

Smoking and risk of breast cancer in the Generations Study cohort

TABLE 1: Characteristics of 102,927* women from the Generations Study, recruited 2003–2013

Study population	N	%
Year of birth		
1908–1939	5917	5.8
1940–1949	21488	20.9
1950–1959	24735	24.0
1960–1969	23749	23.1
1970–1996	27038	26.3
Year of recruitment		
2003–2005	33807	32.9
2006–2007	48489	47.1
2008–2013	20631	20.0
Age at recruitment (years)		
16–34	23289	22.6
35–44	23116	22.5
45–54	24385	23.7
55–64	23837	23.2
65–74	7308	7.1
75–102	992	1.0
Age at menarche (years)		
7–11	20658	20.1
12–14	62291	60.5
15–19	9353	9.1
Not known or anomalous†	10625	10.3
Family history of breast cancer in 1 st degree relatives		
No	87030	84.6
Yes	15897	15.4
Smoking status, at entry to cohort		
Never smoked	66013	64.1
Current smoker	8491	8.3
Former smoker	28300	27.5
Ever-smoker, status unknown at this time	123	0.1
Alcohol consumption, at entry to cohort		
Never regular	10574	10.3
Current drinker (<60g/day)	63690	61.9
Current drinker (≥60g/day)	1280	1.2
Current drinker, amount unknown	4306	4.2
Former drinker	13513	13.1
Ever-drinker, status unknown at this time	9564	9.3
Total number of subjects	102927	100.0

* Excludes 13 women (including one who developed breast cancer) with self-contradictory information for parity or smoking

† Includes 2 women reporting menarche before age 5, 23 at ages 20–33, and 23 reporting never having periods

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TABLE 2: Relative risk of breast cancer in relation to smoking status, intensity, duration, dose, and cessation, by estrogen receptor status

	Estrogen receptor status								All breast cancer*			
	Positive				Negative				Cases	HR [†]	95% CI	P-value
	Cases	HR [†]	95% CI	P-value	Cases	HR [†]	95% CI	P-value				
Ever previously smoked cigarettes ‡												
Never	898	1.00	Baseline		167	1.00	Baseline		1073	1.00	Baseline	
Ever	611	1.12	1.01–1.24	0.035	127	1.25	0.99–1.58	0.063	742	1.14	1.03–1.25	0.010
Ever smoking by estrogen receptor status interaction <i>P</i> =0.40												
Cigarettes per day, averaged over years when smoking §												
Never smoked	898	1.00	Baseline		167	1.00	Baseline		1073	1.00	Baseline	
1–4	216	1.07	0.92–1.25	0.36	41	1.11	0.79–1.56	0.54	258	1.08	0.94–1.24	0.29
5–9	117	1.27	1.05–1.55	0.016	17	0.97	0.59–1.59	0.89	135	1.22	1.02–1.47	0.031
10–14	68	1.37	1.07–1.76	0.013	13	1.34	0.76–2.36	0.31	82	1.37	1.09–1.72	0.0070
15+	51	1.48	1.11–1.97	0.0079	11	1.61	0.87–2.97	0.13	62	1.48	1.14–1.92	0.0031
Amount unknown	159	0.94	0.79–1.12	0.51	45	1.46	1.05–2.03	0.025	205	1.03	0.88–1.20	0.71
Trend <i>P</i> =0.023				Trend <i>P</i> =0.11				Trend <i>P</i> =0.0060				
Trend interaction <i>P</i> =0.52												
Duration of smoking (years) ¶												
Never smoked	898	1.00	Baseline		167	1.00	Baseline		1073	1.00	Baseline	
1–9	139	0.95	0.79–1.13	0.57	37	1.30	0.91–1.85	0.15	177	1.00	0.85–1.18	0.97
10–19	187	1.22	1.04–1.43	0.015	38	1.26	0.88–1.79	0.21	225	1.21	1.05–1.41	0.009
20–29	113	1.16	0.95–1.41	0.15	28	1.59	1.06–2.38	0.025	141	1.21	1.02–1.45	0.033
30+	137	1.23	1.03–1.48	0.024	20	1.07	0.67–1.71	0.78	159	1.22	1.02–1.44	0.026
Duration unknown	35	0.97	0.69–1.36	0.86	4	0.61	0.23–1.66	0.34	40	0.93	0.68–1.28	0.66
Trend§ <i>P</i> =0.17				Trend§ <i>P</i> =0.85				Trend <i>P</i> =0.24				
Trend interaction <i>P</i> =0.44												
Pack-years of smoking §												
Never smoked	898	1.00	Baseline		167	1.00	Baseline		1073	1.00	Baseline	
1–<5	156	1.13	0.95–1.34	0.15	25	0.93	0.61–1.42	0.75	182	1.10	0.94–1.29	0.25
5–<10	84	1.03	0.82–1.29	0.81	19	1.21	0.75–1.94	0.44	103	1.05	0.85–1.28	0.66
10–<20	114	1.25	1.03–1.53	0.027	24	1.42	0.92–2.18	0.11	138	1.27	1.06–1.52	0.010
20+	98	1.48	1.19–1.83	0.0003	14	1.22	0.71–2.13	0.47	114	1.45	1.19–1.77	0.0002
Amount unknown	159	0.95	0.80–1.13	0.59	45	1.47	1.06–2.05	0.022	205	1.03	0.88–1.20	0.70
Trend§ <i>P</i> =0.024				Trend§ <i>P</i> =0.16				Trend <i>P</i> =0.0069				
Trend interaction <i>P</i> =0.66												

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Current or former smoking ‡

Never smoked	898	1.00	Baseline		167	1.00	Baseline		1073	1.00	Baseline	
Current**	73	1.14	0.89–1.45	0.30	14	1.07	0.62–1.86	0.80	87	1.12	0.89–1.39	0.34
Former	538	1.12	1.00–1.25	0.047	113	1.27	1.00–1.62	0.50	655	1.14	1.03–1.26	0.011

Smoking status by estrogen receptor status interaction $P=0.58$

Time since cessation (years) ¶

Never smoked	898	1.00	Baseline		167	1.00	Baseline		1073	1.00	Baseline	
Current** smoker	73	1.14	0.90–1.46	0.28	14	1.08	0.62–1.87	0.79	87	1.12	0.90–1.40	0.31
1–9	100	1.25	1.01–1.54	0.040	26	1.48	0.98–2.23	0.064	127	1.28	1.06–1.55	0.009
10–19	115	1.17	0.96–1.42	0.12	28	1.42	0.94–2.13	0.10	145	1.21	1.02–1.45	0.032
20–29	133	1.10	0.91–1.32	0.33	20	0.94	0.59–1.51	0.81	153	1.07	0.90–1.27	0.46
30+	170	1.05	0.88–1.24	0.61	38	1.43	0.99–2.06	0.058	209	1.10	0.94–1.28	0.24
Duration unknown	20	1.06	0.68–1.65	0.81	1	0.29	0.04–2.08	0.22	21	0.93	0.60–1.43	0.74

Trend ¶ $P=0.055$

Trend ¶ $P=0.85$

Trend ¶ $P=0.071$

Trend interaction $P=0.55$

* Includes 12 breast cancers with unknown or unmeasured ER status

† 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

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

Smoking and risk of breast cancer in the Generations Study cohort

TABLE 3: Relative risk of breast cancer in relation to smoking in relation to age started smoking, by estrogen receptor status

	Estrogen receptor status								All breast cancer*				
	Positive				Negative				Cases	HR [†]	95% CI	P-value	
	Cases	HR [†]	95% CI	P-value	Cases	HR [†]	95% CI	P-value					
Age started smoking (years) ‡													
Never smoked	898	1.00	Baseline		167	1.00	Baseline		1073	1.00	Baseline		
<17	218	1.25	1.08–1.46	0.0032	42	1.22	0.87–1.72	0.25	261	1.24	1.08–1.43	0.0023	
17–19	249	1.13	0.98–1.30	0.093	54	1.32	0.97–1.80	0.077	304	1.15	1.01–1.31	0.030	
20+	122	0.95	0.79–1.15	0.62	28	1.25	0.84–1.87	0.28	151	1.00	0.84–1.18	0.96	
Age unknown	22	0.94	0.62–1.44	0.79	3	0.73	0.23–2.30	0.59	26	0.94	0.64–1.39	0.76	
		Trend§ P=0.17				Trend§ P=0.74				Trend among ever smokers§ P=0.18			
		Trend interaction P=0.30											
Cigarettes per day at ages 16–24 years (among to those ≥25 at entry)													
Never smoked	895	1.00	Baseline		166	1.00	Baseline		1069	1.00	Baseline		
1–4	77	1.10	0.87–1.39	0.42	21	1.65	1.05–2.60	0.032	99	1.19	0.97–1.46	0.10	
5–9	131	1.23	1.02–1.48	0.027	18	0.92	0.57–1.50	0.75	149	1.16	0.99–1.40	0.069	
10–14	170	1.11	0.94–1.31	0.22	31	1.07	0.73–1.57	0.73	203	1.10	0.95–1.29	0.21	
15+	169	1.13	0.96–1.34	0.14	42	1.44	1.02–2.03	0.038	212	1.18	1.01–1.37	0.034	
Started at age 25+	31	0.91	0.64–1.31	0.62	7	1.22	0.57–2.60	0.61	38	0.95	0.69–1.31	0.75	
Unknown	31	0.97	0.68–1.39	0.87	7	1.32	0.62–2.79	0.47	38	1.01	0.73–1.40	0.95	
		Trend§ P=0.70				Trend§ P=0.65				Trend § P=0.78			
		Trend interaction P=0.81											
Starting smoking relative to age at menarche (years)													
Never smoked	898	1.00	Baseline		167	1.00	Baseline		1073	1.00	Baseline		
At or before menarche	32	1.60	1.12–2.28	0.010	2	0.50	0.12–2.02	0.33	34	1.40	0.98–1.99	0.061	
<i>Years started after menarche</i>													
1–4	217	1.21	1.04–1.41	0.015	48	1.38	1.00–1.91	0.049	266	1.23	1.07–1.41	0.0040	
5–9	239	1.09	0.94–1.27	0.23	54	1.35	0.99–1.84	0.060	295	1.13	0.99–1.29	0.071	
10–14	36	1.03	0.74–1.44	0.86	7	1.13	0.53–2.43	0.75	43	1.04	0.76–1.41	0.82	
15+	12	0.64	0.36–1.13	0.12	6	1.92	0.85–4.34	0.12	18	0.81	0.51–1.30	0.39	
Interval unknown	75	1.02	0.79–1.32	0.88	10	0.74	0.38–1.41	0.35	86	0.99	0.77–1.27	0.92	
		Trend§ P=0.041				Trend§ P=0.80				Trend § P=0.031			
		Trend interaction P=0.42											
Starting smoking relative to age at thelarche (years)													
Never smoked	898	1.00	Baseline		167	1.00	Baseline		1073	1.00	Baseline		
At or before thelarche	16	1.45	0.88–2.39	0.14	1	0.45	0.06–3.24	0.43	17	1.27	0.79–2.06	0.33	

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<i>Years started after thelarche</i>													
<i>1–4</i>	160	1.17	0.99–1.39	0.075	31	1.17	0.79–1.72	0.43	192	1.17	1.00–1.37	0.056	
<i>5–9</i>	238	1.06	0.92–1.22	0.47	60	1.42	1.06–1.91	0.020	300	1.11	0.98–1.27	0.10	
<i>10–14</i>	37	0.98	0.70–1.36	0.90	11	1.60	0.87–2.95	0.13	48	1.07	0.80–1.43	0.66	
<i>15+</i>	18	0.94	0.59–1.50	0.79	6	1.83	0.81–4.14	0.14	24	1.06	0.71–1.59	0.77	
Interval unknown	142	1.22	1.02–1.46	0.031	18	0.87	0.53–1.42	0.59	161	1.17	0.99–1.38	0.074	
		Trend§ <i>P</i> =0.58				Trend§ <i>P</i> =0.35				Trend among ever smokers§ <i>P</i> =0.82			
						Trend interaction <i>P</i> =0.28							
Starting smoking relative to 1st childbirth, among parous (follow-up time only from 1st childbirth)													
Never smoked	772	1.00	Baseline		148	1.00	Baseline		927	1.00	Baseline		
After first childbirth	34	1.20	0.85–1.71	0.30	9	1.85	0.94–3.67	0.076	43	1.28	0.94–1.76	0.12	
<i>Interval from starting smoking to 1st childbirth (years)</i>													
<i>1–4</i>	73	1.12	0.88–1.44	0.35	15	1.28	0.74–2.21	0.38	89	1.14	0.91–1.45	0.23	
<i>5–9</i>	177	1.06	0.90–1.25	0.51	42	1.35	0.96–1.90	0.089	220	1.10	0.94–1.28	0.22	
<i>10–14</i>	130	1.08	0.89–1.30	0.42	22	0.89	0.57–1.40	0.62	152	1.04	0.87–1.24	0.65	
<i>15+</i>	77	1.17	0.91–1.51	0.21	16	1.13	0.66–1.92	0.65	94	1.17	0.93–1.47	0.19	
Interval unknown	22	1.07	0.70–1.64	0.75	2	0.54	0.13–2.17	0.38	25	1.02	0.69–1.52	0.92	
		Trend§ <i>P</i> =0.72				Trend§ <i>P</i> =0.33				Trend among ever smokers§ <i>P</i> =0.97			
						Trend interaction <i>P</i> =0.27							

* Includes 21 breast cancers with unknown or unmeasured ER status

† 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

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

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

Strata	Total number of cases in strata	HR for ever-smoking relative to never smoking within strata of alcohol consumption*	95% CI	P-value
Alcohol†				
Non-drinker	110	0.97	0.61–1.52	0.89
Ever drinker	1705	1.18	1.07–1.30	0.0010
Interaction P ‡=0.41				
Alcohol†				
Non-drinker	110	0.97	0.61–1.52	0.89
<20g/day	706	1.17	1.00–1.36	0.049
20–<40g/day	356	1.17	0.95–1.44	0.13
40–<60g/day	87	1.12	0.73–1.72	0.61
≥60g/day	27	1.92	0.78–4.76	0.16
Current, amount unknown	180	1.47	1.09–1.98	0.011
Former drinker	295	0.98	0.78–1.25	0.89
Drinker, details missing	54	0.73	0.38–1.42	0.35
Interaction P ‡=0.33				

* 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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TABLE 5: Relative risk of breast cancer in relation to smoking, by family history of breast cancer

	Family history of breast cancer*							
	No				Yes			
	Cases	HR†	95% CI	P-value	Cases	HR†	95% CI	P-value
Ever previously smoked cigarettes‡								
Never	819	1.00	Baseline		239	1.00	Baseline	
Ever	554	1.07	0.96–1.20	0.22	203	1.35	1.12–1.62	0.0018
				Interaction P=0.038				
Age started smoking (years) ‡								
Never smoked	819	1.00	Baseline		254	1.00	Baseline	
<20	427	1.17	1.04–1.32	0.0098	138	1.26	1.02–1.56	0.029
20+	96	0.82	0.67–1.02	0.076	55	1.56	1.17–2.10	0.0028
Age unknown	16	0.75	0.46–1.23	0.26	10	1.57	0.84–2.96	0.16
			Interaction P=0.0029					
		Trend§ P=0.034				Trend§ P=0.38		
			Trend interaction P=0.044					
Starting smoking relative to age at menarche (years)								
Never smoked	819	1.00	Baseline		254	1.00	Baseline	
Before or <5 years	239	1.30	1.12–1.51	0.0006	61	1.06	0.80–1.41	0.68
5+ years	244	0.97	0.84–1.13	0.70	112	1.53	1.22–1.91	0.0002
Interval unknown	56	0.83	0.62–1.12	0.22	30	1.51	1.02–2.24	0.041
			Interaction P=0.0001					
		Trend§ P=0.0021				Trend§ P=0.40		
			Trend interaction P=0.0079					
Cigarettes per day age among ever smokers, averaged over years when smoking 								
Never smoked	819	1.00	Baseline		254	1.00	Baseline	
1–4	185	1.01	0.86–1.18	0.95	73	1.32	1.01–1.71	0.040
5+	210	1.28	1.09–1.49	0.0019	69	1.42	1.09–1.86	0.010
Unknown	144	0.94	0.79–1.13	0.51	61	1.31	0.99–1.74	0.059
			Interaction P=0.13					
		Trend§ P=0.0019				Trend§ P=0.81		
			Trend interaction P=0.18					
Duration of smoking among ever smokers (years) ¶								
Never smoked	819	1.00	Baseline		254	1.00	Baseline	
1–9	129	0.94	0.78–1.14	0.54	48	1.20	0.88–1.64	0.24
10+	385	1.16	1.03–1.32	0.019	140	1.39	1.13–1.71	0.0020
Duration unknown	25	0.76	0.51–1.13	0.17	15	1.51	0.90–2.55	0.12
			Interaction P=0.094					
		Trend§ P=0.15				Trend§ P=0.86		
			Trend interaction P=0.37					
Pack-years of smoking among ever smokers 								
Never smoked	819	1.00	Baseline		254	1.00	Baseline	
1–10	208	1.02	0.87–1.18	0.84	77	1.28	0.99–1.65	0.060
10+	187	1.30	1.11–1.53	0.0015	65	1.48	1.13–1.95	0.0051
Unknown	144	0.93	0.78–1.12	0.46	61	1.30	0.98–1.72	0.069
			Interaction P=0.16					
		Trend§ P=0.055				Trend§ P=0.54		
			Trend interaction P=0.37					

* First degree relatives, at recruitment

† 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); 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

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menopause (trend, missing).

‡ Time updated through follow-up

§Trend excludes Never smoked and Unknown group

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

¶ Time updated in yearly steps

IN CONFIDENCE