

Supplementary Appendix

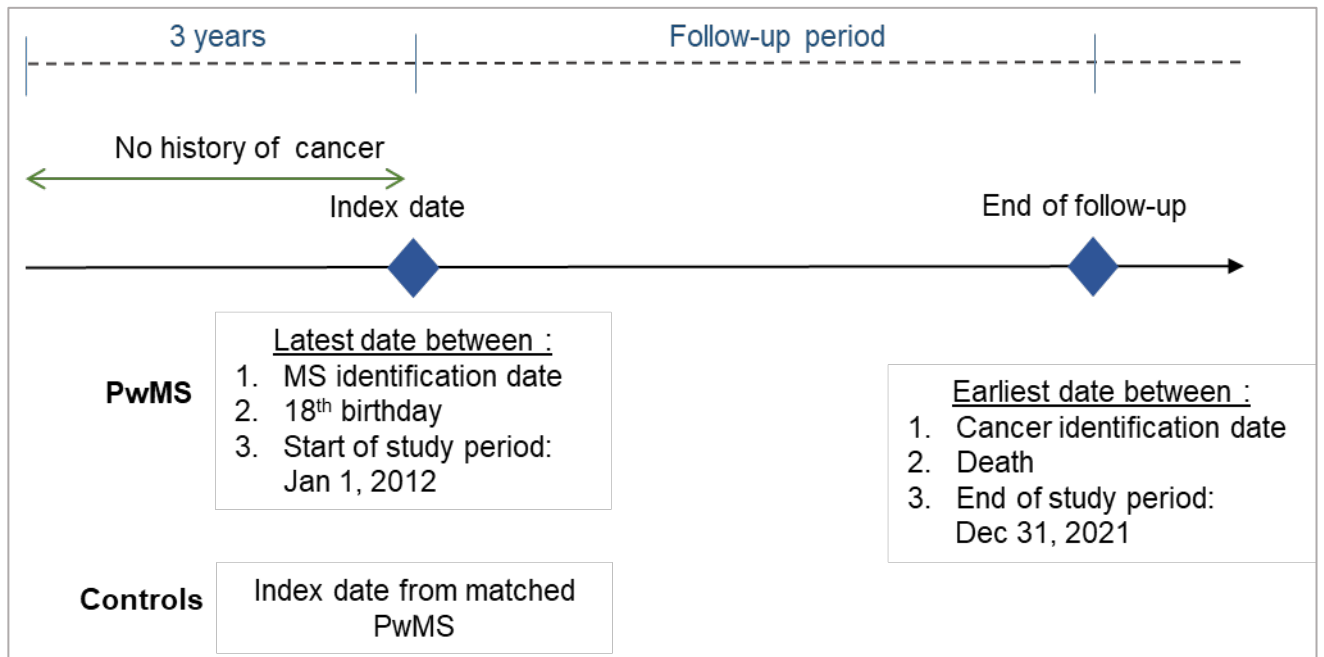
Supplementary data to C. Pierret, A. Mulliez, C. Le Bihan-Benjamin, X. Moisset, P.J. Bousquet, Emmanuelle Leray. Cancer risk among patients with multiple sclerosis: A 10-year nationwide retrospective cohort study submission to *Neurology*.

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eFigure 1: Study design

MS, multiple sclerosis; PwMS, Person with multiple sclerosis



eTable 1: Codes used for cancer identification

Category	Code	Type of code
LTD status	C* ; D0*	ICD-10
Hospitalisations	C* ; D0*	ICD-10
Chemotherapy - hospital	Z511	ICD-10
Radiotherapy - hospital	Z5101	ICD-10
Prostate cancer-specific drugs	L01CD04,L02BX03,L02BX02,L02BB01,L02BB02,L02BB03,L02BB04,L02AE01,L02AE02,L02AE03,L02AE04,G03HA01,L01XX1,L02AA01	ATC class
Radiotherapy - clinic	AANL001, AANL002, AZNL001, BHNL001, EDLL001, EDLL002, FENL001, JGNL001, JKNL001, JKNL002, JKNL003, JKNL004, JKNL005, JKNL006, JLNL001, JLNL002, JLNL003, JLNL004, JLNL005, JLNL006, JLNL007, JLNL008, KCNL003, KCNL004, PANL001, PBLL001, QZNL001, YYYYY016, YYYYY021, YYYYY023, YYYYY045, YYYYY046, YYYYY047, YYYYY048, YYYYY049, YYYYY050, YYYYY051, YYYYY052, YYYYY053, YYYYY054, YYYYY055, YYYYY056, YYYYY080, YYYYY081, YYYYY099, YYYYY101, YYYYY109, YYYYY122, YYYYY128, YYYYY136, YYYYY141, YYYYY151, YYYYY152, YYYYY166, YYYYY175, YYYYY197, YYYYY211, YYYYY223, YYYYY225, YYYYY244, YYYYY256, YYYYY267, YYYYY299, YYYYY301, YYYYY302, YYYYY303, YYYYY304, YYYYY305, YYYYY306, YYYYY307, YYYYY310, YYYYY312, YYYYY313, YYYYY314, YYYYY315, YYYYY316, YYYYY320, YYYYY323, YYYYY324, YYYYY325, YYYYY326, YYYYY327, YYYYY331, YYYYY334, YYYYY335, YYYYY336, YYYYY337, YYYYY338, YYYYY343, YYYYY345, YYYYY346, YYYYY347, YYYYY348, YYYYY349, YYYYY356, YYYYY357, YYYYY358, YYYYY359, YYYYY360, YYYYY365, YYYYY367, YYYYY368, YYYYY369, YYYYY370, YYYYY371, YYYYY377, YYYYY379, YYYYY380, YYYYY381, YYYYY382, YYYYY383, YYYYY387, YYYYY390, YYYYY391, YYYYY392, YYYYY393, YYYYY398, YYYYY450, YYYYY451, YYYYY457, YYYYY458, YYYYY459, YYYYY460, YYYYY468, YYYYY469, YYYYY470, YYYYY471, YYYYY479, YYYYY480, YYYYY481, YYYYY491, YYYYY492, YYYYY493, YYYYY497, YYYYY500, YYYYY511, YYYYY520, YYYYY522, YYYYY533, YYYYY544, YYYYY555, YYYYY566, YYYYY577, YYYYY588, YYYYY599, ZANL001, ZZML001, ZZML002, ZZML003, ZZMP003, ZZMP004, ZZMP015, ZZMP017, ZZNA002, ZZNL001, ZZNL002, ZZNL003, ZZNL004, ZZNL005, ZZNL006, ZZNL007, ZZNL008, ZZNL009, ZZNL010, ZZNL011, ZZNL012, ZZNL013, ZZNL014, ZZNL015, ZZNL016, ZZNL017, ZZNL018, ZZNL019, ZZNL020, ZZNL021, ZZNL022, ZZNL023, ZZNL024, ZZNL025, ZZNL026, ZZNL027, ZZNL028, ZZNL030, ZZNL031, ZZNL033, ZZNL034, ZZNL036, ZZNL037, ZZNL039, ZZNL040, ZZNL042, ZZNL043, ZZNL045, ZZNL046, ZZNL047, ZZNL048, ZZNL049, ZZNL050, ZZNL051, ZZNL052, ZZNL053, ZZNL054, ZZNL055, ZZNL058, ZZNL059, ZZNL060, ZZNL061, ZZNL062, ZZNL063, ZZNL064, ZZNL065, ZZNL066, ZZNL900, ZZNL902, ZZNL903, ZZNL904, ZZNL905, ZZNL906	CCAM code

ICD, International classification of diseases; LTD, Long-term disease; ATC, Anatomical Therapeutic Chemical Classification System; CCAM, *Classification commune des actes médicaux* (French national medical procedure codes)

eTable 2. Codes used for cancer type identification

Cancer type	ICD-10 code
Bladder	C67, C670-C679, D090
Brain and CNS	C70, C71, C72, C700, C701, C709, C710-C725, C728, C729, Z85800
Breast	C50, C501-C509, D05, D050, D051, D057, D059, Z853
Cervix	C53, C530, C531, C538, C539, D06, D060, D061, D067, D069
Colon-rectum	C18, C180-C189, C19, C20, C21, C210, C211, C212, C218, D010-D013, Z850
Kidney	C64, C65, C66
Lung	C33, C34, C340, C341, C342, C343, C348, C349, C3490, C3491, C3492, D021, D022, Z851
Prostate	C61, D075 OR any reimbursement of prostate cancer-specific drugs
Skin	C43, C430-C439, C460, D03, D030-D039, D04, D040-D049, Z85804, C443

ICD, International classification of diseases; CNS, Central Nervous system

eTable 3. Codes used for cancer screening identification

Cancer type	Population	Screening procedure	Code	Type of code
Breast	50 to 74-year-old women	Mammography	QEQK004 QEQK005 QEQK001	CCAM code
Cervix	25 to 65-year-old women	PAP smear	JKQP008 JKQP001 JKQX008 JKQX001 JKQX015 JKQX027 JKQX147 JKQX347 JKQX426 JKQX261	CCAM code
			0013 0026 0027 0028 0029 0030	Laboratory procedure code
		HPV test	ZZQX173 ZZQX628 ZZQX603	CCAM code
			4127 4509 0024 0031	Laboratory procedure code
Colon-rectum	50 to 75-year-old men and women	Occult blood in stool – home test (2015-2021)	9434	Prestation code
		Occult blood in stool - test done by a professional (2012-2021)	1629	Laboratory procedure code

CCAM, *Classification commune des actes médicaux* (French national medical procedure codes); PAP, Papanicolaou test; HPV, Human Papillomavirus

eTable 4. Descriptive table of cancer cases (n=40,164)

Tumour site	Age at cancer diagnosis, mean (sd)			All-cause death				Age at death, mean (sd)		
	Control	PwMS	Difference	Control (N)	Control (%)	PwMS (N)	PwMS (%)	Control	PwMS	Difference
OVERALL	N=31,796	N=8,368								
Brain & CNS	60.1 (13.4)	53.7 (14.4)	-6.4	247	51%	68	34%	64.1 (11.9)	61.6 (13.1)	-2.5
Cervix	45.6 (11.9)	44.6 (11.5)	-1.1	122	9%	37	8%	60.3 (12.6)	60.6 (12.2)	0.3
Colon-rectum	65.3 (11.8)	64.1 (11.3)	-1.2	908	25%	260	32%	70.7 (12.6)	70.1 (11.1)	-0.6
Skin	63.0 (14.3)	60.8 (13.9)	-2.1	122	13%	52	20%	72.0 (16.6)	69.6 (17.4)	-2.4
Lung	63.6 (9.9)	61.8 (9.5)	-1.8	1796	64%	433	62%	65.0 (10.2)	63.0 (9.6)	-2.0
Prostate	67.4 (9.2)	66.3 (9.6)	-1.1	312	12%	95	18%	75.3 (9.8)	73.3 (9.6)	-2.0
Kidney	63.5 (11.5)	61.6 (12.6)	-1.9	208	23%	64	24%	69.8 (11.3)	71.3 (12.3)	1.5
Breast	58.9 (11.8)	58.0 (11.2)	-0.9	668	8%	219	12%	67.4 (14.5)	66.9 (11.7)	-0.5
Bladder	67.2 (10.7)	64.9 (10.9)	-2.3	329	27%	192	38%	73.5 (10.8)	70.4 (9.4)	-3.1
All-cancer	61.8 (12.7)	59.9 (12.9)	-1.9	3548	34%	940	36%	68.1 (12)	67.4 (11.6)	-0.7
No cancer	-	-	-	14,755	3%	10,257	8%	73.1 (15.2)	68.0 (13.6)	-5.0
WOMEN	N=21,454	N= 5,752								
Brain & CNS	60.3 (13.8)	54.4 (14.7)	-6.0	149	47%	41	29%	64.4 (12.3)	63.1 (12.5)	-1.2
Cervix	45.6 (11.9)	44.6 (11.5)	-1.1	122	9%	37	8%	60.3 (12.6)	60.6 (12.2)	0.3
Colon-rectum	65.4 (12.5)	63.7 (11.8)	-1.7	561	25%	164	31%	71.3 (13.6)	69.7 (11.8)	-1.6
Skin	61.6 (14.9)	61 (13.6)	-0.6	72	11%	35	20%	71.1 (18.3)	71.1 (16.7)	0.01
Lung	62.8 (10.4)	61.1 (9.6)	-1.8	874	59%	213	55%	64.2 (10.7)	62.5 (10.2)	-1.8
Prostate	-	-	-	-	-	-	-	-	-	-
Kidney	63.5 (12.2)	62.3 (13.6)	-1.3	95	21%	33	25%	71.2 (11.2)	72.7 (13.3)	1.4
Breast	58.9 (11.8)	58 (11.2)	-0.9	668	8%	219	12%	67.5 (14.4)	66.9 (11.8)	-0.6
Bladder	66.2 (12)	65.2 (11.5)	-0.9	97	25%	107	45%	73.5 (13.1)	70.9 (9.5)	-2.5
All-cancer	60.3 (13.2)	58.7 (13.2)	-1.6	4682	22%	1449	25%	68.1 (12.8)	67.6 (12.0)	-0.5
No cancer	-	-	-	9,219	2%	6,404	7%	76.0 (14.8)	69.9 (13.7)	-6.1
MEN	N=10,342	N=2,616								
Brain & CNS	59.6 (12.6)	52.3 (13.7)	-7.4	98	59%	27	43%	63.7 (11.2)	59.2 (14)	-4.5
Cervix	-	-	-	-	-	-	-	-	-	-
Colon-rectum	65.2 (10.4)	65.0 (10.3)	-0.2	347	26%	96	34%	69.7 (10.7)	70.9 (9.8)	1.2
Skin	65.8 (12.4)	60.5 (14.6)	-5.4	50	17%	17	21%	73.4 (13.8)	66.5 (18.8)	-6.8
Lung	64.6 (9.3)	62.8 (9.3)	-1.8	922	69%	220	70%	65.7 (9.6)	63.5 (9.1)	-2.2
Prostate	67.6 (8.9)	66.3 (9.6)	-1.3	312	12%	95	18%	75.3 (9.8)	73.3 (9.6)	-2.0
Kidney	63.4 (10.8)	61 (11.6)	-2.4	113	24%	31	23%	68.5 (11.3)	69.8 (11.1)	1.3
Breast	-	-	-	-	-	-	-	-	-	-
Bladder	67.7 (10)	64.6 (10.2)	-3.1	232	28%	85	31%	73.5 (9.6)	69.8 (9.3)	-3.8
All-cancer	65.0 (10.7)	62.4 (11.9)	-2.6	3,548	34%	940	36%	68.1 (10.9)	67.2 (10.8)	-0.9
No cancer	-	-	-	5,536	4%	3,853	10%	68.3 (14.7)	64.8 (12.9)	-3.5

CNS, Central Nervous System; PwMS, Person with MS

eTable 5. Fine & Gray analysis adjusted for cancer screening in breast, colorectal and cervical cancer

Outcome	Population eligible	HR 95% CI	p-value
Breast cancer adjusted on mammography	273,870	1.00 [0.94-1.06]	0.8
Colorectal cancer adjusted on occult blood in stool test	394,171	0.92 [0.84-1.01]	0.085
Cervical cancer adjusted on screening (PAP smear or HPV test)	424,171	1.27 [1.15-1.41]	<0.001

*All cancer screening adjustment variables were coded as binary Yes/No

*Unadjusted Fine & Gray analysis on the subgroup eligible at least one day for screening did not differ from main analysis results (Figure 2)

eTable 6. E value analysis

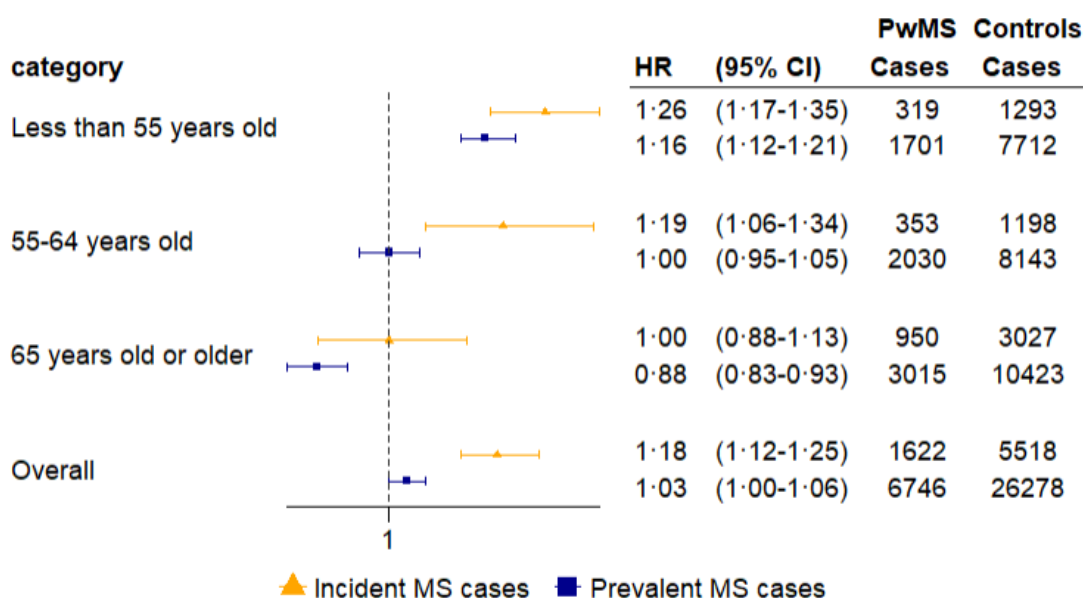
« The E-value represents the extent to which an unmeasured confounder would have to be associated with both treatment and outcome to nullify the observed treatment-outcome association. Greater E-values indicate stronger treatment-outcome associations; as unmeasured confounders would have to have correspondingly large risk ratios to negate the results. The lowest an E-value can be is 1, in which case no unmeasured confounding is necessary to nullify the observed association.” (William T. et al., Journal of Clinical Epidemiology, 2023) <https://doi.org/10.1016/j.jclinepi.2023.09.014>

Overall							
Cancer location		HR	lower	upper	EValue_point	EValue_lower	EValue_upper
All-cancer		1.06	1.03	1.08	1.30	1.21	
Bladder		1,77	1,59	1,96	2.94	2.56	
Brain & CNS		1,63	1,39	1,92	2.64	2.13	
Breast		0,94	0,89	0,99	1.32		1.11
Cervical		1,28	1,15	1,42	1.88	1.57	
Colorectal		0,94	0,87	1,01	1.32		1.00
Kidney		1,21	1,05	1,38	1.71	1.28	
Lung		1	0,92	1,09	1.00	1.00	
Prostate		0,83	0,76	0,91	1.70		1.43
Skin		1,15	1	1,32	1.57	1.00	
By sex							
Cancer location	Sex	HR	lower	upper	EValue_point	EValue_lower	EValue_upper
All-cancer	M	1.01	0.97	1.06	1.14	1.00	
All-cancer	F	1.08	1.05	1.11	1.37	1.27	
Bladder	F	2,60	2,21	3,05	4.64	3.85	
Bladder	M	1,38	1,20	1,58	2.11	1.70	
Brain & CNS	F	1,80	1,47	2,19	2.99	2.31	
Brain & CNS	M	1,59	1,19	2,13	2.56	1.67	
Breast	F	0,94	0,89	0,99	1.33		1.13
Cervical	F	1,28	1,15	1,42	1.87	1.56	
Colorectal	F	0,98	0,89	1,07	1.18		1.00
Colorectal	M	0,87	0,76	0,98	1.58		1.14
Kidney	F	1,17	0,97	1,42	1.62	1.00	
Kidney	M	1,23	1,02	1,49	1.76	1.14	
Lung	F	1,08	0,96	1,21	1.37	1.00	
Lung	M	0,98	0,86	1,11	1.18		1.00
Prostate	M	0,82	0,75	0,90	1.72		1.45
Skin	F	1,13	0,95	1,33	1.51	1.00	
Skin	M	1,17	0,92	1,50	1.62	1.00	
By age							
Cancer location	Age	HR	lower	upper	EValue_point	EValue_lower	EValue_upper
All-cancer	Less than 55	1.20	1.15	1.24	1.68	1.57	
All-cancer	55-64	1.02	0.98	1.07	1.18	1.00	
All-cancer	65+	0.89	0.85	0.94	1.48		1.33
Bladder	Less than 55	2,47	2,01	3,05	4.38	3.43	
Bladder	55-64	1,62	1,37	1,92	2.62	2.08	

Bladder	65+	1,44	1,22	1,71	2.24	1.74	
Brain & CNS	Less than 55	2,24	1,8	2,8	3.91	3.00	
Brain & CNS	55-64	1,34	0,97	1,87	2.01	1.00	
Brain & CNS	65+	1,06	0,72	1,56	1.31	1.00	
Breast	Less than 55	0,96	0,89	1,03	1.25		1.00
Breast	55-64	0,92	0,84	1,01	1.39		1.00
Breast	65+	0,76	0,67	0,86	1.96		1.60
Cervical	Less than 55	1,26	1,12	1,41	1.83	1.49	
Cervical	55-64	1,38	0,97	1,96	2.10	1.00	
Cervical	65+	0,74	0,41	1,34	2.04		1.00
Colorectal	Less than 55	1,01	0,88	1,16	1.11	1.00	
Colorectal	55-64	0,9	0,79	1,02	1.46		1.00
Colorectal	65+	0,82	0,71	0,93	1.74		1.36
Kidney	Less than 55	1,27	1,01	1,58	1.86	1.11	
Kidney	55-64	1,13	0,9	1,43	1.51	1.00	
Kidney	65+	1,06	0,82	1,37	1.31	1.00	
Lung	Less than 55	1,19	1,04	1,36	1.67	1.24	
Lung	55-64	1	0,88	1,14	1.00	1.00	
Lung	65+	0,75	0,63	0,9	2.00		1.46
Prostate	Less than 55	0,89	0,71	1,12	1.50		1.00
Prostate	55-64	0,83	0,72	0,96	1.70		1.25
Prostate	65+	0,72	0,62	0,84	2.12		1.67
Skin	Less than 55	1,3	1,06	1,6	1.92	1.31	
Skin	55-64	1,18	0,9	1,54	1.64	1.00	
Skin	65+	0,85	0,65	1,09	1.63		1.00

eTable 7. Sensitivity analysis, Fine and Gray analysis according to MS identification date

MS participants could either be “prevalent”, i.e. have been identified before the start of the observation period Jan 1, 2012 or be “incident”, i.e. have been identified during the observation period between Jan 1, 2012 and Dec 31, 2021. We compared cancer risk overall and by age between those two groups in Appendix pp 7. We observed that overall “incident” PwMS had a higher increase in cancer risk compared to their matched control than “prevalent” PwMS cases, this increase could be due to an lower age at entry in the “incident” group (10 years younger on average at index date) and a shorter observation period. When looking according to age, the gradient in risk remained in both groups, with an exacerbated risk in the younger group (<55) and a diminished risk in the older group (65 and over).



eTable 8: Sensitivity analysis, Fine and Gray analysis according to MS identification date; descriptive table

Age category	Group	N	Follow-up time in years, mean (sd)	Age at index in years, mean (sd)	Women, n (%)	Cancer cases, MS	Cancer cases, Control
Less than 55	incident	232,670	4.9 (2.9)	36.8 (9.9)	163,496 (70.3)	319	1,293
Less than 55	prevalent	276,060	9.7 (1.3)	42.3 (8.6)	198,105 (71.8)	1,701	7,712
55-64	incident	26,700	4.9 (2.8)	59.4 (2.5)	17,484 (65.5)	353	1,198
55-64	prevalent	86,315	9.2 (2.1)	59.8 (2.6)	60,350 (69.9)	2,030	8,143
65 or older	incident	17,810	4.7 (2.8)	72.0 (6.5)	11,835 (66.5)	950	3,027
65 or older	prevalent	63,690	8.4 (2.7)	72.1 (6.3)	46,875 (73.6)	3,015	10,423
Overall	incident	277,180	4.9 (2.9)	41.3 (14.0)	192,815 (69.6)	1,622	5,518
Overall	prevalent	426,065	9.4 (1.8)	50.3 (13.6)	305,330 (71.7)	6,746	26,278

eTable 9. Cancer screening during the follow-up, according to cancer diagnosis

	Controls	PwMS	Absolute % difference	p-value	Controls	PwMS	Absolute % difference	p-value	
Breast cancer screening					Had a breast cancer				
No breast cancer					Had a breast cancer				
Patients eligible - Women, 50-74 years old	213,062	53,816			5,682	1,310			
Years of eligibility, mean (sd)	6.9 (3.2)	6.6 (3.3)			4.3 (2.8)	4.2 (2.8)			
At least one mammography , all	151,280 (71.0)	34,562 (64.2)	-6.8%	<0.001	5,433 (95.6)	1,199 (91.5)	-4.1%	<0.001	
At least one mammography , by age				<0.001				<0.001	
<55	81,490 (71.3)	19,636 (67.7)	-3.6%		2,143 (97.3)	516 (94.2)	-3.1%		
55-64	50,550 (73.8)	11,153 (65.0)	-8.8%		2,178 (97.4)	474 (93.3)	-4.1%		
65-74	19,240 (63.4)	3,773 (49.4)	-14.0%		1,112 (89.3)	209 (82.3)	-7.6%		
Cervical cancer screening					Had a cervical cancer				
No cervical cancer					Had a cervical cancer				
Patients eligible - Women, 25-64 years old	338,010	84,406			1,329	426			
Years of eligibility, mean (sd)	7.0 (3.3)	6.9 (3.3)			4.3 (2.8)	4.5 (2.8)			
At least one PAP smear or HPV test, all	216,500 (64.1)	53,241 (63.1)	-1.0%	<0.001	1,076 (81.0)	341 (80.0)	-0.9%	0.728	
At least one PAP smear or HPV test, by age				<0.001				0.334	
<35	56,668 (67.7)	14,725 (70.5)	2.8%		376 (86.4)	133 (85.3)	-1.2%		
35-44	65,920 (72.4)	16,722 (73.5)	1.1%		408 (84.1)	122 (86.5)	2.4%		
45-54	64,622 (65.7)	15,442 (62.8)	-2.8%		234 (77.2)	69 (77.5)	0.3%		
55-64	29,290 (45.2)	6,352 (39.2)	-5.9%		58 (54.7)	17 (42.5)	-12.2%		
Colorectal cancer screening					Had a colorectal cancer				
No colorectal cancer					Had a colorectal cancer				
Patients eligible - All, 55-74 years old	312,811	77,928			2,781	651			
Years of eligibility, mean (sd)	6.7 (3.3)	6.5 (3.3)			4.6 (2.8)	4.3 (2.7)			
At least one test, all	115,729 (37.0)	27,050 (34.7)	-2.3%	<0.001	828 (29.8)	171 (26.3)	-3.5%	0.08	
At least one test, by age				<0.001				0.8	
<55	61,775 (36.9)	15,354 (37.0)	0.1%		255 (35.5)	61 (32.1)	-3.4%		
55-64	40,911 (40.5)	9,058 (35.8)	-4.7%		404 (31.6)	76 (26.6)	-5.1%		
65-74	13,043 (29.3)	2,638 (23.7)	-5.6%		169 (21.5)	34 (19.4)	-2.1%		

Eligibility ended at end of follow-up or when participant reached the age limit

^a χ^2 test for proportion comparison

^b ANOVA test

eTable 10. Cancer specific mortality rates and incidence rate ratios

	Cancer-specific mortality rates per 100,000 PY (95%CI)		Incidence rate ratios (95%CI)*	p-value	Significance level
	Control	MS			
All-cancer	2381 (2322-2441)	2378 (2264-2497)	1.06 (1.00-1.12)	0.037	<0.05*
Brain & CNS	5853 (5086-6707)	3872 (2931-5018)	0.76 (0.56-1.02)	0.071	<0.1
Cervical	761 (615-931)	757 (507-1088)	1.17 (0.75-1.75)	0.473	NS
Colorectal	2257 (2090-2433)	2799 (2410-3233)	1.28 (1.08-1.50)	0.003	<0.01*
Skin	882 (691-1110)	1079 (691-1606)	1.24 (0.77-1.94)	0.36	NS
Lung	7771 (7382-8175)	7503 (6746-8321)	0.97 (0.86-1.08)	0.571	NS
Prostate	618 (522-726)	771 (540-1068)	1.31 (0.90-1.87)	0.144	NS
Kidney	1957 (1662-2290)	1396 (948-1982)	0.76 (0.50-1.09)	0.155	NS
Breast	687 (628-750)	741 (614-886)	1.11 (0.91-1.36)	0.284	NS
Bladder	1925 (1665-2214)	2817 (2330-3378)	1.53 (1.21-1.92)	0.0004	<0.001*

* IRR from Poisson models adjusted on age at cancer diagnosis and sex.