Reproductive Factors and Breast Cancer: An Overview

Carlo La Vecchia[1, 2], Eva Negri[2, 3], Peter Boyle[4]

[1] Institute of Social and Preventive Medicine, University of Lausanne
[2] "Mario Negri" Institute for Pharmacological Research, Milan
[3] Inter-University Consortium of Lombardy for Automatic Data Progressing (CILEA), Milan
[4] Unit of Analytical Epidemiology, The International Agency for Research on Cancer, Lyon

It has long been known that reproductive factors influence the risk of breast cancer. Earlier clinical and epidemiological observations showed an inverse association between parity and breast cancer. Overall, breast cancer incidence in nulliparae appears to be about 50% higher than in parous women [1]. The causality of this association, however, tended to be dismissed by the observation, from an international cooperative study conducted in seven areas of the world, that earlier age at first birth could explain the apparent relation between breast cancer and parity [2]. In that study, breast cancer risk was three times greater in women whose first birth was at age 35 or over than in those under 18 years. A more detailed analysis of the same dataset [3] indicated that age at births subsequent to the first had some additional influence on breast cancer risk, although to a more limited extent than the first one. Nulliparous women had a risk approximately comparable to those who first bore a child at age 30, and no protection was conveyed by the number of births after the first, although a small (of the order of 10 percent) reduction in risk was observed in women with five or more births as compared to uniparae [2].

Several subsequent studies confirmed this observation, although some of them showed an independent effect of multiparity even after adjustment for age at first full-term pregnancy. In a prospective investigation from Iceland [4], for instance, an inverse association with parity was observed in each subsequent strata of age at first birth.

This pattern of risk, a major role of age at first birth but a residual protective effect of multiparity, was confirmed by a number of studies, including a prospective one from the United States [5, 6] and several case-control studies from North America, Europe and China [7–13].

Careful consideration of incidence and mortality data led to the suggestion that the effect of parity on breast carcinogenesis would be different at different ages: unmarried (and, hence most frequently nulliparous) women had in fact lower breast cancer incidence below the age of 40, but higher rates at older ages [14]. This different effect of parity at younger and older age was subsequently confirmed by analyses from case-control [15] and cohort [6] studies.

There is, moreover, accumulating evidence from a number of other studies from Scandinavia [16–20],

North and Central America [21, 22] and New Zealand [23] showing no (or very inconsistent) effect of age at first birth, but an inverse relation of parity or multiparity on breast cancer risk, which was independent from that of age at first full-term pregnancy.

Thus, there are at present substantial uncertainties in the definition of the separate roles (and of the interactions) of various reproductive factors in different populations, which are hardly explainable in terms of obvious bias within each study. In order to shed further light in the issue, in this article we present a summary overview of the findings from published studies on age at first birth, parity and breast cancer risk.

Materials and Methods

Articles considered for this overview were formal epidemiological articles on breast cancer published in English since 1970, including information on parity and age at first birth. They were retrieved by reviewing reference lists in relevant papers and by conducting manual and computing (MEDLINE) searches of the literature.

A total of 26 studies was included. For each study, the design, the number of subjects, the age range and the control for confounding were considered, besides the two reproductive variables of specific interest. For a number of studies, some of the above information was missing. In particular, when adjusted relative risks for parity and age at first birth were not given in the papers, they were computed according to the best information available from published material. In all other cases, the relative risk for parity and age at first birth were considered after reciprocal adjustment for these two variables, plus (whenever available) further adjustment for age or other potential confounding factors.

Results

The studies reviewed were grouped in three pairs of tables according to their results: Tables 1a and 1b include the studies showing an association between age at first birth but not parity and breast cancer risk, Tables 2a and 2b those showing a significant association with parity but not age at first birth, and Tables 3a and 3b those reporting associations both with later first birth and (multi)parity.

Among the studies showing a significant association

Tab. 1a. Characteristics of studies showing associations between age at first birth but not parity and breast cancer risk

Study, year, country	Type of study	Numbers of cases and controls	Cases age range (mean/median)	Control of confounding	Other comments
MacMahon et al., 1970, 7 countries [2]	case-control	4,323 12,699	–	age, centre, marital status, education, parity, age at first birth	hospital-based
Herity et al., 1975, Ireland [24]	case-control	100 200	– (57.3/–)	–	cases from outpatients registers, controls from fracture clinics
MacMahon et al., 1982, Estonia [25]	case-control	362 694	30– (–/53)	age, age at first birth	from screening clinics
Trapido, 1983, USA [26]	cohort	454	21–54	age, OC use, age at first birth, parity	–
Brinton et al., 1983, USA [27]	case-control	1,362 1,250	– (–/54)	age, age at first lifebirth, interval first marriage/first lifebirth	from a screening programme (the Breast Cancer Detection Demonstration Project)
Talamini et al., 1985, Italy [28]	case-control	368 373	27–79	age, age at first birth, parity	hospital-based
Brignone et al., 1987, Italy [29]	case-control	853 853	– (54.6/–)	matched for age, area of residence, age at first birth, parity	cases and controls from screening clinics

Tab. 1b. Studies showing association between age at first birth but not parity and breast cancer risk

Study, year, country	Parity					Age at first birth				
	1	2	3	4	≥5	<20	20–24	25–29	30–34	≥35
MacMahon et al., 1970, 7 countries [2]	1#	1.1	1.0	1.0	0.9	1#	1.2	1.6	1.9	2.5
Herity et al., 1975, Ireland [24]		1#			0.9		1#	0.9	1.2	2.3
MacMahon et al., 1982, Estonia [25]	1#	0.7	0.6		1.3	1#	1.8	2.4	2.4	2.4
Trapido, 1983, USA [26]		1#		1.0	0.9	1#	1.5	2.1	2.7	
Brinton et al., 1983, USA [27]	1#	1.0	1.0	0.9	0.8	1#	1.3	1.7	2.5	
Talamini et al., 1985, Italy [28]		1#		0.8			1#	1.3	1.6	
Brignone et al., 1987, Italy [29]		1#	1.2		1.1	1#	1.1	1.8	1.9	

Reference category

with later first birth only, were the original seven-country study by MacMahon et al [2], a case-control study from Ireland [24], one from Estonia [25], a cohort [26] and a case-control [27] investigation from the United States, and two case-control studies from Italy [28, 29]. It is thus difficult to find a common denominator for the various populations studied, although several of them (various components of MacMahon et al study, the Irish and the two Italian ones) are characterized by relatively high parity, but a small proportion of earlier births. Although the trend for parity was not significant, moreover, the point estimate in multiparous women was below unity in five out of seven studies.

The studies showing an effect of parity but not of age at first birth (Table 2), in contrast, came mainly from Scandinavia [three reports 16, 17, 20], although studies from Canada [21], New Zealand [23] and two developing countries (Burma [30] and Costa Rica [22]) showed a similar pattern. In most of these studies (notably the

Tab. 2a. Characteristics of studies showing no significant associations between age at first birth and breast cancer risk

Study, year, country	Type of study	Numbers of cases and controls	Cases age range (mean/median)	Control of confounding	Other comments
Choi et al., 1978, Canada [21]	case-control	400 400	35–74 –	matched for age, area of residence, marital status, education, menopausal status, age at first birth	population-based
Adami et al., 1978, Sweden [16]	case-control	179 179	25–95 (63/64)	matched for age	population-based
Thien H & Thien M-M, 1978, Burma [30]	case-control	193 400	– (–/52)	parity, age at first birth	hospital-based
Adami et al., 1980, Sweden [17]	case-control	1,001 1,001	27–92 (63.5/64)	matched by age. Allowance for parity/age at first birth	population-based
Paul et al., 1986, New Zealand [23]	case-control	433 897	25–54 –	age	population-based
Rosero-Bixby et al., 1987, Costa Rica [22]	case-control	171 826	25–58 –	age, residence, education, menopausal status, parity, breast feeding, age at first birth, birth recency and interval	population-based
Ewertz & Duffy, 1988, Denmark [20]	case-control	1,486 1,336	< 70 (52.9/–)	age, residence, age at menarche, menopausal status, OC use before first pregnancy, parity, age at first birth	population-based

Tab. 2b. Studies showing no significant association between age at first birth and breast cancer risk

Study, year, country	Parity					Age at first birth				
	1	2	3	4	≥5	<20	20–24	25–29	30–34	≥35
Choi et al., 1978, Canada [21]	No significant difference					1*	1.0	0.7	0.8	
Adami et al., 1978, Sweden [16]	1*	0.7	1.0	0.3	0.4	1*	1.6	2.0	1.0	1.6
Thien H & Thien M-M, 1978, Burma [30]		1*		0.6	0.3^{26}	1*	0.9	1.0	1.1	1.5
Adami et al., 1980, Sweden [17]	1*	0.9	0.6	0.7	0.6	1*	1.0	1.0	1.2	1.7
Paul et al., 1986, New Zealand [23]		1*		0.6		1*	1.0	1.0	1.2	
Rosero-Bixby et al., 1987, Costa Rica [22]			1*		0.4	1*	1.5		0.8	
Ewertz & Duffy, 1988, Denmark [20]	1*	0.9	0.9	0.6		1*	0.9	0.9	1.0	

* Reference category

Scandinavian ones) multiparity was less common and restricted to a probably selected fraction of the population.

Finally, Table 3 shows the studies showing effects of both multiparity and age at first birth on breast cancer risk. It includes most American studies [5,6, 8, 9, 12], as well as two large case-control studies from Italy [10, 11], three Scandinavian studies from Finland [4], Iceland [7] and Norway [18, 19], and two Chinese case-control investigations [13, 31].

The differences between these three groups of studies, in terms of characteristics of the population and pattern of exposure to risk factors, are not obvious (see table 4 for a tabulation of available proportions of

early first birth and multiparity in the comparison groups). There was some tendency for the studies showing a strong effect of age at first birth only to include a relatively limited proportion of subjects with early first birth: the percentage of parous women who first gave birth at age 20 or earlier was between 3.3% and 13.9%, but the distribution was only partially different from that of studies showing no significant effect of age at first birth (between 10.2% and 16.0%, excluding the two studies from Burma [30] and Costa Rica [22], whose proportions were 25% and 38% respectively).

An analysis of the distribution of parity between different groups of studies indicated that the proportion of multiparous women (≥ 5 births) in some studies showing no association with parity (between 15% and 43% of the controls) tended to be larger than in studies showing an inverse relation with parity (between 7% and 17%), except, again for the studies conducted in developing countries.

Discussion

The present review summarizes a number of published studies on parity, age at first birth and breast cancer in order to contribute to a debate which, curiously, has become more and more open over the last few years.

Overall, among 26 studies considered, one found no significant association with either variable, seven (including the seven-country study by MacMahon et al. [1]) showed an association between age at first birth but not parity and breast cancer risk, six an association with parity but not age at first birth, and twelve found both variables independently related with breast cancer risk.

Various reasons for these apparent discrepancies could be considered, including publication bias, heterogeneity between populations, differences between studies in terms of criteria for selection of cases and controls, influence of age and other covariates among which the interval between pregnancies and hence the age at subsequent pregnancies may well be of particular importance [3].

Tab. 3a. Characteristics of studies showing associations between both multiparity and age at first birth and breast cancer risk

Study	Type of study	Numbers of cases and controls	Cases age range (mean/median)	Control of confounding	Other comments
Soini, 1977, Finland [7]	case-control	122 534	41–60	–	screening programm
Tulinius et al., 1978, Iceland [4]	cohort	216	20–69 –	year of birth, age at menarche, parity, age at first birth	from a cervical cancer screening program
Paffenbarger et al., 1980, USA [8]	case-control	1,416 2,519	– (58.1/–)	age, race, age at first birth	hospital-based
Bain et al., 1981, USA [5]	case-control	1,159 11,590	< 55	matched on year of birth; allowance for parity, age at first birth and other major risk factors	prevalent cases from the Nurses Health Study
Helmrich et al., 1983, USA [9]	case-control	1,185 3,227	< 70 (–/52)	age, parity, age at first birth, sociodemographic variables and other major breast cancer risk factors	hospital-based; women of all races from the Drug Epidemiology Unit dataset
Toti et al., 1986, Italy [10]	case-control	1,556 1,505	all ages (–/~58)	age, parity, age at first birth	hospital-based
Pathak et al., 1986, USA [6]	cohort	582 106,564	30–59	age, parity, age at first birth and other major breast cancer risk factors	incident cases from the Nurses Health Study
Kvale et al., 1987, Norway [18, 19]	cohort	1,565 61,525	20–89 –	age, parity, age at first birth, age at last birth	recruitment from a screening program
La Vecchia et al., 1987, Italy [11]	case-control	1,108 1,281	26–74 (–/54)	age, parity, age at first birth and other major breast cancer risk factors	hospital-based
Schatzkin et al., 1987, USA [12]	case-control	529 589	< 70 –	age, parity, age at first birth and other major breast cancer risk factors	hospital-based; black women only from the Drug Epidemiology Unit dataset
Yuan et al., 1988, China [13]	case-control	534 534	20–69 (50.8/–)	age, age at first birth	population-based
Tao et al, 1988, China [31]	case-control	497 497	– (47.6/–)	age, age at first birth, parity	population-based

Tab. 3b. Studies showing associations between both multiparity and age at first birth and breast cancer risk

Study, year, country	Parity					Age at first birth				
	1	2	3	4	≥5	<20	20–24	25–29	30–34	≥35
Soini, 1977, Finland [7]	1*	0.9	0.6	0.6	0.4	1*		1.3	1.8	2.0
Tulinius et al., 1978, Iceland [4]		1*	0.6		0.5	1*	1.6	2.6	2.5	4.1
Paffenbarger et al., 1980, USA [8]	1*	1.0	0.9	0.7		1*	1.6	2.0	2.0	
Bain et al., 1981, USA [5]	1*	0.8		0.9	0.7≥6	≤20 1*	1.3	1.7	1.9	2.3
Helmrich et al., 1983, USA [9]		1*	0.9		0.7	1*	1.2	1.8	1.9	
Toti et al., 1986, Italy [10]	1*	1.0	0.8	0.6		1*	1.5	1.6	2.8	
Pathak et al., 1986, USA [6]	1*	0.9	0.8	0.7		Directly associated, estimates not given				
Kvale et al., 1987, Norway [18, 19]	1*	0.9	0.8	0.7	0.5	1*	1.2	1.3	1.4	1.4
La Vecchia et al., 1987, Italy [11]		1*	1.1		0.5	1*	1.8	2.2	2.5	
Schatzkin et al., 1987, USA [12]		1*	0.9		0.6	1*	1.2	2.0	1.7	
Yuan et al., 1988, China [13]	1*	0.7	0.7	0.6	0.4	1*	1.1	1.7	2.7	
Tao et al., 1988, China [31]	1	1.1	0.7	0.6	0.7	1	1.2	1.6	1.4	

* Reference category

Finally, the role of chance cannot be dismissed, since the risk estimates for both variables were relatively moderate, the distribution of women in various strata largely uneven, and the absolute numbers of subjects relatively small in several studies. There is, therefore, ample scope for more formal pooling exercises on the issue, based on the original datasets, in order to derive independently adjusted overall estimates of the separate effects of age at first birth and parity on breast cancer risk, and their interaction.

At present, the conclusions that can be derived from the data considered appear to suggest, from an aetiological viewpoint, that both factors have some independent effect on breast carcinogenesis. From a public health viewpoint, however, age at first birth seems more important, since the trend of increasing risk with older age at first full-term pregnancy is evident and rather linear across all the subsequent levels, while the protection of parity, even in the studies where the association was evident, seems to be quantitatively relevant only for women with four or five births or more.

Summary

Despite extensive research, there is still uncertainty on the separate effects of parity and age at first birth on breast cancer risk. Thus, information on these variables from formal epidemiological articles published in English since 1970 is reviewed in the present article. Among 26 studies considered, one found no significant association with either variable, seven showed an association between age at first birth but not parity and breast cancer risk, six an association with parity but not age at first birth, and in twelve studies both variables appeared to be independently related with breast cancer risk. Various reasons for these apparent differences can be considered, including heterogeneity between various populations (for instance, the proportion of multiparous women in studies showing no association with parity tended to be higher than in studies finding an inverse relation with parity), criteria for selection of cases and controls, influence of age and other covariates (among which the interval between pregnancies is of particular interest) and, of course, the role of chance. The data reviewed suggest, from an aetiological viewpoint, that both parity and age at first birth have some independent effect on breast carcinogenesis. From a public health viewpoint, however, it appears that the importance of age at first birth is greater, since the trend is linear across subsequent age levels, while the protection of parity seems to be quantitatively relevant only for women with four or five births or more.

Résumé

Les facteurs reproductifs et le cancer du sein: un résumé

Malgré des recherches approfondies, des doutes subsistent quant aux effets de parité et d'âge à la première naissance sur le risque du cancer du sein. Différents travaux parus en anglais depuis 1970 sont analysés dans cet article. Des 26 études analysées, une seule ne démontrait pas d'association. Sept ont montré une association avec l'âge à la première naissance mais pas avec la parité. Six ont démontré une association avec la parité mais non avec l'âge à la première naissance et 12 études ont montré une influence indépendante de ces deux facteurs sur le risque de cancer du sein. Différentes hypothèses peuvent être considérées pour ces différences apparentes, y compris

Tab. 4. Percentage of women in the comparison group recording early first birth (< 20 years) or multiparity in selected studies*

Study	Percentage of comparison group with:	
	Early first birth (< 20 years)[.]	Multiparity (≥ 5 births)
Studies showing associations with age at first birth but not parity		
MacMahon et al, 1970 [2]	11.2	15.5
Herity et al, 1975 [24]	3.3	43.1
MacMahon et al, 1982 [25]	5.7	n/a
Brinton et al, 1983 [27]	13.8	n/a
Brignone et al, 1987 (29)	13.9	14.8
Studies showing no significant association with age at first birth		
Choi et al, 1978 [21]	10.9	n/a
Adami et al, 1978 [16]	13.5	8.4
Thien-H & Thien M-M [30]	24.9	42.0 (≥ 6 births)
Adami et al, 1988 [17]	10.2	8.2
Paul et al, 1986 [23]	16.0	n/a
Rosero-Bixby et al, 1987 [22]	38.4	36.7
Ewertz & Duffy, 1988 [20]	11.3	n/a
Studies showing associations between both multiparity and age at first birth		
Tulinius et al, 1978 [4]	8.5	16.7
Helmrich et al, 1983 [9]	28.8	11.7
Kvale et al, 1987 [18, 19]	4.7	n/a
La Vecchia et al, 1987 [11]	8.4	7.5
Schatzkin et al, 1987 [12]	56.8	16.2
Yuan et al, 1988 [13]	18.8	21.9
Tao et al, 1988 [31]	9.1	12.5

*   Only studies relevant information are included
'   Among parous women
n/a   indicates not available

l'hétérogénéité entre les populations étudiées (par exemple la proportion de femmes multipares est plus élevée dans les études démontrant une association avec la parité que dans celles avec une relation inverse), la sélection des cas et des témoins, la structure de l'âge, ainsi que d'autres facteurs comme par exemple l'intervalle entre les grossesses et bien sûr le hasard. Ces données laissent apparaître que la parité, ainsi que l'âge à la première naissance, peuvent influencer d'une manière indépendante le risque du cancer du sein. La corrélation entre l'âge à la première naissance et le cancer du sein est très importante pour la santé publique, étant donné que le risque augmente avec chaque classe d'âge, tandis que la parité n'a un effet protecteur qu'à partir de la quatrième ou de la cinquième naissance.

Zusammenfassung
Fortpflanzungsfaktoren und Brustkrebs: eine Übersicht
Trotz intensiver Forschung bestehen immer noch Zweifel über die einzelnen Auswirkungen von Parität und Alter bei der Erstgeburt auf das Brustkrebsrisiko. Deshalb werden in diesem Artikel die Arbeiten, welche seit 1970 in Englisch veröffentlicht worden sind, analysiert. Von den 26 berücksichtigten Studien fand eine keine eindeutige Beziehung zu diesen beiden Variablen. Sieben wiesen eine Beziehung mit dem Alter bei der Erstgeburt nach, jedoch nicht mit der Parität. Sechs fanden einen Zusammenhang mit der Parität, aber nicht mit Alter bei Erstgeburt und aus 12 Studien ging hervor, dass beide Faktoren unabhängig voneinander mit dem Brustkrebsrisiko verbunden sind. Es gibt verschiedene Hypothesen, diese Diskrepanzen zu erklären, darunter auch die Verschiedenartigkeit in den untersuchten Bevölkerungen (so lag z.B. die Proportion der

Frauen mit mehreren Geburten in jenen Studien, die nicht mit Parität verbunden sind höher, als in jenen, welche eine Verbindung zur Parität fanden), die Auswahlkriterien für Fälle und Kontrollen, der Einfluss des Alters und von anderen Variablen (wobei der Zeitabstand zwischen den Schwangerschaften besonders interessant ist) und natürlich die Rolle des Zufalls. Die gesichteten Resultate deuten vom ätiologischen Sichtpunkt darauf hin, dass Parität und Alter bei der Erstgeburt unabhängig voneinander das Brustkrebsrisiko beeinflussen. Die Beziehung zwischen dem Alter bei der Erstgeburt und der Brustkrebshäufigkeit scheint, vom Standpunkt der Sozialmedizin aus, jedoch von grösserer Bedeutung zu sein, da das Risiko in jeder Altersklasse linear ansteigt. Der Schutzeffekt der Parität hingegen ist erst von der vierten oder fünften Geburt an nachzuweisen.

References
[1] *Boyle P.* Epidemiology of breast cancer. Bailliere's Clin Oncol 1988; *2:* 1–60.

[2] *MacMahon B, Cole P, Lin M,* et al. Age at first birth and breast cancer risk. Bull WHO 1970; *43:* 209–221.

[3] *Trichopoulos D, Hsieh C-c, MacMahon B,* et al. Age at any birth and breast cancer risk. Int J Cancer 1983; *31:* 701–704.

[4] *Tulinius H, Day NE, Johannesson G, Bjarnason O, Gonzales M.* Reproductive factors and risk for breast cancer in Iceland. Int J Cancer 1978; *21:* 724–730.

[5] *Bain C, Willett C, Rosner B, Speizer FE, Belanger C, Hennekens CH.* Early age at first birth and decreased risk of breast cancer. Am J Epidemiol 1981; *114:* 705–709.

[6] *Pathak DR, Speizer FE, Willett WC, Rosner B, Lipnick RJ.* Parity and breast cancer risk: possible effect on age at diagnosis. Int J Cancer 1986; *37:* 21–25.

[7] *Soini I.* Risk factors of breast cancer in Finland. Int J Epidemiol 1977; *6:* 365–373.

[8] *Paffenbarger RS, Kampert JB, Chang HG.* Characteristics that predict risk of breast cancer before and after the menopause. Am J Epidemiol 1980; *112:* 258–268.

[9] *Helmrich S, Shapiro S, Rosenberg L* et al. Risk factors for breast cancer. Am J Epidemiol 1983; *117:* 35–45.

[10] *Toti A, Agugiaro S, Amadori D,* et al. Breast cancer risk factors in Italian women: a multicentric case-control study. Tumori 1986; *72:* 241–249.

[11] *La Vecchia C, Decarli A, Parazzini F* et al. General epidemiology of breast cancer in Northern Italy. Int J Epidemiol 1987; *16:* 347–355.

[12] *Schatzkin A, Palmer JR, Rosenberg L,* et al. Risk factors for breast cancer in black women. JNCI 1987; *78:* 213–217.

[13] *Yuan JM, Yu MC, Ross RK, Gao YT, Henderson BE.* Risk factors for breast cancer in Chinese women in Shanghai. Cancer Research 1988; *48:* 1949–1953.

[14] *Janerich DT, Hoff MB.* Evidence for a cross-over in breast cancer risk factors. Am J Epidemiol 1982; *116:* 211–217.

[15] *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.

[16] *Adami H-O, Rimsten A, Stenkvist B, Vegelius J.* Reproductive history and risk of breast cancer. Cancer 1978; *41:* 747–757.

[17] *Adami H-O, Hansen J, Jung B, Rimsten AJ.* Age at first birth, parity and risk of breast cancer in a Swedish population. Br J Cancer 1980; *42:* 651–658.

[18] *Kvale G, Heuch I, Eide GE.* A prospective study of reproductive factors and breast cancer. I. Parity. Am J Epidemiol 1987; *126:* 831–841.

[19] *Kvale G, Heuch I.* A prospective study of reproductive factors and breast cancer. II. Age at first and last birth. Am J Epidemiol 1987; *126:* 842–850.

[20] *Ewertz M, Duffy SW.* Risk of breast cancer in relation to reproductive factors in Denmark. Br J Cancer 1988; *58:* 99–104.

[21] *Choi NW, Howe GR, Miller AB* et al. An epidemiologic study of breast cancer. Am J Epidemiol 1978; *107:* 510–521.

[22] *Rosero-Bixby L, Oberle MW, Lee NC.* Reproductive history

and breast cancer in a population of high fertility, Costa Rica, 1984-85. Int J Cancer 1987; *40:* 747–754.

[23] *Paul C, Skegg DCG, Spears GFS, Kaldor JM.* Oral contraceptives and breast cancer: a national study. Brit Med J 1986; *293:* 723–726.

[24] *Herity BA, O'Halloran MJ, Bourke GJ, Wilson-Davis K.* A study of breast cancer in Irish women. Brit J Prev Soc Med 1975; *29:* 178–181.

[25] *MacMahon B, Purde M, Cramer D, Hint E.* Association of breast cancer risk with age at first and subsequent births: A study in the population of the Estonian Republic. JNCI 1982; *69:* 1035–1038.

[26] *Trapido EJ.* Age at first birth, parity and breast cancer risk. Cancer 1983; *51:* 946–948.

[27] *Brinton LA, Hoover R, Fraumeni JF, Jr.* Reproductive factors in the aetiology of breast cancer. Br J Cancer 1983; *47:* 757–762.

[28] *Talamini R, La Vecchia C, Franceschi S,* et al. Reproductive and hormonal factors and breast cancer in a Northern Italian population. Int J Epidemiol 1985; *14:* 70–74.

[29] *Brignone G, Cusimano R, Dardanoni G,* et al. A case-control study on breast cancer risk factors in a Southern European population. Int J Epidemiol 1987; *16:* 356–361.

[30] *Thein-Hlaing, Thein-Maung-Myint.* Risk factors of breast cancer in Burma. Int J Cancer 1978; *21:* 432–437.

[31] *Tao SC, Yu MC, Ross RK, Xiu KW.* Risk factors for breast cancer in Chinese women of Bejing. Int J Cancer 1988; *42:* 495–498.

Address for correspondence:

Prof. Carlo La Vecchia
Institute of Social and Preventive Medecine, University of Lausanne
Bugnon 17
CH-1005 Lausanne