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Fifteen-year results of a randomized phase III trial of fenretinide to prevent second breast cancer

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Purpose: The synthetic retinoid fenretinide administered for 5 years for prevention of second breast cancer showed no difference after a median of 8 years, but a possible reduction in premenopausal women. We conducted a long-term analysis in a subgroup of women who were regularly followed up in a single center.
Patients and methods: We analyzed data after a median follow-up of 14.6 years (IQ range, 12.3–16.3 years) from 1739 women aged 30–70 (872 in the fenretinide arm and 867 in the observation arm), representing 60% of the initial cohort of 2867 women. The main efficacy endpoint was second primary breast cancer (contralateral or ipsilateral).
Results: The number of second breast cancers was 168 in the fenretinide arm and 190 in the control arm (hazard ratio = 0.83, 95% CI, 0.67–1.03). There were 83 events in the fenretinide arm and 126 in the observation arm in premenopausal women (HR = 0.62, 95% CI, 0.46–0.83), and 85 and 64 events in postmenopausal women (HR = 1.23, 95% CI, 0.63–2.40). The younger were the women, the greater was the risk reduction associated with fenretinide, which attained 50% in women aged 40 years or younger and disappeared after age 55 (P-age*treatment interaction = 0.023). There was no difference in cancers in other organs, distant metastases or survival.
Conclusions: Fenretinide induces a significant risk reduction of second breast cancer in premenopausal women, which is remarkable at younger ages, and persists several years after treatment cessation. Since adverse events are limited, a trial in young women at high-risk is warranted.
Key words: breast neoplasms, chemoprevention, fenretinide, clinical trial

introduction

Cancer chemoprevention is the use of natural or synthetic agents to reverse or inhibit carcinogenesis at the preclinical stage [1–2]. Retinoids have been studied as chemopreventive agents due to their role in regulating cell growth, differentiation and apoptosis in preclinical models [3–4]. Fenretinide (N-(4-hydroxyphenyl) retinamide), a synthetic derivative of all-trans-retinoic acid, is active in inhibiting mammary carcinogenesis in animal models [5] and can selectively accumulate in human breast tissue [6–7]. This retinoid induces apoptosis *in vitro* [8] and has shown a favorable toxicity profile in clinical studies [9].

In March 1987, we initiated a phase-III trial to assess the efficacy of a 5-year treatment with fenretinide in reducing contralateral or second ipsilateral breast cancer in patients aged 30–70 years with early breast cancer, who had received no systemic treatment after primary treatment. A total of 2867 assessable patients completed the intervention period by July 1998. The main results of the study after 8 years showed no difference in contralateral or ipsilateral breast cancer, but a post-hoc analysis suggested a significant treatment interaction with menopausal status (or age), with a 35% reduction in premenopausal women (or women <50 years) and an opposite trend in postmenopausal women (or women >50 years) [10].

Here we present an updated analysis after a median of nearly 15 years in the subgroup of 1739 women who continued a regular clinical follow-up at the coordinating center.

patients and methods

patients and treatment

A detailed description of the study design and results has been reported previously [10]. Briefly, eligible patients were aged 30–70 years, had stage-I breast cancer (T1–T2 NO) or DCIS, and had received no adjuvant therapy. In the original cohort, approximately half of the eligible subjects were recruited immediately after completion of primary treatment (i.e., surgery with or without radiotherapy). The other half was selected from patients treated with surgery with or without radiotherapy within the previous 10 years, provided that they had no recurrence of cancer, based on the

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notion that the risk of contralateral breast cancer remains stable for at least 10 years after surgery [11–12]. Eligible patients were recruited from 10 centers.

Women were randomly assigned to receive either no treatment (observation) or fenretinide (R.W. Johnson PRI, Springhouse, PA), given orally at a dose of 200 mg/day for 5 years (two capsules at dinner). Since fenretinide treatment is associated with decreased plasma retinol levels [13], a monthly 3-day drug interruption was introduced to minimize diminished adaptation to darkness. Despite some obvious limitations, the use of placebo was not considered appropriate by the IRB because of the large capsule size and the long treatment duration. Treatment compliance by pill count was very high (median value 98%) and stable over time [10]. Serial measurements of plasma fenretinide, its main metabolite N-(4-methoxyphenyl) retinamide, and retinol levels were also obtained to ensure treatment compliance, using the methods previously described [13].

Until completion of the seventh year, when the primary endpoint was assessed, all patients underwent a biannual visit, including clinical examination and blood tests, a mammography and chest X-rays every year and a bone scan every 18 months, as previously described [14]. All tests were blinded to the allocated treatment arm.

follow-up continuation

Upon completion of the seventh year, only the 1739 participants followed at the coordinating center, Istituto Nazionale Tumori, Milan, could regularly be followed-up with the same clinical procedures until the tenth year and every 12 months thereafter. Subjects who had a recurrence were followed every 6 months. The Milan subgroup represents 60% of the whole study population. Information on the remaining 40% participants varied from site to site mainly because of budget limitations and was obtained irregularly until the tenth year. An effort to update disease status and survival from the majority of these subjects is underway.

study endpoints

The primary endpoint of the original study was contralateral breast cancer, and the co-primary endpoint was ipsilateral breast cancer reappearance, be it a recurrence in the same quadrant or a second primary cancer in different quadrants from the original tumor. The occurrence of distant metastasis and death were recorded, but they were not considered to be endpoints for efficacy inasmuch as fenretinide was not thought to be active on breast cancer dissemination.

statistical analysis

In the current analysis, the main efficacy endpoint comprised all second breast cancers regardless of breast origin, i.e., the sum of contralateral and ipsilateral breast cancers. This pooled analysis has recently been reported to assess the effect of tamoxifen after primary treatment of DCIS [15]. All events were included in the analysis, regardless of treatment duration and compliance levels, according to the intention-to-treat principle. The time to occurrence of a second breast cancer was computed from the date of randomization to the date when the diagnosis of the event was firstly made. Observations were censored at the time of second primary cancer in organs other than the breast, progression to distant sites, death without evidence of disease, whichever occurred first, or the date of the last follow-up assessment for the women who were event-free. Crude cumulative hazards curves of second breast cancer were estimated with the Kaplan-Meier method for descriptive purposes, and unadjusted comparisons between the curves were based on the log-rank test.

The Cox model was used to compare the hazard rates between arms while adjusting for the factors known to influence second breast cancer risk, i.e., menopausal status at randomization (pre versus post), type of surgery (quadrantectomy versus radical mastectomy), pT (≤2 cm versus >2 cm) and histology (lobular versus other). The treatment effect was also investigated by menopausal status, as reported in the original publication [10]. While this analysis was post-hoc, several pieces of evidence provided a plausible rationale for a different effect of fenretinide according to menopausal status or age, including the effect on circulating insulin-like growth factor-I (IGF-I) and its main binding protein IGFBP-3 [16]. The effect of the patient's current age on second breast cancers was also investigated by fitting a logistic model with the number of events within each year of the woman's age as the dependent variable (0 = no event; 1 = contralateral and/or ipsilateral breast cancer), and the corresponding age period as the predictor, through a four-knot-restricted cubic spline [17].

results

The current analysis was performed in January 2005 after a median observation of 14.6 years (interquartile range, 12.2–16.2). The main characteristics of the 1739 subjects of the present analysis are shown in Table 1. Compared with the original cohort, the current series showed a higher proportion of women who underwent breast conserving surgery (73.5% versus 62.6%) and entered the trial within a year from surgery (56.8% versus 49.1%). Mean ± SD (years) age was 51 ± 7.6 in the fenretinide arm and 51 ± 7.8 in the observation arm. Premenopausal and postmenopausal patients were equally represented.

second breast cancers

Table 2 shows the number of second breast cancer events in the two treatment arms by site (contralateral or ipsilateral breast cancer) and menopausal status. Overall, there were 168 events in the fenretinide arm versus 190 events in the control arm, accounting for a 17%, borderline statistically significant reduction in the retinoid arm (HR = 0.83, 95% CI, 0.67–1.03). When the analysis was stratified by menopausal status, the number of second breast cancers was 83 in the fenretinide arm versus 126 in the control arm in premenopausal women (HR = 0.62, 95% CI, 0.46–0.83), and 85 versus 64 in postmenopausal women (HR = 1.23, 95% CI, 0.63–2.40).

Figure 1 illustrates the cumulative hazard curves for all second breast cancer events (contralateral breast cancer and ipsilateral breast cancer) by treatment allocated arm. Compared with the observation arm, fenretinide showed a trend to a lower number of second breast neoplasms, which persists up to 15 years. The cumulative hazard curves for all types of second breast cancer stratified by menopausal status are shown in Figure 2. Fenretinide induced clear-cut reduction of second breast cancer compared with no treatment, with a durable benefit up to 15 years, i.e., well beyond the 5-year intervention period. Conversely, an opposite, albeit non-significant, trend was noted in postmenopausal women. As expected, the rate of events in the observation arm was much higher in premenopausal women than in postmenopausal women.

The cumulative hazard curves split for contralateral breast cancer and ipsilateral breast cancer are shown in Figure 3. In premenopausal women, fenretinide treatment exhibited a clear-cut reduction of both events compared with no treatment, which persisted up to 15 years, whereas an opposite, albeit unstable, trend was noted in postmenopausal women on both outcome measures.

Table 1. Baseline subject characteristics of the current series

	Fenretinide arm $n = 872$		Control arm $n = 867$	
Age				
30–35	7	0.8%	11	1.3%
36–40	64	7.3%	69	8.0%
41–45	129	14.8%	127	14.6%
46–50	213	24.4%	226	26.1%
51–55	188	21.6%	174	20.1%
56–60	144	16.5%	130	15.0%
61–65	116	13.3%	114	13.1%
66–70	11	1.3%	16	1.8%
Menopausal status				
Premenopause	420	48%	452	52%
Postmenopause	452	52%	415	48%
Primary tumor site				
Outer quadrant	550	63.1%	556	64.1%
Inner/central quadrant	321	36.8%	310	35.8%
Not reported	1	0.1%	1	0.1%
Primary tumor stage*				
pT1	622	71.3%	660	76.1%
pT2	188	21.6%	159	18.4%
pT1-pT2	14	1.6%	13	1.5%
pTX	37	4.2%	29	3.3%
PTis	11	1.3%	6	0.7%
Primary tumor treatment				
Conservative	652	75%	627	72%
Ablative	220	25%	240	28%
Histology				
Ductal infiltrating	509	58.4%	477	55.0%
Ductal with predominant intraductal component	54	6.2%	48	5.5%
Lobular infiltrating	136	15.6%	149	17.2%
Ductal+Lobular	42	4.8%	44	5.1%
Ductal+DCIS	50	5.7%	60	6.9%
Other	69	7.9%	83	9.6%
DCIS	11	1.3%	6	0.7%
Infiltrating NOS	1	0.1%	–	
Years from surgery to randomization				
<1	490	56.2%	497	57.3%
1–3	214	24.5%	238	27.5%
4–6	133	15.3%	91	10.5%
≥7	35	4.0%	41	4.7%

*International Union Against Cancer tumor-node-metastasis (TNM) classification.

The incidence (annual rate) of contralateral and ipsilateral breast cancers according to the participant's age by allocated arm is illustrated in Figure 4. The younger were the women, the greater was the effect of fenretinide, which tended to disappear after the age of 55 (Wald-P for age*treatment interaction = 0.023). At age 35, the model predicted a mean annual rate of 5.7% in the control arm versus 2.8% in the fenretinide arm, resulting in a 51% risk reduction. At age 40, the mean rate was 4.4% versus 2.3%, a 48% risk reduction.

Table 2. Number of second breast cancers by allocated arm and menopausal status

	Fenretinide ($n = 872$)	Control ($n = 867$)	Hazard ratio (95% CI)
All breast cancer events (contralateral and ipsilateral)			
Premenopausal women	83	126	0.62 (0.46–0.83)
Postmenopausal women	85	64	1.23 (0.63–2.40)
Total	168	190	0.83 (0.67–1.03)
Contralateral Breast Cancer			
Premenopausal women	26	43	0.63 (0.38–1.04)
Postmenopausal women	45	34	1.23 (0.41–3.71)
Total	71	77	0.90 (0.65–1.26)
Ipsilateral Breast Cancer Reappearance			
Premenopausal women	57	83	0.61 (0.43–0.87)
Postmenopausal women	40	32	1.16 (0.49–2.74)
Total	97	115	0.77 (0.58–1.02)

HR, hazard ratio and 95% CI, confidence interval, adjusted for menopausal status at randomization (pre versus post), type of surgery of the primary tumor (quadrantectomy versus mastectomy), pathologic tumor size (≤2 cm versus >2 cm) and histology (lobular versus other). Contralateral and ipsilateral breast cancer do not add up since some patients had both type of events as first recurrence.

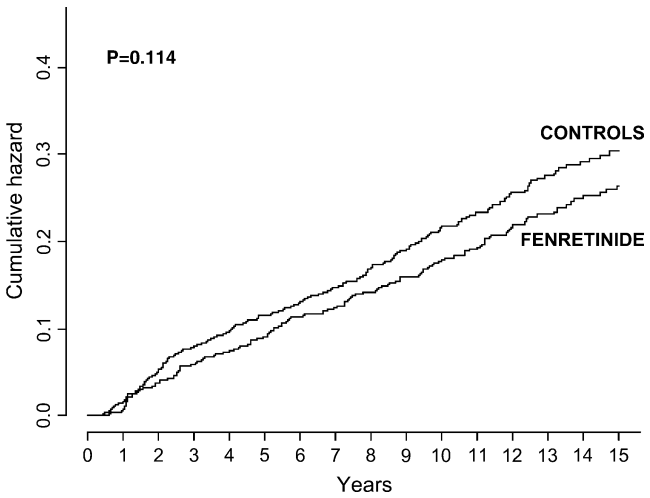

Figure 1. Cumulative hazard curves for all second breast cancers (contralateral and ipsilateral) by treatment allocated arm.

distant metastases

A total of 254 of the 1739 evaluable patients developed distant metastases, without differences between arms: 129 events on fenretinide versus 125 on observation. Two patients also accounted for contralateral breast cancer on fenretinide, and one patient also accounted for ipsilateral breast cancer on observation. No difference was detected by menopausal status either (data not shown).

new primary tumors other than breast

The number of second primary tumors in organs other than the breast was 50 in the fenretinide arm and 52 in the control

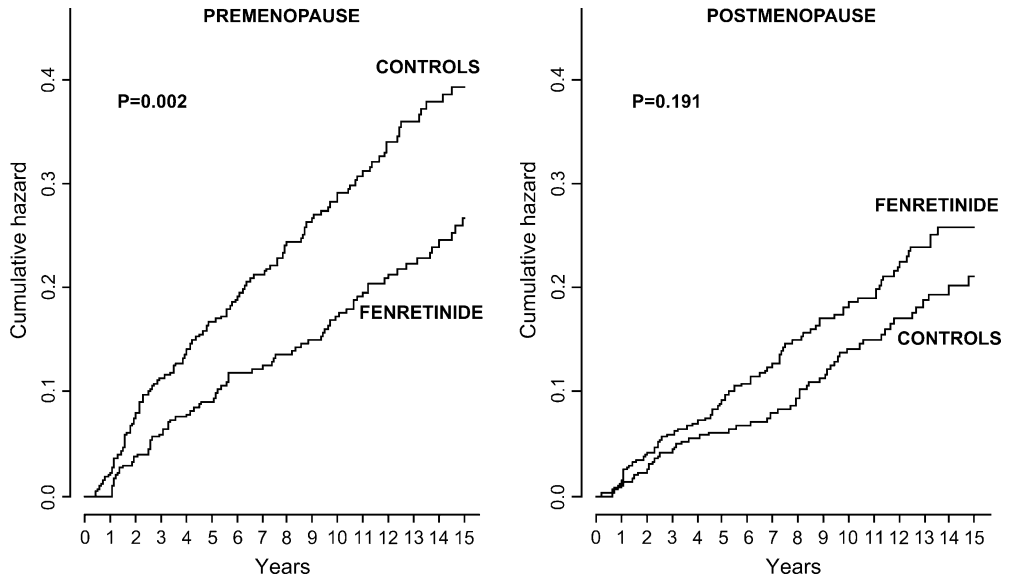

Figure 2. Cumulative hazard curves for all second breast cancers (contralateral and ipsilateral) by allocated arm, stratified for premenopausal women (left panel) and postmenopausal women (right panel).

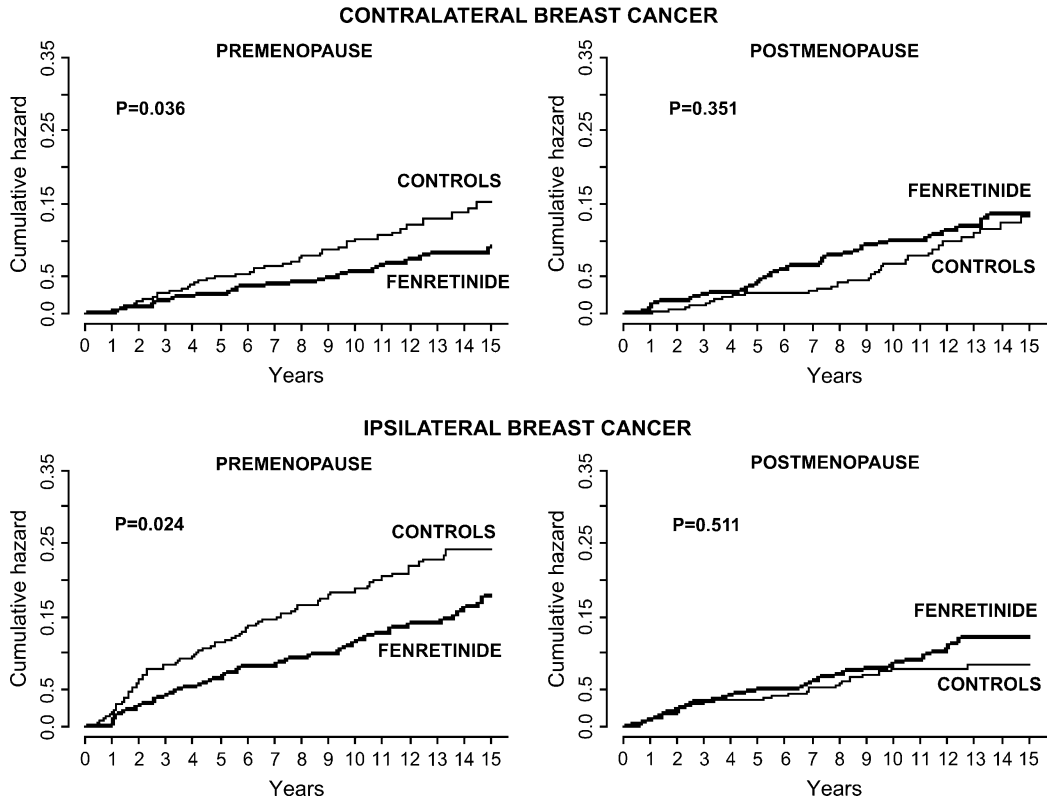

Figure 3. Cumulative hazard curves for contralateral breast cancer (upper panel) and ipsilateral breast cancer (lower panel) by allocated arm, stratified for premenopausal women (left panel) and postmenopausal women (right panel).

arm, without remarkable differences by site (Table 3). The highest number was observed in the lung and the ovary. Although there was a similar number of lung cancers in the fenretinide arm ($n = 9$, eight of which occurred after treatment completion) and the control group ($n = 7$), there were five cases of small cell lung cancers on fenretinide and only 1 case on observation. The overall incidence of ovarian cancer was similar in the two groups. As previously reported [18], however, all ovarian cancers in the fenretinide arm occurred after treatment completion.

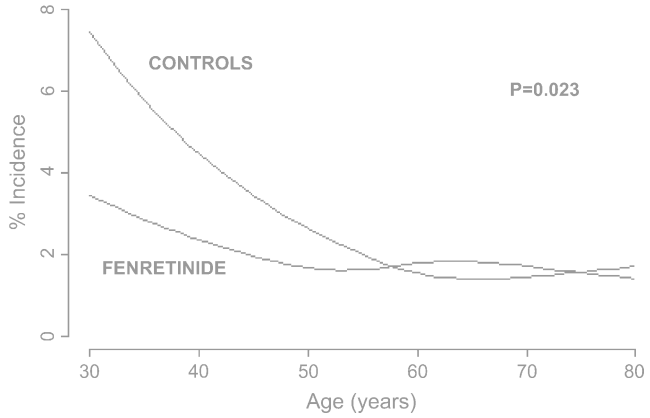

Figure 4. Incidence (% annual rate) of contralateral and ipsilateral breast cancer according to participant's age by treatment allocated arm.

Table 3. Number of second primary tumors in organs other than the breast

Second primary tumors	Fenretinide (n = 872)			Control (n = 867)
	Total	On treatment	Off treatment	Total
Lung	9	1	8	7
Ovary	8	–	8	7
Bowel	4	2	2	6
Kidney	5	4	1	4
Stomach	3	–	3	4
Pancreas	2	1	1	3
Leukemia	1	1	–	4
Endometrium	4	1	3	3
Melanoma	–	–	–	3
Lymphoma	1	–	1	2
Esophagus	1	–	1	2
Cervix	2	–	2	1
Gall bladder	2	1	1	–
Bladder	2	1	1	–
Brain	1	–	1	1
Thyroid	1	–	1	1
Skin	2	–	2	–
Bone – Soft tissue Sarcoma	2	–	2	1
Liver	–	–	–	1
Oral cavity	–	–	–	1
Parotid gland	–	–	–	1
Total	50	12	38	52
Cumulative patient-years of observation	10809	3425	7384	10769

overall mortality

No difference was observed in all-cause mortality between arms. Out of 872 evaluable patients in the fenretinide group, 705 are alive (81%) and 167 are dead (19%), versus 702 (81%) and 165 (19%) of 867 evaluable patients in the control group.

discussion

The aim of this trial was to determine the efficacy of fenretinide in reducing second breast cancer incidence, be it contralateral or ipsilateral, in women with early breast cancer. Because reduction of second breast cancer is a surrogate marker of primary prevention [19], a favorable effect of fenretinide would provide strong rationale for a primary prevention trial in unaffected women at high-risk for breast cancer.

The results of the present analysis in the subgroup of 1739 participants who were regularly followed-up for up to 15 years in a single center indicate that fenretinide induced a 17%, durable reduction of second breast cancer incidence, which approached statistical significance. Moreover, when the analysis was stratified by menopausal status, there was a 38%, statistically significant reduction of second breast cancers in premenopausal women. Importantly, the protective effect persisted for up to 15 years, i.e., 10 years after retinoid cessation. Most notably, the younger were the women, the greater was the benefit of fenretinide, which was associated with a remarkable 50% risk reduction in women aged 40 years or younger, whereas the benefit disappeared after age 55.

Admittedly, our results are limited to a subject subgroup followed in a single center, representing 60% of the original cohort. The subgroup differed slightly from the original cohort as proportionally more women underwent breast conserving surgery and were enrolled within a year from surgery. However, these factors, which are associated with a higher rate of ipsilateral breast cancer and distant metastases, were evenly balanced between arms and were accounted for in the multivariate analysis. Moreover, randomization was stratified by center, and no significant heterogeneity across centers was evident in the initial results [10]. Finally, one strength of the current study is that all women underwent a regular clinical follow-up with uniform procedures in a single center. It is therefore likely that the current results would not change in the whole study population.

The current analysis confirms and further extends the notion that the protective effect of fenretinide occurs exclusively in premenopausal women or women aged 55 or younger. Importantly, this subgroup analysis had not been foreseen when the study was planned. While there are plausible biological explanations for this selective effect, our findings are hypothesis-generating and do not have practical clinical implications, but provide the rationale for a new trial in young women at high-risk for breast cancer.

One explanation for the different effects of fenretinide according to menopausal status or age is a different modulation of circulating IGF-I in premenopausal and postmenopausal women, with a reduction of IGF-I levels only in premenopausal subjects [16]. Since there is an association between high circulating IGF-I or low IGFBP-3 levels and risk of second breast cancer [20], the modulation of the IGF system may at least in part explain the selective effect of fenretinide in premenopausal women. However, a validation study showed that the changes of these biomarkers explained only a limited proportion of the clinical effect of fenretinide [20].

Interestingly, the different effect of fenretinide according to age recalls the effect of first full term pregnancy on breast cancer risk, which is protective at a young age and deleterious at an older age. In animals, this protection can be mimicked by short-term exposure to physiological doses of estrogen and progesterone [21], with p53 and TGF-β as potential mediators

of this protective effect [22]. Using a whole organ culture system, fenretinide, at variance with natural retinoids, worked additively with ovarian hormones to induce apoptosis in ductal epithelial cells in response to DNA damage caused by gamma-radiation. This effect, which was partially dependent on p53 and TGF-β, suggests a sensitizing effect of steroid hormones on fenretinide-induced apoptosis [23]. Thus, fenretinide might enhance the protective or deleterious effects of hormones on breast carcinogenesis depending on the stage (age) of the breast gland development. In mice, fenretinide suppressed spontaneous mammary tumors in 2-month-old nulliparous mice, whereas it was not effective in 4–6-month-old multiparous mice [24]. Likewise, the efficacy of retinoids on mammary carcinogenesis in the rat was inversely related to the delay of carcinogen administration [25]. Therefore, age is a key issue for the effect of fenretinide on mammary tumor development. Because aging is associated with impaired p53 activity in the mammary gland, thus rendering it more susceptible to cumulative DNA damage and cancer, a retinoid intervention early in life may potentiate the protective effect of hormones on mammary gland carcinogenesis whereas a late intervention might even promote it.

An important finding of the present study is the persistence of fenretinide efficacy at 15 years, i.e., 10 years after completion of the retinoid intervention, which suggests the attainment of drug-induced apoptosis in the breast epithelial gland. Apoptosis is the main mechanism of *in vitro* cell growth inhibition induced by fenretinide through different mechanisms, including ceramide production and induction of reactive oxygen species, mostly at concentrations >5 μM [26]. While the plasma concentration attained with 200 mg/day is approximately 1 μM, a selective drug accumulation in the breast with adequate inhibitory and apoptotic concentrations has been described in clinical studies [7, 27]. Mammary glands from fenretinide-fed rats showed a dose-dependent decrease in ductal branching and end-bud proliferation relative to control glands [5, 28]. Similarly to the mammary gland of fenretinide-treated rats, the protective effect of fenretinide in young, premenopausal women might be due to a reduction of breast cells at-risk for transformation. Another possible factor accounting for the age-dependent activity of fenretinide may be a hormone mediated mechanism. In the rat, particularly at young age, fenretinide decreases circulating estradiol and particularly progesterone levels [28]. Unfortunately, in our study we have not measured circulating hormone levels in premenopausal women, so a direct hormonal effect cannot be excluded.

In contrast to tamoxifen, which inhibits only ER-positive tumors [19], fenretinide induces apoptosis both in ER-positive and in ER-negative breast cancer cell lines, although it is more effective in ER positive cells [29]. Interestingly, we have previously shown that fenretinide reduced second tumors in premenopausal women irrespective of the hormone receptor expression of the primary cancer [30], providing the rationale for a combination intervention with a SERM. A biomarker trial of fenretinide and low-dose tamoxifen in premenopausal women at high risk is currently underway [31].

When considering the protective activity of fenretinide on second breast cancer in young women and a similar trend on ovarian cancer, at least during intervention [18], it appears that women with germline BRCA-1 and 2 mutations should be ideal candidates for further investigation of this retinoid. Indeed, fenretinide was highly-effective in inhibiting the growth of BRCA-1 mutated breast cancer cell lines [32].

Although a precise assessment of adverse events is hampered by the lack of placebo, our previous reports showed that the toxicity of fenretinide is manageable, with a nearly 20% cumulative incidence of diminished dark-adaptation and dermatological disorders, mostly of mild grade, as the most frequent adverse events, and only a 4.4% drop-out rate [33]. Like other retinoids, fenretinide may be teratogenic, although available studies show no genotoxic effects *in vitro* and *in vivo* [34, 35], and a lack of storage in the human embryo [36]. Thus, appropriate measures of contraception should be adopted when treating potentially fertile women. This potential toxicity remains an important issue when planning a future trial in young women at high risk.

In conclusion, the 15-year analysis of the Milan subgroup of the phase III trial of fenretinide shows a 17%, borderline significant reduction of second breast cancer associated with the retinoid. Most importantly, the risk reduction is of the order of 50% in women aged 40 or younger, and persists for 10 years after retinoid cessation. As side effects are limited, fenretinide should be investigated further for prevention of breast cancer in young women at high-risk.

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