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Original Paper

Does Age at the Last Birth Affect Breast Cancer Risk?

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We studied the relative importance of age at first and age at last full-term pregnancy (FTP) in a large data set of 3950 cases and 11 510 controls, of whom 2263 cases and 7359 controls had two or more FTPs. We found that a 5-year delay in age at first FTP is associated with an odds ratio of 1.17 (95% confidence interval of 1.05–1.29), whereas a 5-year delay in the age of last FTP is associated with an odds ratio of 1.05 (95% confidence interval 0.96–1.14). Misleading results concerning the relative importance of age at first and last FTP may be obtained when parity is only adjusted in broad categories, uniparous women whose FTP is, simultaneously, both the first and the last are not excluded from the analysis, and age at any FTP between the first and last is not controlled for.

Key words: age at birth, breast cancer, parity
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INTRODUCTION

In a critical examination of the evidence concerning the aetiology of breast cancer, MacMahon suggested that, from the mechanistic point of view, most of the known risk factors for breast cancer can be readily explained in terms of one of two features, the number of potentially susceptible cells in the breast and the level of susceptibility of the cells [1]. He pointed out that there is compelling evidence that mammary gland mass, which may reflect number of stem cells generated during the interuterine life [2], can account for the international differences in the incidence of breast cancer and the pattern of changes observed in migrants, as well as for several other observations assembled by Trichopoulos and Lipman [3]. MacMahon also indicated that the repeatedly demonstrated long-term protective effect of an early full-term pregnancy (FTP), first reported some 25 years ago [4], can be explained by pregnancy-induced differentiation of the terminal end buds of the breast into secretory units, as demonstrated in rats by Russo and associates [5, 6]. This simple and plausible model was challenged by the results of a study by Kalache and associates [7], who reported that the effect of age at last FTP dominated that of age at first FTP. Although the analysis of the data in this report met contemporary statistical standards, Kalache and associates [7] did not address a number of subtle points that appear to be specific to breast cancer epidemiology and biology. It has been reported [8] and confirmed [9] that age at any FTP beyond the first is also positively related to breast cancer risk, although the association is substantially stronger for age at first FTP than for age at any of the subsequent ones. In a population with very high parity, as was the population studied by Kalache and associates [7], the effect of a late last FTP reflects the converging and confounding effects of several FTPs between the first and last which, on average, are also likely to occur late. Furthermore, evaluation of the relative importance of age at first and last FTP should exclude women with only one FTP, since this is both the first and the last, and should control individually for single parities rather than group together multiparous women, in order to avoid residual confounding of unpredictable magnitude and direction. Lastly, the transient, pregnancy oestrogen-dependent, increase in the risk of breast cancer following any birth [10–13] should be taken into account when the effects of age at first and last FTP on breast cancer risk are compared, since the last pregnancy is generally closer to the time of diagnosis of breast cancer. We have compared the independent associations of age at first and age at last FTP with breast cancer risk in the data of the large international case–control study conducted by MacMahon and associates in the 1960s [4, 14]. We have undertaken analyses similar to that used by Kalache and associates [7] as well as an analysis that takes into account the points previously indicated.

PATIENTS AND METHODS

The study was a seven-nation collaborative study which was conducted with a similar protocol in areas with low (Taipei,

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Taiwan; Tokyo, Japan), intermediate (Athens, Greece; São Paulo, Brazil; Slovenia, then part of Yugoslavia) and high (Boston, Massachusetts, U.S.A.; Glamorgan, U.K.) incidence of breast cancer [4, 14]. Except in Tokyo and São Paulo, where the cases represented approximately 50 and 70% of all incident cases, most of the female residents of the study areas who were hospitalised for a first diagnosis of breast cancer during the study period were included. For each case interviewed, 3 eligible patients in the hospital beds closest to that of the index case were interviewed as controls. To be eligible, a control had to be a resident of the study area, had to have never been diagnosed with cancer of the breast and had to be over 35 years of age (when the index case was under 35 years of age the controls were age-matched within 2 years). Details about study design and results concerning lactation, age at first birth, parity and several other variables have been published [8, 14–16].

Information on age at delivery was recorded up to the ninth FTP for each subject in this study. Therefore, age at last FTP can be studied only among those who had nine or fewer FTPs (more than 99% of all women). Analyses which mimic that in Kalache and associates [7] were performed initially. Kalache and associates [7] had included in their analysis women with one or more FTPs and parity was adjusted in broad categories (1, 2–10, 11–18) without accounting for age at any of the intervening FTPs, while estimating the effect of age at first and last FTP. We first examined the effect of age at first FTP and that of age at last FTP, unadjusted for each other. Next, these effects were examined controlling for parity in individual categories (1, 2, 3, ..., 9) as well as age at first and last FTP mutually.

However, as indicated earlier, the effect of age at first FTP cannot be distinguished from that of age at last FTP for women with only one FTP. Therefore, we have restricted the final analysis to those who had between two and nine FTPs. In addition to parity, this analysis attempted to control for age at all intermediate FTPs between the first and the last. The results could assess whether the effect of age at last FTP is confounded by age at first and intermediate FTPs. To adjust for age at intermediate FTPs, a variable representing age at the first possible intermediate FTP was created for subjects with three or more FTPs, and another variable representing age at the second intermediate FTP was created for those with four or more FTPs, and so forth [8]. Age at last FTP was studied both in categorical representations (<25, 25–29, 30–34, 35–39, 40+ years) and in continuous form.

Information on age at menarche, menopausal status, body mass index (weight/height^2) is also available. These variables, as well as study site, hospital and age at diagnosis, were considered as core variables and were always controlled for in the analysis. Subjects were excluded from the present study when information was not available for any one of the variables under consideration.

Since cases and controls were matched for study site and hospital ward, a standard analytical method for a matched case-control study was applied [17, 18]. This method was based on modelling through conditional logistic regression which adjusts for the matched variables inherently, and can also control for additional unmatched variables.

RESULTS

Table 1 shows the distribution of women with nine or fewer FTPs in all seven study centres by case–control status, parity, age at first FTP and age at last FTP. As expected, parity was higher for women with early age at first FTP and late age at last FTP, creating a complex pattern of confounding that necessitates the detailed analytical approach previously outlined.

Table 2 presents the results concerning breast cancer risk associated with age at first and age at last FTP, using alternative approaches with progressively more effective control of confounding by parity and age at any intermediate FTP. When control of confounding was only restricted to risk factors generally accepted for breast cancer (first column odds ratio estimates), both age at first and age at last FTP were positively associated with breast cancer risk, with age at first FTP conveying 3 times as much excess relative risk than age at last FTP. When age at first and last FTP were mutually adjusted and individual FTPs, but not age at intermediate FTPs, were accounted for, both age at first and last FTPs were significant determinants of breast cancer risk (second column odds ratio estimates). However, when a refined analysis restricted to subjects with two or more parities and controlling individually for every FTP as well as for the age of their occurrence was conducted (third column odds ratio estimates), age at first FTP was shown to be substantially more important than age at last FTP. Indeed, age at last FTP was no more important than age at any intermediate FTP with respect to breast cancer risk; the odds ratio for a 5-year increment for age at last FTP was 1.05 which is similar to the antilogarithm of 5×0.0093, as estimated previously [8], for the same increment in age at any FTP beyond the first one.

The refined analysis was also conducted within subgroups of women to examine further the relative importance between age at first and last FTP. Only the matched sets in which the case and controls belonging to the same subgroup contributed to these analyses. Subject's menopausal status did not modify the findings from the refined analysis. For premenopausal women, the adjusted odds ratios were 1.17 (0.91–1.51) and 1.01 (0.81–1.26) associated with a 5-year difference in age at the first and the last FTP, respectively. For postmenopausal women, they were 1.12 (0.96–1.30) and 1.05 (0.93–1.18). A straightforward way to evaluate whether age at first or last FTP is more important is to restrict the analysis to women with two parities. The results from such an analysis would not be confounded by either parity or age at subsequent births. In this subgroup, the adjusted odds ratio associated with a 5-year increment was 1.12 (0.89–1.42) for age at first FTP and 1.08 (0.86–1.34) for age at second (last) FTP.

DISCUSSION

The importance of age at first FTP as a risk factor for breast cancer, first demonstrated in the late 1960s [4], has been confirmed by most subsequent investigations [9, 19–21]. Independent associations of parity or FTPs other than the first with breast cancer risk are quantitatively less important and can be explained by the positive association of age at any FTP beyond the first with the risk for the disease [8, 9], and with the transient short-term increase of breast cancer risk following any FTP [10–13]. Invoking this epidemiological evidence as well as data from experimental animals [5, 6], several authors have concluded that terminal differentiation in the mammary gland epithelium, brought about by a FTP, represents the likely mechanism for the association of parity and age at occurrence of FTPs with breast cancer risk [1, 22]. It seems logical that the breast cancer risk implications would be larger for age at first FTP than for any subsequent FTP, since terminal differentiation is irreversible. However, some studies, notably that by Kvale and Heuch [23] and, in particular, that by Kalache and associates [7], have suggested that age at last FTP may be more important

Table 1. The distribution of women in all seven study sites on parity, age at first FTP and age at last FTP by case–control status

	Number			Age at first FTP (mean ± SD)		Age at last FTP (mean ± SD)	
Parity	Cases	Controls	OR*	Cases	Controls	Cases	Controls
0	1046	2341	1.00	—	—	—	—
1	641	1810	0.78	28.2 ± 6.2	26.9 ± 6.0	28.2 ± 6.2	26.9 ± 6.0
2	898	2436	0.80	26.1 ± 5.0	25.4 ± 4.6	30.3 ± 5.5	29.6 ± 5.2
3	537	1832	0.63	25.1 ± 4.4	24.2 ± 4.2	32.3 ± 5.2	31.5 ± 5.2
4	365	1247	0.62	24.4 ± 4.3	23.4 ± 3.9	34.1 ± 5.4	32.9 ± 5.0
5	200	762	0.55	23.6 ± 4.2	22.6 ± 3.8	34.4 ± 5.2	34.3 ± 5.1
6	126	460	0.56	23.0 ± 3.8	22.3 ± 3.5	36.6 ± 4.7	35.3 ± 4.7
7	62	285	0.46	21.9 ± 4.0	21.6 ± 3.4	36.1 ± 4.1	36.1 ± 4.6
8	46	188	0.52	22.8 ± 4.0	20.6 ± 3.1	38.7 ± 4.4	36.4 ± 4.5
9	29	149	0.39	21.8 ± 3.4	20.8 ± 3.3	39.2 ± 4.1	37.8 ± 4.7

*Odds ratios, adjusted for matching variables (study site and hospital ward).

Table 2. Odds ratios for breast cancer by age at first and last FTP, using progressively refined procedures for adjusting for parity and age at any other FTPs

	Subjects with one or more parities						Subjects with two or more parities			
Variables	Cases (*n*)	Controls (*n*)	Adjusting only for the core variables		Adjusting also for parity status and age at first or last FTP		Cases (*n*)	Controls (*n*)	Adjusting also for individual parity and age at any FTP	
Age at first FTP										
<20	271	1186	1.00	—	1.00	—	227	1019	1.00	—
20–24	1075	3951	1.21	(1.03–1.43)	1.08	(0.91–1.29)	927	3421	1.12	(0.90–1.38)
25–29	920	2633	1.63	(1.37–1.94)	1.30	(1.06–1.59)	736	2099	1.28	(0.99–1.64)
30–34	433	1024	1.98	(1.62–2.42)	1.41	(1.09–1.82)	278	671	1.25	(0.91–1.74)
35+	205	375	2.58	(2.02–3.31)	1.58	(1.12–2.23)	95	149	1.82	(1.16–2.87)
OR per 5-year increase in age at first FTP			1.30	(1.24–1.37)	1.19	(1.09–1.29)			1.17	(1.05–1.29)
Age at last FTP										
<25	378	1359	1.00	—	1.00	—	186	663	1.00	—
25–29	694	2318	1.04	(0.89–1.22)	0.98	(0.82–1.18)	510	1784	0.93	(0.73–1.18)
30–34	875	2796	1.05	(0.90–1.23)	0.95	(0.77–1.18)	720	2442	0.86	(0.66–1.13)
35–39	649	1921	1.18	(1.00–1.39)	1.06	(0.82–1.38)	563	1744	1.00	(0.74–1.36)
40+	308	775	1.48	(1.21–1.81)	1.33	(0.97–1.82)	284	726	1.18	(0.82–1.70)
OR per 5-year increase in age at last FTP			1.09	(1.04–1.13)	1.08	(1.00–1.17)			1.05	(0.96–1.14)

than age at first FTP as a risk factor for breast cancer. These results could be due to chance, since comparative assessment of the magnitude of inherently small relative risk estimates requires substantial statistical power. In the cohort study of Kvale and Heuch [23], there were 1565 cases of breast cancer, whereas the case–control study of Kalache and associates [7] was based on 346 cases of breast cancer and 380 controls. However, it is more likely that exact adjustment for parity and age at occurrence of all FTPs between the first and the last is needed for a valid comparison of the relative importance of age at first and age at last FTP. In a study of a large data set involving 3950 cases of breast cancer and 11 510 controls, among whom 2263 cases and 7359 controls had two or more FTPs, we found that an analysis that mimics that of Kalache and associates [7] and does not adequately control for residual confounding generated results similar to those reported by these authors. By contrast, a more refined analysis has shown that a 5-year delay in age at first FTP is associated with a 17% increase of risk which is statistically highly significant, whereas a 5-year delay in age at last FTP is associated with only a 5% increase of breast cancer risk, which is of borderline statistical significance. The association of age at last FTP with breast cancer risk is no stronger than that of age at any FTP between the first and the last. Analyses within a subgroup of women who were premenopausal, who were postmenopausal, or who had two (the first and the last) FTPs all led to similar observations.

We conclude that age at first FTP is substantially more important than age at any subsequent FTP, including the last FTP, for the modulation of breast cancer risk. Valid demonstration of the relative importance of age at any FTP on breast cancer risk requires strict analytical control of mutual confounding influences. The dominance of age at first FTP as a breast cancer risk factor is likely to be due to irreversible terminal differentiation of mammary epithelium, brought about by the occurrence of this pregnancy.

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