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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.

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

Study (country) ref	Cases/Controls	Cases at diagnosis		Mean age at menarche Cases/Controls	Mean age at natural menopause Cases/Controls	Information on tumour type
		Mean age	Median year			
35 Cohort studies						
Thomas (USA) 3	19/74	49.8	1970	12.5/13.2	†	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
Guernsey 3&4 (UK) 61	84/286	54.0	1986	13.2/13.1	49.6/49.5	No
BCDDP (USA) 46	845/6,079	63.5	1988	12.8/12.9	49.8/49.0	Yes
Icelandic Study (Iceland) 80	897/8,467	56.6	1989	13.4/13.5	48.3/47.8	No
Nurses Health Study I (USA) 113	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	46.1/46.8	No
Amer.Can.Soc. (USA) 89‡	3126/12,236	67.2	1994	12.7/12.9	49.5/49.0	No
Newcomb/Mandelson (USA) 55	34/63	44.5	1994	12.1/12.1	†	Yes
SOF (USA) 98	162/665	76.7	1994	13.1/13.1	48.6/47.9	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	1785/14,360	64.9	2000	12.6/12.7	48.7/48.3	Yes
Nurses Health Study II (USA) 113	1774/6099	45.4	2000	12.3/12.4	†	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	2001	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 controls)						
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	112/152	39.5	1977	12.5/12.6	†	No
Nomura (USA) 9	151/129	57.2	1978	13.2/13.3	48.9/48.9	Yes
Bernstein/Pike (USA) 1	430/418	31.5	1980	12.3/12.5	†	Yes
CASH (USA) 31	3,174/3,138	43.0	1981	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	†	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	†	Yes
Clarke (Canada) 37	456/942	50.1	1984	12.8/12.9	49.6/48.5	Yes
Long Island Study (USA) 30	880/907	54.5	1984	12.7/12.7	48.8/49.2	Yes
Meirik/Lund (Sweden/Norway) 24	386/513	37.2	1984	13.0/13.0	†	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
Wrench/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
Wang/Yu (China) 39	294/294	43.2	1985	14.1/14.4	†	Yes
Bernstein II (USA) 64	676/675	35.5	1986	12.3/12.5	†	No
Daling (USA) 47	659/859	36.5	1987	12.6/12.7	†	Yes
Western New York (USA) 34	547/591	53.6	1987	12.6/12.9	48.8/47.9	Yes
CRC/ICRF (UK) 97	570/564	41.5	1988	12.6/12.7	†	Yes

Dutch OC (Netherlands) 56	823/805	41.6	1988	12.9/13.0	†	Yes
Newcomb (USA) 75	4,600/6,793	56.6	1988	12.9/13.0	49.0/48.3	No
Sanjose (Spain) 53	285/308	55.8	1988	13.1/12.9	49.3/48.3	No
Ross/Pike (USA) 76	799/788	61.2	1989	12.6/12.7	49.9/49.8	Yes
Stanford/Habel (USA) 57	184/205	57.5	1989	12.6/12.5	49.5/49.4	Yes
Yang/Gallagher (Canada) 40	525/523	53.8	1989	12.5/12.6	48.7/48.3	Yes
Zakelj (Slovenia) 49	612/611	44.8	1989	13.8/13.9	†	Yes
ICRF (UK) 104	277/277	49.5	1991	12.9/12.9	†	Yes
WISH (USA) 60	1,635/1,690	40.1	1991	12.4/12.5	†	Yes
4-State Wisconsin (USA) 72	2,813/2,920	65.7	1992	12.9/12.9	49.6/48.9	Yes
McCredie (Australia) 62	431/394	34.8	1993	12.9/12.9	†	Yes
Morabia II (Switzerland) 54	134/665	53.4	1993	13.0/13.4	48.8/48.1	No
ChangClaude (Germany) 87	559/1115	41.8	1994	13.1/13.1	†	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	†	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 controls)						
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	†	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	†	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	621/2,287	55.0	1987	12.7/12.8	49.6/49.1	Yes
Ngelangel (Philippines) 42	271/279	46.1	1988	13.7/13.7	†	Yes
Hulka II (USA) 45	65/125	42.2	1990	12.9/12.6	†	Yes
Katsouyanni (Greece) 48	656/1,263	54.9	1990	12.9/13.1	48.6/47.8	Yes
Franceschi II (Italy) 58	2,243/2,206	53.9	1992	12.9/13.0	49.9/49.1	No
Hamajima (Japan) 66	1338/5441	50.5	1992	13.8/14.0	49.9/49.4	No
Levi (Switzerland) 52	164/375	53.6	1992	13.4/13.5	49.7/49.9	Yes
Gajalakshmi (India) 33	466/485	48.4	1993	13.9/14.0	†	No
Johannesburg (South Africa) 71	1424/1,367	51.0	2003	15.3/15.3	48.2/47.8	Yes
Ghiasvand (Iran) 115	420/460	40.3	2006	13.9/14.0	†	No
Subtotal	24,127/50,172	49.1	1985	13.3/13.7	48.9/47.9	
TOTAL	118,964/306,091	54.0	1993	13.0/13.1	50.0/49.5	

† 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.

‡ 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

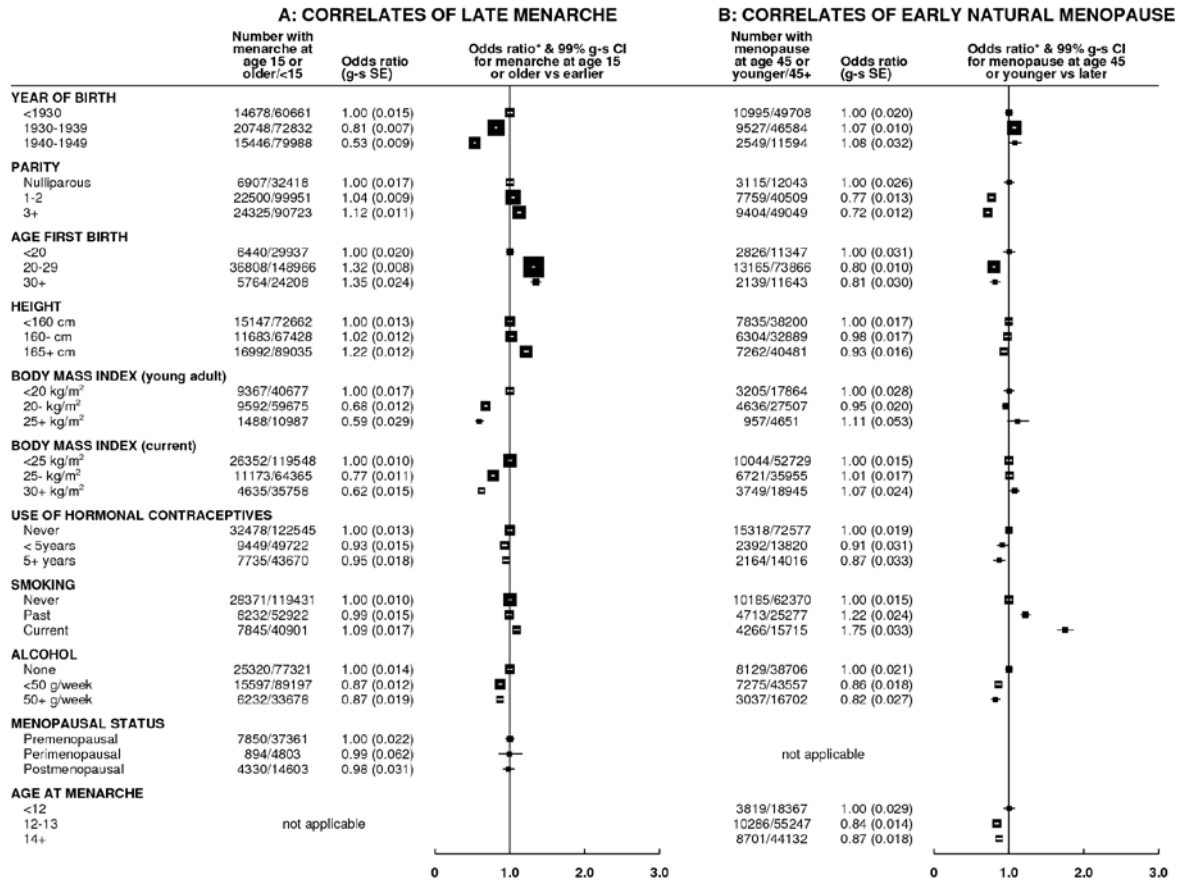
*Relative risk estimates are calculated stratifying, by study, age, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

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)

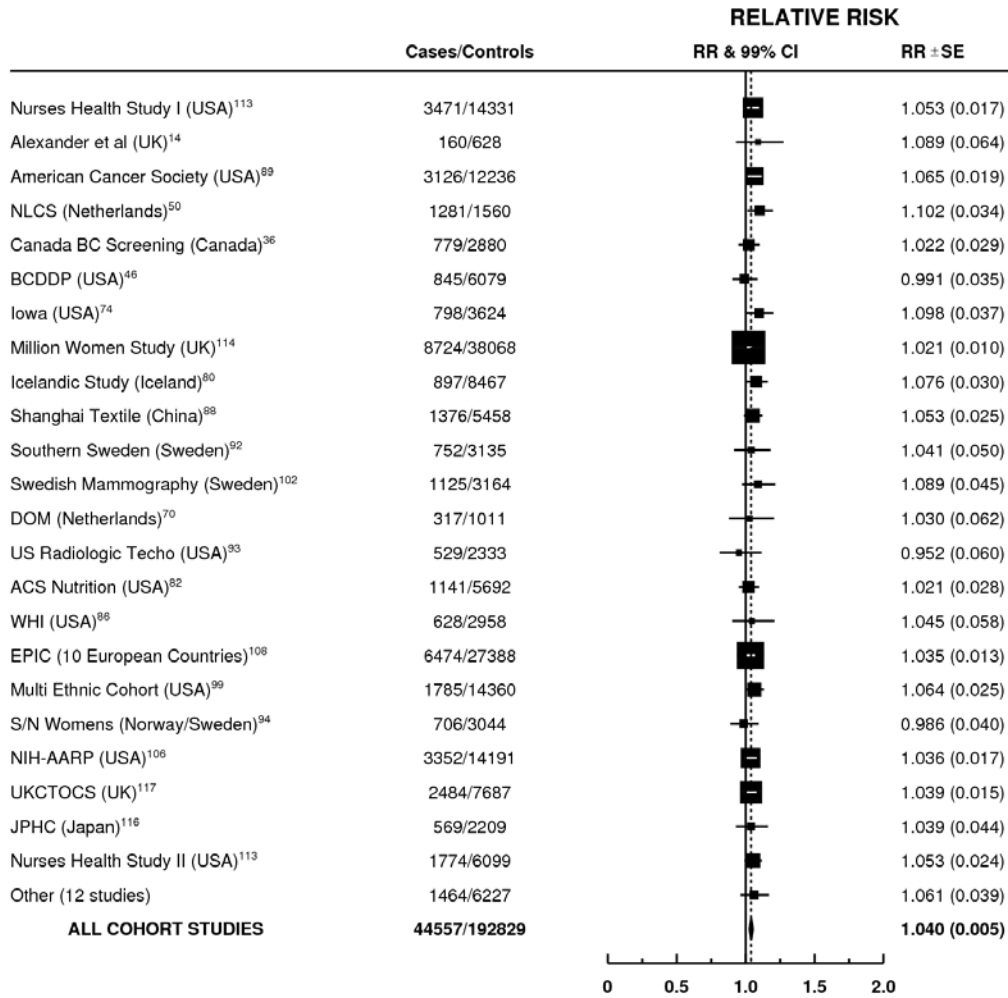
*Relative risk estimates are calculated stratifying, by study, age and year of birth, and adjusting by parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

**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**



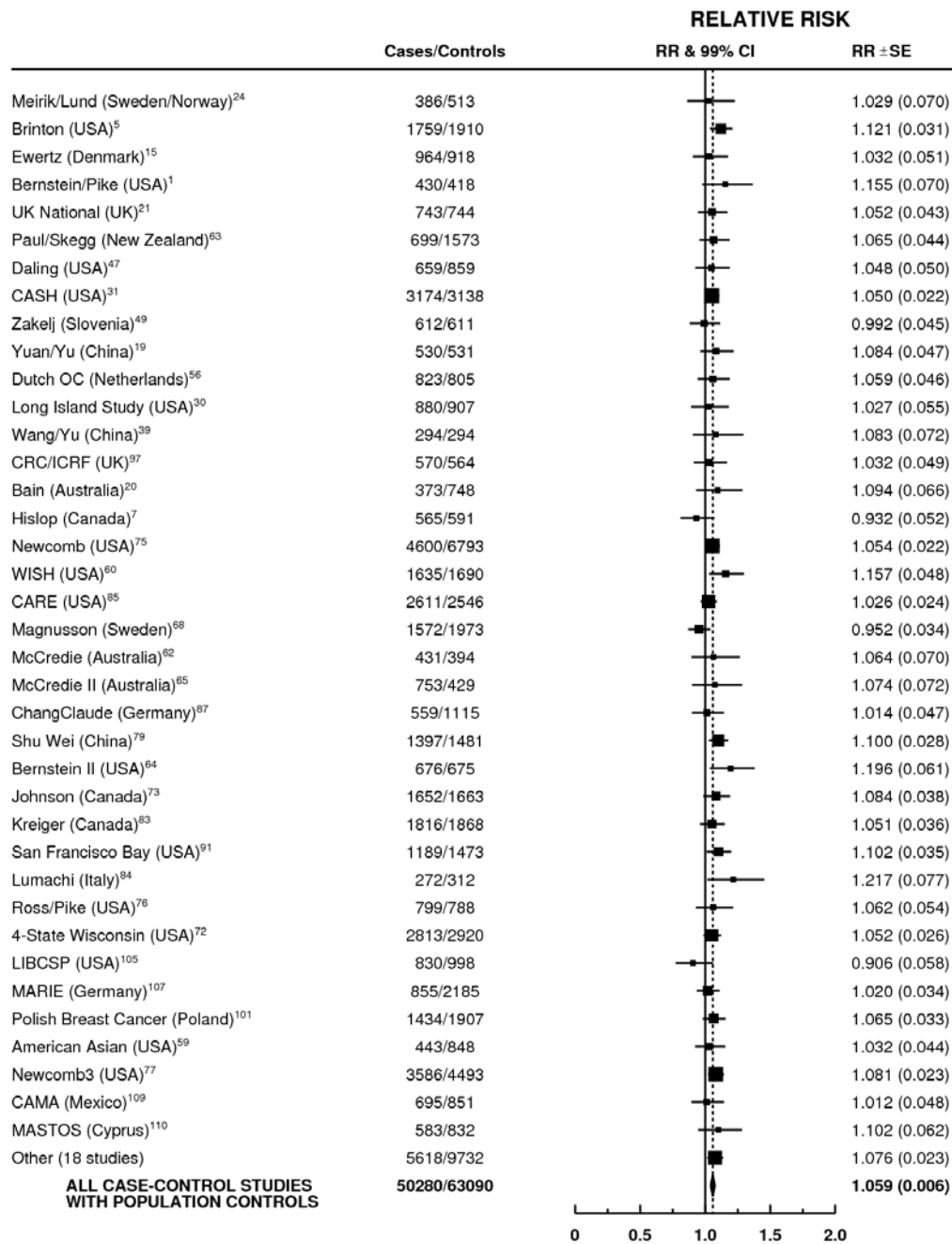
Data are for women without breast cancer, ie controls. Odds ratio calculations were stratified by study and, where appropriate, by age at diagnosis, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index (results for body mass index as a young adult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

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



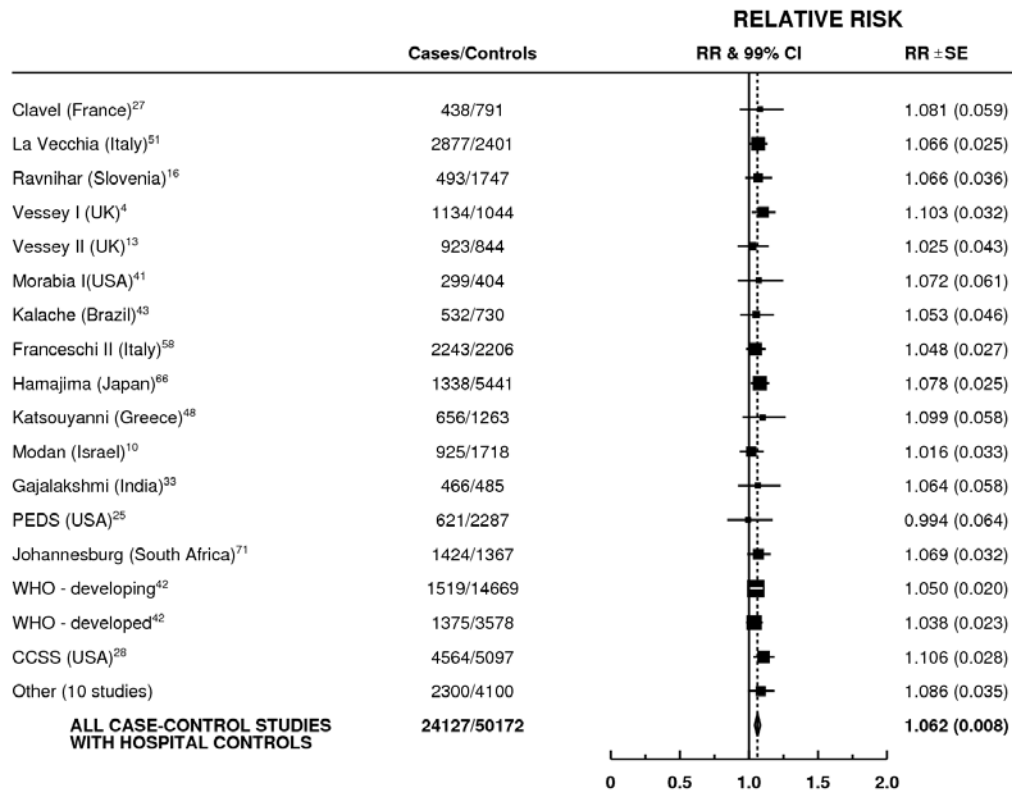
Relative risks are calculated stratifying by age at diagnosis, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

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



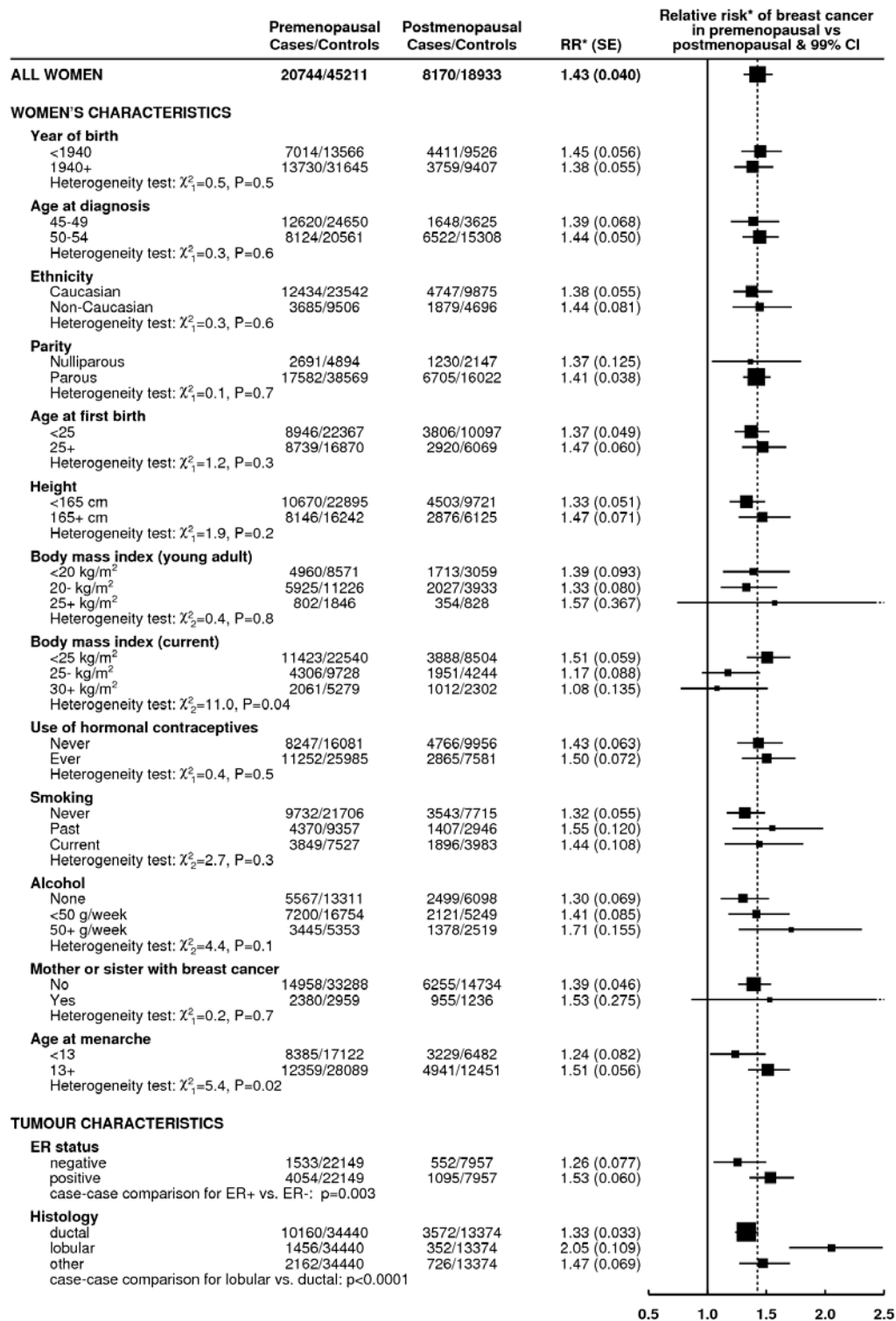
Relative risks are calculated stratifying by age at diagnosis, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

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



Relative risks are calculated stratifying by age at diagnosis, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

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‡

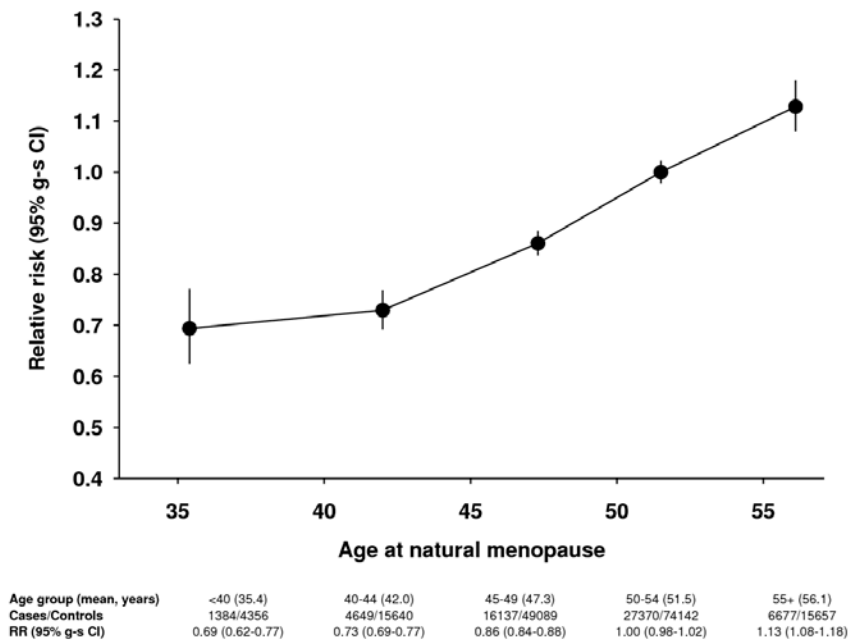


*Relative risks are calculated stratifying by study, age at diagnosis in single years, and, where appropriate, by year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index (results for body mass index as a young adult are not stratified by current body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

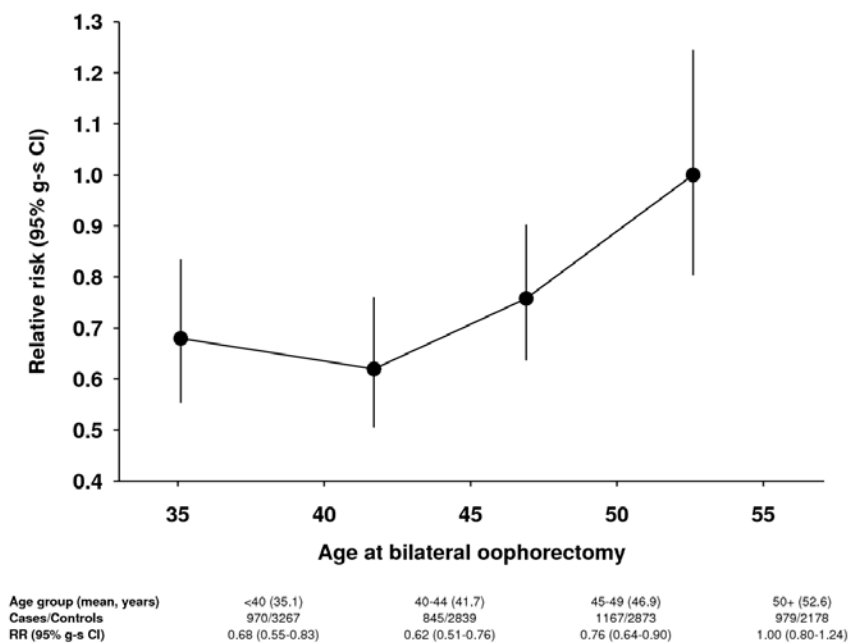
‡Relative risks are calculated stratifying by study, age at diagnosis in single years, and year of birth, and adjusting by parity, age at first birth, smoking, alcohol consumption, height and current body mass index. Case-case comparisons stratified by study, age and year of birth, and adjusted by parity,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



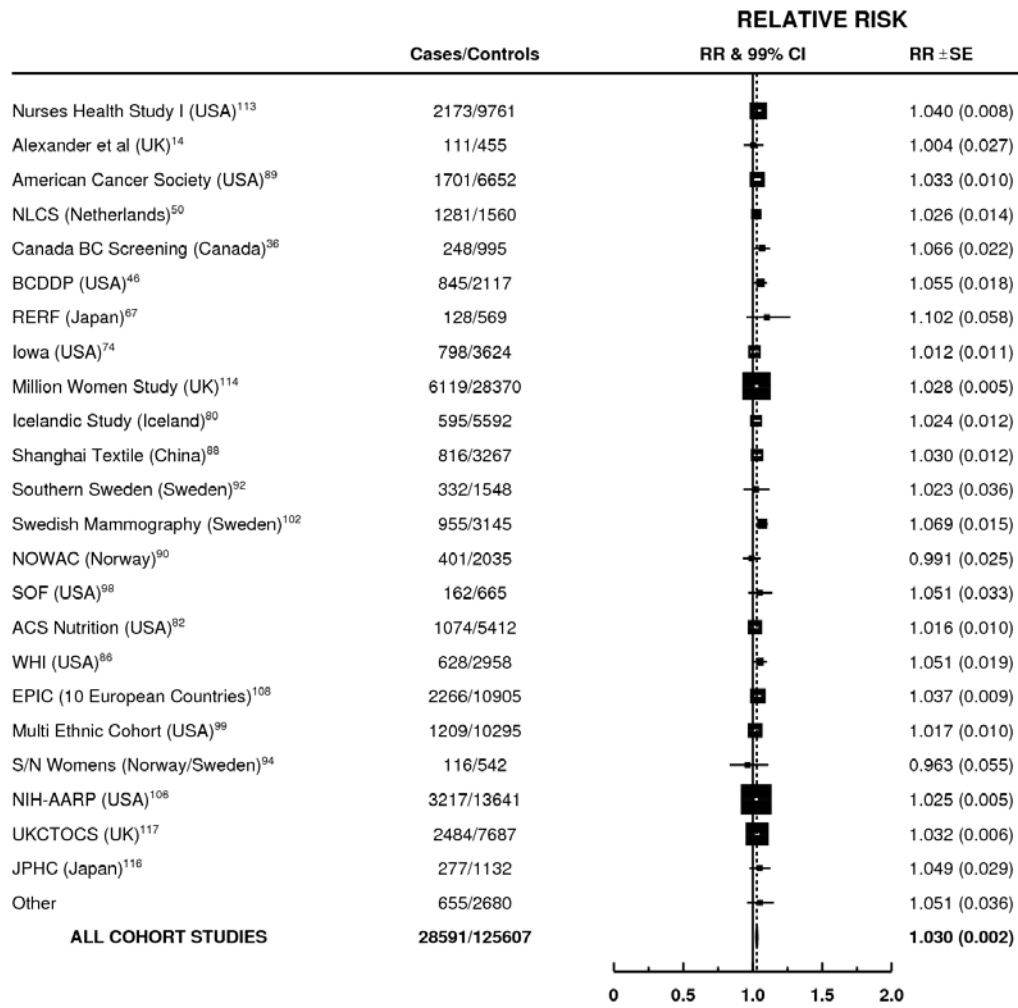
B: Age at bilateral oophorectomy



*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.

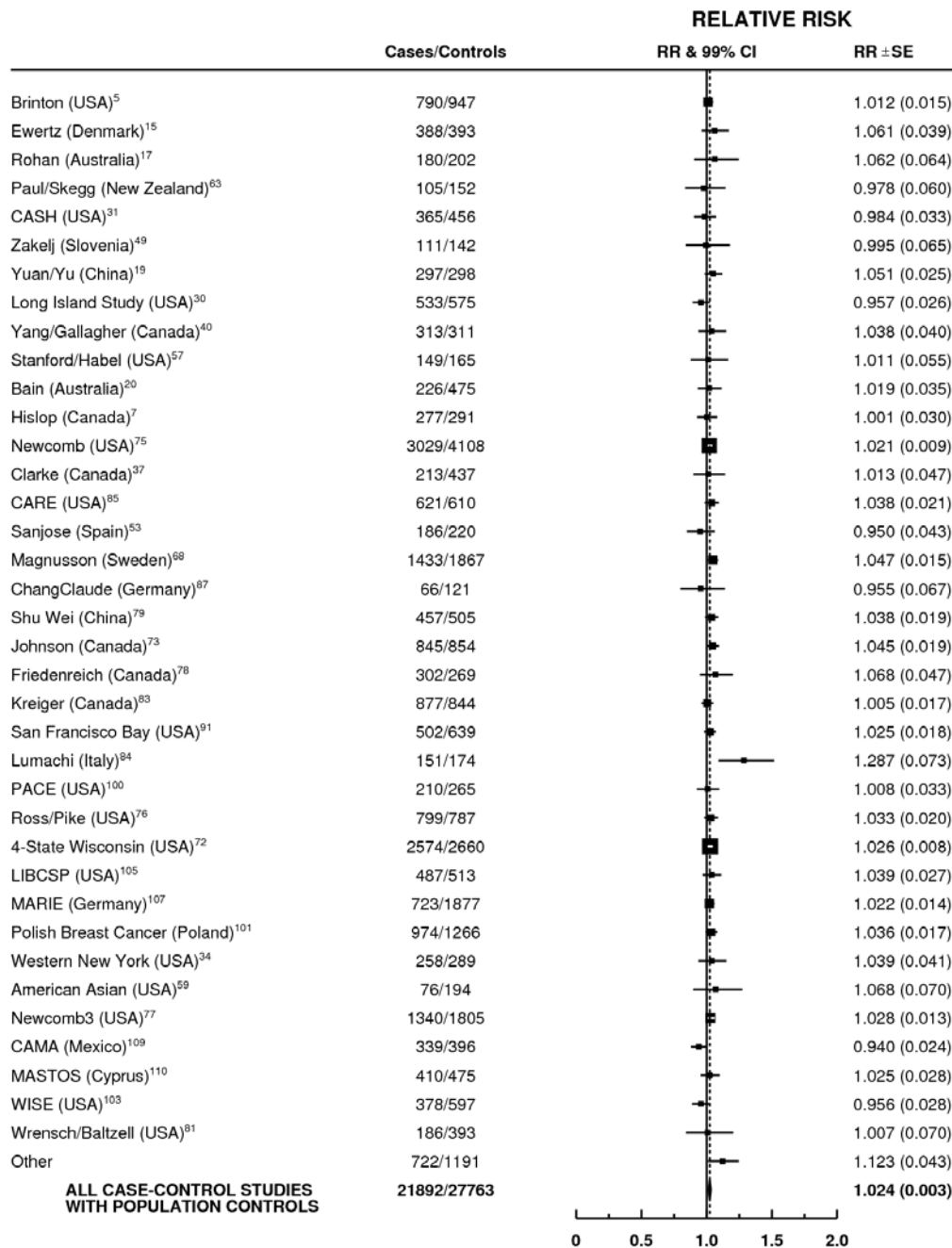
Relative risks in pre-menopausal versus postmenopausal women aged 45-54 years with a natural menopause and with a bilateral oophorectomy were 1.42 (95%CI 1.32-1.52) and 1.53 (95%CI 1.26-1.86), respectively, (p for heterogeneity=0.6).

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



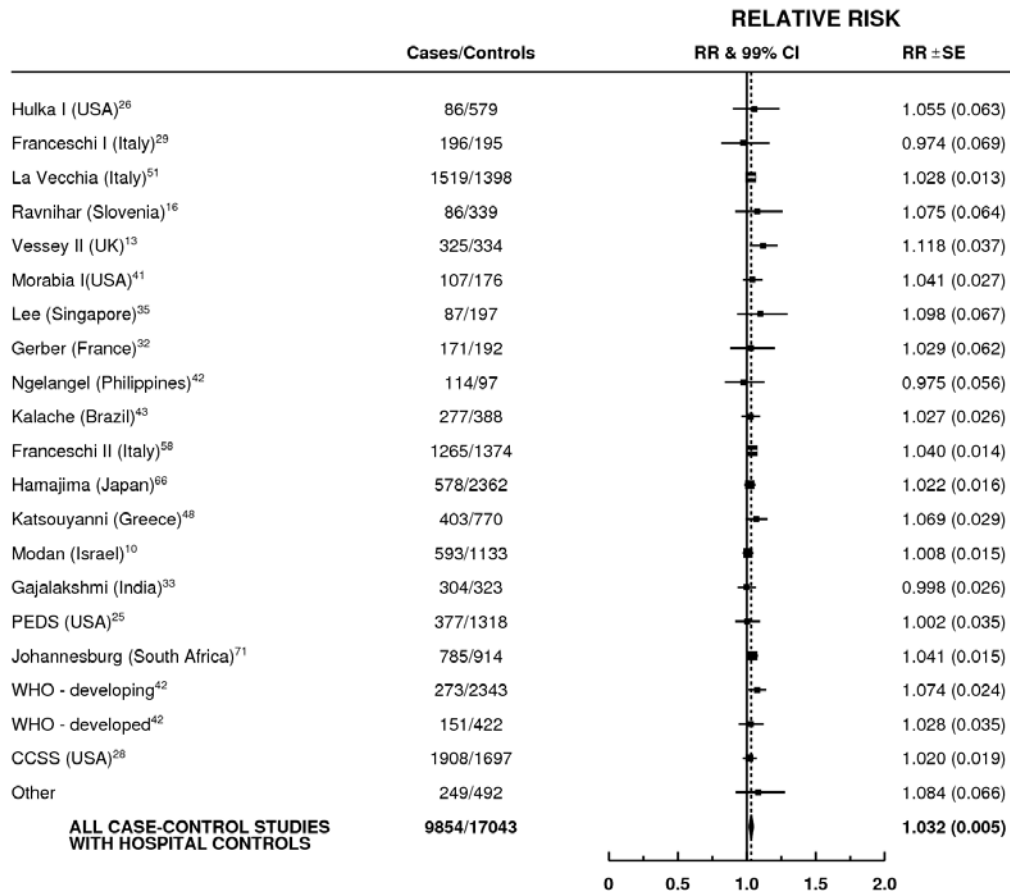
Relative risks are calculated stratifying by age at diagnosis, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

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



Relative risks are calculated stratifying by age at diagnosis, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

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



Relative risks are calculated stratifying by age at diagnosis, year of birth, parity, age at first birth, smoking, alcohol consumption, height, and current body mass index.

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