# THE LANCET Oncology

### Supplementary appendix

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### Menarche, menopause and breast cancer risk: individual participant meta-analysis, including 118,964 women with breast cancer from 117 epidemiological studies

### **Collaborative Group on Hormonal Factors in Breast Cancer**

### Web Appendix

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#### Search strategy and eligibility of studies for the collaboration

This collaboration began in 1992, and since then potentially eligible epidemiological studies have been sought regularly, by searches of review articles, from computer-aided literature searches in MEDLINE, EMBASE and Pubmed, using combinations of the search terms 'breast cancer', 'cohort', 'prospective', 'case-control', 'hormonal contraceptives', 'hormone replacement', 'menarche', 'menopause', and 'reproduct\*'. Studies that had collected relevant data, but had not published on breast cancer were sought by correspondence with colleagues, by discussions at collaborators meetings (in 1993, 1995, 2000, 2005 and 2011), and by electronic searches using additional terms 'cohort', 'prospective', 'women' and 'cancer risk'. To be eligible for the collaboration, epidemiological studies need to have studied at least 400 women with breast cancer (or at least 100 before 2005) and to have collected individual data on women's childbearing history, and use of hormonal therapies.

### Data sought from principal investigators, data checking and collation

Principal investigators were asked to provide individual data from cases and controls on age at menarche, menopausal status, type of and age at menopause (where appropriate), reproductive history, history of hysterectomy and/or bilateral oophorectomy, use of oral contraceptives, use of hormonal therapies for the menopause, height, current weight, weight as a young adult, consumption of alcohol, smoking history, and history of breast cancer in first degree relatives. Principal investigators were also asked to provide information, if available, on tumour histology, estrogen receptor status and a measure of tumour stage.

Data contributed by principal investigators were checked and collated centrally so that analyses could use as similar definitions as possible across studies. Apparent inconsistencies in the data were rectified, where possible, by correspondence with the investigators. After the records had been checked and corrected, investigators were sent summary tables and listings of the variables to be used in analyses for final confirmation that their data had been correctly interpreted.

#### Studies included in these analyses

Studies were included in these analyses if individual data had been provided on women's menopausal status, age at menarche and at menopause, and whether or not they had had a hysterectomy or a bilateral oophorectomy. 117 studies had collected relevant data, and they included 44,557 women with breast cancer (38% of the cases) from cohort studies, 50,280 (42%) from case-control studies with population controls and 24,127 (20%) from case-control studies with hospital controls.

Studies included in these analyses and details of the women and breast cancers included in each study are given in Webtable 1 and references to each study are given on p9-13.

		Cases at diagnosis		Mean age at menarche	Mean age at natural	Information on tumour
		Mean age	Median year	Cases/Controls	menopause Cases/Controls	type
35 Cohort studies	·					
Thomas (USA) 3	19/74	49.8	1970	12.5/13.2	Ť	Yes
Kaiser Permanente (USA) 8	22/16	51.2	1974	13.0/12.4	46.3/45.9	No
Adventist Health Study-1 (USA) 23	47/232	67.0	1979	13.3/13.1	49.6/48.5	Yes
Alexander et al (UK) 14	160/628	55.2	1981	13.4/13.5	48.3/48.0	No
Persson (Sweden) 22	26/57	61.8	1982	13.2/13.6	48.8/49.0	No
Canada BC Screening (Canada) 36	779/2,880	51.1	1985	12.9/12.9	49.0/47.8	No
RERF (Japan) 67	179/774	60.9	1985	14.6/15.0	49.7/48.8	No No
Guernsey 3&4 (UK) 61 BCDDP (USA) 46	84/286 845/6,079	54.0 63.5	1986 1988	13.2/13.1 12.8/12.9	49.6/49.5 49.8/49.0	Yes
Icelandic Study (Iceland) 80	845/0,079	56.6	1988	13.4/13.5	49.3/49.0	No
Nurses Health Study (ICeland) 60	3471/14,331	57.7	1990	12.5/12.6	50.1/50.0	Yes
DOM (Netherlands) 70	317/1,011	55.1	1992	13.3/13.4	45.3/44.7	Yes
Iowa (USA) 74	798/3624	68.5	1992	12.8/12.9	49.8/49.6	Yes
NLCS (Netherlands)50	1281/1560	67.4	1992	13.5/13.7	49.6/49.2	Yes
US Radiologic Techno (USA) 93	529/2333	47.7	1992	12.6/12.6	†	No
Petrakis (USA) 12	204/747	59.0	1993	12.7/12.8 12.7/12.9	46.1/46.8	No
Amer.Can.Soc. (USA) 89‡ Newcomb/Mandelson (USA) 55	3126/12,236	67.2	1994 1994		49.5/49.0	No
SOF (USA) 98	34/63 162/665	44.5	1994	12.1/12.1 13.1/13.1	† 48.6/47.9	Yes Yes
Swedish Mammography (Sweden) 102	1125/3164	63.9	1994	13.2/13.4	50.1/49.7	Yes
Shanghai Textile (China) 88	1376/5458	54.4	1995	15.3/15.5	49.4/48.9	Yes
ACS Nutrition (USA) 82	1141/5692	67.3	1997	12.7/12.8	49.8/49.5	Yes
Danish Nurses (Denmark) 96	99/550	64.3	1997	13.7/13.9	50.8/49.5	Yes
Miyagi (Japan) 112	185/719	55.7	1997	14.4/14.7	50.6/49.8	Yes
NIH-AARP (USA) 106	3352/14,191	66.1	1999	12.0/12.1	48.8/48.3	Yes
JPHC (Japan) 116	569/2209	59.4	2000	14.4/14.6	49.8/49.4	Yes
Multi Ethnic Cohort (USA) 99 Nurses Health Study II (USA) 113	1785/14,360 1774/6099	64.9 45.4	2000 2000	12.6/12.7 12.3/12.4	48.7/48.3	Yes Yes
WHI (USA) 86	628/2958	69.6	2000	12.6/12.7	50.7/50.2	Yes
Southern Sweden (Sweden) 92	752/3135	57.5	2000	13.3/13.4	47.9/48.2	Yes
S/N Womens (Norway/Sweden) 94	706/3044	50.2	2001	13.0/13.0	†	Yes
EPIC (10 European Countries) 108	6474/27,388	57.3	2002	13.0/13.1	49.8/49.2	Yes
Million Women Study (UK) 114	8724/38,068	59.3	2002	12.9/13.0	50.0/49.4	Yes
NOWAC (Norway) 90	403/2,044	63.5	2002	13.3/13.5	49.3/49.2	Yes
UKCTOCS (UK) 117	2484/7687	64.8	2007	12.9/13.0	50.7/50.1	Yes
Subtotal	44,557/192,829	60.2	1999	12.9/13.0	49.8/49.4	
56 Case control studies (with population	/				-	
Leisure World (USA) 2	24/60	69.0	1974	13.2/13.3	46.3/46.7	Yes
Brinton (USA) 5	1,759/1,910	52.6	1976	12.8/12.9	48.2/47.7	No
Ursin (USA ) 38 Nomura (USA) 9	112/152 151/129	39.5 57.2	1977 1978	12.5/12.6 13.2/13.3	† 48.9/48.9	No Yes
Bernstein/Pike (USA) 1	430/418	31.5	1978	12.3/12.5	48.9/48.9 †	Yes
CASH (USA) 31	3,174/3,138	43.0	1980	12.6/12.7	÷	Yes
Hislop (Canada) 7	565/591	50.7	1981	13.1/13.1	49.2/49.2	Yes
Bain (Australia) 20	373/748	54.3	1983	13.1/13.2	48.5/48.2	Yes
Ewertz (Denmark) 15	964/918	49.9	1983	13.6/13.7	ţ	Yes
Oberle (Costa Rica) 11	154/781	44.8	1983	13.4/13.4	†	No
Rohan (Australia) 17	307/324	53.5	1983	13.2/13.2	49.1/48.1	Yes
UK National (UK) 21	743/744	31.9	1983	12.6/12.7	† 10 6/18 5	Yes
Clarke (Canada) 37 Long Island Study (USA) 30	456/942 880/907	50.1 54.5	1984 1984	12.8/12.9 12.7/12.7	49.6/48.5 48.8/49.2	Yes Yes
Meirik/Lund (Sweden/Norway) 24	386/513	37.2	1984	13.0/13.0	48.8/49.2 †	No
Yuan/Yu (China) 19	530/531	50.7	1984	14.6/15.0	48.0/47.5	Yes
American Asian (USA) 59	443/848	44.4	1985	12.9/13.1	†	Yes
Wrensch/Baltzell (USA) 81	459/2,348	50.4	1985	12.5/12.6	48.0/46.2	No
Paul/Skegg (New Zealand) 63	699/1,573	44.2	1985	12.9/13.0	†	No
	294/294	43.2	1985	14.1/14.4	† 1	Yes
Wang/Yu (China) 39			1007	10 2/10 5		I NL-
Bernstein II (USA) 64	676/675	35.5	1986	12.3/12.5	† ,	No
e ,	676/675 659/859 547/591	35.5 36.5 53.6	1986 1987 1987	12.5/12.5 12.6/12.7 12.6/12.9	† † 48.8/47.9	Yes Yes

Webtable 1. Characteristics of the studies and women, and the breast cancers included in the analyses.

Newcomb (USA) 75 Sanjose (Spain) 53 Ross/Pike (USA) 76 Stanford/Habel (USA) 57 Yang/Gallagher (Canada) 40 Zakelj (Slovenia) 49 ICRF (UK) 104 WISH (USA) 60 4-State Wisconsin (USA) 72 McCredie (Australia) 62 Morabia II (Switzerland) 54 ChangClaude (Germany) 87	4,600/6,793 285/308 799/788 184/205 525/523 612/611 277/277 1,635/1,690	56.6 55.8 61.2 57.5 53.8 44.8	1988 1988 1989 1989 1989	12.9/13.0 13.1/12.9 12.6/12.7 12.6/12.5	49.0/48.3 49.3/48.3 49.9/49.8 49.5/49.4	No No Yes Yes
Ross/Pike (USA) 76 Stanford/Habel (USA) 57 Yang/Gallagher (Canada) 40 Zakelj (Slovenia) 49 ICRF (UK) 104 WISH (USA) 60 4-State Wisconsin (USA) 72 McCredie (Australia) 62 Morabia II (Switzerland) 54	799/788 184/205 525/523 612/611 277/277 1,635/1,690	61.2 57.5 53.8 44.8	1989 1989	12.6/12.7 12.6/12.5	49.9/49.8	Yes
Stanford/Habel (USA) 57 Yang/Gallagher (Canada) 40 Zakelj (Slovenia) 49 ICRF (UK) 104 WISH (USA) 60 4-State Wisconsin (USA) 72 McCredie (Australia) 62 Morabia II (Switzerland) 54	184/205           525/523           612/611           277/277           1,635/1,690	57.5 53.8 44.8	1989	12.6/12.5		
Yang/Gallagher (Canada) 40 Zakelj (Slovenia) 49 ICRF (UK) 104 WISH (USA) 60 4-State Wisconsin (USA) 72 McCredie (Australia) 62 Morabia II (Switzerland) 54	525/523 612/611 277/277 1,635/1,690	53.8 44.8			49	
Zakelj (Slovenia) 49 ICRF (UK) 104 WISH (USA) 60 4-State Wisconsin (USA) 72 McCredie (Australia) 62 Morabia II (Switzerland) 54	612/611 277/277 1,635/1,690	44.8	1909	12.5/12.6	48.7/48.3	Yes
ICRF (UK) 104 WISH (USA) 60 4-State Wisconsin (USA) 72 McCredie (Australia) 62 Morabia II (Switzerland) 54	277/277 1,635/1,690		1989	13.8/13.9	+0.7/40.5 †	Yes
WISH (USA) 60 4-State Wisconsin (USA) 72 McCredie (Australia) 62 Morabia II (Switzerland) 54	1,635/1,690	49.5	1991	12.9/12.9	+	Yes
4-State Wisconsin (USA) 72 McCredie (Australia) 62 Morabia II (Switzerland) 54		40.1	1991	12.4/12.5	+	Yes
McCredie (Australia) 62 Morabia II (Switzerland) 54	2,813/2,920	65.7	1991	12.9/12.9	49.6/48.9	Yes
Morabia II (Switzerland) 54	431/394	34.8	1993	12.9/12.9	+	Yes
	134/665	53.4	1993	13.0/13.4	48.8/48.1	No
Changeladde (Germany) 07	559/1115	41.8	1994	13.1/13.1	+0.0/+0.1	Yes
Magnusson (Sweden) 68	1572/1973	62.6	1994	13.6/13.7	50.6/50.1	Yes
Millikan (USA) 69	441/375	41.7	1994	12.5/12.5	+	No
Johnson (Canada) 73	1652/1663	54.5	1995	12.8/12.9	49.0/48.4	Yes
CARE (USA) 85	2611/2546	46.1	1996	12.4/12.4	+9.0/+0.+ †	Yes
Freindenreich (Canada) 78	699/667	52.7	1996	12.7/12.7	51.1/51.0	Yes
McCredie II (Australia) 65	753/429	41.3	1996	12.8/12.8	+	Yes
Kreiger (Canada) 83	1816/1868	53.7	1997	12.8/12.9	49.0/48.8	Yes
LIBCSP (USA) 105	830/998	56.6	1997	12.4/12.4	48.9/48.6	Yes
Lumachi (Italy) 84	272/312	55.0	1997	12.3/12.8	50.8/48.9	Yes
Newcomb3 (USA) 77	3586/4493	50.7	1997	12.7/12.8	49.5/48.9	Yes
San Francisco Bay (USA) 91	1189/1473	52.2	1997	12.6/12.8	47.4/47.0	Yes
Shu Wei (China) 79	1397/1481	47.6	1997	14.5/14.7	†	No
PACE (USA) 100	210/265	72.5	1998	12.9/13.0	49.2/49.0	Yes
WISE (USA) 103	449/711	63.8	2000	12.6/12.8	48.9/48.7	Yes
Polish Breast Cancer (Poland) 101	1,434/1907	56.2	2001	13.5/13.7	49.9/49.5	Yes
Zhou Xin (China) 95	204/409	46.2	2002	13.2/15.0	+	Yes
MARIE (Germany) 107	855/2185	61.8	2003	13.7/13.7	49.8/49.4	Yes
MASTOS (Cyprus) 110	583/832	53.4	2003	13.0/13.2	50.6/50.0	No
CAMA (Mexico) 109	695/851	50.5	2006	12.8/12.9	47.1/47.0	Yes
Subtotal	50,280/ 63,090	50.8	1992	12.9/13.0	49.0/48.5	
	• / /		•			
26 Case control studies (with hospital c	/					
Morabia I(USA) 41	299/404	48.6	1974	12.8/13.0	†	Yes
Vessey I (UK) 4	1134/1044	40.9	1976	12.9/13.2	Ť	Yes
Modan (Israel) 10	925/1718	55.0	1977	13.2/13.2	49.3/48.7	No
Hulka I (USA) 26	154/1285	54.2	1978	13.0/13.0	47.1/46.5	No
Franceschi I (Italy) 29	279/321	57.7	1980	13.4/13.7	48.3/48.0	No
Kalache (Brazil) 43	532/730	48.4	1980	13.6/13.6	47.3/47.1	No
Ravnihar (Slovenia) 16	493/1,747	44.2	1981	14.0/14.2	†	Yes
Vessey II (UK) 13	923/844	47.5	1982	13.1/13.1	†	Yes
WHO - developed 42	1,375/3,578	43.2	1982	13.2/13.2	†	Yes
- developing 42	1,519/14,669	42.8	1984	14.6/14.7	†	Yes
Lê (France) 6	257/249	38.1	1983	12.6/12.9	÷ †	No
CCSS (USA) 28	4564/5097	48.6	1984	12.6/12.7	÷	Yes
Clavel (France) 27	438/791	43.5	1984	12.9/13.2	÷	Yes
Gerber (France) 32	328/427	51.0	1984	13.0/13.1	50.7/48.9	Yes
Marubini (Italy) 18	166/175	48.0	1984	13.0/12.7	† 40 5/48 5	Yes
La Vecchia (Italy) 51	2,877/2,401	52.3	1986	12.9/13.0	49.5/48.5	No
Lee (Singapore) 35	196/404	50.6	1987	13.6/14.1	49.5/48.4	Yes
PEDS (USA) 25 Naslangel (Philippings) 42	621/2,287 271/279	55.0 46.1	1987	12.7/12.8	49.6/49.1	Yes Yes
Ngelangel (Philippines) 42 Hulka II (USA) 45			1988 1990	13.7/13.7	÷ ÷	
Katsouyanni (Greece) 48	65/125 656/1,263	42.2 54.9	1990	<u>12.9/12.6</u> 12.9/13.1	<u>1</u> 48.6/47.8	Yes Yes
Franceschi II (Italy) 58	2,243/2,206	53.9	1990	12.9/13.0	48.0/47.8	No
Hamajima (Japan) 66	2,243/2,206	53.9	1992	13.8/14.0	49.9/49.1	No
Levi (Switzerland) 52	1338/3441 164/375	53.6	1992	13.4/13.5	49.9/49.4	Yes
Gajalakshmi (India) 33	466/485	48.4	1992	13.9/14.0	49.7/49.9 †	No
Johannesburg (South Africa) 71	1424/1,367	51.0	2003		48.2/47.8	
Ghiasvand (Iran) 115	420/460	40.3	2003	<u>15.3/15.3</u> <u>13.9/14.0</u>	48.2/47.8	Yes No
Subtotal	24,127/50,172	40.3 49.1	2006 1985	13.9/14.0 13.3/13.7	T 48.9/47.9	110
Subiotal	27,127/30,172	47.1	1705	13.3/13.7	40.7/4/.7	<u> </u>
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<sup>†</sup> The average age at cancer diagnosis was <50 years, and so the average age at menopause of the few postmenopausal women is uninterpretable, as it reflects the age-restriction of cases and controls. However, all women are included in the analyses. <sup>‡</sup> Cases were of fatal breast cancer

### Webtable 2. Relative risk of breast cancer by age at menarche and age at menopause, by study design

· · · *	Relative risk (95%CI) per year younger at menarche
Women aged <50 years	
Cohort studies	1.047 (1.021-1.074)
Case-control studies, population controls	1.066 (1.049-1.083)
Case-control studies, hospital controls	1.076 (1.057-1.097)
	Heterogeneity by study design, p=0.2
Women aged 50+	
Cohort studies	1.039 (1.029-1.049)
Case-control studies, population controls	1.051 (1.034-1.069)
Case-control studies, hospital controls	1.034 (1.017-1.065)
	Heterogeneity by study design, p=0.5
	Relative risk (95%CI) per year older at menopause
Cohort studies	1.030 (1.025-1.034)
Case-control studies, population controls	1.024 (1.017-1.031)
Case-control studies, hospital controls	1.032 (1.023-1.043)
	Heterogeneity by study design, p=0.3

\*Relative risk estimates are calculated stratifying, by study, age, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

### Webtable 3. Relative risk of breast cancer by age menarche and age at menopause, by ER status and tumour histology

	Relative risk (95%CI) per year younger at menarche
Ductal cancer, ER+ve	1.034 (1.026-1.052)
Ductal cancer, ER-ve	1.024 (1.004-1.044)
Lobular cancer, ER+ve	1.083 (1.052-1.115)
Lobular cancer, ER-ve	1.076 (0.999-1.159)
	Relative risk (95%CI) per year older at menopause
Ductal cancer, ER+ve	1.026 (1.020-1.032)
Ductal cancer, ER-ve	1.010 (1.000-1.020)
Lobular cancer, ER+ve	1.046 (1.031-1.061)
Lobular cancer, ER-ve	1.032 (0.994-1.072)

\*Relative risk estimates are calculated stratifying, by study, age and year of birth, and adjusting by parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

### Webfigure 1. Associations, only among controls, of various factors with: (A) menarche at or after age 15 years vs at younger ages and (B) natural menopause at or before age 45 years vs at older ages

		A: CORRELATES OF LATE MENARCHE			ATES OF EAF	LY NATURAL MENOPAUS
	Number with menarche at age 15 or older/<15	Odds ratio (g-s SE)	Odds ratio* & 99% g-s Cl for menarche at age 15 or older vs earlier	Number with menopause at age 45 or younger/45+	Odds ratio (g-s SE)	Odds ratio* & 99% g-s Cl for menopause at age 45 or younger vs later
YEAR OF BIRTH						
<1930	14678/60661	1.00 (0.015)	<del>_</del>	10995/49708	1.00 (0.020)	<b>•</b>
1930-1939	20748/72832	0.81 (0.007)		9527/46584	1.07 (0.010)	
1940-1949	15446/79988	0.53 (0.009)		2549/11594	1.08 (0.032)	-
PARITY						
Nulliparous	6907/32418	1.00 (0.017)	÷	3115/12043	1.00 (0.026)	+
1-2	22500/99951	1.04 (0.009)		7759/40509	0.77 (0.013)	
3+	24325/90723	1.12 (0.011)		9404/49049	0.72 (0.012)	•
AGE FIRST BIRTH						
<20	6440/29937	1.00 (0.020)	•	2826/11347	1.00 (0.031)	+
20-29	36808/148966	1.32 (0.008)		13165/73866	0.80 (0.010)	
30+	5764/24208	1.35 (0.024)		2139/11643	0.81 (0.030)	•
HEIGHT						
<160 cm	15147/72662	1.00 (0.013)	÷	7835/38200	1.00 (0.017)	÷
160- cm	11683/67428	1.02 (0.012)	E .	6304/32889	0.98 (0.017)	I
165+ cm	16992/89035	1.22 (0.012)	Te	7262/40481	0.93 (0.016)	4
BODY MASS INDEX (young a	dult)	• •			. ,	
<20 kg/m <sup>2</sup>	9367/40677	1.00 (0.017)	4	3205/17864	1.00 (0.028)	1
20- kg/m <sup>2</sup>	9592/59675	0.68 (0.012)	• T	4636/27507	0.95 (0.020)	I
25+ kg/m <sup>2</sup>	1488/10987	0.59 (0.029)		957/4651	1.11 (0.053)	1
•		0.00 (0.020)	-	501/4051	(0.000)	-
BODY MASS INDEX (current)			1	1001100000		1
<25 kg/m <sup>2</sup>	26352/119548	1.00 (0.010)	_ 7	10044/52729	1.00 (0.015)	Ĩ
25- kg/m <sup>2</sup>	11173/64365	0.77 (0.011)		6721/35955	1.01 (0.017)	f
30+ kg/m²	4635/35758	0.62 (0.015)		3749/18945	1.07 (0.024)	-
USE OF HORMONAL CONTR.			1			
Never	32478/122545	1.00 (0.013)	<b>P</b>	15318/72577	1.00 (0.019)	•
< 5years	9449/49722	0.93 (0.015)	-	2392/13820	0.91 (0.031)	•
5+ years	7735/43670	0.95 (0.018)	9	2164/14016	0.87 (0.033)	•
SMOKING						
Never	28371/119431	1.00 (0.010)		10185/62370	1.00 (0.015)	<b>¢</b>
Past	8232/52922	0.99 (0.015)	÷	4713/25277	1.22 (0.024)	•
Current	7845/40901	1.09 (0.017)	•	4266/15715	1.75 (0.033)	-
ALCOHOL						
None	25320/77321	1.00 (0.014)	ė	8129/38706	1.00 (0.021)	•
<50 g/week	15597/89197	0.87 (0.012)		7275/43557	0.86 (0.018)	=
50+ g/week	6232/33678	0.87 (0.019)	=	3037/16702	0.82 (0.027)	•
MENOPAUSAL STATUS						
Premenopausal	7850/37361	1.00 (0.022)	4			
Perimenopausal	894/4803	0.99 (0.062)	<b>→</b>	not apr	olicable	
Postmenopausal	4330/14603	0.98 (0.031)	+	not up;		
AGE AT MENARCHE		. ,				
<12				3819/18367	1.00 (0.029)	+
12-13	not app	licable		10286/55247	0.84 (0.014)	∎⊺
14+	not app			8701/44132	0.87 (0.014)	립
1.11			·	1	0.07 (0.010)	
			0 1.0 2.0 3	.0	c	1.0 2.0 3.

Data are for women without breast cancer, ie controls. Odds ratio calculations were stratified by study and, where appropriate, by age at diagnosis, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index (results for body mass index as a young adult are not stratified by current body mass index).

Webfigure 2A. Relative risk of breast cancer per year younger at menarche in cohort studies.

		RELATIVE RISK			
	Cases/Controls	RR & 99% Cl	RR ±SE		
Nurses Health Study I (USA) <sup>113</sup>	3471/14331		1.053 (0.017)		
Alexander et al (UK) <sup>14</sup>	160/628	<b></b>	1.089 (0.064)		
American Cancer Society (USA) <sup>89</sup>	3126/12236	÷	1.065 (0.019)		
NLCS (Netherlands) <sup>50</sup>	1281/1560	÷ <b>-</b> -	1.102 (0.034)		
Canada BC Screening (Canada) <sup>36</sup>	779/2880	÷	1.022 (0.029)		
BCDDP (USA) <sup>46</sup>	845/6079	+	0.991 (0.035)		
Iowa (USA) <sup>74</sup>	798/3624	-	1.098 (0.037)		
Million Women Study (UK) <sup>114</sup>	8724/38068		1.021 (0.010)		
Icelandic Study (Iceland) <sup>80</sup>	897/8467		1.076 (0.030)		
Shanghai Textile (China) <sup>88</sup>	1376/5458	÷	1.053 (0.025)		
Southern Sweden (Sweden) <sup>92</sup>	752/3135	- <u>+</u> -	1.041 (0.050)		
Swedish Mammography (Sweden) <sup>102</sup>	1125/3164	-	1.089 (0.045)		
DOM (Netherlands) <sup>70</sup>	317/1011		1.030 (0.062)		
US Radiologic Techo (USA) <sup>93</sup>	529/2333		0.952 (0.060)		
ACS Nutrition (USA)82	1141/5692	÷	1.021 (0.028)		
WHI (USA) <sup>86</sup>	628/2958	- <del> -</del> -	1.045 (0.058)		
EPIC (10 European Countries) <sup>108</sup>	6474/27388	-	1.035 (0.013)		
Multi Ethnic Cohort (USA) <sup>99</sup>	1785/14360	-	1.064 (0.025)		
S/N Womens (Norway/Sweden) <sup>94</sup>	706/3044	-	0.986 (0.040)		
NIH-AARP (USA) <sup>106</sup>	3352/14191	÷.	1.036 (0.017)		
UKCTOCS (UK) <sup>117</sup>	2484/7687	÷.	1.039 (0.015)		
JPHC (Japan) <sup>116</sup>	569/2209	- <del> </del> -	1.039 (0.044)		
Nurses Health Study II (USA)113	1774/6099		1.053 (0.024)		
Other (12 studies)	1464/6227	<b>+</b> -	1.061 (0.039)		
ALL COHORT STUDIES	44557/192829	i i	1.040 (0.005)		

## Webfigure 2B. Relative risk of breast cancer per year younger at menarche in case-control studies with population controls.

		RELATIVE RISK			
	Cases/Controls	RR & 99% CI	RR±SE		
Meirik/Lund (Sweden/Norway) <sup>24</sup>	386/513		1.029 (0.070)		
Brinton (USA) <sup>5</sup>	1759/1910		1.121 (0.031)		
Ewertz (Denmark) <sup>15</sup>	964/918	_ <u>+</u>	1.032 (0.051)		
Bernstein/Pike (USA) <sup>1</sup>	430/418	<b></b>	1.155 (0.070)		
UK National (UK) <sup>21</sup>	743/744	- <b>i</b> -	1.052 (0.043)		
Paul/Skegg (New Zealand)63	699/1573		1.065 (0.044)		
Daling (USA) <sup>47</sup>	659/859	_ <b>i</b>	1.048 (0.050)		
CASH (USA) <sup>31</sup>	3174/3138		1.050 (0.022)		
Zakelj (Slovenia) <sup>49</sup>	612/611		0.992 (0.045)		
Yuan/Yu (China) <sup>19</sup>	530/531		1.084 (0.047)		
Dutch OC (Netherlands)56	823/805	- <del> </del>	1.059 (0.046)		
Long Island Study (USA)30	880/907	_ <del></del>	1.027 (0.055)		
Wang/Yu (China) <sup>39</sup>	294/294	_ <b> -</b>	1.083 (0.072)		
CRC/ICRF (UK)97	570/564		1.032 (0.049)		
Bain (Australia) <sup>20</sup>	373/748		1.094 (0.066)		
Hislop (Canada) <sup>7</sup>	565/591	_ <b>_</b>	0.932 (0.052)		
Newcomb (USA) <sup>75</sup>	4600/6793		1.054 (0.022)		
WISH (USA)60	1635/1690	÷	1.157 (0.048)		
CARE (USA)85	2611/2546	li i i i i i i i i i i i i i i i i i i	1.026 (0.024)		
Magnusson (Sweden)68	1572/1973		0.952 (0.034)		
McCredie (Australia)62	431/394	_ <b>i</b>	1.064 (0.070)		
McCredie II (Australia) <sup>65</sup>	753/429	_ <b>i</b>	1.074 (0.072)		
ChangClaude (Germany)87	559/1115		1.014 (0.047)		
Shu Wei (China) <sup>79</sup>	1397/1481	-	1.100 (0.028)		
Bernstein II (USA) <sup>64</sup>	676/675	<b></b>	1.196 (0.061)		
Johnson (Canada) <sup>73</sup>	1652/1663	<b>.</b>	1.084 (0.038)		
Kreiger (Canada) <sup>83</sup>	1816/1868	÷.	1.051 (0.036)		
San Francisco Bay (USA) <sup>91</sup>	1189/1473	÷	1.102 (0.035)		
Lumachi (Italy) <sup>84</sup>	272/312	÷	1.217 (0.077)		
Ross/Pike (USA) <sup>76</sup>	799/788	- <del> </del>	1.062 (0.054)		
4-State Wisconsin (USA)72	2813/2920	÷	1.052 (0.026)		
LIBCSP (USA) <sup>105</sup>	830/998		0.906 (0.058)		
MARIE (Germany) <sup>107</sup>	855/2185	÷.	1.020 (0.034)		
Polish Breast Cancer (Poland) <sup>101</sup>	1434/1907	<b>+</b> -	1.065 (0.033)		
American Asian (USA) <sup>59</sup>	443/848	÷.	1.032 (0.044)		
Newcomb3 (USA)77	3586/4493	<b>.</b>	1.081 (0.023)		
CAMA (Mexico) <sup>109</sup>	695/851	- <del> </del> -	1.012 (0.048)		
MASTOS (Cyprus) <sup>110</sup>	583/832		1.102 (0.062)		
Other (18 studies)	5618/9732	<b>—</b>	1.076 (0.023)		
ALL CASE-CONTROL STUDIES WITH POPULATION CONTROLS	50280/63090		1.059 (0.006)		

Webfigure 2C. Relative risk of breast cancer per year younger at menarche in case-control studies with
hospital controls.

		RELATIVE RISK			
	Cases/Controls	RR & 99% Cl	RR ±SE		
Clavel (France) <sup>27</sup>	438/791		1.081 (0.059)		
La Vecchia (Italy)51	2877/2401	÷	1.066 (0.025)		
Ravnihar (Slovenia) <sup>16</sup>	493/1747	li i i i i i i i i i i i i i i i i i i	1.066 (0.036)		
Vessey I (UK) <sup>4</sup>	1134/1044	<b>—</b>	1.103 (0.032)		
Vessey II (UK) <sup>13</sup>	923/844		1.025 (0.043)		
Morabia I(USA)41	299/404	- <del>  -</del>	1.072 (0.061)		
Kalache (Brazil) <sup>43</sup>	532/730	- <del> </del>	1.053 (0.046)		
Franceschi II (Italy) <sup>58</sup>	2243/2206	÷.	1.048 (0.027)		
Hamajima (Japan) <sup>66</sup>	1338/5441	÷	1.078 (0.025)		
Katsouyanni (Greece) <sup>48</sup>	656/1263		1.099 (0.058)		
Modan (Israel) <sup>10</sup>	925/1718	+	1.016 (0.033)		
Gajalakshmi (India) <sup>33</sup>	466/485		1.064 (0.058)		
PEDS (USA) <sup>25</sup>	621/2287	_ <del> </del>	0.994 (0.064)		
Johannesburg (South Africa) <sup>71</sup>	1424/1367	÷	1.069 (0.032)		
WHO - developing <sup>42</sup>	1519/14669	<b></b>	1.050 (0.020)		
WHO - developed <sup>42</sup>	1375/3578	÷	1.038 (0.023)		
CCSS (USA) <sup>28</sup>	4564/5097	-	1.106 (0.028)		
Other (10 studies)	2300/4100	<b>.</b>	1.086 (0.035)		
ALL CASE-CONTROL STUDIES WITH HOSPITAL CONTROLS	24127/50172	<u> </u>	1.062 (0.008)  2.0		

### Webfigure 3. Relative risk of breast cancer in pre-menopausal versus postmenopausal women aged 45- 54 years in subgroups of women;\* and by tumour characteristics:

	Premenopausal Cases/Controls	Postmenopausal Cases/Controls	RR* (SE)	Relative risk* of breast cance in premenopausal vs postmenopausal & 99% Cl
LL WOMEN	20744/45211	8170/18933	1.43 (0.040)	
VOMEN'S CHARACTERISTICS				
Year of birth				
<1940 1940+ Heterogeneity test: $\chi^2_1$ =0.5, P=0	7014/13566 13730/31645 .5	4411/9526 3759/9407	1.45 (0.056) 1.38 (0.055)	
Age at diagnosis				
45-49 50-54 Heterogeneity test: Χ² <sub>1</sub> =0.3, P=0	12620/24650 8124/20561 .6	1648/3625 6522/15308	1.39 (0.068) 1.44 (0.050)	
Ethnicity	10404/00540	4747/0075	1.00 (0.055)	
Caucasian Non-Caucasian Heterogeneity test: Χ² <sub>1</sub> =0.3, Ρ=0	12434/23542 3685/9506 .6	4747/9875 1879/4696	1.38 (0.055) 1.44 (0.081)	
Parity Nulliparous	2691/4894	1230/2147	1.37 (0.125)	
Parous Heterogeneity test: χ <sub>1</sub> =0.1, P=0	17582/38569	6705/16022	1.41 (0.038)	
Age at first birth	0040/00007	0000/10007	1.07 (0.040)	
<ul> <li>&lt;25</li> <li>25+</li> <li>Heterogeneity test: χ<sup>2</sup><sub>1</sub>=1.2, P=0</li> </ul>	8946/22367 8739/16870 .3	3806/10097 2920/6069	1.37 (0.049) 1.47 (0.060)	
Height <165 cm	10670/22895	4503/9721	1.33 (0.051)	
165+ cm Heterogeneity test: χ <sub>1</sub> =1.9, P=0	8146/16242	2876/6125	1.47 (0.071)	
Body mass index (young adult)	1000/0574	1710/0050	4 00 (0 000)	
<20 kg/m² 20- kg/m² 25+ kg/m² Heterogeneity test: Χ² <sub>2</sub> =0.4, P=0	4960/8571 5925/11226 802/1846	1713/3059 2027/3933 354/828	1.39 (0.093) 1.33 (0.080) 1.57 (0.367)	
Body mass index (current)	.0			
<25 kg/m² 25- kg/m² 30+ kg/m²	11423/22540 4306/9728 2061/5279	3888/8504 1951/4244 1012/2302	1.51 (0.059) 1.17 (0.088) 1.08 (0.135)	
Heterogeneity test: X <sup>2</sup> <sub>2</sub> =11.0, P=	0.04			
Use of hormonal contraceptives Never	8247/16081	4766/9956	1.43 (0.063)	
Ever Heterogeneity test: X <sup>2</sup> <sub>1</sub> =0.4, P=0	11252/25985	2865/7581	1.50 (0.072)	
Smoking				
Never Past	9732/21706 4370/9357	3543/7715 1407/2946	1.32 (0.055) 1.55 (0.120)	
Current Heterogeneity test: X <sub>2</sub> <sup>2</sup> =2.7, P=0	3849/7527	1896/3983	1.44 (0.108)	
Alcohol None	5567/13311	2499/6098	1 20 (0.060)	
<50 g/week	7200/16754	2121/5249	1.30 (0.069) 1.41 (0.085)	
50+ g/week Heterogeneity test: χ <sub>2</sub> =4.4, P=0	3445/5353 .1	1378/2519	1.71 (0.155)	
Mother or sister with breast can				
No Yes Heterogeneity test: Χ <sub>1</sub> =0.2, P=0	14958/33288 2380/2959	6255/14734 955/1236	1.39 (0.046) 1.53 (0.275)	+=
Age at menarche				
<13 13+	8385/17122 12359/28089	3229/6482 4941/12451	1.24 (0.082) 1.51 (0.056)	<b>┝─</b> ╋┿ ┿╋┷
Heterogeneity test: $\chi^2_1$ =5.4, P=0		1011/12101	1.01 (0.000)	-
JMOUR CHARACTERISTICS				
ER status negative positive	1533/22149 4054/22149	552/7957 1095/7957	1.26 (0.077) 1.53 (0.060)	│ <b>─</b> ∎∔ <b>∔</b> ∎─
case-case comparison for ER+	vs. ER-: p=0.003			
Histology ductal	10160/34440	3572/13374	1.33 (0.033)	
lobular	1456/34440	352/13374	2.05 (0.109)	<b>•</b>
other case-case comparison for lobula	2162/34440 ar vs. ductal: p<0.000	726/13374	1.47 (0.069)	<b>_</b> ₽
sase case companson for lobuli	a +3. duotai. p<0.000			1 1

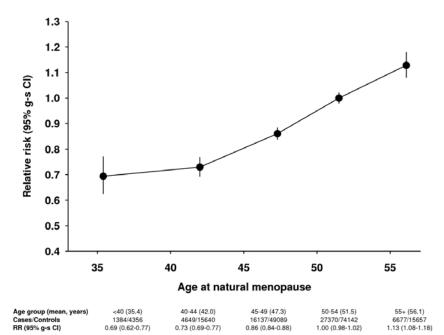
\*Relative risks are calculated stratifying by study, age at diagnosis in single years, and, where appropriate, by year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index (results for body mass index as a young adult are not stratified by current body mass index).

Relative risks are calculated stratifying by study, age at diagnosis in single years, and year of birth, and adjusting by parity, age at first birth, smoking, alcohol consumption, height and current body mass index. Case-case comparisons stratified by study, age and year of birth, and adjusted by parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

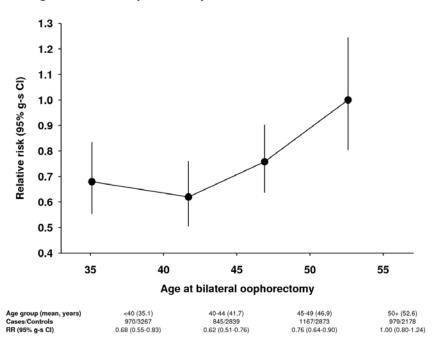
#### Webfigure 4. Relative risk of breast cancer by:

(A) age at natural menopause, and (B) age at bilateral oophorectomy.

#### A: Age at natural menopause







\*Relative risk estimates are calculated stratifying by study, age, year of birth, parity, age at first birth, smoking, alcohol consumption, height and current body mass index.

Relative risks in pre-menopausal versus postmenopausal women aged 45-54 years with a natural menopause and with a bilateral oophorectomy were 1.42 (95% CI 1.32-1.52) and 1.53 (95% CI 1.26-1.86), respectively, (p for heterogeneity=0.6).

		ISK	
	Cases/Controls	RR & 99% Cl	RR ±SE
Nurses Health Study I (USA) <sup>113</sup>	2173/9761		1.040 (0.008)
Alexander et al (UK) <sup>14</sup>	111/455	÷	1.004 (0.027)
American Cancer Society (USA) <sup>89</sup>	1701/6652	÷	1.033 (0.010)
NLCS (Netherlands) <sup>50</sup>	1281/1560		1.026 (0.014)
Canada BC Screening (Canada) <sup>36</sup>	248/995	-	1.066 (0.022)
BCDDP (USA) <sup>46</sup>	845/2117	+	1.055 (0.018)
RERF (Japan) <sup>67</sup>	128/569	<b></b>	1.102 (0.058)
Iowa (USA) <sup>74</sup>	798/3624	÷.	1.012 (0.011)
Million Women Study (UK) <sup>114</sup>	6119/28370		1.028 (0.005)
Icelandic Study (Iceland) <sup>80</sup>	595/5592		1.024 (0.012)
Shanghai Textile (China) <sup>88</sup>	816/3267	-	1.030 (0.012)
Southern Sweden (Sweden) <sup>92</sup>	332/1548	+	1.023 (0.036)
Swedish Mammography (Sweden) <sup>102</sup>	955/3145	-	1.069 (0.015)
NOWAC (Norway)90	401/2035	+	0.991 (0.025)
SOF (USA) <sup>98</sup>	162/665	<b>-</b>	1.051 (0.033)
ACS Nutrition (USA)82	1074/5412	ė.	1.016 (0.010)
WHI (USA) <sup>86</sup>	628/2958	-	1.051 (0.019)
EPIC (10 European Countries) <sup>108</sup>	2266/10905		1.037 (0.009)
Multi Ethnic Cohort (USA) <sup>99</sup>	1209/10295	÷	1.017 (0.010)
S/N Womens (Norway/Sweden)94	116/542	_ <b>_</b>	0.963 (0.055)
NIH-AARP (USA) <sup>108</sup>	3217/13641		1.025 (0.005)
UKCTOCS (UK)117	2484/7687		1.032 (0.006)
JPHC (Japan) <sup>116</sup>	277/1132	-	1.049 (0.029)
Other	655/2680	<b>!-</b> -	1.051 (0.036)
ALL COHORT STUDIES	28591/125607	i i	1.030 (0.002)

### Webfigure 5A. Relative risk of breast cancer per year older at menopause in cohort studies.

Webfigure 5B. Relative risk of breast cancer per year older at menopause in case-control studies with population controls.

	RELATIVE RISK			
	Cases/Controls	RR & 99% Cl	$RR \pm SE$	
Brinton (USA)⁵	790/947		1.012 (0.015	
Ewertz (Denmark) <sup>15</sup>	388/393	<b>-</b>	1.061 (0.039	
Rohan (Australia) <sup>17</sup>	180/202	_ <b>_</b>	1.062 (0.064	
Paul/Skegg (New Zealand) <sup>63</sup>	105/152		0.978 (0.060	
CASH (USA) <sup>31</sup>	365/456	-	0.984 (0.033	
Zakelj (Slovenia) <sup>49</sup>	111/142	_ <b>_</b>	0.995 (0.065	
Yuan/Yu (China) <sup>19</sup>	297/298	+	1.051 (0.025	
Long Island Study (USA) <sup>30</sup>	533/575		0.957 (0.026	
Yang/Gallagher (Canada)40	313/311	<b>∔</b>	1.038 (0.040	
Stanford/Habel (USA)57	149/165		1.011 (0.055	
Bain (Australia) <sup>20</sup>	226/475	+	1.019 (0.035	
Hislop (Canada) <sup>7</sup>	277/291		1.001 (0.030	
Newcomb (USA) <sup>75</sup>	3029/4108	ģ.	1.021 (0.009	
Clarke (Canada) <sup>37</sup>	213/437		1.013 (0.047	
CARE (USA)85	621/610	÷.	1.038 (0.021	
Sanjose (Spain) <sup>53</sup>	186/220		0.950 (0.043	
Magnusson (Sweden)68	1433/1867		1.047 (0.015	
ChangClaude (Germany)87	66/121	_ <b>_</b>	0.955 (0.067	
Shu Wei (China) <sup>79</sup>	457/505	÷	1.038 (0.019	
Johnson (Canada) <sup>73</sup>	845/854	-	1.045 (0.019	
Friedenreich (Canada)78	302/269	<b></b>	1.068 (0.047	
Kreiger (Canada) <sup>83</sup>	877/844	La construction de la constructi	1.005 (0.017	
San Francisco Bay (USA) <sup>91</sup>	502/639		1.025 (0.018	
Lumachi (Italy) <sup>84</sup>	151/174		1.287 (0.073	
PACE (USA) <sup>100</sup>	210/265	+	1.008 (0.033	
Ross/Pike (USA) <sup>76</sup>	799/787	÷.	1.033 (0.020	
4-State Wisconsin (USA)72	2574/2660	ė.	1.026 (0.008	
LIBCSP (USA) <sup>105</sup>	487/513	Į.	1.039 (0.027	
MARIE (Germany) <sup>107</sup>	723/1877		1.022 (0.014	
Polish Breast Cancer (Poland) <sup>101</sup>	974/1266	-	1.036 (0.017	
Western New York (USA) <sup>34</sup>	258/289		1.039 (0.041	
American Asian (USA) <sup>59</sup>	76/194		1.068 (0.070	
Newcomb3 (USA)77	1340/1805	i i	1.028 (0.013	
CAMA (Mexico) <sup>109</sup>	339/396	-	0.940 (0.024	
MASTOS (Cyprus) <sup>110</sup>	410/475	. ↓	1.025 (0.028	
WISE (USA) <sup>103</sup>	378/597	-	0.956 (0.028	
Wrensch/Baltzell (USA) <sup>81</sup>	186/393	_	1.007 (0.070	
Other	722/1191	<b></b>	1.123 (0.043	
ALL CASE-CONTROL STUDIES	21892/27763		1.024 (0.003	

Webfigure 5C. Relative risk of breast cancer per year older at menopause in case-control studies with
hospital controls.

		RELATIVE RISK	
	Cases/Controls	RR & 99% Cl	RR ±SE
Hulka I (USA) <sup>26</sup>	86/579	<b>—</b>	1.055 (0.063)
Franceschi I (Italy) <sup>29</sup>	196/195	_ <b>-</b>	0.974 (0.069)
La Vecchia (Italy)51	1519/1398	÷	1.028 (0.013)
Ravnihar (Slovenia) <sup>16</sup>	86/339		1.075 (0.064)
Vessey II (UK) <sup>13</sup>	325/334	-	1.118 (0.037)
Morabia I(USA)41	107/176	-	1.041 (0.027)
Lee (Singapore) <sup>35</sup>	87/197		1.098 (0.067)
Gerber (France) <sup>32</sup>	171/192		1.029 (0.062)
Ngelangel (Philippines) <sup>42</sup>	114/97	_ <b>_</b>	0.975 (0.056)
Kalache (Brazil)43	277/388	÷	1.027 (0.026)
Franceschi II (Italy)58	1265/1374	÷	1.040 (0.014)
Hamajima (Japan) <sup>66</sup>	578/2362	i.	1.022 (0.016)
Katsouyanni (Greece) <sup>48</sup>	403/770	-	1.069 (0.029)
Modan (Israel) <sup>10</sup>	593/1133	÷	1.008 (0.015)
Gajalakshmi (India) <sup>33</sup>	304/323	+	0.998 (0.026)
PEDS (USA) <sup>25</sup>	377/1318	+	1.002 (0.035)
Johannesburg (South Africa) <sup>71</sup>	785/914	-	1.041 (0.015)
WHO - developing <sup>42</sup>	273/2343	-	1.074 (0.024)
WHO - developed <sup>42</sup>	151/422		1.028 (0.035)
CCSS (USA) <sup>28</sup>	1908/1697	÷	1.020 (0.019)
Other	249/492		1.084 (0.066)
ALL CASE-CONTROL STUDIES WITH HOSPITAL CONTROLS	9854/17043	<u>с.                                    </u>	1.032 (0.005) ـــــا 2.0

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