malignant neoplasm of cystic duct
Ampulla of Vater cancer			
	10949	B162.00	Malignant neoplasm of ampulla of Vater
	21792	B808600	Carcinoma in situ of ampulla of Vater
	105613	B161300	Malignant neoplasm of sphincter of Oddi
Mixed			
	54103	B16.00	Malignant neoplasm gallbladder and extrahepatic bile ducts
	15907	B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
	60312	B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
	38978	B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
	8918	B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
	35039	B163.00	Malignant neoplasm, overlapping lesion of biliary tract
	54103	B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
	70516	BB5D.11	[M]Biliary tract adenomas and adenocarcinomas
	107299	BB5D700	[M]Combined hepatocellular carcinoma and cholangiocarcinoma
	110147	BB5D711	[M]Hepatocholangiocarcinoma
	36031	BB5D.00	[M]Hepatobiliary tract adenomas and carcinomas
	66673	B808.00	Carcinoma in situ of liver and biliary system
	51934	B808.11	Carcinoma in situ of biliary system
	98540	B808z00	Carcinoma in situ of liver or biliary system NOS

Supplemental Table 2. Read codes used to identify history of gallbladder disease and cholecystectomy in CPRD

Diagnosis	medcode	readcode	readterm
Gallbladder disease			
	29663	J503000	Gallstone ileus
	42278	J671100	Gallstone chronic pancreatitis
	17901	1J5..00	Suspected gallstones
	109379	8CMWD00	On gallstone care pathway
	12316	J670500	Gallstone acute pancreatitis
	760	J64..15	Gallstones
	17959	7648700	Enterotomy and removal of gallstone
	45836	4G22.00	O/E: pigment gall stone
	4429	4G2..00	O/E: gall stone
	42694	4G2Z.00	O/E: gall stone NOS
	61996	4G21.00	O/E: cholesterol gall stone
	12140	14CE.00	H/O: gall stones
	94302	4775	Faeces: gall stones present
	47888	J64z000	Cholelithiasis without obstruction NOS
	34063	J64zz00	Cholelithiasis NOS
	62988	J64z100	Cholelithiasis with obstruction NOS
	96795	Jyu8000	[X]Other cholelithiasis
	27437	J64z.00	Cholelithiasis NOS
	3599	J64..00	Cholelithiasis
	17323	J64..16	Stone - biliary
	40075	J64..12	Calculus - biliary
Cholecystectomy			
	2968	7810511	Laparoscopic cholecystectomy
	26137	J66y700	Post cholecystectomy bile leakage
	49318	7810300	Partial cholecystectomy and exploration of common bile duct
	61185	7810000	Total cholecystectomy and excision of surrounding tissue
	49604	7810100	Total cholecystectomy and exploration of common bile duct
	73258	J660.00	Postcholecystectomy syndrome
	100084	14ND.00	History of cholecystectomy
	9574	7810211	Cholecystectomy NEC
	214	7810.11	Cholecystectomy
	7879	7810500	Endoscopic cholecystectomy
	8291	7810200	Total cholecystectomy NEC

Supplemental Table 3. ICD-10 codes used to identify gallbladder disease in the NHS Hospital Episode Statistics Admitted Patient Care data link¹

ICD-10	Description
K80.0	Calculus of gallbladder with acute cholecystitis
K80.1	Calculus of gallbladder with other cholecystitis
K80.2	Calculus of gallbladder without cholecystitis
K80.3	Calculus of bile duct with cholangitis
K80.4	Calculus of bile duct with cholecystitis
K80.5	Calculus of bile duct without cholangitis or cholecystitis
K80.6	Calculus of gallbladder and bile duct with cholecystitis
K80.7	Calculus of gallbladder and bile duct without cholecystitis
K80.8	Other cholelithiasis
K81.0	Acute cholecystitis
K81.1	Chronic cholecystitis
K81.2	Acute cholecystitis with chronic cholecystitis
K81.9	Cholecystitis, unspecified

Abbreviations: ICD-10, International Classification of Diseases, Tenth Revision; and NHS, National Health Service

¹Only patients from practices in England were eligible for linkage.

Supplemental Table 4. OPCS-4 codes used to identify cholecystectomy in the NHS Hospital Episode Statistics Admitted Patient Care data link¹

OPCS Code	Description
J181	Total cholecystectomy and excision of surrounding tissue
J182	Total cholecystectomy and exploration of common bile duct
J183	Total cholecystectomy NEC

Abbreviations: NEC, not elsewhere classified; NHS, National Health Service; and OPCS-4, Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision)

^aOnly patients from practices in England were eligible for linkage.

Supplemental Table 5. Odds ratios for the association between menopausal hormone therapy use and odds of gallbladder cancer by hysterectomy/oophorectomy status

Variable	Women <u>with</u> a history of hysterectomy or oophorectomy			Women <u>without</u> a history of hysterectomy or oophorectomy		
	Cases n = 86 (%)	Controls n = 380 (%)	OR (95% CI)	Cases n = 397 (%)	Controls n = 1,850 (%)	OR (95% CI)
Ever MHT use^a						
No use	51 (59)	226 (60)	1.00 (Reference)	332 (84)	1,550 (84)	1.00 (Reference)
Ever	35 (41)	154 (40)	1.47 (0.21, 10.62)	65 (16)	300 (16)	1.84 (0.92, 3.66)
MHT formulation^a						
No use	51 (59)	226 (60)	1.00 (Reference)	332 (84)	1,550 (84)	1.00 (Reference)
Estrogen only	25 (29)	99 (26)	1.89 (0.33, 10.86)	7 (2)	43 (2)	1.00 (0.39, 2.55)
Estrogen and progesterone	10 (12)	53 (14)	0.63 (0.08, 5.02)	57 (14)	251 (14)	1.67 (0.83, 3.36)
Progesterone only	0 (0)	2 (0)	--	1 (0)	6 (0)	1.18 (0.12, 11.45)
MHT administration^{a,b}						
No use	51 (59)	226 (60)	1.00 (Reference)	332 (84)	1,550 (84)	1.00 (Reference)
Pill	28 (32)	112 (29)	1.42 (0.33, 6.11)	58 (14)	258 (14)	1.51 (0.77, 2.92)
Patch	13 (15)	65 (17)	1.63 (0.44, 6.03)	7 (2)	36 (2)	1.10 (0.44, 2.75)
Other ^c	5 (9)	31 (8)	0.91 (0.20, 4.09)	5 (1)	39 (2)	0.67 (0.25, 1.84)
MHT dose^a						
No use	51 (59)	226 (60)	1.00 (Reference)	332 (84)	1,550 (84)	1.00 (Reference)
Pill low dose	24 (30)	83 (24)	1.00 (0.09, 11.73)	42 (11)	179 (10)	1.47 (0.69, 3.13)
Pill high dose	3 (4)	29 (8)	0.10 (0.00, 2.31)	8 (2)	73 (4)	0.67 (0.26, 1.79)
Patch low dose	9 (14)	47 (16)	0.14 (0.00, 10.21)	7 (2)	26 (2)	1.03 (0.26, 4.10)
Patch high dose	1 (2)	11 (4)	0.15 (0.00, 61.92)	1 (0)	5 (0)	0.54 (0.04, 7.84)
Number of prescriptions^d						
No use (0–1 prescriptions)	51 (59)	226 (60)	1.00 (Reference)	332 (84)	1,550 (84)	1.00 (Reference)
2–9 prescriptions	17 (20)	69 (18)	1.44 (0.17, 11.90)	42 (10)	160 (8)	1.31 (0.32, 5.31)
≥10 prescriptions	18 (21)	85 (22)	0.88 (0.06, 12.14)	23 (6)	140 (7)	0.66 (0.14, 3.18)
<i>P</i> –trend ^e			0.80			0.08

Duration of use^d						
No use (0–1 month)	51 (59)	226 (60)	1.00 (Reference)	332 (84)	1,550 (84)	1.00 (Reference)
>1–<24 months	14 (16)	46 (12)	1.18 (0.13, 10.83)	35 (9)	134 (7)	1.38 (0.34, 5.59)
24–<48 months	6 (7)	26 (7)	2.21 (0.14, 32.75)	11 (3)	55 (3)	0.89 (0.18, 4.41)
≥48 months	15 (18)	82 (21)	0.90 (0.15, 13.49)	19 (5)	111 (6)	0.83 (0.17, 4.09)
<i>P</i> –trend ^e			0.84			0.20
Time since last use^d						
No use	51 (59)	226 (60)	1.00 (Reference)	332 (84)	1,550 (84)	1.00 (Reference)
>1–<24 months	2 (2)	45 (12)	0.16 (0.01, 8.31)	13 (3)	70 (4)	0.77 (0.15, 3.86)
24–<36 months	5 (6)	18 (5)	3.91 (0.16, 94.83)	5 (1)	40 (2)	0.65 (0.11, 3.78)
36–<84 months	9 (10)	34 (9)	0.52 (0.03, 7.93)	13 (3)	54 (3)	1.34 (0.30, 6.10)
≥84 months	19 (22)	57 (15)	1.16 (0.13, 10.47)	34 (9)	136 (7)	1.38 (0.33, 5.71)
<i>P</i> –trend ^e			0.48			0.12

Controls were individually matched to cases on year of birth, index year, and number of years in the general practice and in the CPRD prior to diagnosis/selection date.

All models were analyzed with conditional logistic regression.

^aModel adjusted for age at index date, index year, duration of MHT use, BMI, diabetes, gallstones, hysterectomy, and oophorectomy.

^bCells do not add up to the total as women could have taken more than one type of MHT.

^cOther includes cream, nasal spray, implant, ring, or suppository.

^dModel adjusted for age at index date, index year, MHT administration, BMI, diabetes, gallstones, hysterectomy, and oophorectomy.

^eThe Wald test was used to test for a linear trend across categories of exposure and biliary tract cancer site.

Supplemental Table 6. Odds ratios for the association between menopausal hormone therapy use and odds of cholangiocarcinoma by hysterectomy/oophorectomy status

Variable	Women <u>with</u> a history of hysterectomy or oophorectomy			Women <u>without</u> a history of hysterectomy or oophorectomy		
	Cases n = 175 (%)	Controls n = 774 (%)	OR (95% CI)	Cases n = 695 (%)	Controls n = 3,586 (%)	OR (95% CI)
Ever MHT use^a						
No use	120 (69)	457 (59)	1.00 (Reference)	574 (83)	2,968 (83)	1.00 (Reference)
Ever	55 (31)	317 (41)	0.43 (0.11, 1.64)	121 (17)	618 (17)	0.86 (0.52, 1.44)
MHT formulation^a						
No use	120 (69)	457 (59)	1.00 (Reference)	574 (83)	2,968 (83)	1.00 (Reference)
Estrogen only	34 (19)	217 (28)	0.40 (0.10, 1.61)	12 (2)	93 (3)	0.61 (0.30, 1.24)
Estrogen and progesterone	19 (11)	95 (12)	0.40 (0.09, 1.77)	108 (15)	511 (14)	1.07 (0.62, 1.85)
Progesterone only	2 (1)	5 (1)	1.18 (0.05, 29.70)	1 (0)	14 (0)	0.33 (0.04, 2.72)
MHT administration^{a,b}						
No use	120 (69)	457 (59)	1.00 (Reference)	574 (83)	2,968 (83)	1.00 (Reference)
Pill	40 (23)	220 (28)	0.76 (0.27, 2.15)	107 (15)	530 (15)	0.93 (0.56, 1.56)
Patch	28 (16)	130 (17)	0.95 (0.36, 2.55)	12 (2)	71 (2)	0.71 (0.36, 1.40)
Other ^c	5 (3)	53 (7)	0.43 (0.13, 1.48)	13 (2)	99 (3)	0.61 (0.32, 1.14)
MHT dose^a						
No use	120 (69)	457 (59)	1.00 (Reference)	332 (84)	1,550 (84)	1.00 (Reference)
Pill low dose	26 (16)	155 (23)	0.24 (0.05, 1.27)	69 (10)	384 (11)	0.67 (0.38, 1.17)
Pill high dose	12 (7)	70 (10)	0.18 (0.02, 1.60)	26 (4)	125 (4)	0.67 (0.34, 1.30)
Patch low dose	20 (13)	105 (18)	0.69 (0.25, 1.90)	9 (1)	59 (2)	0.49 (0.16, 1.52)
Patch high dose	6 (4)	16 (3)	0.77 (0.15, 3.88)	1 (0)	3 (0)	0.65 (0.05, 8.77)
Number of prescriptions^d						
No use (0–1 prescriptions)	120 (69)	457 (59)	1.00 (Reference)	574 (83)	2,968 (83)	1.00 (Reference)
2–9 prescriptions	19 (11)	124 (16)	0.48 (0.21, 1.12)	62 (9)	319 (9)	0.99 (0.72, 1.35)
≥10 prescriptions	36 (20)	193 (25)	0.63 (0.30, 1.29)	59 (8)	299 (8)	0.97 (0.69, 1.35)
<i>P</i> –trend ^e			0.12			0.84
Duration of use^d						

No use (0–1 month)	120 (69)	457 (59)	1.00 (Reference)	574 (83)	2,968 (83)	1.00 (Reference)
>1–<24 months	12 (7)	84 (11)	0.61 (0.24, 1.53)	48 (7)	265 (7)	0.91 (0.64, 1.28)
24–<48 months	11 (6)	56 (7)	0.29 (0.09, 0.91)	19 (3)	97 (3)	1.06 (0.62, 1.80)
≥48 months	32 (18)	177 (23)	0.73 (0.33, 1.60)	54 (8)	256 (7)	1.03 (0.73, 1.47)
<i>P</i> –trend ^e			0.16			0.91
Time since last use^d						
No use	120 (69)	457 (59)	1.00 (Reference)	574 (83)	2,968 (83)	1.00 (Reference)
>1–<24 months	15 (8)	87 (11)	0.46 (0.08, 2.57)	27 (4)	136 (4)	1.60 (0.59, 4.38)
24–<36 months	6 (3)	45 (6)	0.68 (0.09, 4.89)	17 (2)	99 (3)	1.28 (0.45, 3.64)
36–<84 months	15 (9)	76 (10)	0.69 (0.13, 3.60)	24 (3)	144 (3)	1.22 (0.44, 3.34)
≥84 months	19 (11)	108 (14)	0.46 (0.09, 2.25)	53 (8)	239 (7)	1.56 (0.61, 4.00)
<i>P</i> –trend ^e			0.65			0.66

Controls were individually matched to cases on year of birth, index year, and number of years in the general practice and in the CPRD prior to diagnosis/selection date.

All models were analyzed with conditional logistic regression.

^aModel adjusted for age at index date, index year, duration of MHT use, BMI, diabetes, smoking status, alcohol use, hysterectomy, oophorectomy, aspirin use, and statin use.

^bCells do not add up to the total as women could have taken more than one type of MHT.

^cOther includes cream, nasal spray, implant, ring, or suppository.

^dModel adjusted for age at index date, index year, MHT administration, BMI, diabetes, smoking status, alcohol use, hysterectomy, oophorectomy, aspirin use, and statin use.

^eThe Wald test was used to test for a linear trend across categories of exposure and biliary tract cancer site.

Supplemental Table 7. Odds ratios for the association between menopausal hormone therapy use and odds gallbladder cancers among CPRD patients eligible for linkage to NHS Hospital Episode Statistics Admitted Patient Care data link^a

	Gallbladder Cancer – adjusted for gallbladder disease			Gallbladder Cancer – excluding gallbladder disease		
	Cases n = 262 (%)	Controls n = 1,184 (%)	OR (95% CI)	Cases n = 124 (%)	Controls n = 1,114 (%)	OR (95% CI)
Ever MHT use^b						
Never	209 (80)	919 (78)	1.00 (Reference)	105 (85)	862 (77)	1.00 (Reference)
Ever	53 (20)	265 (22)	2.22 (0.89, 5.54)	19 (15)	252 (23)	2.31 (0.68, 7.87)
MHT formulation^b						
Non-use	209 (80)	919 (78)	1.00 (Reference)	105 (85)	862 (77)	1.00 (Reference)
Estrogen only	18 (7)	81 (7)	2.19 (0.75, 6.46)	5 (4)	74 (7)	2.14 (0.51, 8.89)
Estrogen and progesterone	34 (13)	178 (15)	2.39 (0.91, 6.29)	14 (11)	173 (15)	2.66 (0.70, 10.07)
Progesterone only	1 (0)	6 (0.5)	0.79 (0.05, 13.04)	0 (0)	5 (1)	--
MHT administration^{b,c}						
None	209 (80)	919 (78)	1.00 (Reference)	105 (85)	862 (77)	1.00 (Reference)
Pill	45 (17)	217 (18)	1.96 (0.85, 4.52)	16 (13)	207 (19)	2.17 (0.65, 7.29)
Patch	12 (4)	61 (5)	1.28 (0.39, 4.19)	2 (2)	57 (5)	0.66 (0.12, 3.50)
Other ^d	10 (4)	45 (4)	1.05 (0.35, 3.09)	4 (3)	41 (6)	1.79 (0.54, 5.98)
MHT dose						
No use	209 (80)	919 (78)	1.00 (Reference)	105 (85)	862 (77)	1.00 (Reference)
Pill low dose	36 (14)	164 (14)	1.44 (0.55, 3.77)	12 (10)	157 (15)	1.37 (0.37, 5.07)
Pill high dose	4 (1)	62 (5)	0.45 (0.11, 1.88)	2 (2)	57 (5)	0.61 (0.10, 3.80)
Patch low dose	10 (4)	43 (4)	0.72 (0.13, 4.05)	3 (3)	42 (5)	0.58 (0.07, 4.80)
Patch high dose	1 (0)	10 (1)	0.12 (0.01, 2.74)	0 (0)	8 (1)	--
Number of MHT prescriptions^e						
Non-use (0 – 1 prescriptions)	209 (80)	919 (78)	1.00 (Reference)	105 (85)	862 (77)	1.00 (Reference)
2 – 9 prescriptions	30 (11)	117 (10)	0.85 (0.23, 3.12)	11 (9)	114 (10)	1.03 (0.47, 2.28)
≥10 prescriptions	23 (9)	148 (12)	0.43 (0.10, 1.83)	8 (6)	138 (12)	0.53 (0.23, 1.23)
<i>P</i> -Trend ^f			0.10			0.18
Duration of use^e						

None	209 (80)	919 (78)	1.00 (Reference)	105 (85)	862 (77)	1.00 (Reference)
>1 – <24 months	28 (11)	92 (8)	0.95 (0.26, 3.52)	12 (10)	89 (8)	0.64 (0.08, 5.37)
24 – <48 months	5 (2)	50 (4)	0.25 (0.04, 1.49)	1 (0)	50 (4)	0.05 (0.00, 1.37)
≥48 months	20 (7)	123 (10)	0.29 (0.06, 1.33)	6 (5)	113 (10)	0.18 (0.02, 2.11)
<i>P-Trend</i> ^f			0.08			0.07

Time since last use^e

No use	209 (80)	919 (78)	1.00 (Reference)	105 (85)	862 (77)	1.00 (Reference)
>1 – <36 months	13 (5)	105 (9)	0.38 (0.08, 1.68)	4 (3)	100 (9)	0.32 (0.03, 3.21)
≥36 months	40 (15)	160 (13)	0.87 (0.24, 3.18)	15 (12)	152 (14)	0.86 (0.11, 6.78)
<i>P-Trend</i> ^f			0.18			0.39

Controls were individually matched to cases on year of birth, diagnosis year, and number of years in the general practice and in the CPRD prior to diagnosis/selection date. All models were analyzed with conditional logistic regression and controls with a history of cholecystectomy were excluded.

^aOnly patients from practices in England were eligible for linkage.

^bModel adjusted for age at index date, index year, duration of MHT use, BMI, diabetes, gallbladder disease, hysterectomy, and oophorectomy.

^cCells do not add up to the total as women could have taken more than one type of MHT.

^dOther includes cream, nasal spray, implant, ring, or suppository.

^eModel adjusted for age at index date, index year, MHT administration, BMI, diabetes, gallstones, hysterectomy, and oophorectomy.

^fThe Wald test was used to test for a linear trend across categories of exposure and biliary tract cancer site.

Supplemental Table 8. E-values representing the needed minimum strength of associations of an unmeasured confounder with both the outcome and exposure to completely explain observed associations between MHT use and GBC and cholangiocarcinoma, respectively

	Gallbladder^a	Cholangiocarcinoma
Variable	E-value	E-value
Ever MHT use		
No use	Ref	Ref
Ever	2.96	1.96
MHT formulation		
No use	Ref	Ref
Estrogen only	2.58	2.78
Estrogen and progesterone	3.35	1.43
Progesterone only	4.44	2.35
MHT administration		
No use	Ref	Ref
Pill	3.08	1.25
Patch	1.21	1.25
Other	2.00	2.90
MHT dose		
No use	Ref	Ref
Pill low dose	1.59	1.85
Pill high dose	1.60	1.21
Patch low dose	1.32	1.81
Patch high dose	1.37	1.74
Number of prescriptions		
No use (0–1 prescriptions)	Ref	Ref
2–9 prescriptions	2.08	1.67
≥10 prescriptions	1.63	1.53
Duration of use		
No use (0–1 month)	Ref	Ref
>1–<24 months	2.06	1.81
24–<48 months	1.11	1.46
≥48 months	1.92	1.43
Time since last use		
No use	Ref	Ref
>1–<24 months	2.40	1.60
24–<36 months	1.24	1.92
36–<84 months	2.17	1.81
≥84 months	2.08	1.25
Among MHT users only		
Age at initiation		
<50 years	Ref	Ref

50–55 years	2.87	1.59
56–60 years	3.68	2.01
>60 years	2.32	2.50

Time since last use

>1–<24 months	Ref	Ref
24–<36 months	1.46	2.12
36–<84 months	1.56	2.04
≥84 months	2.17	1.21

^a Controls with history of cholecystectomy were excluded