

Smoking and risk of breast cancer in the Generations Study cohort

SUPPLEMENTARY TABLE 1: Further characteristics of 102,927 women from the Generations Study who were recruited 2003–2013

Study population	N	%
Age started smoking (years)		
Never smoker	66013	64.1
<16	13773	13.4
17–19	14351	13.9
20+	7306	7.1
Smoker, age started unknown	1484	1.4
Age at thelarche (years)		
7–11	33251	32.3
12–14	48089	46.7
15–19	3440	3.3
Not known	18147	17.6
Parity, at entry to cohort		
Nulliparous	29209	28.4
Parous	73718	71.6
Age at 1st parous birth (years)		
13–19	4170	5.7
20–24	20520	27.8
25–29	30108	40.8
30–34	14721	20.0
35–49	4199	5.7
Menopausal status at entry to cohort		
Pre-menopausal	59841	58.1
Post-menopausal	43086	41.9
BMI at age 20		
<20	22808	22.2
20–<25	51217	49.8
25–<30	7463	7.3
30–<35	1307	1.3
35+	396	0.4
Unknown	19746	19.2
Post-menopausal BMI at entry to cohort (N=43,086)		
<20	1671	3.9
20–<25	19064	44.3
25–<30	14856	34.5
30–<35	4710	10.9
35+	1741	4.0
Unknown	1044	2.4
Total number of subjects	102927	100.0

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SUPPLEMENTARY TABLE 2: Characteristics of incident invasive breast cancer cases arising in 102,927 women from the Generations Study

Study population	N	%
Age at breast cancer diagnosis (years)		
24–44	247	13.6
45–54	474	26.1
55–64	610	33.6
65–74	404	22.3
75–95	80	4.4
Year of breast cancer diagnosis		
2004–2006	130	7.2
2007–2009	550	30.3
2010–2012	697	38.4
2013–2015	438	24.1
Confirmation of breast cancer		
Confirmed*	1813	99.9
Self-reported only†	2	0.1
Morphological type		
Ductal	1430	78.8
Lobular	298	16.4
Tubular	31	1.7
Mucinous or colloid	18	1.0
Adenocarcinoma (not otherwise specified)	15	0.8
Other known types	16	0.9
Missing	7	0.4
Estrogen receptor status		
Positive	1509	82.7
Negative	294	16.1
Not tested	6	0.3
Missing	6	0.3
Total number of cases	1815	100.0

* Confirmation through national cancer registration or medical records

† With reported treatments that imply self-reported diagnosis of breast cancer is correct

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SUPPLEMENTARY TABLE 3: Relative risk of breast cancer in relation to smoking, by morphological type

	Morphological type*												
	Ductal				Lobular				Other types, and missing				
	Cases	HR [†]	95% CI	P-value	Cases	HR [†]	95% CI	P-value	Cases	HR [†]	95% CI	P-value	
Ever previously smoked cigarettes[‡]													
Never	849	1.00	Baseline		174	1.00	Baseline		50	1.00	Baseline		
Ever	581	1.12	1.01–1.25	0.033	124	1.16	0.92–1.47	0.20	37	1.24	0.81–1.90	0.33	
					Ever smoking by morphological type interaction P=0.63								
Cigarettes per day, averaged over years when smoking [§]													
Never smoked	849	1.00	Baseline		174	1.00	Baseline		50	1.00	Baseline		
1–4	204	1.08	0.93–1.26	0.34	40	1.01	0.71–1.42	0.98	14	1.29	0.71–2.34	0.40	
5–9	107	1.22	0.99–1.50	0.058	17	0.96	0.58–1.58	0.88	11	2.17	1.13–4.16	0.020	
10–14	58	1.21	0.93–1.59	0.16	22	2.36	1.51–3.68	0.0001	2	0.71	0.17–2.93	0.64	
15+	52	1.56	1.17–2.07	0.0023	9	1.39	0.71–2.71	0.34	1	0.51	0.07–3.66	0.50	
Unknown	160	1.02	0.86–1.21	0.84	36	1.09	0.76–1.57	0.64	9	0.99	0.49–2.02	0.98	
			Trend P=0.034				Trend P=0.0090				Trend P=0.27		
					Trend interaction P=0.075								
Duration of smoking (years) ¶													
Never smoked	849	1.00	Baseline		174	1.00	Baseline		50	1.00	Baseline		
1–9	145	1.03	0.87–1.23	0.72	21	0.75	0.48–1.18	0.22	11	1.35	0.70–2.63	0.37	
10–19	176	1.19	1.01–1.41	0.039	36	1.24	0.87–1.78	0.24	13	1.52	0.83–2.80	0.18	
20–29	105	1.14	0.93–1.41	0.21	30	1.58	1.07–2.34	0.022	6	1.13	0.48–2.65	0.77	
30+	126	1.24	1.03–1.50	0.026	28	1.20	0.80–1.80	0.37	5	0.84	0.34–2.12	0.72	
Duration unknown	29	0.86	0.59–1.24	0.42	9	1.25	0.64–2.45	0.52	2	1.03	0.25–4.27	0.96	
			Trend§ P=0.35				Trend§ P=0.15				Trend § P=0.55		
					Trend interaction P=0.48								
Pack-years of smoking §													
Never smoked	849	1.00	Baseline		174	1.00	Baseline		50	1.00	Baseline		
1–<5	149	1.13	0.95–1.34	0.18	24	0.91	0.60–1.40	0.68	9	1.18	0.58–2.41	0.65	
5–<10	77	0.99	0.78–1.25	0.90	16	1.02	0.61–1.71	0.93	10	2.20	1.12–4.35	0.023	
10–<20	104	1.21	0.98–1.49	0.078	26	1.47	0.97–2.22	0.069	8	1.60	0.76–3.38	0.22	
20+	91	1.49	1.19–1.85	0.0004	22	1.61	1.03–2.51	0.035	1	0.28	0.04–2.06	0.21	
Unknown	160	1.02	0.86–1.21	0.83	36	1.09	0.76–1.57	0.63	9	0.99	0.49–2.01	0.98	
			Trend§ P=0.0221				Trend§ P=0.026				Trend P=0.12		
					Trend interaction P=0.063								

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Current or former smoking ‡

Never smoked	849	1.00	Baseline		174	1.00	Baseline		50	1.00	Baseline	
Current**	68	1.09	0.85–1.40	0.512	15	1.28	0.75–2.17	0.36	4	1.06	0.38–2.98	0.91
Former	513	1.13	1.01–1.26	0.033	109	1.15	0.90–1.46	0.26	33	1.26	0.81–1.97	0.31

Smoking status by morphological type interaction $P=0.97$

Time since cessation (years) ¶

Never smoked	849	1.00	Baseline		174	1.00	Baseline		50	1.00	Baseline	
Current** smoker	68	1.09	0.85–1.40	0.49	15	1.30	0.76–2.20	0.34	4	1.07	0.38–2.99	0.90
1–9	102	1.27	1.03–1.56	0.026	17	1.23	0.75–2.02	0.42	8	1.70	0.82–3.49	0.15
10–19	105	1.09	0.89–1.34	0.40	33	1.85	1.27–2.70	0.0013	7	1.24	0.56–2.73	0.60
20–29	126	1.12	0.93–1.36	0.23	21	0.87	0.55–1.36	0.53	6	0.88	0.37–2.08	0.77
30+	165	1.12	0.94–1.33	0.20	32	0.90	0.62–1.32	0.60	12	1.52	0.78–2.96	0.22
Duration unknown	15	0.84	0.51–1.40	0.51	6	1.59	0.70–3.61	0.26	0			

Trend§ $P=0.26$

Trend§ $P=0.039$

Trend § $P=0.90$

Trend heterogeneity $P=0.38$

Age started smoking among ever smokers (years)

Never smoked	849	1.00	Baseline		174	1.00	Baseline		50	1.00	Baseline	
<17	205	1.22	1.05–1.43	0.012	38	1.17	0.82–1.66	0.38	18	1.83	1.07–3.14	0.027
17–19	239	1.15	0.99–1.33	0.062	54	1.24	0.91–1.69	0.17	11	0.92	0.48–1.76	0.81
20+	116	0.98	0.80–1.19	0.81	29	1.12	0.75–1.67	0.57	6	0.87	0.37–2.03	0.74
Age unknown	21	0.97	0.63–1.49	0.88	3	0.64	0.20–2.01	0.44	2	1.63	0.39–6.77	0.50

Trend§ $P=0.22$

Trend§ $P=0.74$

Trend among ever smokers§ $P=0.95$

Trend interaction $P=0.95$

* Based the International Classification of Diseases for Oncology: Morphology of Neoplasms codes (Ductal: 850_/3 ; Lobular: 852_/3 except 8521/3 ; Other types, and missing includes 8 cases where morphology is missing)

† Adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); age at menarche (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); duration of breastfeeding (trend, missing); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1– <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); physical activity (log(metabolic equivalent) trend, missing); pre-menopausal body mass index at age 20 years (trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); menopausal status (pre- or post-menopausal) and age at menopause (trend, missing).

‡ Time updated through follow-up period

§ Time updated at the point renewed information was available from follow-up questionnaire

¶ Trend excludes Never smoked and Unknown group

¶¶ Time updated in yearly steps

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** Includes current smokers and <1 year immediately after stopping

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SUPPLEMENTARY TABLE 4: Relative risk of breast cancer in relation to former-smoking, by level of alcohol consumption

Strata	Total number of cases in strata	HR for former-smoking relative to never smoking within strata of alcohol consumption*	95% CI	P-value
Alcohol[†]				
Non-drinker	103	0.83	0.49–1.39	0.48
Ever drinker	1625	1.18	1.07–1.31	0.0010
Interaction P ‡=0.19				
Alcohol[†]				
Non-drinker	103	0.83	0.49–1.39	0.47
<20g/day	685	1.18	1.01–1.38	0.041
20–<40g/day	339	1.20	0.97–1.49	0.091
40–<60g/day	77	1.07	0.68–1.67	0.78
≥60g/day	24	2.04	0.81–5.15	0.13
Current, amount unknown	170	1.49	1.10–2.04	0.011
Former drinker	278	0.96	0.75–1.24	0.76
Drinker, details missing	52	0.72	0.35–1.48	0.37
Interaction P ‡=0.21				

* Adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); age at menarche (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); duration of breastfeeding (trend, missing); current oral contraceptive use before menopause (yes, no); physical activity (log(metabolic equivalent) trend, missing); pre-menopausal body mass index at age 20 years (trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); menopausal status (pre- or post-menopausal) and age at menopause (trend, missing).

[†] Time updated through follow-up period

[‡] Interaction across all categories, including missing groups

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SUPPLEMENTARY TABLE 5: Relative risk of breast cancer in relation to smoking, by parity*

	Parity							
	Nulliparous				Parous			
	Cases	HR†	95% CI	P-value	Cases	HR†	95% CI	P-value
Ever previously smoked cigarettes*								
Never	146	1.00	Baseline		927	1.00	Baseline	
Ever	119	1.37	1.07–1.75	0.012	623	1.09	0.99–1.21	0.089
								Ever smoking by parity interaction $P=0.095$
Age started smoking *								
Never smoked	146	1.00	Baseline		927	1.00	Baseline	
<20	90	1.51	1.16–1.97	0.0022	475	1.13	1.01–1.27	0.033
20+	28	1.15	0.77–1.73	0.49	123	0.99	0.82–1.20	0.91
Age unknown	1	0.32	0.04–2.28	0.25	25	1.01	0.68–1.51	0.95
								Age started smoking by parity interaction $P=0.10$
Starting smoking relative to age at menarche (years)								
Never smoked	146	1.00	Baseline		927	1.00	Baseline	
Before or <5 years	48	1.64	1.18–2.28	0.0032	252	1.16	1.00–1.34	0.050
5+ years	58	1.27	0.94–1.73	0.12	298	1.08	0.94–1.24	0.26
Interval unknown	13	1.07	0.60–1.91	0.82	73	0.97	0.75–1.27	0.84
								Age started smoking relative to menarche by parity interaction $P=0.10$

* Time updated through follow-up

† Adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); age at menarche (trend, missing); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1– <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); physical activity (log(metabolic equivalent) trend, missing); pre-menopausal body mass index at age 20 years (trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); menopausal status (pre- or post-menopausal) and age at menopause (trend, missing).

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SUPPLEMENTARY TABLE 6: Relative risk of breast cancer in relation to smoking, by menopausal status*

	Menopausal status							
	Premenopausal				Postmenopausal			
	Cases	HR†	95% CI	P-value	Cases	HR†	95% CI	P-value
Ever previously smoked cigarettes*								
Never	323	1.00	Baseline		750	1.00	Baseline	
Ever	198	1.17	0.98–1.40	0.088	544	1.13	1.01–1.26	0.040
Ever smoking by menopausal status interaction $P=0.73$								
Age started smoking*								
Never smoked	323	1.00	Baseline		750	1.00	Baseline	
<20	162	1.21	1.00–1.46	0.051	403	1.19	1.05–1.34	0.0069
20+	28	0.93	0.63–1.36	0.70	123	1.02	0.84–1.23	0.86
Age unknown	8	1.56	0.77–3.14	0.22	18	0.80	0.50–1.28	0.35
Age started smoking by menopausal status interaction $P=0.49$								
Starting smoking relative to age at menarche (years)								
Never smoked	323	1.00	Baseline		750	1.00	Baseline	
Before or <5 years	102	1.36	1.08–1.70	0.0080	198	1.19	1.01–1.40	0.035
5+ years	76	1.07	0.83–1.37	0.61	280	1.11	0.96–1.28	0.15
Interval unknown	20	0.87	0.55–1.40	0.58	66	1.03	0.78–1.35	0.86
Age started smoking relative to menarche by menopausal status interaction $P=0.66$								

* Time updated through follow-up

† Adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); age at menarche (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); duration of breastfeeding (trend, missing); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1– <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); physical activity (log(metabolic equivalent) trend, missing); pre-menopausal body mass index at age 20 years (trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing).