Supplementary Table 1 Cohort size and follow-up

Exposure	Outcome	N	Events	Women	Men	Median years	Person-years	Lost
MSDP	All-cause cancer	402,849	59,241	218,975	183,874	14.11	5,248,919	1,048
MSDP	Oropharyngeal	432,190	800	236,798	195,392	14.32	6,017,273	1,126
MSDP	Esophageal	432,524	788	236,928	195,596	14.32	6,024,151	1,126
MSDP	Gastric	432,518	541	236,915	195,603	14.32	6,024,902	1,126
MSDP	Colorectal	430,714	4,506	236,152	194,562	14.31	5,975,973	1,122
MSDP	Liver	432,604	474	236,942	195,662	14.32	6,026,606	1,126
MSDP	Gallbladder	432,631	96	236,952	195,679	14.32	6,027,614	1,126
MSDP	Pancreatic	432,589	946	236,936	195,653	14.32	6,026,244	1,126
MSDP	Lung	432,384	2,991	236,828	195,556	14.32	6,017,812	1,122
MSDP	Breast (women)	229,309	7,279	229,309	0	14.31	3,171,185	583
MSDP	Renal	432,248	1,140	236,812	195,436	14.32	6,016,613	1,125
MSDP	Bladder	432,163	810	236,852	195,311	14.32	6,017,086	1,125
MSDP	Prostate (men)	193,090	8,701	0	193,090	14.22	2,598,928	520
MSDP	Cervical (women)	236,182	90	236,182	0	14.35	3,319,882	599
MSDP	Endometrial (women)	236,239	1,187	236,239	0	14.35	3,313,164	601
MSDP	Ovarian (women)	236,393	925	236,393	0	14.35	3,319,862	600
MSDP	Cutaneous melanoma	430,961	2,034	235,889	195,072	14.32	5,989,456	1,118
MSDP	Keratinocyte carcinoma	424,546	19,148	232,815	191,731	14.26	5,776,128	1,107
MSDP	Basal cell carcinoma	421,787	16,389	231,748	190,039	14.27	5,755,543	1,107
MSDP	Squamous cell carcinoma	407,988	2,590	224,989	182,999	14.31	5,663,512	1,104
MSDP	Brain	432,517	614	236,898	195,619	14.32	6,025,574	1,125
MSDP	Thyroid	432,282	329	236,677	195,605	14.32	6,020,518	1,124
MSDP	Hematological malignancies	430,934	3,449	236,193	194,741	14.32	5,986,412	1,122
MSDP	Hodgkin lymphoma	432,331	118	236,812	195,519	14.32	6,023,155	1,126
MSDP	Non-Hodgkin lymphoma	431,815	1,635	236,588	195,227	14.32	6,007,171	1,124
MSDP	Multiple myeloma	432,485	701	236,898	195,587	14.32	6,022,714	1,126
MSDP	Leukemia	432,230	922	236,769	195,461	14.32	6,017,606	1,124
DOSE	All-cause cancer	467,333	69,647	252,245	215,088	14.10	6,078,382	1,209
DOSE	Oropharyngeal	501,723	934	273,039	228,684	14.32	6,978,647	1,297
DOSE	Esophageal	502,101	921	273,193	228,908	14.32	6,986,556	1,297

Exposure	Outcome	N	Events	Women	Men	Median years	Person-years	Lost
DOSE	Gastric	502,094	643	273,173	228,921	14.32	6,987,246	1,296
DOSE	Colorectal	499,980	5,296	272,269	227,711	14.31	6,930,045	1,292
DOSE	Liver	502,200	565	273,208	228,992	14.32	6,989,351	1,297
DOSE	Gallbladder	502,228	108	273,218	229,010	14.32	6,990,531	1,297
DOSE	Pancreatic	502,183	1,141	273,200	228,983	14.32	6,988,914	1,297
DOSE	Lung	501,936	3,653	273,082	228,854	14.32	6,978,638	1,293
DOSE	Breast (women)	264,301	8,422	264,301	0	14.31	3,652,273	672
DOSE	Renal	501,775	1,358	273,060	228,715	14.32	6,977,416	1,296
DOSE	Bladder	501,664	951	273,098	228,566	14.32	6,978,058	1,296
DOSE	Prostate (men)	225,964	10,203	0	225,964	14.22	3,038,223	600
DOSE	Cervical (women)	272,314	111	272,314	0	14.35	3,824,933	689
DOSE	Endometrial (women)	272,379	1,397	272,379	0	14.35	3,816,874	691
DOSE	Ovarian (women)	272,565	1,048	272,565	0	14.35	3,825,105	690
DOSE	Cutaneous melanoma	500,298	2,361	271,991	228,307	14.32	6,946,366	1,289
DOSE	Keratinocyte carcinoma	492,708	22,528	268,387	224,321	14.26	6,694,196	1,274
DOSE	Basal cell carcinoma	489,472	19,292	267,140	222,332	14.27	6,670,190	1,274
DOSE	Squamous cell carcinoma	473,220	3,040	259,231	213,989	14.31	6,561,880	1,271
DOSE	Brain	502,102	734	273,159	228,943	14.32	6,988,195	1,296
DOSE	Thyroid	501,836	387	272,906	228,930	14.32	6,982,430	1,295
DOSE	Hematological malignancies	500,247	4,063	272,353	227,894	14.32	6,942,358	1,292
DOSE	Hodgkin lymphoma	501,886	139	273,062	228,824	14.32	6,985,421	1,296
DOSE	Non-Hodgkin lymphoma	501,285	1,926	272,803	228,482	14.32	6,966,716	1,295
DOSE	Multiple myeloma	502,058	804	273,156	228,902	14.32	6,984,910	1,297
DOSE	Leukemia	501,746	1,103	273,012	228,734	14.32	6,978,592	1,295
ASI	All-cause cancer	404,584	60,160	218,295	186,289	14.11	5,263,895	1,037
ASI	Oropharyngeal	434,185	812	236,171	198,014	14.32	6,037,219	1,107
ASI	Esophageal	434,516	813	236,302	198,214	14.32	6,044,074	1,107
ASI	Gastric	434,508	571	236,284	198,224	14.32	6,044,626	1,106
ASI	Colorectal	432,715	4,611	235,530	197,185	14.32	5,995,419	1,105
ASI	Liver	434,600	492	236,315	198,285	14.32	6,046,582	1,107
ASI	Gallbladder	434,625	92	236,324	198,301	14.33	6,047,538	1,107
ASI	Pancreatic	434,585	1,013	236,308	198,277	14.32	6,046,152	1,107
ASI	Lung	434,355	3,376	236,196	198,159	14.32	6,036,642	1,103

Exposure	Outcome	N	Events	Women	Men	Median years	Person-years	Lost
ASI	Breast (women)	228,659	7,180	228,659	0	14.32	3,160,555	568
ASI	Renal	434,234	1,177	236,185	198,049	14.32	6,036,278	1,107
ASI	Bladder	434,126	828	236,217	197,909	14.32	6,036,583	1,106
ASI	Prostate (men)	195,694	8,701	0	195,694	14.22	2,630,618	516
ASI	Cervical (women)	235,539	96	235,539	0	14.35	3,308,216	584
ASI	Endometrial (women)	235,572	1,231	235,572	0	14.35	3,300,720	586
ASI	Ovarian (women)	235,777	904	235,777	0	14.35	3,308,697	585
ASI	Cutaneous melanoma	432,954	1,998	235,256	197,698	14.32	6,009,634	1,102
ASI	Keratinocyte carcinoma	426,494	19,326	232,225	194,269	14.26	5,794,155	1,090
ASI	Basal cell carcinoma	423,744	16,576	231,163	192,581	14.27	5,773,690	1,090
ASI	Squamous cell carcinoma	409,746	2,578	224,357	185,389	14.31	5,680,335	1,087
ASI	Brain	434,525	617	236,278	198,247	14.33	6,045,614	1,106
ASI	Thyroid	434,287	351	236,048	198,239	14.32	6,040,398	1,106
ASI	Hematological malignancies	432,898	3,498	235,566	197,332	14.32	6,005,910	1,103
ASI	Hodgkin lymphoma	434,324	120	236,181	198,143	14.33	6,043,053	1,106
ASI	Non-Hodgkin lymphoma	433,797	1,680	235,964	197,833	14.32	6,026,795	1,105
ASI	Multiple myeloma	434,475	685	236,269	198,206	14.32	6,042,664	1,107
ASI	Leukemia	434,214	938	236,145	198,069	14.32	6,037,415	1,106

Person-years sum the stored follow-up times, measured in days/365. Lost denotes participants whose recorded loss date was the analysis censoring date, not all records with a loss date. Original cancer-specific Ns excluded the relevant baseline cancer; the all-cause Ns excluded all baseline cancers. Female-only and male-only rows have zero participants of the other sex.

Supplementary Table 2 MSDP estimates

Outcome	Unadjusted HR (CI)	Model 1 HR (CI)	Model 2 HR (CI)	M2 P	M2 FDR
All-cause cancer	1.03 (1.01–1.05)	1.06 (1.04–1.08)	1.05 (1.03–1.07)	<0.001	<0.001
Oropharyngeal	1.25 (1.08–1.45)	1.20 (1.04–1.39)	1.17 (1.01–1.36)	0.034	0.155
Esophageal	1.17 (1.01–1.35)	1.16 (1.00–1.35)	1.10 (0.94–1.28)	0.228	0.488
Gastric	1.20 (1.00–1.43)	1.20 (1.01–1.44)	1.17 (0.98–1.41)	0.084	0.314
Colorectal	1.02 (0.96–1.09)	1.05 (0.99–1.12)	1.04 (0.97–1.11)	0.266	0.513
Liver	1.11 (0.92–1.35)	1.13 (0.93–1.37)	1.06 (0.87–1.30)	0.531	0.683
Gallbladder	0.90 (0.57–1.41)	0.92 (0.59–1.46)	0.90 (0.57–1.42)	0.649	0.741

Outcome	Unadjusted HR (CI)	Model 1 HR (CI)	Model 2 HR (CI)	M2 P	M2 FDR
Pancreatic	1.00 (0.87–1.16)	1.07 (0.93–1.23)	1.03 (0.89–1.18)	0.702	0.758
Lung	1.44 (1.34–1.56)	1.44 (1.33–1.55)	1.29 (1.19–1.39)	<0.001	<0.001
Breast (women)	0.96 (0.92–1.02)	0.98 (0.93–1.03)	0.97 (0.92–1.02)	0.189	0.488
Renal	1.00 (0.88–1.13)	0.99 (0.87–1.13)	0.95 (0.83–1.08)	0.408	0.589
Bladder	1.11 (0.96–1.29)	1.14 (0.98–1.32)	1.10 (0.95–1.28)	0.199	0.488
Prostate (men)	0.94 (0.90–0.98)	1.02 (0.97–1.07)	1.02 (0.97–1.07)	0.382	0.589
Cervical (women)	1.20 (0.77–1.86)	1.17 (0.75–1.83)	1.21 (0.77–1.91)	0.402	0.589
Endometrial (women)	1.00 (0.88–1.13)	1.04 (0.91–1.18)	1.03 (0.91–1.17)	0.632	0.741
Ovarian (women)	0.89 (0.76–1.03)	0.91 (0.78–1.05)	0.93 (0.80–1.08)	0.356	0.589
Cutaneous melanoma	1.15 (1.05–1.27)	1.16 (1.06–1.28)	1.14 (1.04–1.25)	0.006	0.033
Keratinocyte carcinoma	1.04 (1.01–1.07)	1.07 (1.04–1.11)	1.06 (1.03–1.10)	<0.001	<0.001
Basal cell carcinoma	1.06 (1.02–1.09)	1.09 (1.05–1.13)	1.08 (1.05–1.12)	<0.001	<0.001
Squamous cell carcinoma	0.91 (0.83–0.99)	0.97 (0.89–1.06)	0.95 (0.87–1.04)	0.235	0.488
Brain	0.94 (0.78–1.12)	0.94 (0.78–1.12)	0.94 (0.79–1.12)	0.485	0.654
Thyroid	0.78 (0.61–1.00)	0.81 (0.63–1.05)	0.81 (0.62–1.04)	0.097	0.314
Hematological malignancies	0.96 (0.89–1.03)	1.00 (0.92–1.07)	0.98 (0.91–1.06)	0.659	0.741
Hodgkin lymphoma	1.20 (0.82–1.76)	1.18 (0.80–1.74)	1.18 (0.80–1.74)	0.415	0.589
Non-Hodgkin lymphoma	0.98 (0.88–1.09)	1.01 (0.91–1.13)	1.00 (0.90–1.12)	0.978	0.978
Multiple myeloma	0.83 (0.70–0.98)	0.88 (0.74–1.04)	0.87 (0.73–1.03)	0.105	0.314
Leukemia	1.02 (0.89–1.17)	1.04 (0.90–1.20)	1.02 (0.89–1.18)	0.765	0.794

Exposure contrast is MSDP yes versus no. Estimates are matched by cancer identifier and coefficient name. Full coefficients, standard errors, CIs, nominal and adjusted P values, Ns, and event counts are in Supplementary_model_output.csv. For original coefficients without separately saved standard errors, SEs are reconstructed from their 95% CIs; newly fitted coefficients use model-based SEs.

Supplementary Table 3 Initiation-age contrasts and initiator-only trends

Primary ASI contrasts: Model 1

Outcome	Adult HR (CI)	Adolescent HR (CI)	Childhood HR (CI)	Childhood FDR
All-cause cancer	1.14 (1.11–1.16)	1.19 (1.17–1.21)	1.29 (1.19–1.40)	<0.001
Oropharyngeal	2.51 (2.10–3.00)	2.25 (1.90–2.67)	3.34 (2.11–5.28)	<0.001
Esophageal	2.03 (1.69–2.43)	2.12 (1.80–2.50)	2.91 (1.80–4.71)	<0.001

Outcome	Adult HR (CI)	Adolescent HR (CI)	Childhood HR (CI)	Childhood FDR
Gastric	1.34 (1.06–1.69)	1.69 (1.39–2.04)	NE (<10 events)	NE
Colorectal	1.31 (1.21–1.41)	1.33 (1.24–1.43)	1.21 (0.90–1.65)	0.377
Liver	1.51 (1.17–1.94)	2.20 (1.79–2.70)	NE (<10 events)	NE
Gallbladder	1.45 (0.85–2.48)	1.29 (0.77–2.16)	NE (<10 events)	NE
Pancreatic	1.40 (1.19–1.65)	1.42 (1.22–1.65)	1.64 (0.92–2.91)	0.232
Lung	6.53 (5.86–7.28)	9.07 (8.20–10.04)	11.40 (9.12–14.23)	<0.001
Breast (women)	1.10 (1.03–1.17)	1.03 (0.97–1.10)	1.15 (0.81–1.64)	0.670
Renal	1.31 (1.12–1.53)	1.32 (1.15–1.52)	2.10 (1.36–3.23)	0.003
Bladder	1.69 (1.39–2.05)	2.42 (2.06–2.85)	3.66 (2.36–5.68)	<0.001
Prostate (men)	0.87 (0.82–0.93)	0.85 (0.81–0.89)	0.79 (0.64–0.97)	0.086
Cervical (women)	1.50 (0.88–2.56)	1.17 (0.67–2.02)	NE (<10 events)	NE
Endometrial (women)	0.77 (0.65–0.91)	0.64 (0.53–0.77)	NE (<10 events)	NE
Ovarian (women)	0.99 (0.82–1.19)	1.11 (0.93–1.33)	NE (<10 events)	NE
Cutaneous melanoma	0.85 (0.74–0.96)	0.75 (0.66–0.85)	0.67 (0.37–1.21)	0.374
Keratinocyte carcinoma	0.94 (0.90–0.98)	0.92 (0.88–0.95)	0.89 (0.75–1.05)	0.361
Basal cell carcinoma	0.91 (0.87–0.95)	0.90 (0.87–0.94)	0.84 (0.70–1.01)	0.190
Squamous cell carcinoma	1.17 (1.05–1.29)	0.99 (0.90–1.10)	1.23 (0.83–1.81)	0.509
Brain	1.01 (0.80–1.26)	0.99 (0.81–1.21)	NE (<10 events)	NE
Thyroid	0.89 (0.65–1.22)	0.91 (0.68–1.22)	NE (<10 events)	NE
Hematological malignancies	0.95 (0.87–1.05)	1.06 (0.97–1.15)	1.49 (1.11–2.00)	0.031
Hodgkin lymphoma	1.09 (0.64–1.84)	1.26 (0.81–1.96)	NE (<10 events)	NE
Non-Hodgkin lymphoma	0.92 (0.80–1.05)	1.03 (0.91–1.16)	1.23 (0.77–1.97)	0.602
Multiple myeloma	0.99 (0.80–1.22)	0.89 (0.73–1.09)	1.81 (0.99–3.32)	0.162
Leukemia	0.99 (0.82–1.20)	1.25 (1.07–1.46)	1.45 (0.81–2.58)	0.377

Primary ASI contrasts: Model 2 (smoking status omitted)

Outcome	Adult HR (CI)	Adolescent HR (CI)	Childhood HR (CI)	Childhood FDR
All-cause cancer	1.11 (1.09–1.14)	1.16 (1.13–1.18)	1.24 (1.15–1.35)	<0.001
Oropharyngeal	2.35 (1.96–2.81)	2.11 (1.77–2.50)	3.01 (1.90–4.78)	<0.001
Esophageal	1.92 (1.60–2.31)	1.96 (1.66–2.32)	2.45 (1.51–3.97)	0.001
Gastric	1.33 (1.05–1.68)	1.67 (1.37–2.02)	NE (<10 events)	NE
Colorectal	1.25 (1.15–1.35)	1.26 (1.17–1.36)	1.12 (0.83–1.52)	0.744
Liver	1.38 (1.07–1.78)	1.96 (1.59–2.42)	NE (<10 events)	NE

Outcome	Adult HR (CI)	Adolescent HR (CI)	Childhood HR (CI)	Childhood FDR
Gallbladder	1.47 (0.85–2.53)	1.29 (0.76–2.17)	NE (<10 events)	NE
Pancreatic	1.31 (1.11–1.55)	1.31 (1.12–1.53)	1.43 (0.80–2.56)	0.500
Lung	6.38 (5.72–7.12)	8.78 (7.93–9.72)	10.50 (8.40–13.13)	<0.001
Breast (women)	1.07 (1.00–1.14)	1.01 (0.95–1.08)	1.12 (0.78–1.60)	0.803
Renal	1.26 (1.08–1.48)	1.24 (1.08–1.43)	1.86 (1.21–2.87)	0.021
Bladder	1.63 (1.34–1.98)	2.31 (1.96–2.72)	3.41 (2.19–5.30)	<0.001
Prostate (men)	0.88 (0.82–0.93)	0.85 (0.81–0.90)	0.80 (0.65–0.99)	0.134
Cervical (women)	1.44 (0.84–2.49)	1.11 (0.63–1.95)	NE (<10 events)	NE
Endometrial (women)	0.75 (0.64–0.89)	0.66 (0.55–0.79)	NE (<10 events)	NE
Ovarian (women)	1.01 (0.84–1.22)	1.17 (0.97–1.40)	NE (<10 events)	NE
Cutaneous melanoma	0.83 (0.72–0.94)	0.72 (0.64–0.82)	0.65 (0.36–1.17)	0.386
Keratinocyte carcinoma	0.93 (0.90–0.97)	0.91 (0.88–0.94)	0.91 (0.77–1.08)	0.590
Basal cell carcinoma	0.91 (0.87–0.95)	0.90 (0.86–0.94)	0.87 (0.72–1.05)	0.386
Squamous cell carcinoma	1.14 (1.03–1.26)	0.96 (0.87–1.06)	1.20 (0.81–1.78)	0.645
Brain	1.00 (0.80–1.26)	0.98 (0.80–1.21)	NE (<10 events)	NE
Thyroid	0.91 (0.66–1.24)	0.91 (0.68–1.22)	NE (<10 events)	NE
Hematological malignancies	0.94 (0.86–1.04)	1.04 (0.95–1.13)	1.41 (1.05–1.89)	0.088
Hodgkin lymphoma	1.13 (0.66–1.92)	1.29 (0.82–2.01)	NE (<10 events)	NE
Non-Hodgkin lymphoma	0.91 (0.79–1.05)	1.02 (0.90–1.15)	1.19 (0.74–1.91)	0.744
Multiple myeloma	0.97 (0.79–1.20)	0.87 (0.71–1.07)	1.71 (0.93–3.13)	0.254
Leukemia	0.97 (0.80–1.17)	1.20 (1.03–1.41)	1.34 (0.75–2.39)	0.624

These primary contrasts use self-reported never smoking as the reference. ASI Model 2 omits smoking status; Model 1 and other extended covariates are as specified in the Methods. Fewer than 10 category-specific events produce NE and no CI or P value; a suppressed zero-event contrast must not be described as a null or protective effect. Each contrast and model has a separate 27-outcome FDR family. Full adult/adolescent FDR values are in the CSV.

Trend tests restricted to initiators

Outcome	Initiators N	Events	M1 P	M1 FDR	ASI M2 P	ASI M2 FDR	+status P	+status FDR
All-cause cancer	147,078	25,603	<0.001	0.007	0.004	0.038	<0.001	0.008
Oropharyngeal	158,730	501	0.721	0.923	0.693	0.970	0.847	0.986
Esophageal	158,906	501	0.480	0.763	0.782	0.970	0.660	0.986
Gastric	158,910	311	0.258	0.497	0.285	0.551	0.247	0.485
Colorectal	158,086	2,134	0.881	0.972	0.970	0.970	0.946	0.986

Outcome	Initiators N	Events	M1 P	M1 FDR	ASI M2 P	ASI M2 FDR	+status P	+status FDR
Liver	158,966	287	0.009	0.064	0.026	0.142	0.022	0.146
Gallbladder	158,977	44	0.900	0.972	0.928	0.970	0.919	0.986
Pancreatic	158,959	488	0.868	0.972	0.744	0.970	0.890	0.986
Lung	158,762	2,866	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Breast (women)	70,506	2,282	0.249	0.497	0.316	0.569	0.373	0.629
Renal	158,793	567	0.542	0.770	0.863	0.970	0.752	0.986
Bladder	158,658	523	<0.001	<0.001	<0.001	0.002	<0.001	0.001
Prostate (men)	84,613	3,707	0.344	0.581	0.396	0.669	0.348	0.626
Cervical (women)	72,817	35	0.194	0.477	0.193	0.465	0.184	0.451
Endometrial (women)	72,988	304	0.075	0.254	0.110	0.371	0.099	0.325
Ovarian (women)	73,025	295	0.332	0.581	0.207	0.465	0.217	0.485
Cutaneous melanoma	158,464	634	0.178	0.477	0.127	0.381	0.108	0.325
Keratinocyte carcinoma	155,894	7,174	0.512	0.767	0.597	0.948	0.514	0.816
Basal cell carcinoma	154,726	6,006	0.974	0.974	0.844	0.970	0.995	0.995
Squamous cell carcinoma	149,826	1,106	0.026	0.119	0.023	0.142	0.032	0.146
Brain	158,943	242	0.962	0.974	0.956	0.970	0.949	0.986
Thyroid	158,872	111	0.672	0.907	0.774	0.970	0.769	0.986
Hematological malignancies	158,295	1,407	0.025	0.119	0.038	0.171	0.032	0.146
Hodgkin lymphoma	158,858	53	0.150	0.451	0.178	0.465	0.162	0.437
Non-Hodgkin lymphoma	158,645	655	0.257	0.497	0.285	0.551	0.252	0.485
Multiple myeloma	158,916	262	0.752	0.923	0.827	0.970	0.828	0.986
Leukemia	158,818	412	0.049	0.191	0.060	0.232	0.059	0.229

Initiators are current or former smokers with recorded initiation age. Ordinal scores are adult = 0, adolescence = 1, childhood = 2. The two-sided Wald test evaluates this score among initiators only, not an ever/never contrast. A significant score test is not evidence of strict monotonicity in every categorical estimate. ASI M2 omits smoking status. The +status sensitivity additionally adjusts for current/former status among initiators, which is estimable without a never-smoking reference. Primary categorical ASI results are above and in ASI_primary_model_output.csv. Status-adjusted categorical fits using a true-never reference are retained only as flagged diagnostics in the full output CSV and are not used for inference.

Supplementary Table 4 Smoking-dose estimates

PYS per original SD

Outcome	M1 HR (CI)	M1 FDR	M2 HR (CI)	M2 P	M2 FDR
All-cause cancer	1.09 (1.08–1.09)	<0.001	1.06 (1.05–1.07)	<0.001	<0.001
Oropharyngeal	1.28 (1.24–1.33)	<0.001	1.17 (1.12–1.23)	<0.001	<0.001
Esophageal	1.25 (1.21–1.30)	<0.001	1.16 (1.11–1.21)	<0.001	<0.001
Gastric	1.19 (1.14–1.25)	<0.001	1.15 (1.08–1.21)	<0.001	<0.001
Colorectal	1.12 (1.09–1.14)	<0.001	1.08 (1.05–1.10)	<0.001	<0.001
Liver	1.21 (1.15–1.27)	<0.001	1.08 (1.02–1.15)	0.013	0.024
Gallbladder	1.06 (0.91–1.23)	0.553	0.96 (0.80–1.16)	0.691	0.704
Pancreatic	1.16 (1.11–1.21)	<0.001	1.08 (1.03–1.14)	0.003	0.006
Lung	1.44 (1.43–1.46)	<0.001	1.32 (1.30–1.34)	<0.001	<0.001
Breast (women)	1.06 (1.03–1.09)	<0.001	1.03 (1.00–1.06)	0.081	0.121
Renal	1.13 (1.09–1.18)	<0.001	1.05 (1.00–1.11)	0.034	0.061
Bladder	1.23 (1.19–1.28)	<0.001	1.14 (1.09–1.19)	<0.001	<0.001
Prostate (men)	0.94 (0.93–0.96)	<0.001	0.96 (0.94–0.98)	<0.001	<0.001
Cervical (women)	1.04 (0.83–1.30)	0.756	0.94 (0.70–1.25)	0.655	0.704
Endometrial (women)	0.86 (0.79–0.92)	<0.001	0.92 (0.84–1.00)	0.051	0.081
Ovarian (women)	1.03 (0.95–1.10)	0.553	1.02 (0.93–1.11)	0.704	0.704
Cutaneous melanoma	0.90 (0.86–0.95)	<0.001	0.92 (0.87–0.98)	0.005	0.011
Keratinocyte carcinoma	0.94 (0.93–0.95)	<0.001	0.95 (0.94–0.97)	<0.001	<0.001
Basal cell carcinoma	0.93 (0.91–0.94)	<0.001	0.95 (0.93–0.96)	<0.001	<0.001
Squamous cell carcinoma	1.01 (0.98–1.04)	0.729	0.98 (0.94–1.02)	0.317	0.389
Brain	0.95 (0.88–1.02)	0.206	0.91 (0.83–1.00)	0.043	0.072
Thyroid	0.99 (0.88–1.11)	0.848	1.04 (0.91–1.19)	0.581	0.681
Hematological malignancies	1.03 (1.00–1.06)	0.070	1.01 (0.97–1.04)	0.670	0.704
Hodgkin lymphoma	1.17 (1.03–1.32)	0.021	1.12 (0.97–1.29)	0.137	0.195
Non-Hodgkin lymphoma	1.03 (0.99–1.08)	0.140	1.03 (0.98–1.08)	0.207	0.267
Multiple myeloma	0.91 (0.84–0.98)	0.016	0.86 (0.79–0.94)	0.001	0.003
Leukemia	1.08 (1.03–1.13)	0.004	1.04 (0.98–1.10)	0.172	0.233

PYSP per original SD

Outcome	M1 HR (CI)	M1 FDR	M2 HR (CI)	M2 P	M2 FDR
All-cause cancer	1.09 (1.08–1.10)	<0.001	1.06 (1.05–1.07)	<0.001	<0.001
Oropharyngeal	1.30 (1.26–1.35)	<0.001	1.17 (1.12–1.23)	<0.001	<0.001
Esophageal	1.29 (1.24–1.34)	<0.001	1.18 (1.12–1.24)	<0.001	<0.001
Gastric	1.21 (1.15–1.28)	<0.001	1.16 (1.09–1.24)	<0.001	<0.001
Colorectal	1.12 (1.10–1.15)	<0.001	1.08 (1.05–1.11)	<0.001	<0.001
Liver	1.24 (1.17–1.30)	<0.001	1.09 (1.02–1.17)	0.015	0.029
Gallbladder	1.06 (0.89–1.25)	0.578	0.96 (0.78–1.17)	0.663	0.716
Pancreatic	1.18 (1.13–1.24)	<0.001	1.10 (1.04–1.17)	<0.001	0.001
Lung	1.50 (1.48–1.51)	<0.001	1.35 (1.33–1.37)	<0.001	<0.001
Breast (women)	1.05 (1.03–1.08)	<0.001	1.02 (0.99–1.06)	0.164	0.246
Renal	1.15 (1.10–1.20)	<0.001	1.06 (1.01–1.12)	0.021	0.039
Bladder	1.27 (1.22–1.32)	<0.001	1.15 (1.10–1.21)	<0.001	<0.001
Prostate (men)	0.94 (0.92–0.96)	<0.001	0.96 (0.94–0.98)	<0.001	0.001
Cervical (women)	1.04 (0.84–1.28)	0.772	0.94 (0.71–1.23)	0.642	0.716
Endometrial (women)	0.85 (0.79–0.92)	<0.001	0.91 (0.83–1.00)	0.043	0.068
Ovarian (women)	1.02 (0.95–1.10)	0.691	1.00 (0.92–1.10)	0.917	0.917
Cutaneous melanoma	0.90 (0.85–0.94)	<0.001	0.92 (0.87–0.97)	0.005	0.010
Keratinocyte carcinoma	0.94 (0.92–0.95)	<0.001	0.95 (0.93–0.97)	<0.001	<0.001
Basal cell carcinoma	0.92 (0.91–0.94)	<0.001	0.94 (0.92–0.96)	<0.001	<0.001
Squamous cell carcinoma	1.02 (0.98–1.05)	0.432	0.99 (0.95–1.03)	0.606	0.712
Brain	0.95 (0.88–1.02)	0.208	0.91 (0.83–1.00)	0.042	0.068
Thyroid	0.99 (0.89–1.11)	0.925	1.05 (0.92–1.20)	0.459	0.563
Hematological malignancies	1.03 (1.00–1.06)	0.089	1.01 (0.97–1.04)	0.771	0.800
Hodgkin lymphoma	1.16 (1.02–1.32)	0.039	1.11 (0.94–1.30)	0.208	0.281
Non-Hodgkin lymphoma	1.03 (0.99–1.08)	0.172	1.03 (0.98–1.08)	0.265	0.341
Multiple myeloma	0.90 (0.84–0.98)	0.020	0.86 (0.78–0.94)	0.001	0.003
Leukemia	1.08 (1.03–1.14)	0.005	1.04 (0.98–1.11)	0.200	0.281

PYS = cigarettes/day divided by 20 multiplied by smoking duration. PYSP = PYS/(recruitment age − 16). One original SD equals 14.869 pack-years and 0.34118 pack-years/year, respectively. The original data replace some missing dose values with zero; zero is not a verified never-smoking category. The regression SD was calculated before baseline-cancer exclusions; cohort-specific descriptive SDs are in Table 1 and Dose_distributions_and_SD.csv.

Supplementary Table 5 Models without smoking status

Exposure	Outcome	HR (CI)	P	FDR
MSDP MSDP1	All-cause cancer	1.05 (1.03–1.07)	<0.001	<0.001
MSDP MSDP1	Oropharyngeal	1.20 (1.04–1.39)	0.015	0.067
MSDP MSDP1	Esophageal	1.11 (0.95–1.29)	0.185	0.454
MSDP MSDP1	Gastric	1.18 (0.99–1.42)	0.072	0.278
MSDP MSDP1	Colorectal	1.04 (0.97–1.11)	0.256	0.495
MSDP MSDP1	Liver	1.07 (0.88–1.31)	0.474	0.617
MSDP MSDP1	Gallbladder	0.90 (0.57–1.43)	0.668	0.765
MSDP MSDP1	Pancreatic	1.04 (0.90–1.20)	0.596	0.732
MSDP MSDP1	Lung	1.37 (1.27–1.48)	<0.001	<0.001
MSDP MSDP1	Breast (women)	0.97 (0.92–1.02)	0.215	0.484
MSDP MSDP1	Renal	0.95 (0.84–1.08)	0.441	0.617
MSDP MSDP1	Bladder	1.11 (0.96–1.29)	0.159	0.431
MSDP MSDP1	Prostate (men)	1.02 (0.98–1.07)	0.367	0.597
MSDP MSDP1	Cervical (women)	1.23 (0.78–1.93)	0.376	0.597
MSDP MSDP1	Endometrial (women)	1.02 (0.90–1.16)	0.721	0.765
MSDP MSDP1	Ovarian (women)	0.93 (0.80–1.08)	0.358	0.597
MSDP MSDP1	Cutaneous melanoma	1.14 (1.04–1.25)	0.007	0.037
MSDP MSDP1	Keratinocyte carcinoma	1.06 (1.03–1.10)	<0.001	<0.001
MSDP MSDP1	Basal cell carcinoma	1.08 (1.05–1.12)	<0.001	<0.001
MSDP MSDP1	Squamous cell carcinoma	0.95 (0.87–1.04)	0.257	0.495
MSDP MSDP1	Brain	0.94 (0.78–1.12)	0.480	0.617
MSDP MSDP1	Thyroid	0.80 (0.62–1.03)	0.087	0.294
MSDP MSDP1	Hematological malignancies	0.98 (0.91–1.06)	0.686	0.765
MSDP MSDP1	Hodgkin lymphoma	1.18 (0.80–1.75)	0.399	0.599
MSDP MSDP1	Non-Hodgkin lymphoma	1.00 (0.90–1.12)	0.954	0.954
MSDP MSDP1	Multiple myeloma	0.87 (0.73–1.03)	0.102	0.305
MSDP MSDP1	Leukemia	1.02 (0.89–1.18)	0.737	0.765
DOSE PYS_perSD	All-cause cancer	1.07 (1.07–1.08)	<0.001	<0.001
DOSE PYS_perSD	Oropharyngeal	1.26 (1.22–1.31)	<0.001	<0.001
DOSE PYS_perSD	Esophageal	1.22 (1.17–1.26)	<0.001	<0.001
DOSE PYS_perSD	Gastric	1.17 (1.12–1.23)	<0.001	<0.001
DOSE PYS_perSD	Colorectal	1.09 (1.07–1.12)	<0.001	<0.001

Exposure	Outcome	HR (CI)	P	FDR
DOSE PYS_perSD	Liver	1.14 (1.09–1.21)	<0.001	<0.001
DOSE PYS_perSD	Gallbladder	1.03 (0.88–1.20)	0.718	0.776
DOSE PYS_perSD	Pancreatic	1.11 (1.06–1.16)	<0.001	<0.001
DOSE PYS_perSD	Lung	1.43 (1.41–1.45)	<0.001	<0.001
DOSE PYS_perSD	Breast (women)	1.04 (1.02–1.07)	0.001	0.002
DOSE PYS_perSD	Renal	1.09 (1.05–1.14)	<0.001	<0.001
DOSE PYS_perSD	Bladder	1.21 (1.16–1.25)	<0.001	<0.001
DOSE PYS_perSD	Prostate (men)	0.95 (0.93–0.97)	<0.001	<0.001
DOSE PYS_perSD	Cervical (women)	1.01 (0.80–1.28)	0.913	0.913
DOSE PYS_perSD	Endometrial (women)	0.84 (0.78–0.90)	<0.001	<0.001
DOSE PYS_perSD	Ovarian (women)	1.03 (0.96–1.11)	0.374	0.459
DOSE PYS_perSD	Cutaneous melanoma	0.89 (0.85–0.94)	<0.001	<0.001
DOSE PYS_perSD	Keratinocyte carcinoma	0.95 (0.93–0.96)	<0.001	<0.001
DOSE PYS_perSD	Basal cell carcinoma	0.93 (0.92–0.95)	<0.001	<0.001
DOSE PYS_perSD	Squamous cell carcinoma	1.01 (0.97–1.04)	0.754	0.783
DOSE PYS_perSD	Brain	0.94 (0.87–1.01)	0.112	0.152
DOSE PYS_perSD	Thyroid	0.97 (0.87–1.09)	0.664	0.747
DOSE PYS_perSD	Hematological malignancies	1.01 (0.98–1.04)	0.475	0.558
DOSE PYS_perSD	Hodgkin lymphoma	1.13 (1.00–1.29)	0.049	0.070
DOSE PYS_perSD	Non-Hodgkin lymphoma	1.02 (0.98–1.07)	0.306	0.393
DOSE PYS_perSD	Multiple myeloma	0.89 (0.82–0.96)	0.002	0.003
DOSE PYS_perSD	Leukemia	1.05 (1.00–1.11)	0.034	0.052
DOSE PYSP_perSD	All-cause cancer	1.08 (1.07–1.08)	<0.001	<0.001
DOSE PYSP_perSD	Oropharyngeal	1.28 (1.23–1.33)	<0.001	<0.001
DOSE PYSP_perSD	Esophageal	1.25 (1.20–1.30)	<0.001	<0.001
DOSE PYSP_perSD	Gastric	1.19 (1.13–1.26)	<0.001	<0.001
DOSE PYSP_perSD	Colorectal	1.10 (1.07–1.12)	<0.001	<0.001
DOSE PYSP_perSD	Liver	1.16 (1.10–1.23)	<0.001	<0.001
DOSE PYSP_perSD	Gallbladder	1.03 (0.87–1.22)	0.730	0.775
DOSE PYSP_perSD	Pancreatic	1.14 (1.08–1.19)	<0.001	<0.001
DOSE PYSP_perSD	Lung	1.48 (1.46–1.50)	<0.001	<0.001
DOSE PYSP_perSD	Breast (women)	1.04 (1.01–1.07)	0.003	0.004
DOSE PYSP_perSD	Renal	1.10 (1.06–1.15)	<0.001	<0.001

Exposure	Outcome	HR (CI)	P	FDR
DOSE PYSP_perSD	Bladder	1.24 (1.19–1.29)	<0.001	<0.001
DOSE PYSP_perSD	Prostate (men)	0.94 (0.93–0.96)	<0.001	<0.001
DOSE PYSP_perSD	Cervical (women)	1.01 (0.81–1.26)	0.912	0.912
DOSE PYSP_perSD	Endometrial (women)	0.83 (0.77–0.90)	<0.001	<0.001
DOSE PYSP_perSD	Ovarian (women)	1.03 (0.95–1.10)	0.516	0.593
DOSE PYSP_perSD	Cutaneous melanoma	0.89 (0.85–0.93)	<0.001	<0.001
DOSE PYSP_perSD	Keratinocyte carcinoma	0.94 (0.93–0.96)	<0.001	<0.001
DOSE PYSP_perSD	Basal cell carcinoma	0.93 (0.91–0.94)	<0.001	<0.001
DOSE PYSP_perSD	Squamous cell carcinoma	1.02 (0.98–1.05)	0.407	0.499
DOSE PYSP_perSD	Brain	0.94 (0.87–1.02)	0.115	0.155
DOSE PYSP_perSD	Thyroid	0.98 (0.88–1.10)	0.746	0.775
DOSE PYSP_perSD	Hematological malignancies	1.01 (0.98–1.04)	0.527	0.593
DOSE PYSP_perSD	Hodgkin lymphoma	1.13 (0.99–1.29)	0.076	0.107
DOSE PYSP_perSD	Non-Hodgkin lymphoma	1.02 (0.98–1.07)	0.353	0.454
DOSE PYSP_perSD	Multiple myeloma	0.88 (0.81–0.96)	0.002	0.004
DOSE PYSP_perSD	Leukemia	1.06 (1.00–1.11)	0.039	0.059

No-status models retain the other Model 2 covariates but omit smoking status. The primary ASI Model 2 already omits smoking status; its categorical results are in Supplementary Table 3 and Figure 3, and initiator-only trends are in eFigure 2. These models address one overlapping adjustment variable; other potential mediators remain in the extended model and therefore their estimates are not identified total causal effects.

Fit messages are retained by exposure and outcome in Additional_model_fit_warnings.csv. The structurally overlapping, status-adjusted true-never categorical ASI fit is not used for inference.

Supplementary Table 6 Legacy-reference ASI sensitivity

These analyses preserve the original mixed no-recorded-age reference and original exposure eligibility. They are not primary results and must not be interpreted as comparisons with never smoking. Model 1 and the extended model without smoking status use the same covariate sets as the primary ASI analysis. Thus, differences reflect the changed reference and eligibility, not a change in smoking-status adjustment. Original metadata and category counts are included as separate CSVs.

Legacy reference: Model 1

Outcome	Adult HR (CI)	Adolescent HR (CI)	Childhood HR (CI)	Childhood FDR
All-cause cancer	1.13 (1.10–1.15)	1.18 (1.15–1.20)	1.28 (1.18–1.39)	<0.001
Oropharyngeal	2.29 (1.94–2.71)	2.06 (1.76–2.40)	3.05 (1.94–4.80)	<0.001
Esophageal	1.93 (1.62–2.30)	2.01 (1.72–2.35)	2.75 (1.71–4.44)	<0.001
Gastric	1.34 (1.07–1.68)	1.70 (1.42–2.04)	NE (<10 events)	NE
Colorectal	1.29 (1.20–1.39)	1.32 (1.23–1.41)	1.20 (0.89–1.63)	0.447
Liver	1.42 (1.12–1.81)	2.08 (1.71–2.51)	NE (<10 events)	NE
Gallbladder	1.37 (0.82–2.30)	1.19 (0.72–1.94)	NE (<10 events)	NE
Pancreatic	1.43 (1.22–1.67)	1.45 (1.25–1.67)	1.67 (0.94–2.97)	0.195
Lung	5.46 (4.96–6.02)	7.57 (6.94–8.26)	9.48 (7.64–11.77)	<0.001
Breast (women)	1.07 (1.01–1.14)	1.01 (0.95–1.08)	1.12 (0.79–1.59)	0.799
Renal	1.28 (1.10–1.49)	1.30 (1.14–1.48)	2.07 (1.35–3.17)	0.004
Bladder	1.57 (1.30–1.89)	2.22 (1.92–2.58)	3.37 (2.19–5.21)	<0.001
Prostate (men)	0.87 (0.82–0.92)	0.85 (0.81–0.89)	0.78 (0.63–0.97)	0.078
Cervical (women)	1.44 (0.86–2.42)	1.08 (0.63–1.85)	NE (<10 events)	NE
Endometrial (women)	0.81 (0.69–0.96)	0.67 (0.56–0.80)	NE (<10 events)	NE
Ovarian (women)	0.99 (0.82–1.19)	1.10 (0.92–1.32)	NE (<10 events)	NE
Cutaneous melanoma	0.84 (0.74–0.96)	0.75 (0.67–0.85)	0.67 (0.37–1.21)	0.389
Keratinocyte carcinoma	0.94 (0.90–0.98)	0.91 (0.88–0.95)	0.88 (0.75–1.05)	0.341
Basal cell carcinoma	0.91 (0.87–0.95)	0.90 (0.87–0.94)	0.84 (0.70–1.02)	0.195
Squamous cell carcinoma	1.13 (1.02–1.25)	0.96 (0.88–1.06)	1.19 (0.81–1.76)	0.594
Brain	0.99 (0.79–1.23)	0.97 (0.80–1.18)	NE (<10 events)	NE
Thyroid	0.96 (0.70–1.30)	0.97 (0.73–1.29)	NE (<10 events)	NE
Hematological malignancies	0.95 (0.87–1.04)	1.05 (0.97–1.14)	1.48 (1.10–1.99)	0.034
Hodgkin lymphoma	1.05 (0.63–1.75)	1.23 (0.80–1.88)	NE (<10 events)	NE
Non-Hodgkin lymphoma	0.94 (0.82–1.08)	1.06 (0.94–1.19)	1.28 (0.80–2.05)	0.519
Multiple myeloma	0.97 (0.79–1.19)	0.88 (0.72–1.06)	1.79 (0.98–3.26)	0.177
Leukemia	0.96 (0.80–1.15)	1.19 (1.02–1.38)	1.35 (0.76–2.40)	0.519

Legacy reference: extended model without smoking status

Outcome	Adult HR (CI)	Adolescent HR (CI)	Childhood HR (CI)	Childhood FDR
All-cause cancer	1.10 (1.08–1.13)	1.15 (1.12–1.17)	1.24 (1.14–1.34)	<0.001

Outcome	Adult HR (CI)	Adolescent HR (CI)	Childhood HR (CI)	Childhood FDR
Oropharyngeal	2.17 (1.83–2.57)	1.94 (1.65–2.27)	2.79 (1.77–4.40)	<0.001
Esophageal	1.84 (1.55–2.20)	1.87 (1.60–2.19)	2.34 (1.45–3.78)	0.003
Gastric	1.33 (1.06–1.66)	1.67 (1.39–2.01)	NE (<10 events)	NE
Colorectal	1.24 (1.15–1.34)	1.25 (1.17–1.34)	1.12 (0.83–1.52)	0.734
Liver	1.30 (1.02–1.66)	1.85 (1.53–2.25)	NE (<10 events)	NE
Gallbladder	1.37 (0.82–2.31)	1.17 (0.71–1.92)	NE (<10 events)	NE
Pancreatic	1.34 (1.14–1.57)	1.34 (1.15–1.55)	1.47 (0.83–2.61)	0.431
Lung	5.30 (4.81–5.84)	7.27 (6.65–7.93)	8.66 (6.97–10.76)	<0.001
Breast (women)	1.04 (0.98–1.11)	0.99 (0.93–1.06)	1.09 (0.77–1.56)	0.940
Renal	1.23 (1.06–1.44)	1.21 (1.06–1.39)	1.83 (1.19–2.82)	0.025
Bladder	1.51 (1.25–1.82)	2.11 (1.82–2.45)	3.12 (2.02–4.82)	<0.001
Prostate (men)	0.87 (0.83–0.93)	0.85 (0.81–0.90)	0.80 (0.65–0.99)	0.136
Cervical (women)	1.40 (0.83–2.37)	1.04 (0.61–1.80)	NE (<10 events)	NE
Endometrial (women)	0.79 (0.67–0.93)	0.69 (0.57–0.82)	NE (<10 events)	NE
Ovarian (women)	1.00 (0.83–1.21)	1.16 (0.97–1.38)	NE (<10 events)	NE
Cutaneous melanoma	0.83 (0.73–0.94)	0.73 (0.65–0.82)	0.66 (0.36–1.19)	0.405
Keratinocyte carcinoma	0.94 (0.90–0.98)	0.91 (0.88–0.94)	0.91 (0.77–1.08)	0.582
Basal cell carcinoma	0.91 (0.87–0.95)	0.90 (0.87–0.94)	0.88 (0.73–1.06)	0.405
Squamous cell carcinoma	1.11 (1.00–1.23)	0.94 (0.85–1.04)	1.18 (0.80–1.74)	0.734
Brain	0.99 (0.79–1.23)	0.97 (0.80–1.18)	NE (<10 events)	NE
Thyroid	0.97 (0.71–1.32)	0.97 (0.73–1.29)	NE (<10 events)	NE
Hematological malignancies	0.94 (0.85–1.03)	1.02 (0.94–1.11)	1.39 (1.03–1.86)	0.112
Hodgkin lymphoma	1.05 (0.63–1.76)	1.22 (0.79–1.87)	NE (<10 events)	NE
Non-Hodgkin lymphoma	0.93 (0.81–1.07)	1.04 (0.92–1.17)	1.23 (0.77–1.96)	0.734
Multiple myeloma	0.95 (0.77–1.17)	0.84 (0.69–1.02)	1.65 (0.90–3.02)	0.313
Leukemia	0.93 (0.78–1.12)	1.14 (0.98–1.33)	1.24 (0.70–2.21)	0.734

NE indicates fewer than 10 category events. Full nominal and adjusted P values, Ns, and case counts are in Supplementary_model_output.csv under analysis = original_reference. Each model and category contrast has a separate 27-outcome FDR family. Archived status-adjusted original-reference outputs remain in the full CSV for audit but are not the primary ASI Model 2.

Supplementary Table 7 Restricted cubic spline tests

Original smoking-dose cohorts and four-knot spline models; reference dose = 0. Overall association is tested with 3 degrees of freedom and nonlinearity with 2. All P values are nominal and exploratory. Complete coefficients, covariance matrices, prediction coordinates, and exact knot locations are provided in the accompanying RCS CSV files. Female-specific cancers were not included in the original spline series; prostate analyses include men only. Other spline outcomes include both sexes.

PYS spline models

Outcome	N	Events	Overall P	Nonlinear P	Four knots
All-cause cancer	467,333	69,647	<0.0001	0.0002	0.05; 3.25; 19.125; 57.75
Oropharyngeal	501,723	934	<0.0001	0.6420	0.05; 3.3; 19.25; 58
Esophageal	502,101	921	<0.0001	0.0764	0.05; 3.3; 19.25; 58
Gastric	502,094	643	<0.0001	0.0240	0.05; 3.3; 19.25; 58
Colorectal	499,980	5,296	<0.0001	0.1889	0.05; 3.3; 19.2; 58
Liver	502,200	565	0.0123	0.0911	0.05; 3.3; 19.25; 58
Gallbladder	502,228	108	0.4327	0.2770	0.05; 3.3; 19.25; 58
Pancreatic	502,183	1,141	0.0043	0.1370	0.05; 3.3; 19.25; 58
Lung	501,936	3,653	<0.0001	<0.0001	0.05; 3.3; 19.2; 57.75
Renal	501,775	1,358	0.2038	0.9432	0.05; 3.3; 19.25; 58
Bladder	501,664	951	<0.0001	0.7355	0.05; 3.3; 19.2; 58
Prostate (men)	225,964	10,203	0.0002	0.0296	0.05; 4; 21.5; 66
Cutaneous melanoma	500,298	2,361	0.0037	0.0850	0.05; 3.3; 19.25; 58
Keratinocyte carcinoma	492,708	22,528	<0.0001	0.2082	0.05; 3.3; 19.25; 58
Basal cell carcinoma	489,472	19,292	<0.0001	0.0692	0.05; 3.3; 19.2; 58
Squamous cell carcinoma	473,220	3,040	0.3538	0.4668	0.05; 3.3; 19.25; 58
Brain	502,102	734	0.1341	0.4891	0.05; 3.3; 19.25; 58
Thyroid	501,836	387	0.4569	0.3299	0.05; 3.3; 19.25; 58
Hematological malignancies	500,247	4,063	0.3303	0.1982	0.05; 3.3; 19.25; 58
Hodgkin lymphoma	501,886	139	0.2376	0.3561	0.05; 3.3; 19.25; 58
Non-Hodgkin lymphoma	501,285	1,926	0.3808	0.4850	0.05; 3.3; 19.25; 58
Multiple myeloma	502,058	804	0.0035	0.2148	0.05; 3.3; 19.25; 58
Leukemia	501,746	1,103	0.0195	0.0179	0.05; 3.3; 19.25; 58

PYSP spline models

Outcome	N	Events	Overall P	Nonlinear P	Four knots
All-cause cancer	467,333	69,647	<0.0001	0.0012	0.0011628; 0.078947; 0.47059; 1.3208
Oropharyngeal	501,723	934	<0.0001	0.6138	0.0011628; 0.078947; 0.46939; 1.319
Esophageal	502,101	921	<0.0001	0.2155	0.0011628; 0.078947; 0.46939; 1.32
Gastric	502,094	643	<0.0001	0.0069	0.0011628; 0.078947; 0.46939; 1.32
Colorectal	499,980	5,296	<0.0001	0.1243	0.0011628; 0.078947; 0.46939; 1.3192
Liver	502,200	565	0.0056	0.0371	0.0011628; 0.078947; 0.46939; 1.32
Gallbladder	502,228	108	0.3883	0.2403	0.0011628; 0.078947; 0.46939; 1.32
Pancreatic	502,183	1,141	0.0014	0.1349	0.0011628; 0.078947; 0.46939; 1.32
Lung	501,936	3,653	<0.0001	<0.0001	0.0011628; 0.078947; 0.46875; 1.319
Renal	501,775	1,358	0.1216	0.8036	0.0011628; 0.078947; 0.46939; 1.32
Bladder	501,664	951	<0.0001	0.8144	0.0011628; 0.078947; 0.46875; 1.32
Prostate (men)	225,964	10,203	0.0002	0.0204	0.0011628; 0.091463; 0.5; 1.4821
Cutaneous melanoma	500,298	2,361	0.0045	0.1088	0.0011628; 0.078947; 0.4697; 1.3207
Keratinocyte carcinoma	492,708	22,528	<0.0001	0.0537	0.0011628; 0.079194; 0.47024; 1.3214
Basal cell carcinoma	489,472	19,292	<0.0001	0.0219	0.0011628; 0.079167; 0.47059; 1.3214
Squamous cell carcinoma	473,220	3,040	0.7974	0.9179	0.0011628; 0.079546; 0.47297; 1.3281
Brain	502,102	734	0.2106	0.8496	0.0011628; 0.078947; 0.46951; 1.32
Thyroid	501,836	387	0.4643	0.3524	0.0011628; 0.078947; 0.46951; 1.32
Hematological malignancies	500,247	4,063	0.4565	0.2847	0.0011628; 0.078947; 0.46951; 1.32
Hodgkin lymphoma	501,886	139	0.2701	0.3311	0.0011628; 0.078947; 0.46948; 1.32
Non-Hodgkin lymphoma	501,285	1,926	0.4277	0.4779	0.0011628; 0.078947; 0.46951; 1.32
Multiple myeloma	502,058	804	0.0040	0.2056	0.0011628; 0.078947; 0.46951; 1.32
Leukemia	501,746	1,103	0.0297	0.0249	0.0011628; 0.078947; 0.46939; 1.32

Adjustment: age, sex where applicable, race/ethnicity, BMI, income, alcohol category, physical activity, deprivation category, education, smoking status, heart disease, stroke, diabetes, hypertension, CRP, and diet. Prostate models additionally include PSA testing and prostate-cancer family history and omit sex. Unlike the linear skin-cancer models, these original spline models do not include skin-specific covariates. Dose units are pack-years for PYS and pack-years/year for PYSP. Knots follow the original rms tied-value handling and therefore are reported numerically rather than assigned nominal whole-cohort percentiles.

Supplementary figure legends

eFigure 1. Extended-model sensitivity for MSDP without smoking-status adjustment. Reference contrasts and SD units are as in the main figures. Points and bars show HRs and 95% CIs, the dashed line denotes HR = 1, and the horizontal scale is logarithmic. Cohort Ns and model definitions are in Supplementary Table 1 and the Methods; each exposure or initiation contrast has a separate 27-outcome FDR family. Exact numerical results are supplied in the model CSV.

eFigure 2. Initiator-only ASI trend estimates for Model 1 and primary ASI Model 2, which omits smoking status. Current/former smokers with recorded initiation age are scored adult = 0, adolescence = 1, childhood = 2. HRs represent one category-score increase toward earlier initiation. These are not category-versus-never contrasts; sparse childhood contrasts suppressed in Figure 3 are not plotted separately here. Points and bars indicate HRs and 95% CIs; the dashed line is HR = 1 and the axis is logarithmic. Each model has a separate 27-outcome FDR family. Exact estimates and the additional current/former-status-adjusted sensitivity are in Supplementary Table 3 and the model CSV.

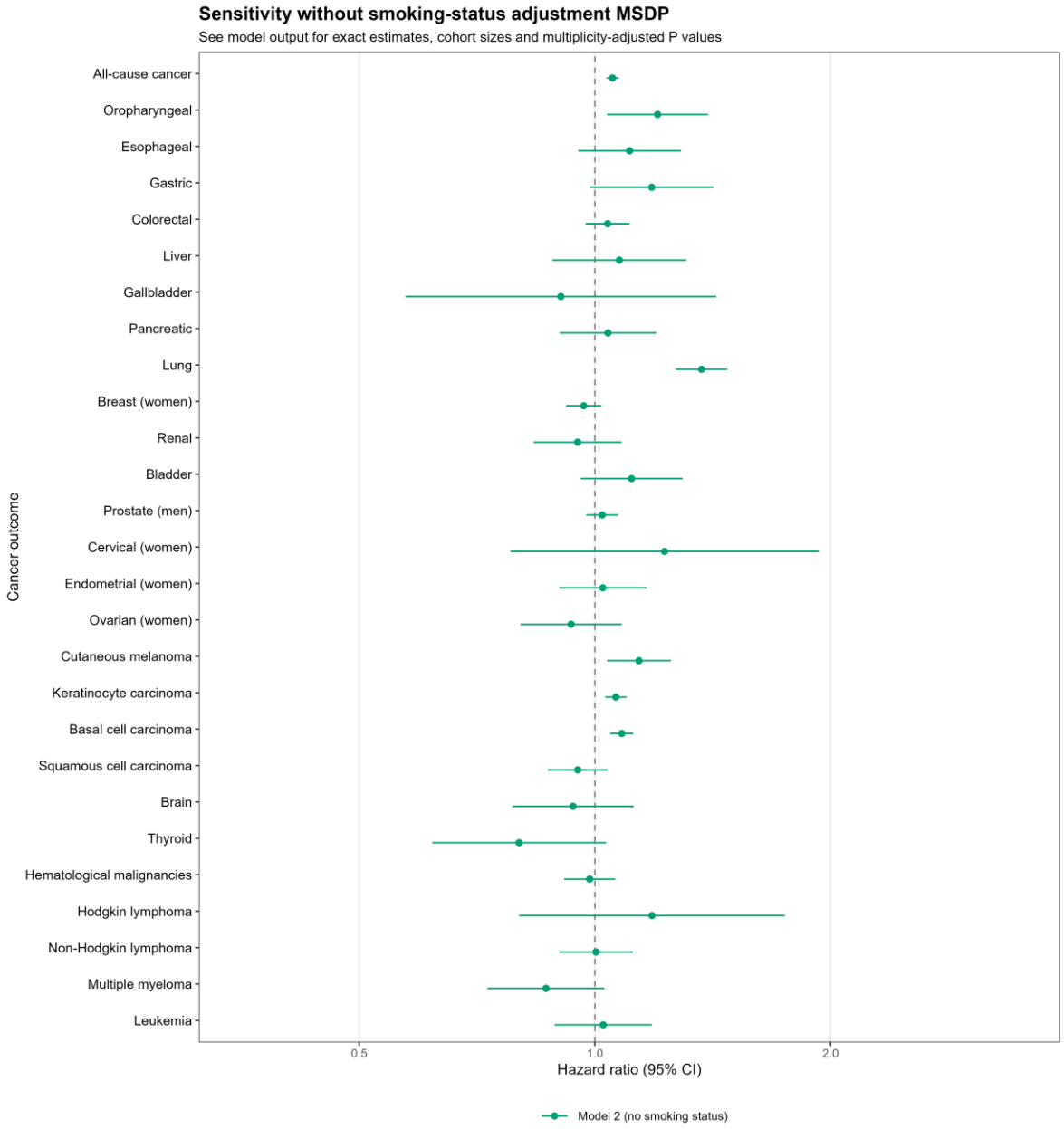
eFigure 3. Extended-model sensitivity for Smoking dose without smoking-status adjustment. Reference contrasts and SD units are as in the main figures. Points and bars show HRs and 95% CIs, the dashed line denotes HR = 1, and the horizontal scale is logarithmic. Cohort Ns and model definitions are in Supplementary Table 1 and the Methods; each exposure or initiation contrast has a separate 27-outcome FDR family. Exact numerical results are supplied in the model CSV.

eFigure 4. Legacy-reference ASI sensitivity using the original no-recorded-initiation-age category as reference. This mixed category includes current/former smokers with missing initiation age and must not be called never smoking. Model 1 and the extended model omitting smoking status are shown, matching the primary ASI covariate sets. The original all-cause sample has 466,292 participants; outcome-specific sample sizes are in ASI_original_reference_metadata.csv. Differences from the primary analysis reflect both reference composition and eligibility. The dashed line denotes HR = 1; panels share a logarithmic scale. Right-hand numbers are category events and NE denotes suppression below 10 events. Each contrast/model has a separate 27-outcome FDR family. Numerical results are in Supplementary Table 6.

eFigure 5. Hypothesised pathways relevant to MSDP adjustment. Arrows denote assumptions, not estimated effects. Familial and social background may cause maternal smoking and adult cancer; own smoking and adult BMI, inflammation, or chronic disease may be downstream of prenatal exposure. The simplified diagram illustrates possible over-adjustment, not a sufficient adjustment set for identifying causal effects. See Schisterman EF et al. Epidemiology. 2009;20:488–495. doi:10.1097/EDE.0b013e3181a819a1.

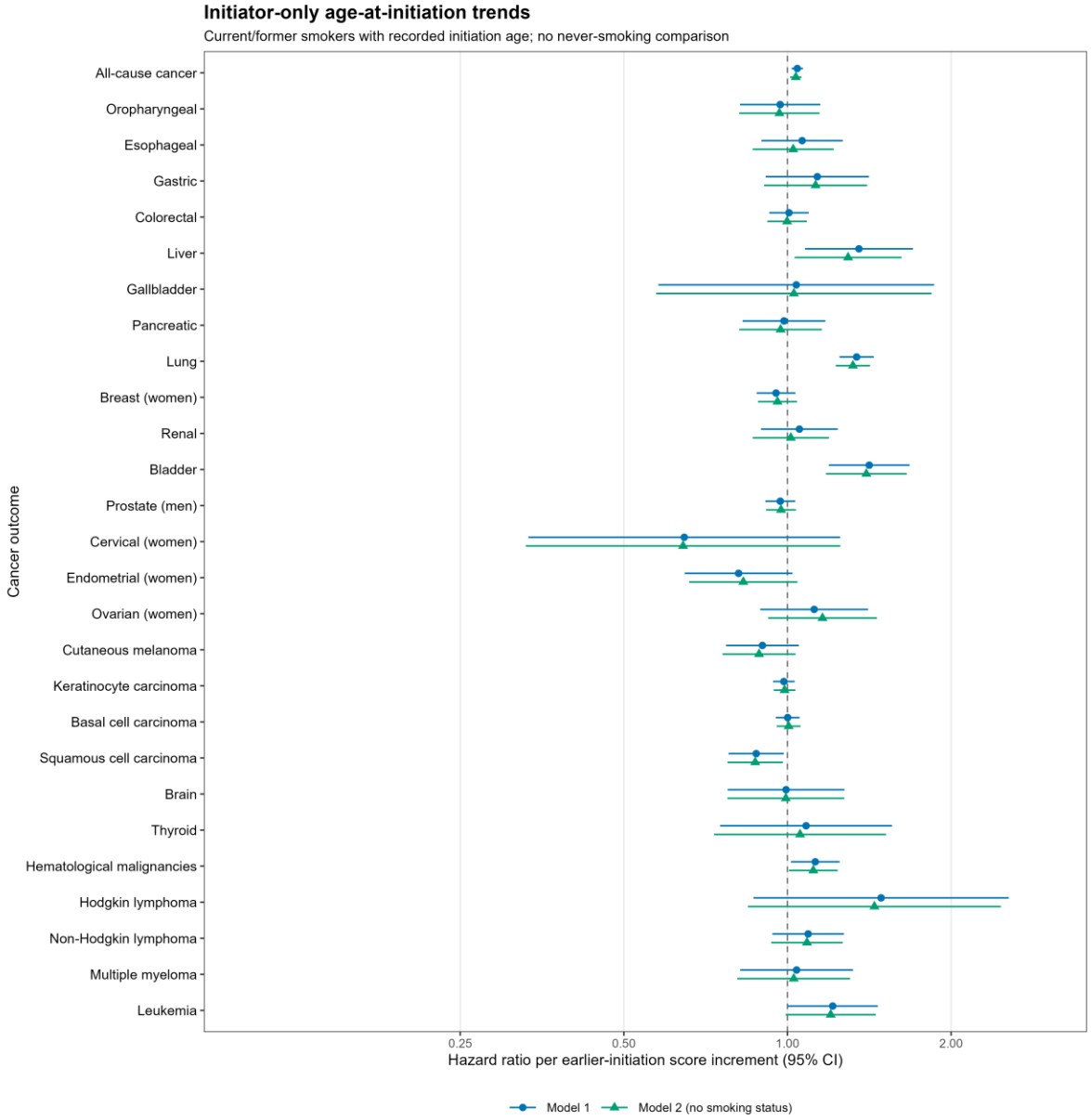
eFigures 6A–6B and 7A–7B. Complete restricted cubic spline curves for PYS (eFigure 6) and PYSP (eFigure 7), each covering 23 outcomes across two pages. The solid curve is the adjusted HR, the shaded band the 95% CI, and the dashed horizontal line HR = 1; reference dose is zero. Axes give the dose units and HR, with outcome-specific vertical scales. The four-knot model, adjustment covariates, exploratory nominal Wald tests, sample sizes, event counts, and knots are described in Supplementary Table 7. Prostate analyses include men only. Both significant and nonsignificant nonlinear tests are displayed; curve crossings are not interpreted as safe-exposure thresholds.

eFigure 1 MSDP without smoking-status adjustment



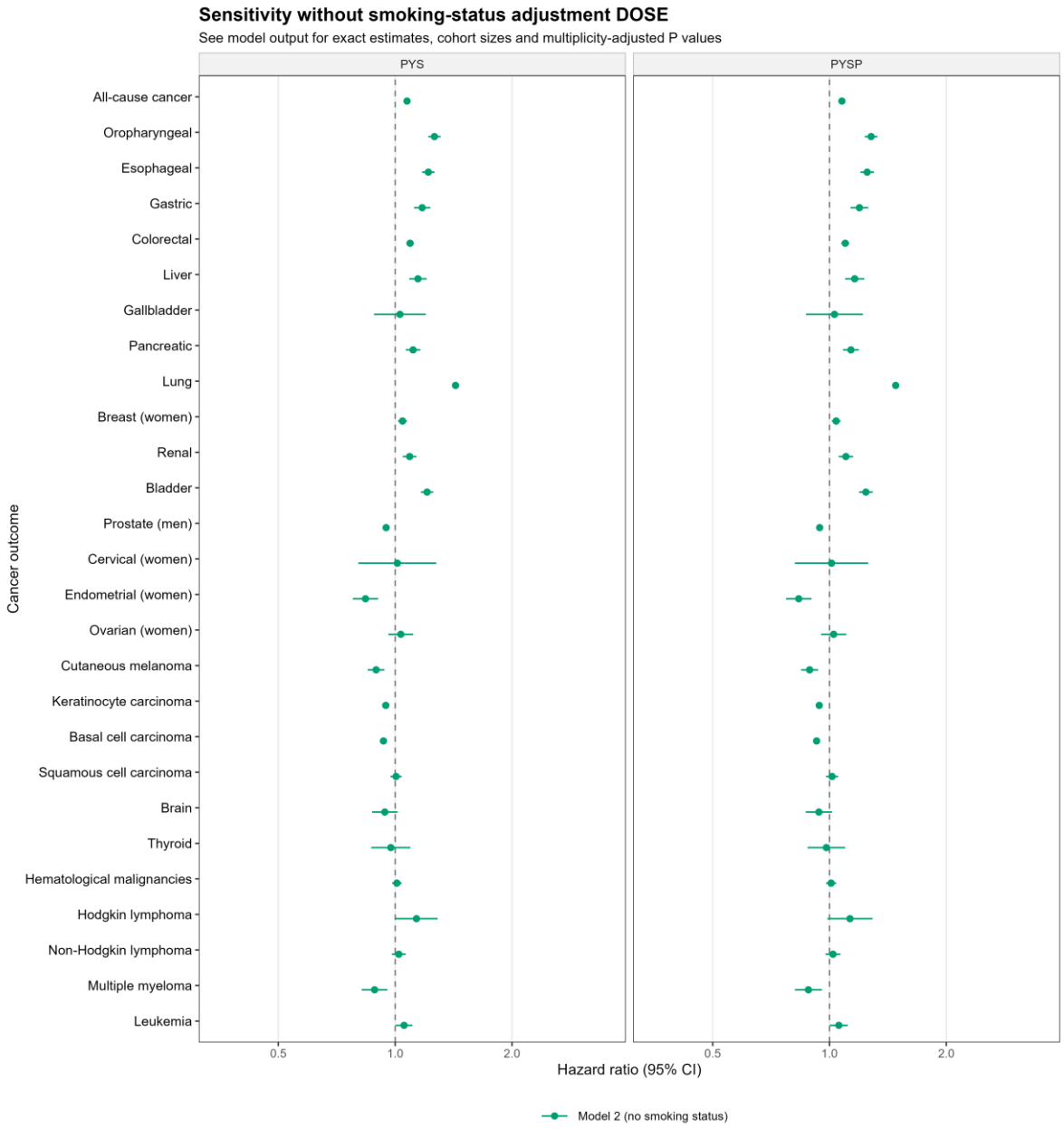
See the supplementary figure legends for contrasts, adjustment sets, sex restrictions, multiplicity families, and suppression rules.

eFigure 2 Initiator-only ASI trends



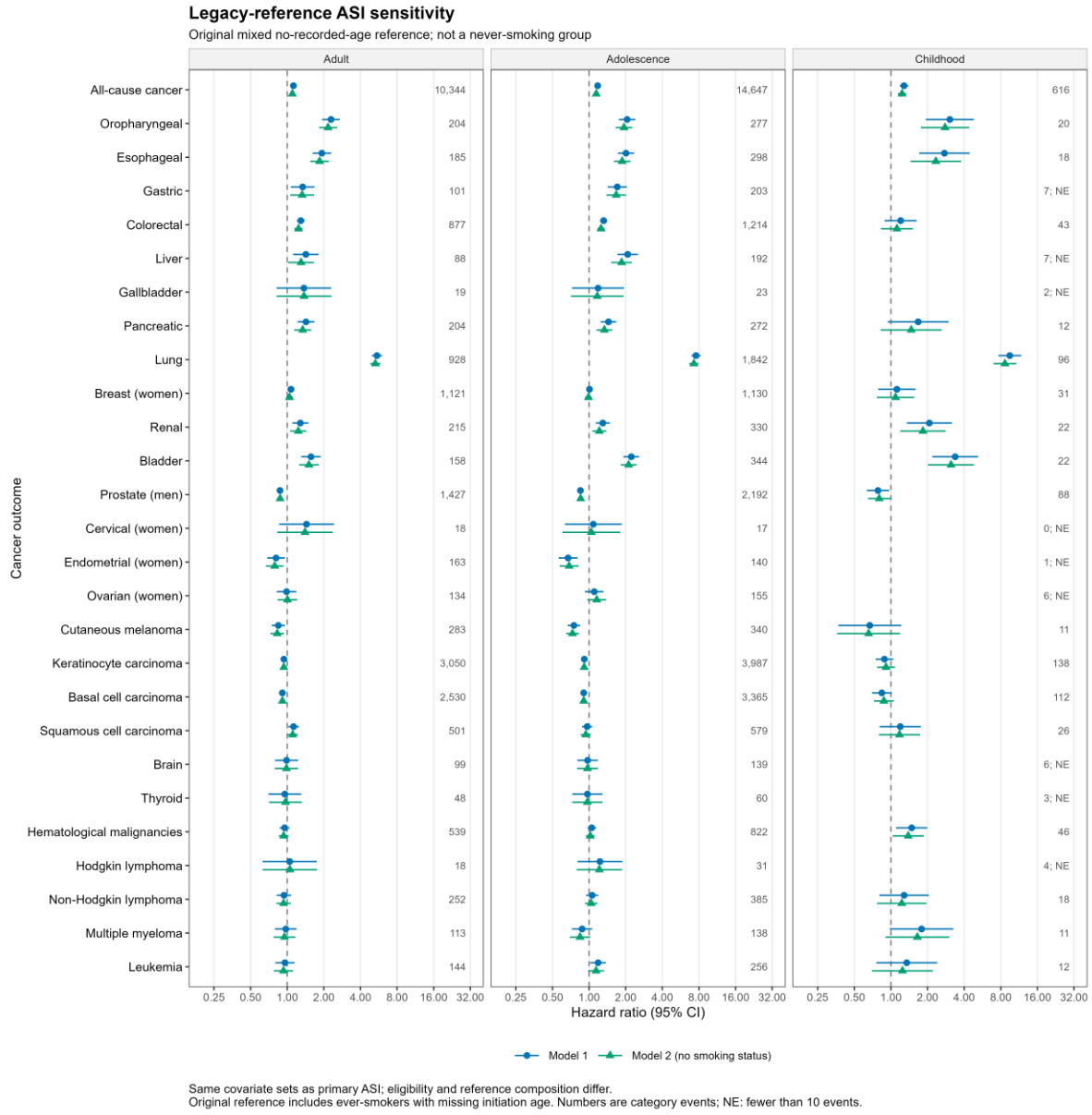
See the supplementary figure legends for contrasts, adjustment sets, sex restrictions, multiplicity families, and suppression rules.

eFigure 3 Smoking dose without smoking-status adjustment



See the supplementary figure legends for contrasts, adjustment sets, sex restrictions, multiplicity families, and suppression rules.

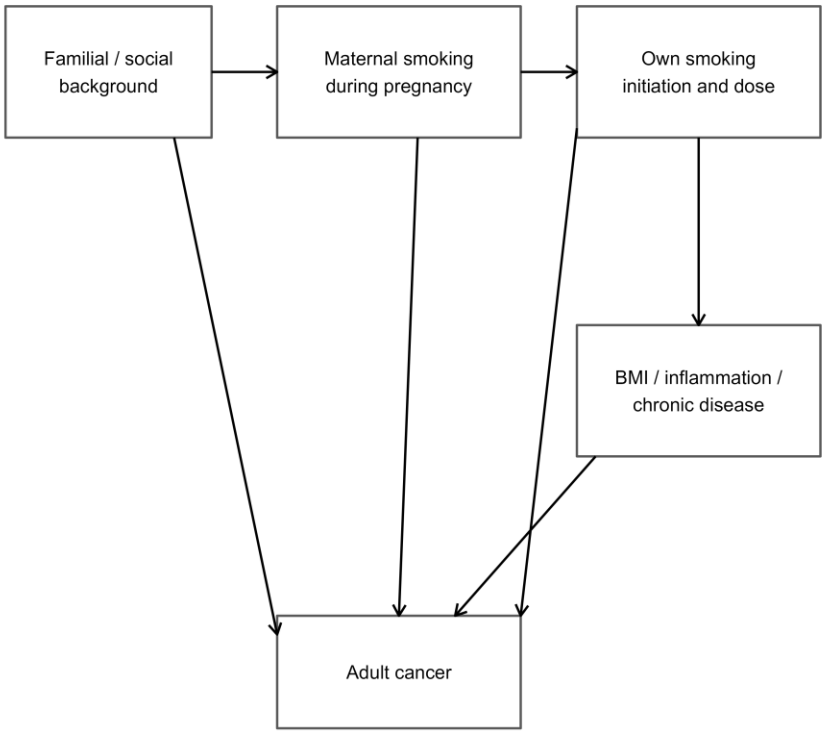
eFigure 4 Legacy-reference ASI sensitivity



See the supplementary figure legends for contrasts, adjustment sets, sex restrictions, multiplicity families, and suppression rules.

eFigure 5 Hypothesised pathways and potential over-adjustment

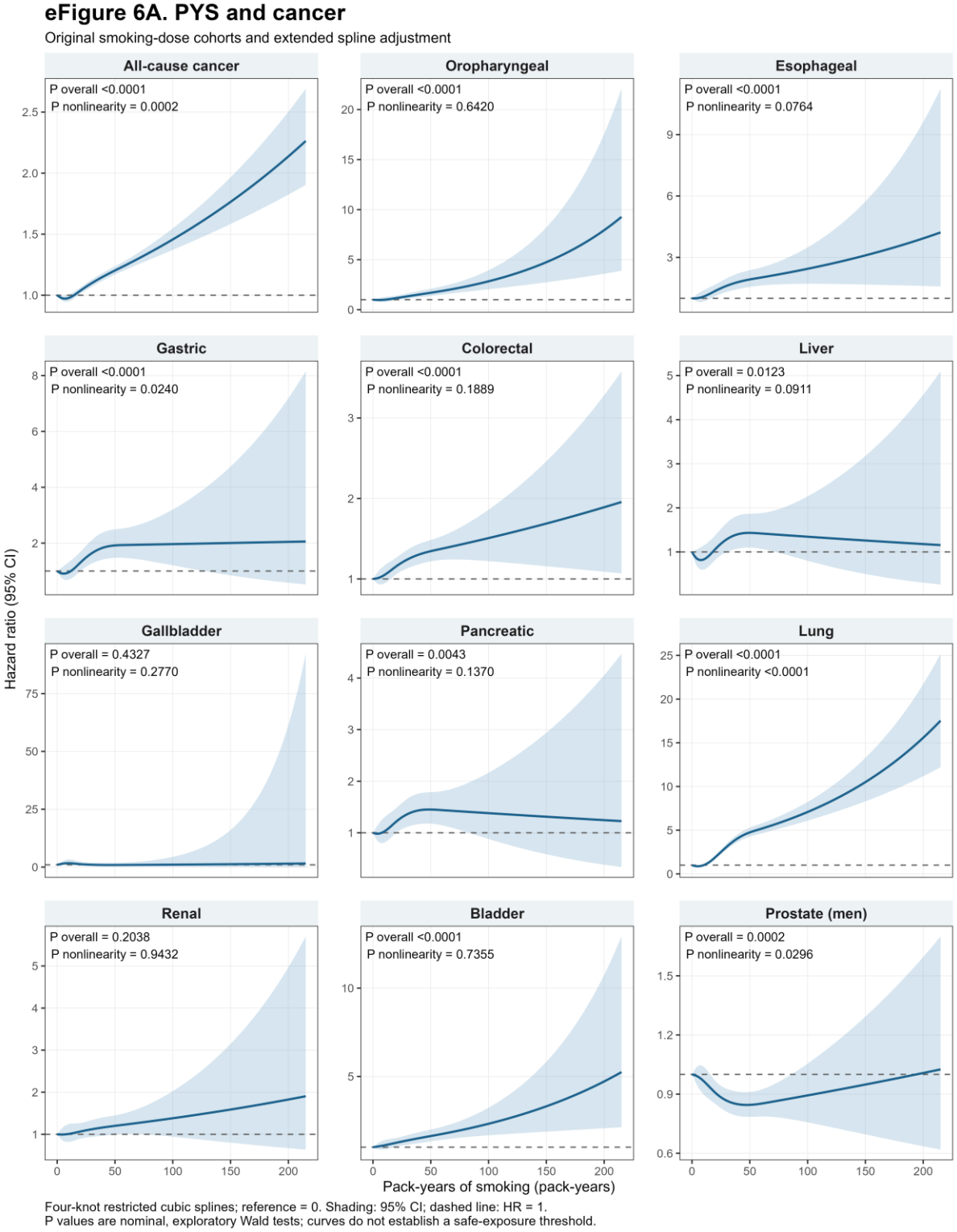
Hypothesized pathways and potential over-adjustment



Arrows are assumptions, not findings. Familial and social background includes unmeasured factors.
Own smoking and adult health variables can lie downstream of maternal exposure.
Smoking status overlaps with initiation and dose definitions. Conditional HRs are not identified causal effects.

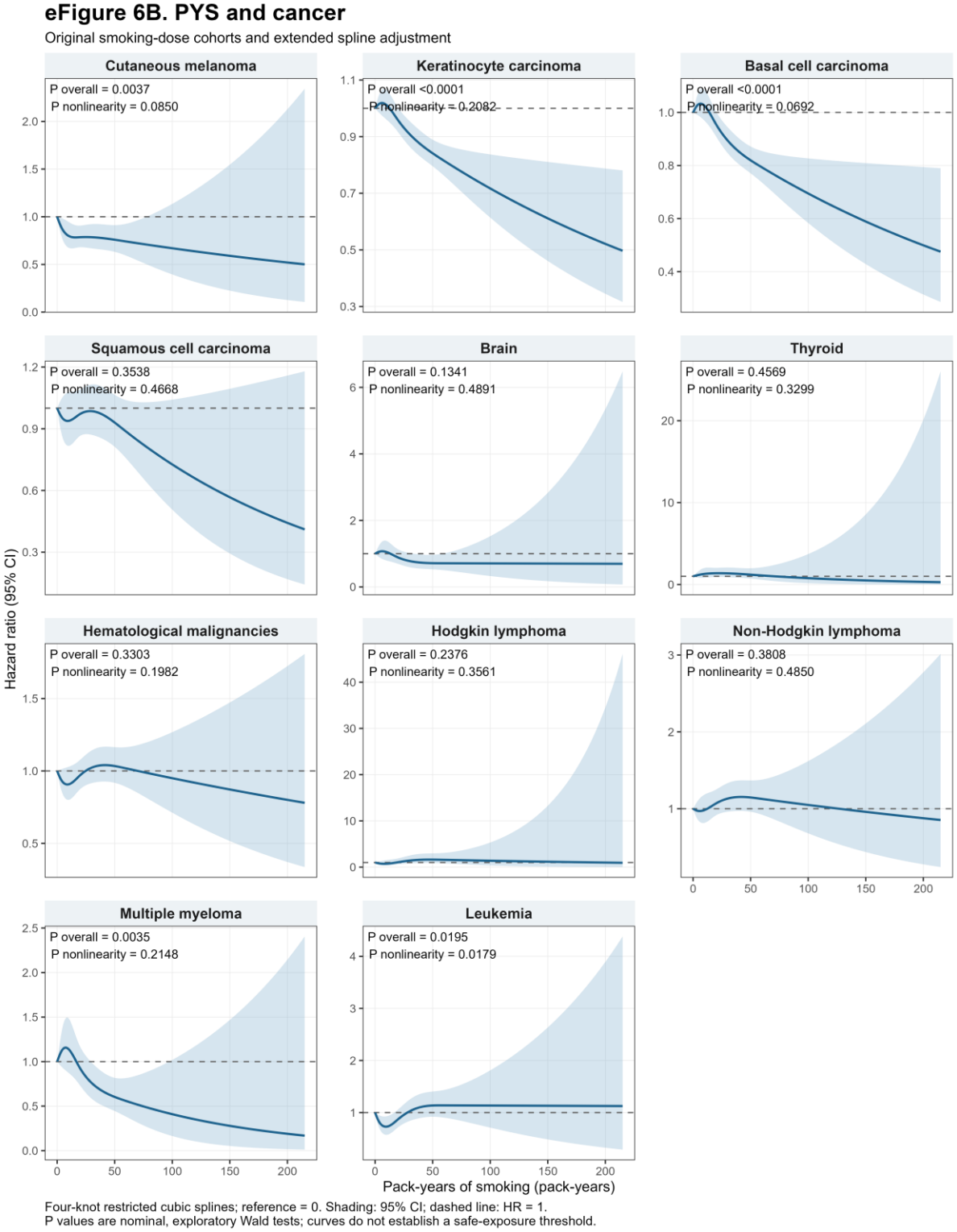
See the supplementary figure legends for contrasts, adjustment sets, sex restrictions, multiplicity families, and suppression rules.

eFigure 6A PYS restricted cubic splines



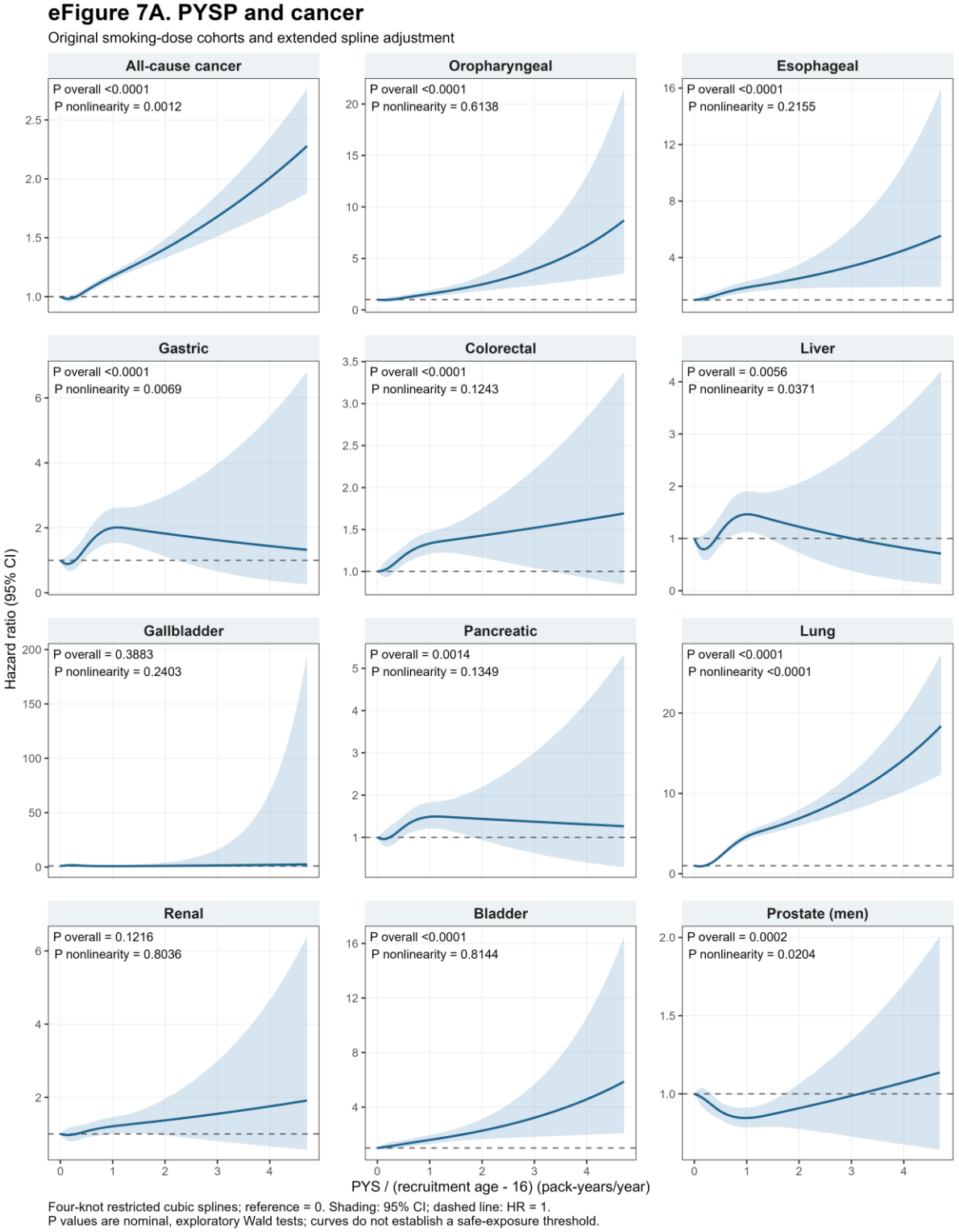
Full model definitions, sample sizes, and nominal tests: Supplementary Table 7.

eFigure 6B PYS restricted cubic splines



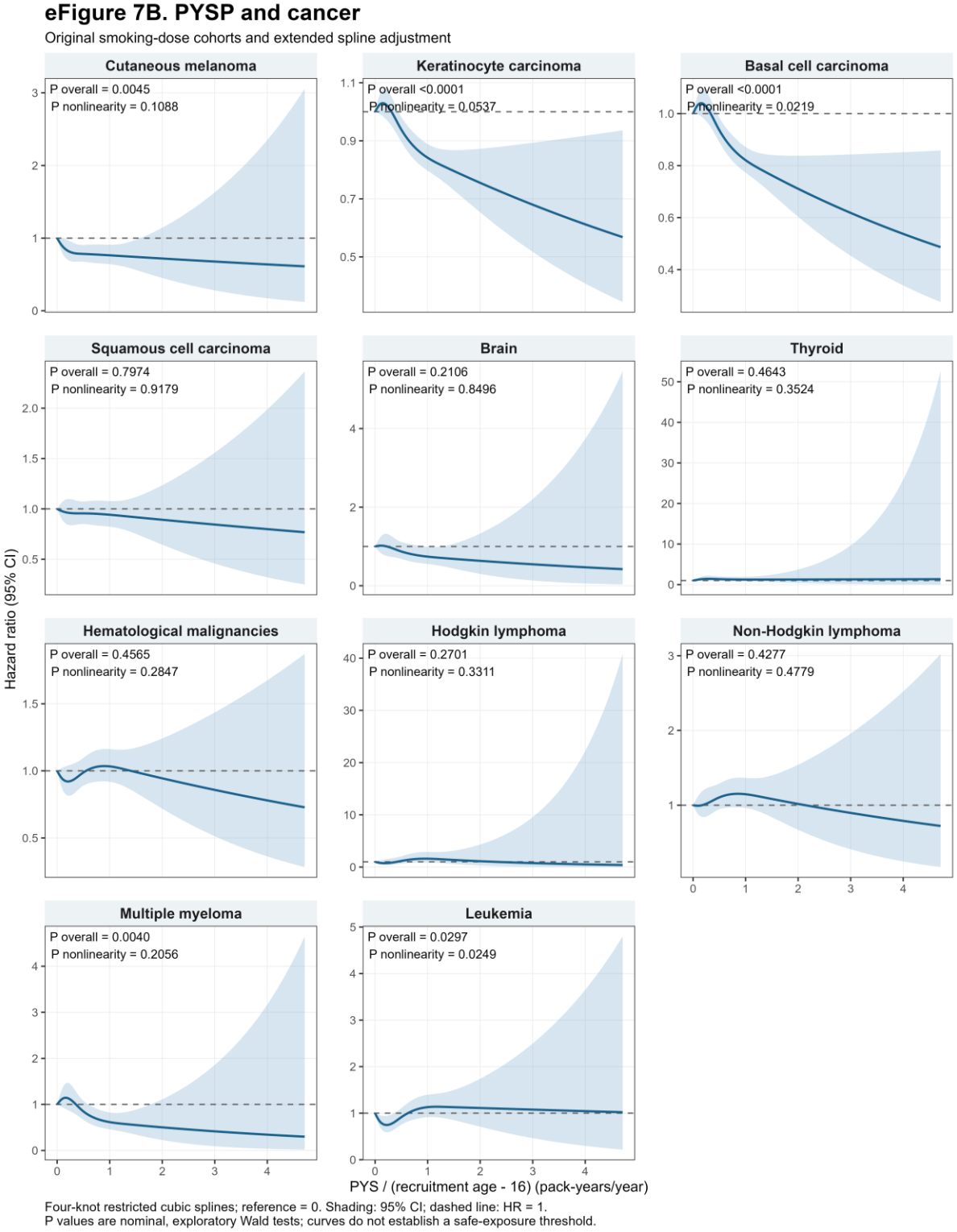
Full model definitions, sample sizes, and nominal tests: Supplementary Table 7.

eFigure 7A PYSP restricted cubic splines



Full model definitions, sample sizes, and nominal tests: Supplementary Table 7.

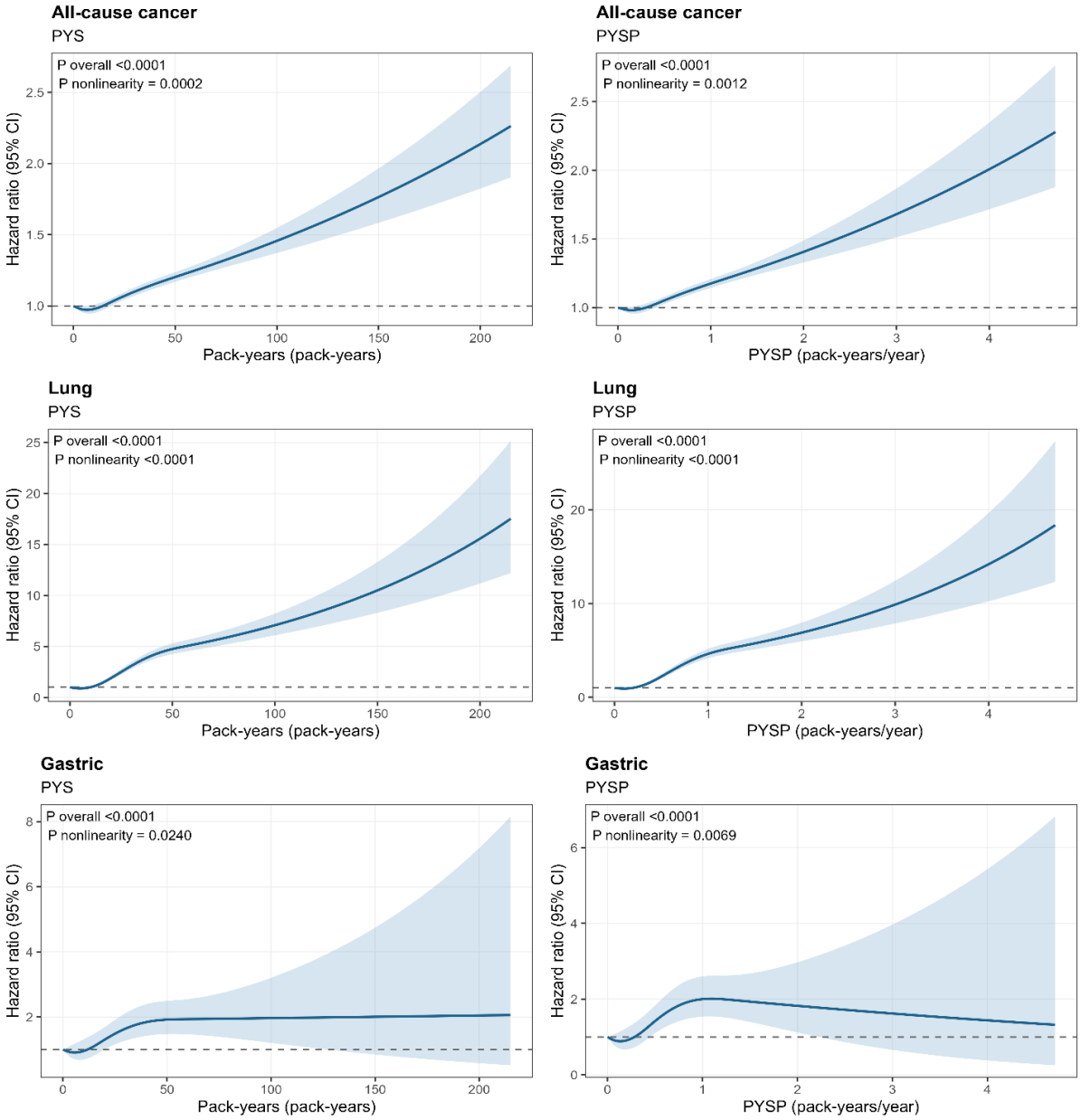
eFigure 7B PYSP restricted cubic splines



Full model definitions, sample sizes, and nominal tests: Supplementary Table 7.

Supplementary file Figure 8. Restricted cubic spline associations of PYS and PYSP with all-cause, lung, and gastric cancer. Curves show adjusted HRs relative to PYS = 0 or PYSP = 0; shading indicates 95% CIs, and the horizontal dashed line denotes HR = 1. The left column uses PYS in pack-years; the right uses PYSP = PYS/(recruitment age − 16), in pack-years/year. Four-knot Cox spline models use the original dose cohorts and the extended spline covariates specified in the Methods, including smoking status. Overall and nonlinear P values are nominal Wald tests with 3 and 2 degrees of freedom; they are exploratory and unadjusted for multiplicity. Knot locations, sample sizes, event counts, and full output are in Supplementary file Table 7 and the RCS model files. Complete curves for 23 outcomes appear in eFigures 6–7. The panels have outcome-specific vertical scales. A curve crossing HR = 1 does not define a safe-exposure threshold. CI, confidence interval; HR, hazard ratio; PYS, pack-years of smoking; PYSP, scaled pack-years.

Figure 8. Restricted cubic spline dose-response associations



Four knots; reference = 0; shading = 95% CI; dashed line = HR 1.
Nominal Wald P values. Complete outcome curves: eFigures 6-7.