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Reproductive factors and breast cancer risk. Do they differ according to age at diagnosis?

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Summary

Studies yielding results on risk factors stratified by age at diagnosis or menopausal status were reviewed to better understand the role of hormonal factors and to determine whether reproductive events influence breast cancer risk differently according to age at diagnosis of breast cancer. Through a Medline/Pubmed search, 26 articles providing risk estimates by age at diagnosis of breast cancer or by menopausal status were analysed. A decrease of about 9% of breast cancer risk was found for each additional year at menarche when breast cancer was diagnosed early or before the menopause, and of about 4% when diagnosed late or after. Breast cancer risk increased with increasing age at FFTP by 5% per year for breast cancer diagnosed early or before the menopause and by 3% for cancers diagnosed late or after the menopause. Each full term pregnancy (or child) led to a 3% reduction in the risk of breast cancer diagnosed early or before the menopause, whereas the reduction attained 12% for the breast cancers diagnosed later. No change in the effect of these three factors with time (date of diagnosis of the breast cancer before 1980 or after) was observed. These results support the hypothesis of an age-specific effect of the three breast cancer risk factors considered herein, based on the time of initiation of the carcinogenic process. These observations underline the importance of the time of initiation of the carcinogenic process in determining the effect of promoters such as reproductive factors. This largely unexplored aspect of breast carcinogenesis might open the way for new prevention approaches.

Introduction

Breast cancer is the most frequent cancer among females in France, with 35 000 new cases each year. Its incidence has increased regularly and substantially (+60%) between 1975 and 1995, whereas a less marked increase has been observed in mortality (+8%). Early diagnosis resulting from screening programs and more effective treatments may explain these observations [1].

Apart from genetic susceptibility, the main risk factors for breast cancer are related to endogenous and exogenous hormones. Estrogens are known to induce mammary tumours in animals. Several epidemiological studies support the hypothesis that estrogens play an important role in the development of breast cancer in women [2]. Indeed, breast cancer risk increases with exposure to ovarian hormones : early menarche and late menopause were found to be risk factors whereas premenopausal oophorectomy decreases the risk. Although breast cancer incidence increases with age, the rate at which it increases slows down after the menopause. Other observations, although still controversial, support the role of hormones in the aetiology of breast cancer : spontaneous or induced abortions may increase breast cancer risk ; hormone plasma levels are higher in post-menopausal women with breast cancer than in controls ; exogenous hormones (the contraceptive pill or hormone replacement therapy) seem to increase breast cancer risk during use, and 5 to 10 years after. Finally, certain factors (such as diet, alcohol, physical activity and obesity) are supposed to play a role through their effect on hormone metabolism.

These epidemiological data are supported by biological data which show that estrogens and progesterone, together with other hormones (ovarian androgens, polypeptide hormones and growth factors) act as promoters by stimulating mammary cell proliferation. Other risk factors such as ionising radiation or

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inherited breast cancer genes are not hormone-related, but, are considered instrumental in the initiation of carcinogenesis.

Although the hormonal hypothesis is a generally admitted explanation for the role of reproductive events as risk factors, how these events interact with the hormonal metabolism, and why their effect appears to vary with age, is poorly understood.

We reviewed studies yielding results on risk factors stratified by age at diagnosis or menopausal status to better understand the role of hormonal factors and to determine whether reproductive events influence breast cancer risk differently according to age at diagnosis of breast cancer.

We investigated age at menarche, age at first full term pregnancy (FFTP), also described in some studies as age at first child, and parity (the number of pregnancies, deliveries or children according to the studies), the reproductive factors most often described in epidemiological studies on breast cancer.

Material and methods

Study selection criteria

Articles providing risk estimates by age at diagnosis of breast cancer or by menopausal status (used as a proxy variable for age at diagnosis) were obtained through a Medline/Pubmed search. When results in a specific article were given in several age categories, only extreme age categories were retained in order to better illustrate the effect of age. The literature search yielded 25 articles that were then analysed.

Statistical methods

Dose-response graphs have been prepared as a means of summarising the results of case-control and cohort studies, as used elsewhere [3]. The graphs show changes in the relative risk (or odds ratio) of breast cancer (the y variable) for different levels of the considered reproductive factor (the x variable). The points correspond to the relative risk (or odds ratio) for different categories of the factor studied, as given in each study reviewed. The plots show not only the direction of the association, that is whether the risk of cancer increases or decreases with exposure, but also allow estimations of the magnitude of the effect, by estimating the slope of the linear regression. A logarithmic scale was used so that the visual distance above and below the reference category line is comparable. The individual plots were adjusted to a common baseline, by moving each curve to pass through RR or OR=1 at this exposure. This allows comparisons between studies. The results of each study were weighed by the number of breast cancer cases in that particular study.

Results

The characteristics of the studies are detailed in Table 1. Figure 1 shows the results of 21 studies on the relationship between breast cancer and age at menarche. Breast cancer risk decreased with increasing age at menarche. Breast cancer risk decreased by about 9% (95% CI: 7-11%) for each additional year in age at menarche when breast cancer was diagnosed early or before menopause and of about 4% (95% CI: 2-5%) when diagnosed later.

Figure 2 shows the results obtained from 18 studies that investigated the FFTP as a risk factor for breast cancer. Breast cancer risk increased with increasing age at FFTP by 5% (95% CI: 5-6%) per year for breast cancer diagnosed early or before menopause and by 3% (95% CI: 2-4%) for cancers diagnosed late or after the menopause.

The relationship between breast cancer and parity was investigated in 20 studies (Figure 3). Each full term pregnancy (or child) led to a 3% (95% CI: 1-6%) reduction in the risk of breast cancer diagnosed early or before menopause, whereas the reduction attained 12% (95% CI: 10-14%) for the breast cancers diagnosed later.

For each reproductive factor, the slopes of the regression lines differed according to whether breast cancer was diagnosed early or late in life (Table 2). To test a possible change in the effect of these three factors with time, the data were computed for two different periods according to the time of diagnosis of breast: before 1980, and after (Table 2). Overall, they were similar, whatever the period of time.

Discussion

Our statistical analysis of pooled studies from the literature showed a stronger effect of an early age at menarche and of a late age at FFTP on the risk of breast cancers diagnosed at a young age (or before the

menopause) than at an older age (or after the menopause). In contrast, the protective effect of multiparity was stronger on late breast cancers. These observations were independent of the study period.

Table 1. **Main characteristics of epidemiological studies on reproductive factors and breast cancer**

Author [ref]	Date of diagnosis of breast cancer	Factors available *	Early breast cancers		Late breast cancers	
			n	Definition of age (or status) for the selection	n	Definition of age (or status) for the selection
Stavraky et al. [4]	06/67-02/71	M,F,P	95	Pre-menopausal	278	Post-menopausal
Burns et al. [5]	1/71-12/75	M,F	355	Pre-menopausal	669	Post-menopausal
J Lubin et al. [6]	76-77	M,F,P	99	Age: 30-44	158	Age: 55-64
Helmrich et al. [7]	76-12/80	M	471	Pre-menopausal	692	Post-menopausal
Lipnick et al. [8]	< 06/76	F,P	714	Pre-menopausal	130	Post-menopausal
Pathak et al. [9]	76-80	P	109	Age: 30-39	182	Age: 50-55
Brignone et al. [10]	72-83	M,F,P	374	Pre-menopausal	479	Post-menopausal
Schatzkin et al. [11]	76-11/85	M	224	Pre-menopausal	299	Post-menopausal
Brinton et al. [12]	1/73-11/80	M	344	Age: <45	-	-
Negri et al. [13]	1st study: 80-83 2nd: 72-84 3rd: >01/83	M,F,P	1,447	Age <50	2,625	Age: 50+
Kampert et al. [14]	70-77	M,F,P	762	Pre-menopausal	866	Post-menopausal
Layde et al. [15]	12/80-12/82	F,P	1,666	Pre-menopausal	471	Post-menopausal
Bouchardy et al. [16]	10/76-05/80	M,F,P	154	Age : 25-44	223	Age: 55-64
Ewertz et al. [17]	83-84; 5 Nordic countries	F,P	≈1,000	Age: 35-44	≈1,000	Age: 55-64
Hsieh et al. [18]	7 countries	M	-[1]	Pre-menopausal	-[1]	Post-menopausal
Segala et al. [19]	02/83-04/87	M,F,P	85	Age: <45	210	Age: 55+
Peng Lee et al. [20]	86-88	M,F,P	109	Pre-menopausal	89	Post-menopausal
De Stavola et al. [21]	61-15/4/92	M,F,P	73	Pre-menopausal	95	Post-menopausal
Mayberry et al. [22]	12/80-12/82	M,P	177	Age: 20-39]	-	-
Clavel-Chapelon et al. [23]	83-87	M,F,P	121	Age: <40	141	Age: 50+
Talamini et al. [24]	06/91-02/94	M,F,P	989	Pre-menopausal	1,574	Post-menopausal
Gilliland et al. [25]	1/92-12/94	M,F,P	36[2] 29[3]	Pre-menopausal	44[2] 57[3]	Post-menopausal
McCredie et al. [26]	11/83-10/87	M,P	184	Age: 25-39	245	Age: 50-54
Titus-Ernstoff et al. [27]	4/88-12/91	M,F,P	1,636	Pre-menopausal	4,992	Post-menopausal
Magnusson et al. [28]	10/93-3/95	M,F,P	-	-	2,731	Age: 50+

* M=age at menarche, F=first full-term pregnancy, P=parity

[1] numbers of pre-and post-menopausal women not indicated; 1,610 women are under 49 years of age and 6,470 are 50 and over

[2] Hispanic

[3] Non Hispanic

Convincing evidence exists for the overall role of age at menarche and the FFTP in breast cancer risk. A younger age at menarche is associated with an earlier onset of ovulatory cycles and consequently with longer exposure to estrogens, which increases cell proliferation [29, 30]. The earlier the FFTP, the earlier in life cells undergo differentiation, thus decreasing the risk of mammary cell transformation and/or proliferation. The multi-step process of carcinogenesis [31] that is initiation, promotion, tumour and progression, sheds light on how these factors modify the risk differentially according to the age at diagnosis. During the first step, cells that have not undergone the maturation process may become initiated under the influence of a carcinogen, whereas differentiated cells are either less sensitive or insensitive to initiating agents. During the second step, the initiated cell may evolve into a cancerous cell after promotion, that will give rise to a breast tumour several years later. The proliferation of mammary cells, which is at a maximum between 10 and 20 years of age, facilitates the promotion of the carcinogenic process. Early menarche and a late FFTP may therefore increase the risk of breast cancer only if mammary cells are initiated at a young age. Early menarche would then induce early proliferation of mammary cells through exposure to estrogen whereas a late FFTP would delay the protective effect of differentiation. In contrast, cancers initiated late in life cannot be modified by these factors. Although early initiation cannot be excluded for some late cancers,

the difference in tumour development may be related to other environmental factors (body mass index**,** food intake, etc.).

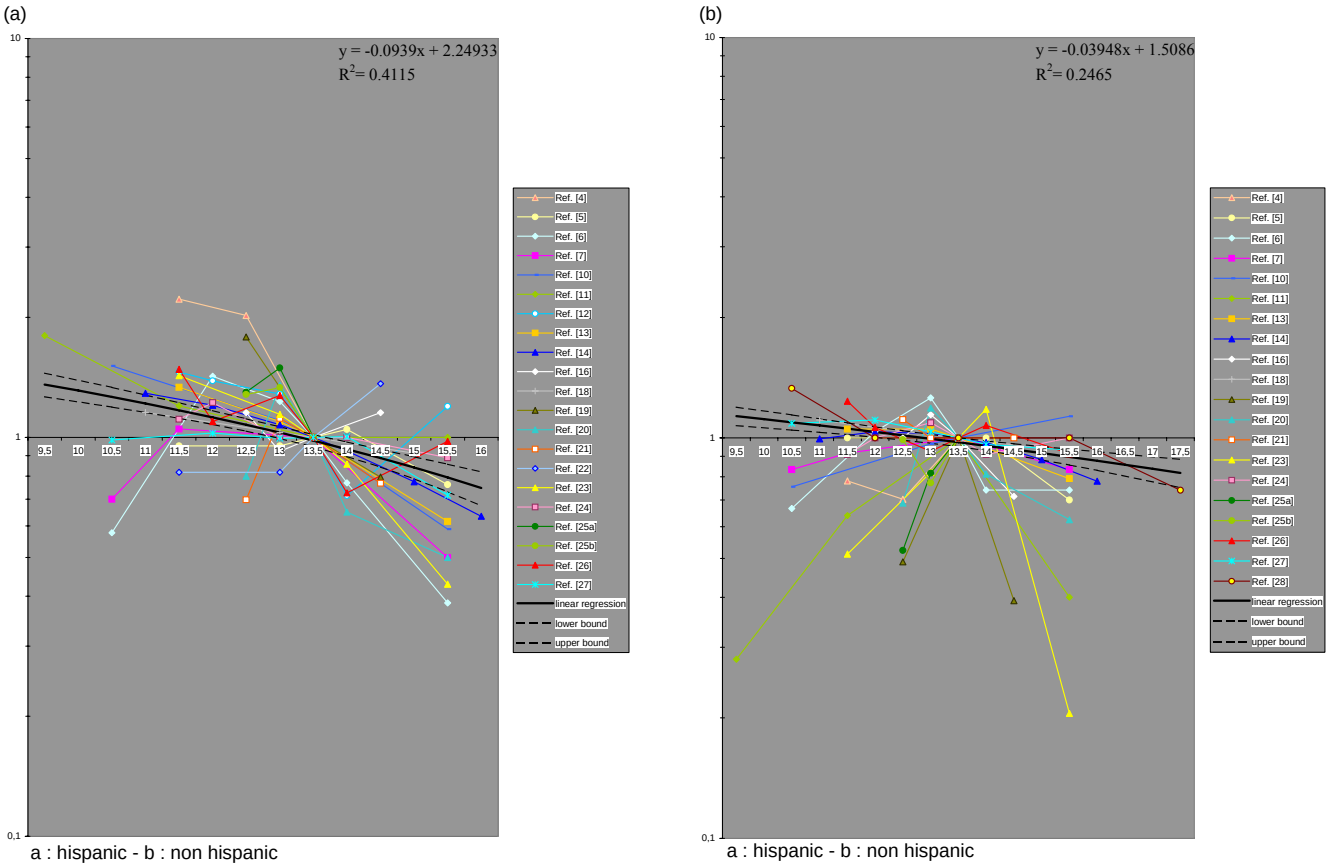

Fig. 1. Relation between age at menarche and risk of (a) early breast cancer and (b) late breast cancer.

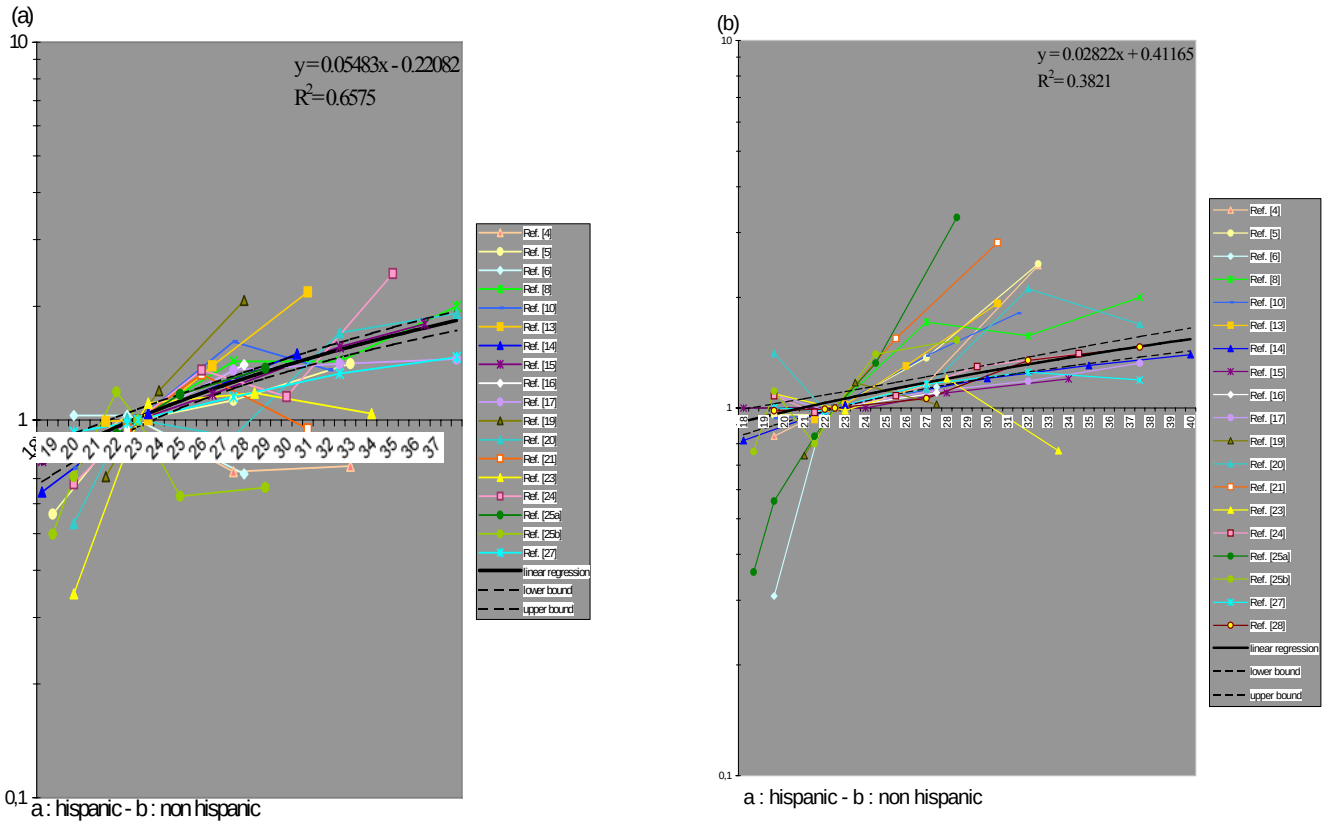

Fig. 2. Relation between age at first full term pregnancy and risk of (a) early breast cancer and (b) late breast cancer.

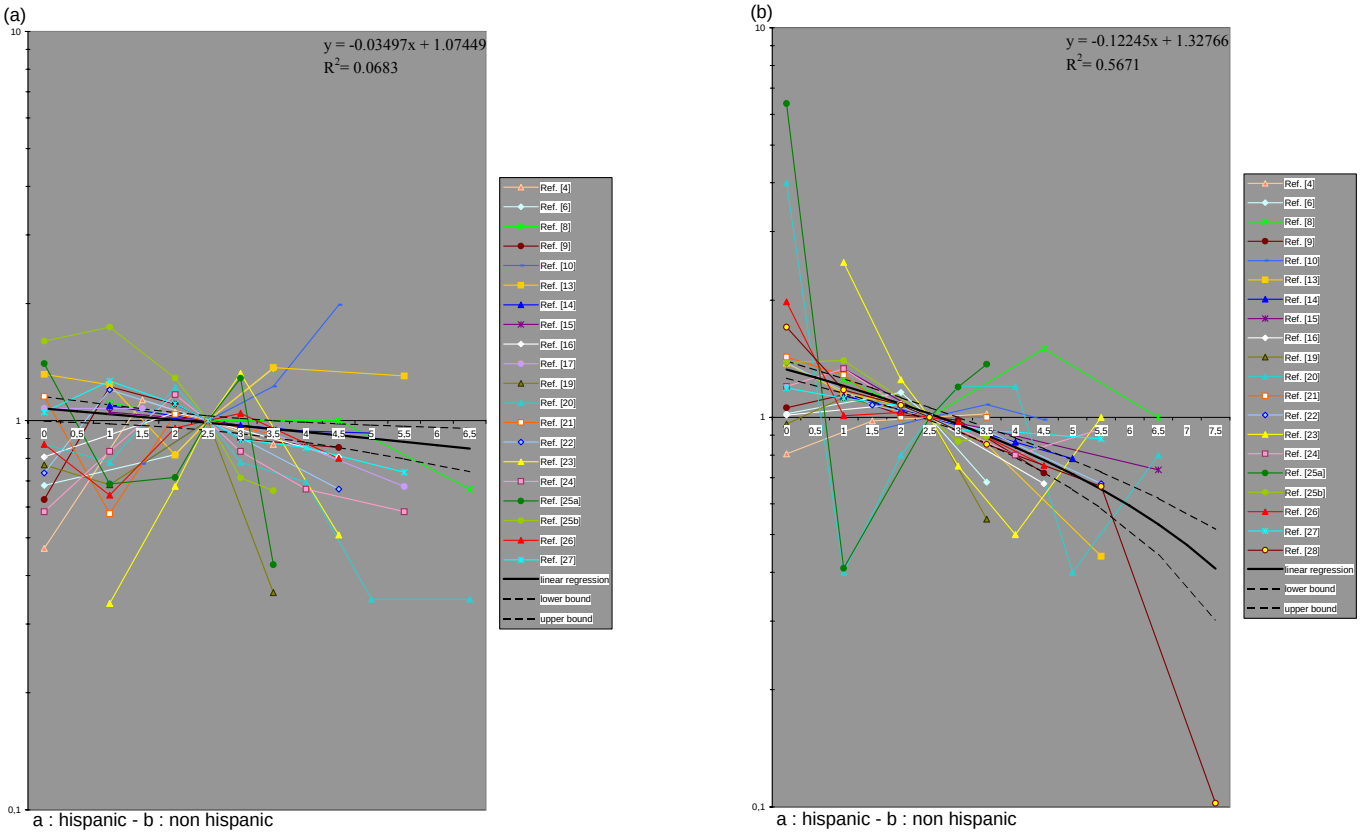

Fig. 3. Relation between parity and risk of (a) early breast cancer and (b) late breast cancer.

Table 2 . **Summary of the results on the relationship between breast cancer and reproductive factors according to age at diagnosis**

Risk factor	(n) studies	(n) cases	Regression Coefficients (95% CI)	p-value*	Cases included before** 1980	Cases included after** 1980
Age at menarche				$<10^{-4}$		
early breast cancers	19	7,764	-0.09 (0.07-0.11)		-0.09 (0.04-0.13)	-0.06 (0.03-0.09)
late breast cancers	18	16,467	-0.04 (0.02-0.05)		-0.03 (0.01-0.06)	-0.05 (0.03-0.06)
Age at first full-term pregnancy				$<10^{-4}$		
early breast cancers	17	9,744	+0.05 (0.05-0.06)		+0.06 (0.05-0.07)	+0.05 (0.04-0.06)
late breast cancers	18	16,832	+0.03 (0.02-0.04)		+0.04 (0.02-0.07)	+0.02 (0.02-0.03)
Parity				$<10^{-3}$		
early breast cancers	19	9,859	-0.03 (0.01-0.06)		-0.04 (0.01-0.07)	-0.06 (0.03-0.09)
late breast cancers	19	16,590	-0.12 (0.10-0.14)		-0.05 (0.02-0.08)	-0.12 (0.09-0.15)

* of the comparison of regression coefficients between early and late breast cancers
** other studies had cases included both before and after 1980

We demonstrated that the protective effect of multiparity is higher for cancers emerging late in life. Recent studies found a transient increase in breast cancer risk immediately after each pregnancy [32-34]. The multiparity effect could therefore be derived from a short-term increase in risk followed by a long-term protective effect against late cancers. It could also be argued that the protective effect of multiparity may not be observed among young women simply because multiparity is uncommon in this population.

Consideration must be given to the validity of the data on reproductive factors. Few authors have reported on the validity of reproductive factors. In a sub-study on 700 women from the E3N study [35] who twice completed the same self-administered questionnaire, we found a high reproducibility rate for answers on age at menarche, age at first pregnancy and the number of live births with percentages of identical answers respectively equal to 71%, 64% and 98%. It might be argued that a differential error with age is

likely, since women may have a better recall of a recent event than of the remote past. In our reproducibility study, we found similar results, whatever the length of time between the event and the interview.

As indicated in Material and methods, the articles reviewed herein represent all the Medline/Pubmed references that provided risk estimates by age or menopausal status. However, some studies may not have been taken into account, either because they were not referenced in Medline/Pubmed, or, because these risk factors, although studied, were not mentioned in the abstract or as keywords. The potential bias of negative unpublished studies cannot be excluded, but cannot be estimated.

Although pooling results is a simple and fast approach not requiring original data from all studies, it should not be considered a panacea. This approach is open to criticism because confounding factors cannot be taken into consideration when data are aggregated. However, one would expect each author to have taken them into account.

Together, these results support the hypothesis of an age-specific effect of the three breast cancer risk factors considered herein, based on the time of initiation of the carcinogenic process. These observations underline the importance of the time of initiation of the carcinogenic process in determining the effect of promoters such as reproductive factors. This largely unexplored aspect of breast carcinogenesis might open the way for new prevention approaches.

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