Induced and spontaneous abortion and breast cancer risk: results from the E3N cohort study.

Xavier Paoletti, Françoise Clavel-Chapelon

Induced and spontaneous abortion and breast cancer risk: results from the E3N cohort study

Xavier PAOLETTI, Françoise CLAVEL-CHAPELON[*] and the E3N group
INSERM, Equipe E3N, Institut Gustave Roussy, Villejuif, France

Recent reviews reach conflicting conclusions on breast cancer risk after spontaneous or induced abortion. E3N is a large-scale cohort study collecting detailed information on environmental and reproductive factors. We investigated the relation between breast cancer and a history of induced and/or spontaneous abortion, using the data from the 100,000 women aged 40–65 at entrance in 1990. Among them, over 2,600 new invasive breast cancers had been diagnosed by June 2000. Multivariate analysis, adjusted for known potential confounders, showed no association between a history of induced abortion and breast cancer risk either in the whole population (relative risk [RR] = 0.91, 95% confidence interval [CI] 0.82–0.99) or in subgroups defined by parity or by menopausal status. Overall, the association between spontaneous abortion and breast cancer was not significant (RR = 1.05, 95% CI 0.95–1.15). However, there is a suggestion of increased risk with increased number of miscarriages (RR = 1.20, 95% CI 0.92–1.56 after 3 or more). Moreover, an interaction with menopausal status was observed. In premenopause, the risk decreased with increasing number of spontaneous abortions, whereas it increased in postmenopause. Among nulliparous and parous women, the relative risk estimates were respectively equal to 1.16 (95% CI 1.04–1.30, p trend < 0.0008) and 1.14 (95% CI 1.01–1.28, p trend = 0.005). Premenopausal breast cancer, on the other hand, appeared to be less frequent in women who had had repeated miscarriages. We conclude that there is no relationship between breast cancer and induced abortion but that an association with spontaneous abortion is possible and may depend on menopausal status.

Key words: *induced abortion; spontaneous abortion; cohort study; breast neoplasm; menopause; risk factor*

Since induced abortion was legalized in France in 1975, approximately 250,000 medical terminations of pregnancy have been reported yearly (250,000 in 1976 and 220,000 in 1994) for a population of about 14.5 million French women between 15 and 50 years old. One in 5 French women are estimated to have had at least 1 induced abortion during their reproductive lives and approximately 32 pregnancies are aborted for 100 living births.[1] It is difficult to estimate spontaneous abortions, as they are often not detected even by the woman concerned. Rough estimates are that 12% to 17% of pregnancies in France end in a spontaneous abortion.[2] The health consequences of abortion are a public heath concern, and whether or not abortion affects breast cancer risk remains a major issue of debate.

Some hypotheses based on animals or endocrine data suggest that such an association is plausible.[3] As an incomplete pregnancy, abortion may affect the breast cancer risk in 2 ways. It has been shown that there is a transient excess in risk during the months after a full-term birth.[4–6] Hormone rates rise steadily during the gestational period and high hormone levels are suspected to promote carcinogenesis. Is a smaller, shorter cumulative exposure to hormones remain a risk factor? Conversely, cell differentiation observed after the first full-term pregnancy (FTP) contributes to the protective effect of a first birth on breast cancer risk. Do women aborting during the first trimester experience the growth-enhancing effects of the early secretion of hormones without benefiting from the protection of a completed pregnancy? Both hypotheses are plausible, even though supported by limited animal data.

Grant sponsor: French League against Cancer; Grant sponsor: European Community; Grant sponsor: 3M Company; Grant sponsor: the Mutuelle Générale de l'Education Nationale; Grant sponsor: Institut Gustave-Roussy; Grant sponsor: Institut National de la Santé et de la Recherche Médicale.

[*] Correspondence to: INSERM, Equipe E3N, Institut Gustave Roussy, 24 rue C. Desmoulins, 94805 Cedex Villejuif, France. Fax: +33-1-42-11-40-00. E-mail: clavel@igr.fr

Recent reviews of breast cancer risk associated with spontaneous or induced abortion reach conflicting conclusions,[7–9] ranging from null to a moderately strong effect. More recent cohort studies[10–12] and case-control studies[13–17] point to the absence of any relation. Concern has been raised with regard to the difficulty of drawing definitive conclusions about spontaneous or induced abortion, [7,18] as biases, particularly those related to case-control design and to inadequate choices of the reference group,[8] can create spurious associations or obscure genuine relations.

The present study used the data from the E3N cohort to investigate the relationship between breast cancer risk and a history of abortion. As miscarriages may be the consequence of hormonal or genetic defects, which is not the case of induced abortion, authors[7,8] recommend to investigate both types separately. Relations between breast cancer and both types of pregnancy interruption were assumed to be independent. Both overall and subgroup associations were explored, in particular *(i)* in parous and nulliparous women, *(ii)* before first FTP and *(iii)* before and after menopause.

Material and methods

E3N is a prospective cohort study on cancer risk factors, conducted in France.[19] Part of the E3N cohort (i.e., women who replied to a dietary questionnaire) is also included in the European Prospective Investigation on Cancer (EPIC).[20]

The cohort consists of around 100,000 French women insured with the Mutuelle Générale de l'Education Nationale (MGEN), a national health insurance scheme primarily covering teachers. They were aged 40–65 at inclusion. The main objective of the study is to investigate risk factors for cancer and other serious illnesses. Participants were enrolled in the study between June 1990 and November 1991 after replying to a baseline questionnaire. Follow-up questionnaires are sent out at approximately 24-month intervals.

Reproductive events were recorded in the first 2 questionnaires. The first inquired about the overall number of pregnancies, deliveries, abortions (either induced or spontaneous, before or after first FTP), the date of first pregnancy and first delivery. The second requested details of each pregnancy, up to a maximum of 12: age at pregnancy, duration, outcome (i.e., live birth, stillbirth, miscarriage, ectopic pregnancy or induced abortion) and lactation period.

As in the first questionnaire, ectopic pregnancies were grouped together with spontaneous abortions and they were analysed together with the latter. In case of a discrepancy between the 2 questionnaires, the figures from the first were used. Menopausal status was recorded in each questionnaire. Five hundred and seven women reported to have had abortions between questionnaire 1 and questionnaire 2. Postmenopause was defined as the cessation of periods for natural reasons or due to surgery (total oophorectomy).

Women who had self-reported a history of cancer other than basal cell carcinoma at baseline (n = 4,540) or for whom no date of diagnostic was available (n = 39) were excluded from the initial pool of 98,997 subjects. Those with missing pregnancy outcomes (n = 1,651) were also excluded from analysis. This left 92,767 women for the main analysis.

All questionnaires asked participants whether breast cancer had been diagnosed, requesting the addresses of their physicians and permission to contact them. Deaths in the cohort were detected from reports by family members or by the postal service and by searching in the insurance company (MGEN) file, which contains information on vital status. Information on cause of death was obtained from the National Service on Causes of Deaths (INSERM). Information on the reimbursement of hospital fees of nonrespondents (n = 688) was obtained from the MGEN file. In this case, the subject's physician was contacted for diagnostic information, making it possible to find additional breast cancer cases. Only 1,815 women could not be traced in the MGEN file (names misspelled, names changed after divorce, no longer insured with the MGEN, etc.), and nonrespondents in this group were considered lost to follow-up.

A total of 3,022 incident breast cancer cases were reported by participants since their entry into the study. Of these, about 100 were only self-reported cases, the remaining being confirmed by a pathology report. After exclusion of 376 cases of carcinoma *in situ*, 2,646 cases of invasive breast cancer were available for analysis. Cases that were only self-reported were also included, as self-reporting proved to be extremely accurate (1.67% false positive).

The person-years of each participant were calculated from the date of return of the first questionnaire (or of the second one for the 507 women who aborted between the 2 questionnaires) up to the date of breast cancer

diagnosis, date of death, date of last questionnaire returned or end of June 2000 (for replies received after June 2000), whichever occurred first. The mean follow-up time for the present study was 9.6 years (SD =1.45 years).

To investigate the relationship between abortion and breast cancer risk, a proportional hazards regression model with age as the time scale was used.[21] The estimated relative risk (RR) and the corresponding 95% confidence interval (CI) are presented, adjusted for potential confounders (see Table I): educational level, body mass index, age at first menarche, parity, age at first birth (FTP), marital status, oral contraceptive use, infertility problems, personal history of benign mastopathy, family history of breast cancer and menopausal status. The menopausal status of 38,407 women changed during follow-up. These contributed to each of the 2 subgroups in accordance with the period of follow-up during which they were pre- or postmenopausal. Missing data for adjustment factors were imputed to the mode among the population with complete data. In stratified analysis, subjects with missing data for stratification factors were excluded from the analysis. Induced and spontaneous abortions were considered separately in the analysis. No adjustment was made for miscarriages when looking at the effect of induced abortions, and *vice versa*. This point is discussed in greater detail in the last part of the article.

The effect of abortion was investigated in all women. In view of the fundamental role of the first FTP, the data were also stratified on nulliparity and the relation between abortion before first FTP and breast cancer was explored. In addition, a possible differential effect of abortion was analyzed according to menopausal status.

Results

Of the 92,767 women studied, 22.1% had 1 or more induced abortions (15.3% had 1, 4.6% had 2 and 2.1% had 3 or more) and 23.0% had 1 or more spontaneous abortions (16.8% had 1, 4.4% had 2 and 1.8% had 3 or more). The mean duration of gestation was 7.1 (SD = 4.8) weeks before an induced abortion and 9.8 (SD = 6.0) weeks before a spontaneous abortion. The latter figure is of course strongly overestimated as many spontaneous abortions occurring during the first weeks of pregnancy are not detected by the woman concerned. Five hundred twenty-nine of the women who had 1 or more induced abortions and 607 of those who had 1 or more spontaneous abortions developed breast cancer during follow-up.

The main characteristics of the study population are shown in Table I. The proportions of induced and spontaneous abortions in the E3N population are quite comparable and they have similar distributions for the different adjustment variables used in the analysis. The great majority of the women were married with 2 children. Thirty-two percent had a personal history of benign breast disease, while 10.5% had a family history of breast cancer. Forty percent had, at one time or another, used oral contraceptives.

Table II shows the RR of breast cancer after spontaneous or induced abortion. Point estimates are given for the breast cancer risk of abortion in general and for the risk specific to spontaneous and induced abortion. In addition to the "Ever" group, we also studied the effect of repeated outcomes. Women with a history of (induced or spontaneous) abortion had the same breast cancer risk as women with no such history (RR = 0.97, 95% CI 0.90 –1.08). Induced abortions reduced the risk of breast cancer (RR = 0.91 95% CI 0.82– 0.99), but no pattern of risk with increasing number of outcomes was observed. A history of spontaneous abortion was not statistically related to breast cancer (RR = 1.05, 95%), though the risk slightly increased with repeated miscarriages (p trend = 0.16).

Data were analyzed according to parity status (Table III). Results are presented separately for nulliparous and for parous women. Among parous women, the effect of abortion before first FTP was examined. In none of the subgroups considered was there any relation between a history of induced abortion and breast cancer, except for a statistically significant decrease associated with 2 induced abortions in parous subjects (RR=0.75 95%CI 0.60–0.93). Spontaneous abortions did not affect breast cancer risk either in the entire parous women group or among those who had a spontaneous abortion before their first FTP. However, a trend of increasing risk with an increasing number of spontaneous abortions was observed in nulliparous women with point estimates of 1.28 (95% CI 0.84 –1.96) and 1.37 (0.79 –2.36), respectively, for histories of 1 and 2 or more miscarriages.

Table I. **Main characteristics of the population under study (n=92,767 women)**

Characteristics at inclusion	All women n	Never aborted %	Ever aborted (%) Induced[1]	Ever aborted (%) Spontaneous[2]
Age at inclusion (years)				
40-45	32,135	60.1	23.6	22.5
45-50	22,495	59.7	23.9	22.8
50-55	17,813	61.1	21.9	23.2
55-60	12,131	62.1	19.3	24.3
60-65	8,076	65.7	15.4	23.5
Missing	117	66.0	14.2	23.4
Number of years at school				
<12	12,312	63.4	18.9	23.9
12-16	60,752	60.5	22.7	22.8
>16	15,821	59.7	22.7	23.8
Missing	3,882	64.7	19.9	20.5
Body Mass Index (kg/m^2)				
<18	2,212	65.3	19.6	21.3
18-22	43,660	60.4	23.2	22.5
≥22	46,524	61.2	21.1	23.6
Missing	371	62.4	22.8	23.8
Age at menarche (years)				
≤11	16,122	59.6	23.4	23.5
11-13	46,451	60.9	22.0	22.9
>13	29,416	61.4	21.4	23.0
Missing	778	67.1	22.6	19.6
Parity				
0	11,159	79.0	15.0	8.7
1	14,885	61.3	23.5	21.0
2	39,193	59.7	23.6	22.7
3	19,831	56.1	22.7	28.3
4 or more	7,699	52.4	19.9	36.0
Missing	0			
Age at 1st birth (years)				
≤20	8,726	55.8	29.5	22.3
20 – 30	64,788	59.6	21.9	24.5
30 – 35	5,612	54.6	23.1	29.4
>35	1,641	50.0	25.6	32.5
Missing	841	38.7	39.5	50.8
Marital status				
Not living with a partner	16,334	63.4	25.0	17.8
Living with a partner	72,506	60.1	21.5	24.4
Missing	3,927	66.7	19.5	19.2
Oral contraceptive use[3]				
Never	55,167	62.8	20.0	23.1
Ever	37,600	58.2	25.1	23.0
Infertility treatments[3]				
Never	86,164	61.6	22.4	21.9
Ever	6,603	52.2	17.7	38.1
Benin breast disease history[3]				
No	62,484	61.3	21.5	23.2
Yes	30,283	60.3	23.2	22.6
Breast cancer among 1st degree relatives				
No	81,448	60.8	22.1	23.1
1	9,647	61.0	22.1	22.8
2 or more	879	60.1	21.1	24.9
Missing	793	71.5	15.7	17.6

[1]92,666 women had data on induced abortion - [2] 92,649 women had data on spontaneous abortion - [3] For these categories, missing data were undistinguishable from "no" responses.

Table II. **History of spontaneous or induced abortion and breast cancer risk. E3N cohort study, 1990-2000.**

Abortion history	Number of cases	PY[1]	Multivariate RR (95% CI)[2]	
Experienced an abortion				
Never	1,617	543,992	1.00	(reference)
Ever	991	348,944	0.97	0.90-1.08
1	607	211,940	0.99	0.90-1.09
2	231	87,027	0.91	0.79-1.04
3+	153	49,977	1.02	0.86-1.21
Experienced an induced abortion				
Never[3]	2,079	696,960	1.00	(reference)
Ever	529	197,057	0.91	0.82-0.99
1	379	136,960	0.94	0.84-1.05
2	90	41,287	0.73	0.59-0.90
3+	60	18,809	1.00	0.77-1.29
Experienced a spontaneous abortion				
Never[4]	2,003	687,935	1.00	(reference)
Ever	607	205,943	1.05	0.95-1.15
1	430	150,194	1.02	0.92-1.13
2	120	39,181	1.08	0.90-1.30
3+	57	16,566	1.20	0.92-1.56
			p trend=0.16	

[1]Person-years of follow-up - [2]Adjusted for the variables of Table I – [3]Including women with a history of spontaneous abortions (464 breast cancer cases, 153,380 person-years). – [4]Including women with a history of induced abortions (386 breast cancer cases, 144,495 person-years).

Table III. **History of spontaneous or induced abortion and breast cancer risk stratified on parity status. E3N cohort study, 1990-2000.**

Abortion history	Number of cases	PY[1]	Multivariate RR (95% CI)[2]	
Among nulliparous women				
Induced abortion				
Never [3]	319	90,794	1.00	(Reference)
Ever	51	15,958	0.92	0.68-1.25
1	36	11,120	0.95	0.67-1.34
2+	15	4,838	0.87	0.52-1.46
			p trend=0.13	
Spontaneous abortion				
Never [4]	332	97,475	1.00	(Reference)
Ever	38	9,228	1.31	0.93-1.86
1	24	5,943	1.28	0.84-1.96
2+	14	3,284	1.37	0.79-2.36
Among parous women				
Induced abortion				
Never[5]	1,760	606,165	1.00	(Reference)
Ever	478	181,099	0.91	0.82-1.01
1	343	125,840	0.94	0.84-1.06
2	83	38,138	0.75	0.60-0.93
3+	52	17,120	1.00	0.76-1.32
Spontaneous				
Never aborted[6]	1,671	590,460	1.00	(Reference)
Ever aborted	569	194,715	1.02	0.93-1.13
1	406	144,251	1.00	0.90-1.11
2	111	37,235	1.05	0.87-1.28
3+	52	15,228	1.20	0.91-1.59
			p trend=0.30	
Among parous women and before first FTP				
Induced				
Never aborted	1,760	732,352	1.00	(Reference)
Ever aborted before FFTP	150	52,573	0.96	0.81-1.13
1	119	41,341	0.98	0.81-1.18
2+	31	11,232	0.87	0.61-1.25
Spontaneous				
Never aborted	1,671	707,946	1.00	(Reference)
Ever aborted before FFTP	233	75,149	1.06	0.92-1.22
1	195	62,753	1.07	0.92-1.25
2+	38	12,395	1.01	0.73-1.40

[1]Person-years of follow-up - [2] Adjusted for all variables of Table I but parity - [3]Including women with a history of spontaneous abortion (29 breast cancer cases, 6,727 person-years) - [4]Including women with a history of induced abortion (44 breast cancer cases, 13,457 person-years) - [5]Including women with a history of spontaneous abortion (435 breast cancer cases, 146,653 person-years) - [6]Including women with a history of induced abortion (344 breast cancer cases, 131,037 person-years)

The relation between abortion and breast cancer risk was also investigated in subgroups defined by menopausal status (Table IV). No association was found between breast cancer and induced abortion. This was not the case with spontaneous abortion, which was associated with a decrease in the risk of premenopausal breast cancer (p trend = 0.06) followed by an increase in risk of postmenopausal breast cancer (p trend < 10^{-3}). The decrease in risk in premenopause was confined to parous women, though the small number of nulliparous did not allow us to reach firm conclusions. Among postmenopausal women, the increase in risk with an increasing number of spontaneous abortions was observed in both nulliparous and parous women (p for trend = 0.05 and 0.005, respectively).

Table IV. **History of spontaneous or induced abortion and breast cancer risk according to menopausal status. E3N cohort study, 1990-2000.**

	Pre-menopausal women[1]				Post-menopausal women[2]			
	No. of cases	PY[3]	RR[4]	95% CI	No. of cases	PY[3]	RR[4]	95% CI
All women								
Induced								
Never aborted	589	226,460	1.00	(Ref.)	1,355	394,790	1.00	(Ref.)
Ever aborted	167	71,476	0.89	0.75-1.06	331	104,227	0.92	0.81-1.03
1	129	52,637	0.94	0.78-1.14	228	68,825	0.95	0.83-1.10
2	27	14,141	0.73	0.50-1.07	59	23,008	0.75	0.58-0.97
3+	11	4,697	0.84	0.46-1.50	44	12,392	1.02	0.75-1.37
Spontaneous								
Never aborted	604	230,058	1.00	(Ref.)	1,264	382,966	1.00	(Ref.)
Ever aborted	152	67,774	0.87	0.72-1.05	424	115,989	1.16	1.04-1.30
1	118	50,172	0.92	0.75-1.12	287	83,305	1.09	0.96-1.25
2	27	12,414	0.83	0.57-1.23	90	23,047	1.24	1.00-1.54
3+	7	5,187	0.52	0.25-1.10	47	9,636	1.52	1.14-2.04
			p trend=0.06				p trend<10^{-3}	
Nulliparous								
Induced								
Never aborted	82	26,018	1.00	(Ref.)	221	55,035	1.00	(Ref.)
Ever aborted	11	5,865	0.60	0.32-1.13	38	8,256	1.08	0.76-1.54
1	10		N/A		24	5,474	1.07	0.68-1.59
2+	1		N/A		14	2,781	1.17	0.68-2.01
Spontaneous								
Never aborted	85	28,739	1.00	(Ref.)	231	58,038	1.00	(Ref.)
Ever aborted	8	3,068	1.06	0.50-2.25	28	5,320	1.39	0.93-2.10
1	7		N/A		15	3,370	1.18	0.69-2.01
2+	1		N/A		13	1,949	1.78	1.00-3.17
							p trend = 0.05	
Parous women								
Induced								
Never aborted	507	200,441	1.00	(Ref.)	1,134	339,755	1.0	(Ref.)
Ever aborted	156	65,611	0.93	0.78-1.12	293	95,970	0.90	0.79-1.02
1	119	48,332	0.97	0.79-1.18	204	63,351	0.94	0.81-1.10
2	26	13,005	0.79	0.53-1.17	53	21,288	0.74	0.56-0.98
3+	11	4,273	0.96	0.53-1.76	36	11,331	0.94	0.67-1.31
Spontaneous								
Never aborted	519	201,319	1.00	(Ref.)	1,033	324,928	1.00	(Ref.)
Ever aborted	144	64,707	0.86	0.71-1.03	396	110,669	1.14	1.01-1.28
1	111	48,147	0.89	0.73-1.10	272	79,934	1.08	0.95-1.24
2	26	11,783	0.84	0.56-1.25	82	21,932	1.19	0.95-1.49
3+	7	4,776	0.55	0.26-1.14	42	8,802	1.50	1.10-2.05
			p trend=0.05				p trend = 0.005	

[1]For the pre-menopausal group, patients follow-up was censored at the date of menopause if no event had occurred before. - [2]For the post-menopausal group, the date of entry was either the date on which the first questionnaire was completed if the woman was menopausal at inclusion, or the date of menopause. - [3]Person-years of follow-up - [4]Adjusted for all variables of Table I but parity and menopausal status - N/A, Not available

Discussion

Our study revealed an increase in risk with a history of spontaneous abortion. This increase was observed both among nulliparous and parous women. Moreover, as for other risk factors,[22,23] an interaction with menopausal status was apparent. In premenopause, the risk decreased with increasing number of spontaneous abortions, whereas it increased in postmenopause, both among nulliparous and parous women. A history of induced abortion was not associated to breast cancer risk, either in the whole population or in subgroups defined by parity or by menopausal status.

The E3N data comes from self-administered questionnaires. This raises the question of the accuracy of the responses. The reproducibility of the E3N data was assessed in a substudy on 751 women who completed the first questionnaire twice, 18 months apart. There was a high percentage of identical responses concerning the number of births, number of induced abortions and number of miscarriages: 95%, 87% and 97%, respectively. Moreover, the prospective design of the study should avoid differential reports of pregnancy outcomes between cases and noncases. The fact that over 85% of the initial cohort continue to participate in the study more than 10 years after inclusion also shows its high degree of interest and argues for the quality of the individual responses.

It is nevertheless likely that induced abortions are underreported. This has been extensively discussed in several studies.[24] Induced abortion was legalized in France in 1975. As the women in our study were born between 1925 and 1950 and had a median age of 31 in 1975, it cannot be excluded that abortions performed before 1975 were underreported because of their illegal nature. The same may possibly be true of those performed in later years, as abortion remains a taboo topic. Even though the French 1975 law requires that women should anonymously declare the abortion via a form provided by the hospital, Blayo[1] estimated that 35% of all induced abortions in France are not reported. It can be supposed that this figure is lower among women with a high educational level, as is the case with those in the E3N study. In any event, no differences were found in the RR estimates when the data was stratified on birth cohort (results not presented here) to detect any possible effect of the 1975 law. Although underreporting is likely and may result in the dilution of any effect of induced abortion on breast cancer risk, such an effect will in no way be differential.

The absence of any relationship between induced abortion and breast cancer risk in the E3N population corroborates the 3 previously published cohort studies. In the Iowa cohort, the age-adjusted risk among women who had experienced induced abortion compared to those who never had was 1.1 (95% CI 0.8 –1.6).[11] In a record linkage study between a birth certificate registry and a cancer surveillance system, Tang *et al*.[12] also found no association between breast neoplasm and induced abortion (RR = 0.9, 95% CI 0.7–1.2). The largest study published so far,[10] based on a record linkage between Danish induced abortion registries and cancer registries, yielded similar conclusions. In that cohort of 1.5 million women, among whom around 370,000 induced abortions and 10,000 breast cancer cases were identified, a relative risk of 1.00 (95% CI 0.94 –1.06) was estimated in women with a history of induced abortion as compared to those without such a history. Because of the nature of the information collected in the registries, this high-quality study was unable to take into account such factors as spontaneous abortion, age at first birth or menopausal status.

The risk associated with induced abortion before first FTP has been investigated in case-control studies only.[7,14,17,25–27] No overall relation was found in any of these studies. Michels *et al*.[26] found a positive association in women under 50 years of age and a negative association in older subjects. However, induced and spontaneous abortions were grouped together in this last study, which limits its conclusions.

Contrary to our own findings, most studies have described spontaneous abortion as unrelated to breast cancer risk.[7] Only 2 cohort studies have been published so far.[28,29] Calle *et al*.[28] found a statistically insignificant decrease in risk of fatal breast cancer related to a history of spontaneous abortion, with RRs of 0.95 (95% CI 0.81–1.10), 0.74 (95% CI 0.56–0.98) and 0.85 (95% CI 0.60 –1.20) corresponding to 1, 2 and 3 or more miscarriages, respectively. Sellers *et al*.[29] found in postmenopausal women that there was little evidence of an increase in risk associated with a history of spontaneous abortion (RR = 1.1, 95% CI 0.9 –1.4) and that the risk was not higher among women reporting 2 or more spontaneous abortions in consecutive pregnancies (RR = 1.0, 95% CI 0.7–1.4).

However, these results require cautious interpretation as biases may affect risk estimates. First of all, many spontaneous abortions, especially those occurring during the first weeks of gestation, may be identified as delayed menstruation and not as spontaneous abortion, or may simply be less well remembered. This effect

biases results towards the null. Of greater importance may be the difference in detection between early and late miscarriages. It is questionable whether they have the same etiology and the same effect on breast cancer risk and whether they concern the same women. Indeed, women who have had repeated unsuccessful pregnancies can have a completely different profile with regard to hormonal levels, blood pressure, etc. In our analysis, we adjusted for use of an infertility treatment (this concerned 1,291 of the 11,159 nulliparous women). Nevertheless, the excess of risk observed in nulliparous women may be attributable to confounding factors that would also induce an abortion, such as environmental factors (certain chemicals, irradiation, etc.) and genetic factors.[30,31] Detailed information was recorded, which enabled a large number of potential confounders to be taken into account, thus avoiding significant dilution of any effect. None of the confounders interacted significantly in the association under study. In particular, results were similar in both the subgroups defined according to whether or not there was a family history of breast cancer.[32]

Our results support the idea that the protective effect of an FTP is not acquired during the first trimester. The absence of any long-term protective effect after interrupted pregnancies favors the idea that the differentiation of breast cells takes place during the last few months. A study on preterm deliveries[33] revealed a doubling of the risk in parous women with a gestation period under 32 weeks, with a decrease in risk with increasing duration of gestation. The clear trend highlighted in our study suggests that the protective effect is obtained gradually, late in gestation. Hsieh *et al*.[34] also found that delivery before the 37th week of gestation resulted in reduced increments in the short-term risk and a smaller reduction in the long-term risk compared to full-term delivery. These publications are complemented by the study of Liu *et al*.,[6] which models the transient effect over time. The latter study found that the risk reaches a peak 5 years after the birth and eventually disappears after 15 years.

The decrease in premenopausal breast cancer risk observed in our population, followed by an increase in postmenopause that mirrored that effect, indicated that pregnancy interruption might give transient protection. We found no such effect after induced abortion, even though the mean period of gestation before abortion is shorter. Indeed, a spontaneous abortion may affect the risk as a result of an abnormally low production of progesterone by the corpus luteum. It is likely that spontaneous abortion is more an indicator of hormonal disorders than an independent risk factor.

In our study, spontaneous abortion and induced abortion were analyzed separately. To estimate the breast cancer risk of 1 type of abortion, women who had experienced the other type of abortion were included in the reference group. We double-checked for a possible interaction between these 2 outcomes. We first analyzed both the correlation between the 2 variables 'history of spontaneous abortion' and 'history of induced abortion' and that between the number of induced abortions and the number of spontaneous abortions. The Pearson coefficients were very low, 0.05 and 0.07, respectively. We then reanalyzed our data using women who had never had any abortion as reference. The second analysis (not presented here) gave very similar results. Both factors can therefore be regarded as independent.

We conclude that there is no relationship between breast cancer and induced abortion but that there is a possible association with spontaneous abortion. This association is inverted before and after the menopause and this may explain why published studies exploring the overall relation without precisely taking into account the menopausal status failed to find a relation. It is usually hypothesized that an interrupted pregnancy might affect breast cancer risk. Nevertheless, this hypothesis fails to explain the increase in breast cancer risk associated with spontaneous abortion if no similar increase is observed after induced abortion involving the same duration of gestation. Promoters of breast cancer: progesterone deficiency, inadequate estrogen/progesterone balance, or other hormonal disorders resulting in a miscarriage may affect breast cancer risk. It can be supposed that a genetic influence also prevails. Some genes may be related both to miscarriages and to breast cancer. Further studies focusing on women at high risk of spontaneous abortion might lead to the detection of genes or environmental factors also associated with breast cancer carcinogenesis.

Acknowledgements

The authors are indebted to all the participants for providing the data. They are grateful to Garth Evans for his assistance with English and to Sébastien Chaillou for his help in preparing the data.

References

1. Blayo C. Le point sur l'avortement en France. Population et Société, Institut National d'Etudes Démographiques 1997;325:1–5.
2. Mauvais-Jarvis P, Schaison G, Touraine P. Médecine de la reproduction, 3rd éd. Médecine Sciences: Flammarion France. 1997. 624 p.
3. Russo J, Russo IH. Biology of disease: Biological and molecular bases of mammary carcinogenesis. Lab Invest 1987;57:112–37.
4. Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. N Engl J Med 1994;331:5–9.
5. Kroman N, Wohlfahrt J, Andersen KW, Mouridsen HT, Westergaard T, Melbye M. Parity, age at first childbirth and the prognosis of primary breast cancer. Br J Cancer 1998;78:1529 –33.
6. Liu Q, Wuu J, Lambe M, Hsieh SF, Ekbom A, Hsieh CC. Transient increase in breast cancer risk after giving birth: postpartum period with the highest risk (Sweden). Cancer Causes Control 2002;13:299–305.
7. Wingo PA, Newsome K, Marks JS, Calle EE, Parker SL. The risk of breast cancer following spontaneous or induced abortion. Cancer Causes and Control 1997;8:93–108.
8. Michels KB, Willett WC. Does induced or spontaneous abortion affect the risk of breast cancer? Epidemiology 1996;7:521–8.
9. Brind J, Chinchilli VM, Severs WB, Summy-Long J. Induced abortion as an independent risk factor for breast cancer: a comprehensive review and meta-analysis. J Epidemiol Community Health 1996;50:481–96.
10. Melbye M, Wohlfart J, Olsen JH, Frisch M, Westergaard T, Helweg-Larsen K, Andersen PK. Induced abortion and the risk of breast cancer. New Engl J Med 1997;336:81– 85.
11. Lazovich D, Thompson JA, Mink PJ, Sellers TA, Anderson KE. Induced abortion and breast cancer risk. Epidemiology 2000;11:76–80.
12. Tang MT, Weiss NS, Malone KE. Induced abortion in relation to breast cancer among parous women: a birth certificate registry study. Epidemiology 2000;11:177– 80.
13. Goldacre MJ, Kurina LM, Seagroatt V, Yeates D. Abortion and breast cancer: a case-control record linkage study. J Epidemiol Community Health 2001;55:336 –7.
14. Sanderson M, Shu XO, Jin F, Dai Q, Wen W, Hua Y, Gao YT, Zheng W. Abortion history and breast cancer risk: results from the Shanghai breast cancer study. Int J Cancer 2001;92:899 –905.
15. Newcomb PA, Mandelson MT. A record-based evaluation of induced abortion and breast cancer risk (United States). Cancer Causes Control 2000;11:777– 81.
16. Fioretti F, Tavani A, Bosetti C, La Vecchia C, Negri E, Barbone F, Talamini R, Franceschi S. Risk factors for breast cancer in nulliparous women. Br J Cancer 1999;79:1923–8.
17. Palmer JR, Rosenberg L, Rao RS, Zauber A, Strom BL, Warshauer ME, Stolley PD, Shapiro S. Induced and spontaneous abortion in relation to risk of breast cancer (United States). Cancer Causes Control 1997;8:841–9.
18. Davidson T. Abortion and breast cancer: a hard decision made harder. Lancet Oncol 2001;2:756–8.
19. Clavel-Chapelon F, E3N group. E3N, a French cohort study on cancer risk factors. Eur J Cancer Prev 1997;6:473–8.
20. Riboli E. Nutrition and cancer: background and rationale of the European prospective investigation into cancer and nutrition (EPIC). Ann Oncol 1992;3:783–91.
21. Commenges D, Letenneur L, Joly P, Alioum A, Dartigues JF. Modelling age-specific risk: application to dementia. Stat Med 1998;17:1973–88.
22. Clavel-Chapelon F, E3N group. Differential effects of reproductive factors on the risk of pre- and postmenopausal breast cancer. Results from a large cohort of French women. Br J Cancer 2002;86:723–7.
23. Clavel-Chapelon F, Gerber M. Reproductive factors and breast cancer risk. Do they differ according to age at diagnosis? Breast Cancer Res Treat 72:107–15.
24. Tang MT, Weiss NS, Daling JR, Malone KE. Case-control differences in the reliability of reporting a history of induced abortion. Am J Epidemiol 2000;151:1139–43.
25. Daling JR, Brinton LA, Voigt LF, Weiss NS, Coates RJ, Malone KE, Schoenberg JB, Gammon M. Risk of breast cancer among white women following induced abortion. Am J Epidemiol 1996;144:373–80.
26. Michels KB, Hsieh C-c, Trichopoulos D and Willett WC. Abortion and breast cancer risk in seven countries. Cancer Causes Control 1995;6:75– 82.
27. Hadjimichael OC, Boyle CA, Meigs JW. Abortion before first livebirth and risk of breast cancer. Br J Cancer 1986;53:281–4.
28. Calle EE, Mervis CA, Wingo PA, Thun MJ, Rodriguez C, Heath CW. Spontaneous abortion and risk of fatal breast cancer in a prospective cohort of United States women. Cancer Causes Control 1995;6:460–468.

29. Sellers TA, Potter JD, Severson JK, Bostnick RM, Nelson CL, Kushy LH, Folsom AR. Difficulty becoming pregnant and family history as interactive risk factors for post-menopausal breast cancer: the Iowa women's heath study. Cancer Causes Control 1993;4:21–8.
30. Watier L, Richardson S, Hemon D. Accounting for pregnancy dependence in epidemiologic studies of reproductive outcomes. Epidemiology 1997;8:629 –36.
31. Chaudru V, Laing A, Dunston GM, Adams-Campbell LL, Williams R, Lynch JJ, Leffall LD, DeWitty RL, Gause BL, Bonney GE, Demenais F. Interactions between genetic and reproductive factors inbreast cancer risk in a population-based sample of African-American families. Genet Epidemiol 2002;22:285–97.
32. Andrieu N, Clavel F, Gairard B, Piana L, Bremond A, Lansac J, Flamant R, Renaud R. Familial risk of breast cancer and abortion. Cancer Detect Prev 1994;18:51–5.
33. Melbye M, Wohlfahrt J, Andersen AM, Westergaard T, Andersen PK. Preterm delivery and risk of breast cancer. Br J Cancer 1999;80:609–13.
34. Hsieh CC, Wuu J, Lambe M, Trichopoulos D, Adami HO, Ekbom A. Delivery of premature newborns and maternal breast-cancer risk. Lancet 1999;353:1239.