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Original Paper

Risk Factors for Breast Cancer in Women Under 40 Years

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The relation between hormonal and lifestyle factors and breast cancer risk in women younger than 40 years was investigated using data from two case–control studies conducted in Italy between 1983 and 1994. Cases were 579 women with histologically confirmed, incident breast cancer and controls were 668 women admitted to hospital for acute, non-neoplastic, non-hormone-related diseases. Breast cancer risk was inversely related to age at menarche with a multivariate odds ratio (OR) of 0.53 (95% confidence interval, CI, 0.31–0.89) for women reporting menarche at the age of ≥15 years compared with <12 years. Breast cancer risk was significantly higher in parae than in nulliparae (OR 1.58), and was directly associated with age at first birth (OR 5.31 among women aged ≥30 years at first birth compared with those aged <20), and inversely with time since last birth (OR 3.80 for <3 years compared with ≥12). Compared with women reporting no abortion, the OR were 1.10 for any spontaneous, 0.87 for any induced and 0.90 for ≥2 abortions. With reference to oral contraceptive use, the OR was 1.05 for ever users compared with never users, and no material association was evident with duration, time since first and last use. The OR was 1.79 for more than 13 years of education compared with <9, 1.85 for a family history of breast cancer and 1.85 for a history of benign breast disease. Breast cancer risk was inversely related to body mass index with an OR of 0.51 (95% CI 0.26–0.97) for ≥30 kg/m^2 compared to <20. Total energy and alcohol intake were directly related to the risk (OR 1.38 and 1.27 for the highest tertiles of intake compared with the lowest), although the estimates were not significant, whilst raw vegetable and beta-carotene consumption were inversely related to breast cancer risk (OR 0.57 and 0.67 for the highest tertile of intake compared with the lowest). Thus, most risk factors in this large dataset of women aged less than 40 years were similar to those described in breast cancer epidemiology at any age. Of interest are the inverse associations with body mass index, age at menarche and time since last birth, the direct ones with age at first and last birth, and the higher risk of parous women compared with nulliparae. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: breast neoplasms, case–control studies, diet, hormonal factors, oral contraceptives, reproductive factors, risk factors
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INTRODUCTION

WOMEN UNDER 40 years of age account for less than 10% of breast cancer cases [1], but any risk factor for breast cancer at younger age is of interest for individual risk assessment and in a public health perspective. The Surveillance Epidemiology and End Results (SEER) Program for the period 1973–1989 [2] showed that trends in breast cancer among women under 40 years of age were more favourable than for older women, although similar patterns of mortality by age were observed in Italian women [3]. Several risk factors for breast cancer may differ in relation to age at diagnosis [4–8].

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Nulliparity and overweight have been related to reduced risk at younger age and to elevated risk in the elderly [5], and the associations with age at menarche [9–12] and a family history of breast cancer [13, 14] were reportedly stronger in younger patients, although the evidence is still controversial. Likewise, the association with age at first birth and the potential role of age at last birth and time since last birth may be quantitatively different in younger women [9–11]. Abortions—and, specifically, induced abortion [15]—have been related to increased breast cancer risk in young women [16, 17], although the evidence is still controversial [18, 19]. As for oral contraceptive use, re-analysis of individual data from 54 epidemiological studies [20] showed an association at younger age, which was largely explained in terms of recent use. The potential effects of alcohol intake [5, 21, 22], diet [23] and height [24–26] on breast carcinogenesis in relation to age at diagnosis are still debated.

To provide further information on these issues, we analysed the relationship of hormonal, reproductive and general lifestyle factors with breast cancer risk in women younger than 40 years, using the combined data from two case–control studies conducted in Italy.

PATIENTS AND METHODS

The data were derived from two case–control studies of breast cancer, the first conducted between January 1983 and May 1991 in the greater Milan area [27], and the second between June 1991 and February 1994 in six Italian areas: greater Milan, the province of Pordenone, the urban area of Genoa and the province of Forlì, in northern Italy; the province of Latina, in central Italy; and the urban area of Naples, in southern Italy [28]. The interviewers were centrally trained, and some sections of the structured questionnaires had been tested for reliability and reproducibility [29, 30]. All interviews for cases and controls were conducted in hospital; on average, less than 4% of cases and controls approached refused the interview. The overall dataset included 5984 cases and 5504 controls; for the present report, only women younger than 40 years were considered.

Cases were 579 women aged 22–39 years (median age 36 years) with incident (i.e. diagnosed within the year before interview), histologically confirmed breast cancer, admitted to the major teaching and general hospitals in the areas under surveillance.

Controls were 668 women aged 22–39 years (median age 34 years), residing in the same areas and admitted to the same network of hospitals where cases had been identified, for a wide spectrum of acute, non-neoplastic conditions unrelated to known or likely risk factors for breast cancer. Of these, 33% had traumatic conditions (mostly fractures and sprains), 30% non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 19% were admitted for acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 18% for miscellaneous other illnesses, such as eye, ear, nose, throat and dental disorders. Women were not included if they had been admitted for gynaecological, hormonal or neoplastic diseases.

The questionnaires included information on personal characteristics and lifestyle habits, including education, marital status and other socio-economic indicators, smoking, alcohol and coffee drinking, anthropometric variables, diet, menstrual and reproductive factors (such as age at menarche, menstrual pattern, number of abortions and births, and age at each birth), selected medical conditions, history of lifelong use of oral contraceptives, history of benign breast disease and family history of breast and ovarian cancer. Body mass index was computed according to Quetelet's index (weight, kg/height^2, m^2). Information on alcohol included the number of drinks per day and the number of days per week for each type of alcoholic beverage, and total alcohol consumption was computed as the average number of all alcoholic drinks per day (each approximately 12–15 g of ethanol).

The latest study also collected information on physical activity, and more detailed dietary information using a food frequency questionnaire including average weekly frequency of consumption of 78 foods, food groups, or recipes [29]. Italian food composition tables were used to compute energy and selected nutrient intake [31].

Data analysis

Odds ratios (OR) of breast cancer, and the corresponding 95% confidence intervals (CI) were derived using unconditional multiple logistic regression models, fitted by the method of maximum likelihood [32]. All the regression equations included terms for study, centre, calendar year of recruitment, single year of age, education, body mass index, family history of breast cancer in first-degree relatives, parity and age at first birth.

RESULTS

Table 1 gives the distribution of 579 breast cancer cases and 668 controls according to age, education, marital status, family history of breast cancer and history of benign breast

Table 1. *Distribution of* 579 *cases of breast cancer and* 668 *controls in women aged* < 40 *years, and corresponding odds ratios (OR) with* 95% *confidence intervals (CI), according to selected covariates: Italy*, 1983–1994

	Breast cancer	Controls	OR (95% CI)*
Age (years)			
<25	10	50	
25–29	59	100	
30–34	157	188	
35–39	353	330	
Education (years)			
<9	247	346	1†
9–13	212	232	1.27 (0.96–1.68)
>13	120	90	1.79 (1.24–2.58)
Marital status			
Ever married	492	498	1†
Never married	87	170	0.72 (0.45–1.14)
Family history of breast cancer			
No	533	644	1†
Yes	46	24	1.85 (1.08–3.16)
History of benign breast disease			
No	492	615	1†
Yes	87	53	1.85 (1.26–2.73)

*Estimates from multiple logistic regression equations including terms for study, centre, year of recruitment, age, education, body mass index, family history of breast cancer, parity and age at first birth. †Reference category.

disease. Compared with controls, cases were significantly more educated, with an OR of 1.79 for >13 years of education compared with <9 years, and less often never married (OR 0.72 compared with ever married). Breast cancer cases more frequently reported a history of breast cancer in first-degree relatives (OR 1.85); the OR was 4.76 (95% CI 0.93–24.37) for women (7 cases and 2 controls) with more than one first-degree relative affected. A history of ovarian cancer in first-degree relatives was reported by 4 cases (0.6%) and 3 controls (0.4%), corresponding to an OR of 0.90 (95% CI 0.18–4.40), and a history of breast and/or ovarian cancer was reported by 48 (8%) cases and 25 (4%) controls, corresponding to an OR of 1.82 (95% CI 1.08–3.06). The OR was also significantly elevated (OR 1.85) among women with a personal history of benign breast disease.

Menstrual and reproductive factors are shown in Table 2. There was a significant inverse relation with age at menarche, with an OR of 0.53 for women reporting menarche when aged ≥15 years compared with those aged <12 years. Women reporting irregular menstrual cycles (defined as frequent menstrual-like episodes less than 21 or more than 35 days apart) were at non-significantly reduced breast cancer risk (OR 0.73). Only 12 cases (2.1%) and 9 controls (1.3%) were postmenopausal, and the corresponding OR was 1.37 (95% CI 0.55–3.42).

Spontaneous and induced abortions were not related to breast cancer risk: compared with women reporting no abortion, the OR was 1.10 for any spontaneous, 0.87 for any induced, 1.10 for one abortion (either spontaneous or induced) and 0.90 for two or more. Breast cancer risk was higher in parous women than in nulliparae (OR 1.58, 95%CI 1.17–2.14), the OR was 1.53 for one and 1.70 for two children, but tended to level off for three and four children, with OR, respectively, of 1.42 and 1.13 (Figure 1). Older age at first pregnancy and at first birth was strongly associated with breast cancer risk: the OR were respectively, 4.14 and 5.31 for women aged ≥30 years versus those aged <20 years at first pregnancy and birth. Older women at last birth had a non-significantly increased risk of breast cancer, with an OR of 2.39 for last birth when aged 35 years or older. Breast cancer risk was not related to time since first birth, but inversely with time since last birth in pluriparae, the OR being 3.80 for women with <3 years since last birth compared with ≥12 years, and the trend in risk was significant.

We computed the OR for pluriparous women according to number of children, age at first birth and time since last birth when these three variables were included simultaneously in the same logistic regression model. Compared with women with two births, the OR was 0.79 for those with three and 0.70 for those with four or more children. Breast cancer risk was strongly and directly associated with age at first birth (OR 9.31 in women aged ≥30 years compared with those aged <20 at first birth) (Figure 2a) and inversely with time since last birth (OR 3.79 for <3 years compared with ≥10) (Figure 2b), indicating that at 5 years since the last birth the risk was still significantly elevated.

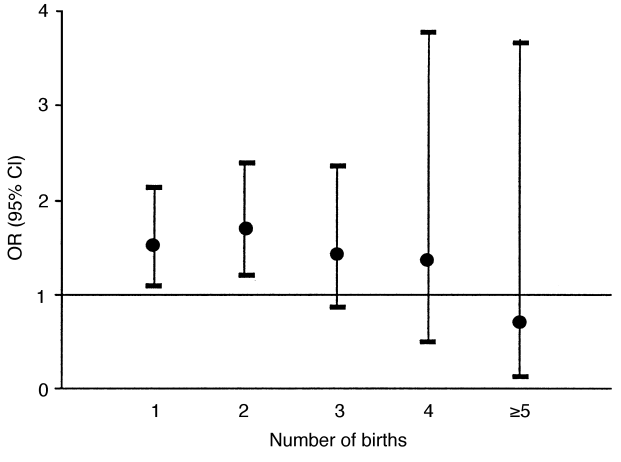

Figure 1. The relationship of number of births with breast cancer risk. Points are odds ratios (OR) with 95% confidence intervals (CI) according to number of births. OR were estimated from multiple logistic regression equations including terms for study, centre, year of recruitment, age, education, body mass index, family history of breast cancer and age at first birth. Nulliparae were the reference category.

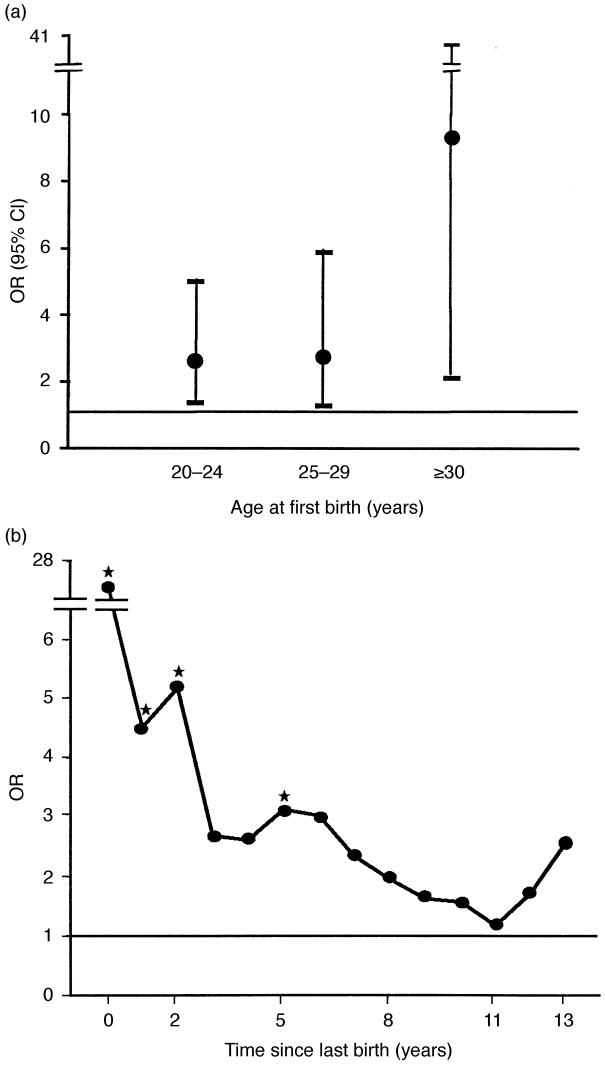

Figure 2. The relationship of timing of births with breast cancer risk. Points are odds ratios (OR) with 95% confidence intervals (CI) for pluriparous women according to age at first birth (a) and time since last birth (b). OR were estimated from a multiple logistic regression equation including terms for study, centre, year of recruitment, age, education, body mass index, family history of breast cancer, number of births, age at first birth and time since last birth. The reference category was women aged <20 years at first birth (a), or women ≥14 years since last birth (b). *Lower CI value >1.

Table 2. Distribution of 579 cases of breast cancer and 668 controls in women aged <40 years, and corresponding odds ratios (OR) with 95% confidence intervals (CI), according to menstrual and reproductive factors, and oral contraceptive use: Italy, 1983–1994

	Breast cancer	Controls	OR (95% CI)*
Age at menarche (years)			
<12	157	160	1†
12	155	167	0.85 (0.61–1.18)
13	145	180	0.79 (0.56–1.10)
14	91	104	0.89 (0.61–1.31)
≥15	31	57	0.53 (0.31–0.89)
χ^2 trend			3.62 ($P=0.057$)
Menstrual pattern‡			
Regular	484	526	1†
Irregular	38	61	0.73 (0.46–1.14)
Spontaneous abortions			
No	483	569	1†
Yes	96	99	1.10 (0.79–1.54)
Induced abortions			
No	492	560	1†
Yes	87	108	0.87 (0.63–1.22)
Total abortions			
No	410	485	1†
1	113	106	1.10 (0.80–1.51)
>1	56	77	0.90 (0.60–1.33)
Number of children			
Nulliparae	130	220	1†
1	181	180	1.53 (1.09–2.13)
2	215	196	1.70 (1.21–2.40)
3	43	55	1.42 (0.86–2.36)
≥4	10	17	1.13 (0.47–2.71)
χ^2 trend			3.73 ($P=0.054$)
Age at first pregnancy (years)§			
<20	28	89	1†
20–24	192	209	2.58 (1.58–4.21)
25–29	184	137	3.37 (2.00–5.66)
≥30	61	31	4.14 (2.14–8.02)
χ^2 trend			19.37 ($P<0.001$)
Age at first birth (years)‡§			
<20	22	80	1†
20–24	176	202	2.84 (1.66–4.86)
25–29	185	134	4.19 (2.38–7.36)
≥30	66	31	5.31 (2.66–10.62)
χ^2 trend			25.36 ($P<0.001$)
Age at last birth (years)‡‖			
<25	33	67	1†
25–29	99	113	1.43 (0.77–2.64)
30–34	111	74	2.00 (0.98–4.09)
≥35	21	14	2.39 (0.81–7.06)
χ^2 trend			4.08 ($P=0.043$)
Time since first birth (years)§			
≥15	80	142	1†
12–14	102	92	1.40 (0.73–2.70)
9–11	99	91	1.19 (0.45–3.13)
6–8	80	60	1.18 (0.31–4.48)
3–5	54	41	1.08 (0.19–6.03)
<3	34	22	1.00 (0.12–8.09)
Time since last birth (years)‡‖			
≥12	27	61	1†
9–11	44	65	1.08 (0.56–2.08)
6–8	68	63	1.65 (0.82–3.31)
3–5	73	58	1.87 (0.88–3.98)
<3	52	21	3.80 (1.46–9.87)
χ^2 trend			8.02 ($P=0.005$)

*Estimates from multiple logistic regression equations including terms for study, centre, year of recruitment, age, education, body mass index, family history of breast cancer, parity and age at first birth. †Reference category. ‡The sum does not add up to the total because of some missing values. §Parae only. ‖Pluriparae only.

Table 3. Distribution of 579 cases of breast cancer and 668 controls in women aged < 40 years, and corresponding odds ratios (OR) with 95% confidence intervals (CI), according to oral contraceptive use: Italy, 1983–1994

	Breast cancer	Controls	OR (95% CI)*
Never oral contraceptive use	358	441	1†
Ever oral contraceptive use	221	227	1.05 (0.81–1.36)
Duration of oral contraceptive use (years)‡			
≤2	128	120	1.19 (0.87–1.62)
>2–5	53	59	0.96 (0.63–1.48)
>5	40	46	0.86 (0.53–1.40)
χ^2 trend			0.09 ($P = 0.770$)
Time since first oral contraceptive use (years)			
<10	113	115	1.19 (0.86–1.64)
≥10	108	112	0.92 (0.66–1.28)
Time since last oral contraceptive use (years)‡			
≥10	45	51	0.85 (0.54–1.36)
5–9	73	62	1.11 (0.75–1.65)
<5	102	108	1.17 (0.84–1.63)
χ^2 trend			1.04 ($P = 0.308$)
Age at first oral contraceptive use (years)			
<20	25	34	1.09 (0.61–1.96)
20–22	38	73	0.60 (0.38–0.95)
23–25	49	40	1.28 (0.80–2.05)
≥26	109	80	1.26 (0.89–1.78)
χ^2 trend			1.17 ($P = 0.279$)
First oral contraceptive use in relation to first birth			
Before	59	48	0.90 (0.57–1.44)
In the same year	22	17	1.19 (0.60–2.37)
After	95	98	0.95 (0.67–1.33)

*Estimates from multiple logistic regression equations including terms for study, centre, year of recruitment, age, education, body mass index, family history of breast cancer, parity and age at first birth. †Reference category. ‡The sum does not add up to the total because of some missing values.

Ever use of oral contraceptives was reported by 221 (38%) cases and 227 (34%) controls, with a corresponding OR of 1.05 (Table 3). No significant relationship emerged with several other measures of oral contraceptive use: the OR were 0.86 for more than 5 years use, 1.17 for less than 5 years since last use, 1.09 for starting use when younger than 20 years and 0.90 for having started use before first birth.

A significant inverse relationship emerged with body mass index, the OR being 0.51 (95% CI 0.26–0.97) for women whose body mass index was $\geq 30\,kg/m^2$ compared with $< 20\,kg/m^2$. Non-significant associations of breast cancer risk were observed with alcohol and total energy intake: the OR for more than two drinks per day compared with non-drinkers was 1.27 (95% CI 0.93–1.72), and the OR for the highest tertile of total calorie intake compared to the lowest was 1.38 (95% CI 0.83–2.29). We also evaluated the risk in relation to the intake of raw vegetables and beta-carotene (data not shown). A significant decrease in risk was observed with raw vegetable intake, with an OR of 0.57 (95% CI 0.33–0.98) for more than eight servings a week, and a non-significant decrease with beta-carotene consumption (an indicator of fruit and vegetable intake) with an OR of 0.67 (95% CI 0.38–1.17) for the highest tertile of intake.

DISCUSSION

The present study confirms that in women under the age of 40 years at diagnosis breast cancer risk is inversely related to body mass, age at menarche and time since last birth, and directly to age at first and last birth. No association emerged with abortion and oral contraceptive use, and the associations with education, family history of breast cancer, history of benign breast disease and some nutritional factors were consistent with our knowledge of the general epidemiology of breast cancer [4, 23, 33].

A strength of this study is the relatively large size, which provided reasonably stable risk estimates. Although the study was not population-based, cases were identified in the major teaching and general hospitals; only incident cases were included, which limited any potential modifying effect of treatment [34]; only acute conditions unrelated to known or potential risk factors for breast cancer were included in the comparison group; less than 4% of cases and controls refused interview, and the hospital-based design may improve the comparability of recall of several covariates by cases and controls [32, 35]. Reproducibility and validity of the questionnaires were satisfactory [29, 30, 36], and the results were similar in the two studies [27, 37], confirming their consistency.

The association of breast cancer risk with various menstrual and reproductive factors is of specific interest in young women [38–40]. Age at menarche and irregular menstrual periods were both inversely related to breast cancer risk, in agreement with the results of the American Nurses' Cohort [41] and another large Italian case–control study [42], and parity, which is protective later in life, increases breast cancer risk in younger women. Still, multiparity tended to lower the risk also at younger ages [9–11]. The risk estimates for parity in young women are probably influenced by recent last birth, since birth has been reported to induce a short-term increase in breast cancer risk [43]. Likewise, most menstrual factors

appear to have more influence in younger than older women [4]. This is consistent with a short-term (i.e. promoting) effect of hormone-related factors on the process of breast carcinogenesis [44–47].

The lack of association with spontaneous or induced abortion is in agreement with most current epidemiological evidence, and offers a useful contribution to a still open debate [18, 19]. The inverse association of breast cancer risk with body mass index in young premenopausal women has been extensively reported [4, 5, 8] and has been related to anovulation in overweight and obese women [38]. The lack of association with oral contraceptive use and duration of use is also relevant, although the association was somewhat above unity in recent users, consistently with the results of a systematic re-analysis of individual data [20].

The identification of *BRCA1* and *BRCA2* genes associated with familial breast cancer at young ages [48] aroused interest in the relation between breast cancer risk and family history in young women. Studies of the risks of breast cancer according to age at diagnosis generally showed higher risk at younger age [4, 13], and a meta-analysis gave relative risks of 2.7 in women under the age of 50 years, and 1.8 in those aged $\geq$50 years [14]. Our estimates of an approximately 80% increase in the risk of breast cancer is relatively low [5] and suggests that the role of *BRCA1* and *BRCA2* or other high penetrance genes is relatively limited in this population.

In line with the general evidence on breast cancer epidemiology [5] our data show a direct association with educational level and with history of benign breast disease [4], as well as with alcohol drinking and nutritional factors [23, 33].

Thus, this study confirms that some recognised risk factors, including age at menarche and reproductive factors, are strong determinants of breast cancer in young women, while other factors seem to play a role comparable with that suggested by our general knowledge of the epidemiology of breast cancer at any age.

1. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. eds. *Cancer Incidence in Five Continents*, vol. 7 (IARC Scientific Publication No. 143). Lyon, IARC, 1997.
2. Hankey BF, Miller B, Curtis R, Kosary C. Trends in breast cancer in younger women in contrast to older women. *Monogr Natl Cancer Inst* 1994, **16**, 7–14.
3. La Vecchia C, Decarli A, Cislaghi C. Changes in breast cancer mortality in Italy. *Eur J Cancer* 1988, **24**, 275–276.
4. Velentgas P, Daling JR. Risk factors for breast cancer in younger women. *Monogr Natl Cancer Inst* 1994, **16**, 15–22.
5. Lipworth L. Epidemiology of breast cancer. *Eur J Cancer Prev,* 1995, **4**, 7–30.
6. Lubin JH, Burns PE, Blot WJ, *et al.* Risk factors for breast cancer in women in Northern Alberta, Canada, as related to age at diagnosis. *J Natl Cancer Inst* 1982, **68**, 211–217.
7. Fraser GE, Shavlik D. Risk factors, lifetime risk, and age at onset of breast cancer. *Ann Epidemiol* 1997, **7**, 375–382.
8. Cold S, Hansen S, Overvad K, Rose C. A woman's build and the risk of breast cancer. *Eur J Cancer* 1998, **34**, 1163–1174.
9. Kampert JB, Whittemore AS, Paffenbarger RS Jr. Combined effect of childbearing, menstrual events, and body size on age-specific breast cancer risk. *Am J Epidemiol* 1988, **128**, 962–979.
10. Negri E, La Vecchia C, Bruzzi P, *et al.* Risk factors for breast cancer: pooled results from three Italian case–control studies. *Am J Epidemiol* 1988, **128**, 1207–1215.
11. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev* 1993, **15**, 36–47.
12. Titus-Ernstoff L, Longnecker MP, Newcomb PA, *et al.* Menstrual factors in relation to breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1998, **7**, 783–789.
13. Claus EB. Genetic epidemiology of breast cancer in younger women. *Monogr Natl Cancer Inst* 1994, **16**, 49–53.
14. Pharoah PDP, Day NE, Duffy S, Easton DF, Ponder BAJ. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* 1997, **71**, 800–809.
15. Howe HL, Senie RT, Bzduch H, Herzfeld P. Early abortion and breast cancer risk among women under age 40. *Int J Epidemiol* 1989, **18**, 300–304.
16. Daling JR, Malone KE, Voigt LF, White E, Weiss NS. Risk of breast cancer among young women: relationship to induced abortion. *J Natl Cancer Inst* 1994, **86**, 1584–1592.
17. Daling JR, Brinton LA, Voigt LF, *et al.* Risk of breast cancer among white women following induced abortion. *Am J Epidemiol* 1996, **144**, 373–380.
18. Adami H-O, Bergström R, Lund E, Meirik O. Absence of association between reproductive variables and the risk of breast cancer in young women in Sweden and Norway. *Br J Cancer* 1990, **62**, 122–126.
19. Wingo PA, Newsome K, Marks JS, Calle EE, Parker SL. The risk of breast cancer following spontaneous or induced abortion. *Cancer Causes Control* 1997, **8**, 93–108.
20. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996, **347**, 1713–1727.
21. Smith SJ, Deacon JM, Chilvers CED, and members of the U.K. National Case–Control Study Group. Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. *Br J Cancer* 1994, **70**, 112–119.
22. Swanson CA, Coates RJ, Malone KE, *et al.* Alcohol consumption and breast cancer risk among women under age 45 years. *Epidemiology* 1997, **8**, 231–237.
23. World Cancer Research Fund in association with American Institute for Cancer Research. *Food, Nutrition and the Prevention of Cancer: A Global Perspective*, ch. Breast. Washington, World Cancer Research Fund, American Institute for Cancer Research 1997, 252–287.
24. Lund E, Adami H-O, Bergstrøm R, Meirik O. Anthropometric measures and breast cancer in young women. *Cancer Causes Control* 1990, **1**, 169–172.
25. Swanson CA, Coates RJ, Schoenberg JB, *et al.* Body size and breast cancer risk among women under age 45 years. *Am J Epidemiol* 1996, **143**, 698–706.
26. McCredie MRE, Dite GS, Giles GG, Hopper JL. Breast cancer in Australian women under the age of 40. *Cancer Causes Control* 1998, **9**, 189–198.
27. La Vecchia C, Decarli A, Parazzini F, *et al.* General epidemiology of breast cancer in Northern Italy. *Int J Epidemiol* 1987, **16**, 347–355.
28. La Vecchia C, Negri E, Franceschi S, *et al.* Oral contraceptives and breast cancer: a cooperative Italian study. *Int J Cancer* 1995, **60**, 163–167.
29. Decarli A, Franceschi S, Ferraroni M, *et al.* Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. *Ann Epidemiol* 1996, **6**, 110–118.
30. D'Avanzo B, La Vecchia C, Katsouyanni K, Negri E, Trichopoulos D. An assessment, and reproducibility of food frequency data provided by hospital controls. *Eur J Cancer Prev* 1997, **6**, 288–293.
31. Salvini S, Parpinel M, Gnagnarella P, Maisonneuve P, Turrini A, eds. *Banca Dati di Composizione degli Alimenti per Studi Epidemiologici in Italia*. Milano, Istituto Europeo di Oncologia, 1998.
32. Breslow NE, Day NE. Statistical methods in cancer research. The analysis of case–control studies. Vol. 1. *IARC* Sci Publ 1980, **32**.
33. Young TB. A case–control study of breast cancer and alcohol consumption habits. *Cancer* 1989, **64**, 552–558.
34. Potischman N, Swanson CA, Coates RJ, *et al.* Dietary relationships with early onset (under age 45) breast cancer in a case–control study in the United States: influence of chemotherapy treatment. *Cancer Causes Control* 1997, **8**, 713–721.
35. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959, **22**, 719–748.
36. Franceschi S, Barbone F, Negri E, *et al.* Reproducibility of an Italian food frequency questionnaire for cancer studies. Results for specific nutrients. *Ann Epidemiol* 1995, **5**, 69–75.

37. Talamini R, Franceschi S, La Vecchia C, *et al.* The role of reproductive and menstrual factors in cancer of the breast before and after menopause. *Eur J Cancer* 1996, **32A**, 303–310.
38. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. *Nature* 1983, **303**, 767–770.
39. Thompson WD. Age at and time since: modeling temporal aspects of exposure. *Epidemiology* 1997, **8**, 471–473.
40. Cummings P, Weiss NS, McKnight B, Stanford JL. Estimating the risk of breast cancer in relation to the interval since last term pregnancy. *Epidemiology* 1997, **8**, 488–494.
41. Garland M, Hunter DJ, Colditz GA, *et al.* Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. *Am J Epidemiol* 1998, **147**, 636–643.
42. Parazzini F, La Vecchia C, Negri E, Franceschi S, Tozzi L. Lifelong menstrual pattern and risk of breast cancer. *Oncology* 1993, **50**, 222–225.
43. Bruzzi P, Negri E, La Vecchia C, *et al.* Short term increase in risk of breast cancer after full term pregnancy. *Br Med J* 1988, **297**, 1096–1098.
44. Pike MC. Age-related factors in cancers of the breast, ovary, and endometrium. *J Chron Dis* 1987, **40**(Suppl. 2), 59S–69S.
45. Decarli A, La Vecchia C, Negri E, Franceschi S. Age at any birth and breast cancer in Italy. *Int J Cancer* 1996, **67**, 187–189.
46. Hsieh C-C, Chan H-W, Lambe M, Ekbom A, Adami H-O, Trichopoulos D. Does age at the last birth affect breast cancer risk? *Eur J Cancer* 1996, **32A**, 118–121.
47. Robertson C, Boyle P. Age at any birth and breast cancer risk. *Stat Med* 1998, **17**, 431–445.
48. Ford D, Easton DF. The genetics of breast and ovarian cancer. *Br J Cancer* 1995, **72**, 805–812.

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