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Original article

Pathological features and survival outcomes of very young patients with early breast cancer: How much is “very young”?

Giuseppe Cancello [a, *], Patrick Maisonneuve [b], Manuelita Mazza [a], Emilia Montagna [a], Nicole Rotmensz [b], Giuseppe Viale [c, d], Giancarlo Pruneri [c, d], Paolo Veronesi [d, e], Alberto Luini [e], Oreste Gentilini [e], Aron Goldhirsch [a], Marco Colleoni [a]

[a] Division of Medical Senology, Department of Medicine, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
[b] Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy
[c] Division of Pathology, European Institute of Oncology, Italy
[d] University of Milan School of Medicine, Milan, Italy
[e] Division of Senology, European Institute of Oncology, Milan, Italy

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ABSTRACT

We collected information on 497 consecutive breast cancer patients aged less than 35 years operated at the European Institute of Oncology. The main aim of the study is to compare biological and clinical features dividing the population by age: <25 years, 25–29 and 30–34 years old. Pattern of recurrence and survival were also analyzed.

Patients aged <25 years had 81.8% poorly differentiated tumors compared with 66.7% and 56.5% in the 25–29 and 30-34 groups, respectively; no other significant difference were found in the distribution of clinical and immunohistochemical features The distribution of Luminal A and B, Triple Negative and HER2 subtypes (immunohistochemically defined) was not statistically different among the three age groups. No difference was found in the incidence of loco-regional relapses, distant metastases, disease-free survival ($p = 0.79$) and overall survival ($p = 0.99$) between the three age groups. This latter findings was confirmed using age as a continuous variable assuming a linear association between age and the outcomes considered, too.

In conclusion, our data indicate that the group of patients with breast cancer below 35 years is essentially a homogenous group when classical clinical and immunohistochemical features were considered.

Introduction

Breast cancer in young age is a topic issue in oncology for many reasons. First, the sharp increase in the number of breast cancers diagnosed in pre-menopausal women reported in several countries over the last years [1,2]. Moreover, the management of breast cancer in young patients (<35 or <40 years) solicits an integrated approach taking into account relevant issues such as fertility preservation and pregnancy.

Some old and historical studies but also more recent analyses used cut-off of 40 years or the cut-off of 35 years to define a woman with breast cancer “young” or “very young”. In all these cases they found that young patients (below 35 or 40 years) had a different pattern of recurrence with an increased risk of death and more aggressive clinical and tumor biological characteristics if compared to the older women [3–11].

In a previous recent publication we evaluated biological and clinical features and pattern of recurrence of two groups of young patients (below 35 years and 35–50 aged) with early breast cancer; we analyzed data according to an immunohistochemical classification in four subtypes.

We found that very young patients (below 35 years) with Triple Negative, Luminal B, or HER2-positive breast cancer have a worse prognosis when compared with older patients with similar characteristics of disease [12].

However the choice of a cut-off of age to define a limit for a different clinical and biological behavior may be arbitrary particularly because the biological, hormonal and environmental milieu modeling tumor biology, is continuously modifying during lifetime. Moreover, it is still unclear whether young age as prognostic factor

* Corresponding author. Tel.: +39 02 57489502; fax: +39 02 574829212.
E-mail address: giuseppe.cancello@ieo.it (G. Cancello).

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represents a continuous variable or it may be an inherent characteristic of wider subgroups, i.e. premenopausal (less than 50 years) or very young patients (below 35 years) [13–15].

By now we updated our previous information about very young patients with breast cancer and decided to evaluate three subgroups of patients according to three different age ranges, below 25 years, 25–29 years and 30–34 years.

Aim of our study was to analyze biological and clinical features and pattern of recurrence and survival of these three age-groups of very young patients (below 35 years) with early breast cancer.

The reason to select 3 specific age groups can be seen as arbitrary. However the choice to define a priori categorical variables is in general considered easily acceptable by the physicians.

Moreover some previous analyses have already provided results according to age strata (13, 15).

Nonetheless no studies have evaluated both the clinical/biological features and relapse and survival of different strata of very young women with early breast cancer.

Nevertheless we performed an analysis using age as continuous variable to verify and confirm the results about outcome considered, too.

Patients and methods

We extracted information from our prospectively collected institutional database on all consecutive breast cancer patients operated at the European Institute of Oncology (EIO) between January 1995 and December 2006.

Data on the patient's medical history, concurrent diseases, type of surgery, pathological evaluation, and results of staging procedures were available for all patients. Pathological assessment included evaluation of the primary tumor size, histological type and of lymph nodes status including a sentinel node biopsy [16], when applicable. Tumor grade was evaluated according to Elston and Ellis [17] and peritumoral vascular invasion (PVI) was assessed according to Rosen [18]. Estrogen (ER) and progesterone receptor (PgR) status, Ki-67 labeling index (assessed with the MIB 1 monoclonal antibody), and HER2/neu over-expression were evaluated immunohistochemically as previously reported [19]. The threshold for ER and PgR positivity was 1% [18,20,21]. Moreover we used an immunohistochemical classification to define different subtypes of tumors as follows: Luminal A (ER > 0 or PgR > 0) and (Ki-67 < 14%) and (HER2 0/+/++), Luminal B (ER > 0 or PgR > 0) and (Ki-67 ≥ 14%) and/or (HER2 +++), HER2-positive (ER = 0 and PgR = 0) and (HER2 +++), and Triple Negative (ER = 0 and PgR = 0) and (HER2 0/+/++) [12,22,23].

Statistical analysis

The Fisher exact test and the Mantel–Haenszel Chi–Square test for trend were used to assess the association between categorical and ordinal variables, respectively.

The primary endpoints were the incidence of locoregional relapse (LRR), distant metastasis (DM), breast cancer related events (BCE), disease-free survival (DFS) and overall survival (OS). DFS was defined as the length of time from the date of surgery to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. OS was determined as the time from surgery until the date of death (from any cause) or the date of last follow-up. Cumulative incidence and survival plots according to age were drawn using the Kaplan–Meier method. The log-rank test was used to assess the survival difference between strata.

Table 1
Characteristics of breast cancer patients according to age at diagnosis.

	All patients	Age at diagnosis			*P* value (trend)
		<25	25–29	30–34	
All	497	22	123	352	
Histology					
Ductal	456	21	118	317	0.46
Lobular	7	0	1	6	
Ductal + lobular	7	0	0	7	
Other	27	1	4	22	
Tumor size					
≤1 cm	58	4	9	45	0.005 (0.06)
1–2 cm	190	6	34	150	
2–4 cm	188	8	64	116	
>4 cm	51	3	14	34	
Unknown	10				
Tumor grade					
G1	33	0	3	30	0.01 (0.0007)
G2	154	3	36	115	
G3	299	18 (81.8%)	82 (66.7%)	199 (56.5%)	
Unknown					
Number of positive nodes					
None	229	9	63	157	0.75 (0.28)
1-3	174	10	41	123	
4-9	51	2	10	39	
10 or more	43	1	9	33	
PVI					
Absent	286	15	71	200	0.59 (0.38)
Present	208	7	51	150	
Unknown	3				
ER					
Absent	126	4	41	81	0.06 (0.36)
Present	371	18	82	271	
PgR					
Absent	175	6	51	118	0.21 (0.65)
Present	322	16	72	234	
CA153					
Absent	268	12	56	20	0.04 (0.06)
Present	152	8	48	96	
Unknown	77				
Ki67					
<14%	48	2	4	42	0.04 (0.02)
14–30%	188	6	47	135	
>30%	260	14 (63.6%)	72 (58.5%)	174 (49.4%)	
Unknown	1				
Her2/Neu					
0/+/++	341	18	78	250	0.15 (0.70)
+++	102	3	32	67	
Unknown	49				
IHC classification					
Luminal A	38	2	3	33	0.06 (0.36)
Luminal B	336	17	80	239	
HER2	29	0	11	18	
Triple negative	94	3	29	62	
Surgery					
Quadrantectomy	345	15	81	249	0.59 (0.44)
Mastectomy	152	7	42	103	

We performed an analysis using age as a continuous variable assuming a linear association between outcomes/endpoints considered and age with a univariate and multivariate analysis.

All analyses were performed with the SAS software, version 8.2 (Cary, NC).

Results

We selected female patients, aged less 35 years (770 patients) presenting with a diagnosis of primary breast cancer.

We excluded patients having had a previous cancer at another site (14 patients), patients receiving neoadjuvant treatment (167 patients), metastatic disease at surgery (20 patients) and presentation with bilateral breast cancer (6 patients).

Table 2a
Adjuvant treatment modalities in breast cancer patients according to age at diagnosis and IHC classification.

	Luminal A				Luminal B			
	<25	25–29	30–34	*P*-value[a]	<25	25–29	30–34	*P*-value[a]
ALL	2	3	33		17	80	239	
Hormonotherapy	*N* (%)	*N* (%)	*N* (%)	0.40	*N* (%)	*N* (%)	*N* (%)	0.70
None	1	0	2		1	8	12	
TAM alone	0	0	2		0	3	9	
LHRH alone	0	1	2		2	10	29	
TAM + LHRH	1	2	26		13	58	175	
Other/NOS	0	0	1		1	1	13	
Chemiotherapy								
None	1	2	25	0.69	4	17	67	0.46
Antracycline	1	1	8		11	45	127	
CMF	0	0	0		2	5	18	
Other/NOS	0	0	0		0	13	26	

[a] Fisher's exact test; NOS: Not otherwise specified; IHC: immunohistochemical.

Finally we excluded from the analysis patients not having full immunohistochemical information allowing IHC classification (66 patients).

As far as FISH is concerned, on 103 HER2++, 31 were Fished, and 2 showed amplification. The others were not "fished" because the diagnosis for this cases were made in the last years of 1990's, when there was no therapy available and the role of HER2 was not completely clear and routinely defined. According to the results of FISH test in other cases, we expected a relatively low rate of amplification (5–10%) also in the other HER2++ cases. So we presumed that the missed few cases with FISH amplification couldn't significantly modify the distribution of breast cancer subtypes in the three age-groups.

We selected 497 premenopausal breast cancer patients aged <35 years.

The number and characteristics of evaluable patients are given in Table 1

Patients aged <25 years showed a higher percentage of T1a,b,mic tumors (18%) compared to other two subgroups, but this feature was balanced by an also higher percentage of tumors >4 cm (13.6%) in the youngest patients; no significant difference was found among the subgroups for the nodal status.

Patients aged <25 years had 81.8% poorer differentiated tumors compared to 66.7% and 56.5% of the 25–29 and 30–34 group, respectively. The group <25 years had also tumors with higher ki-67 (with labeling index more than 30%) compared with the other two age subgroups below 35 years. However, no significant difference was found among the three age-strata in the distribution of ki-67 when the cut-off of 14% was considered.

We found a higher percentage of Luminal B subtype breast cancer in the youngest patients than the other two subgroups; in the same age-subgroup no cases of HER2 subtypes breast cancer were found.

However our analysis didn't show a statistical significant different distribution of the four immunohistochemical-defined subtypes among the three age groups.

Analysis of adjuvant treatment received didn't show any statistical significant difference in the distribution of the chemotherapy regimens and hormonal therapies among the three patients groups (Tables 2a and 2bb).

Median follow-up was 5.7 years for DFS and 6.8 years for OS.

No difference in LRR, DM and contralateral breast cancer were found; also DFS ($p = 0.79$) and OS ($p = 0.99$) were the same in the three age groups of very young breast cancer patients (Fig. 1).

We performed an analysis using age as a continuous variable assuming a linear association between age and the outcomes considered. In the supplementary table are depicted the HRs at univariate analysis for 1 year age increase (Supplementary Table).

No association between age and any of the outcomes considered was observed when we considered age as a continuous variable instead of a categorical variable. There is no association after further adjustments for different clinical and biological parameters, too (*data not shown*).

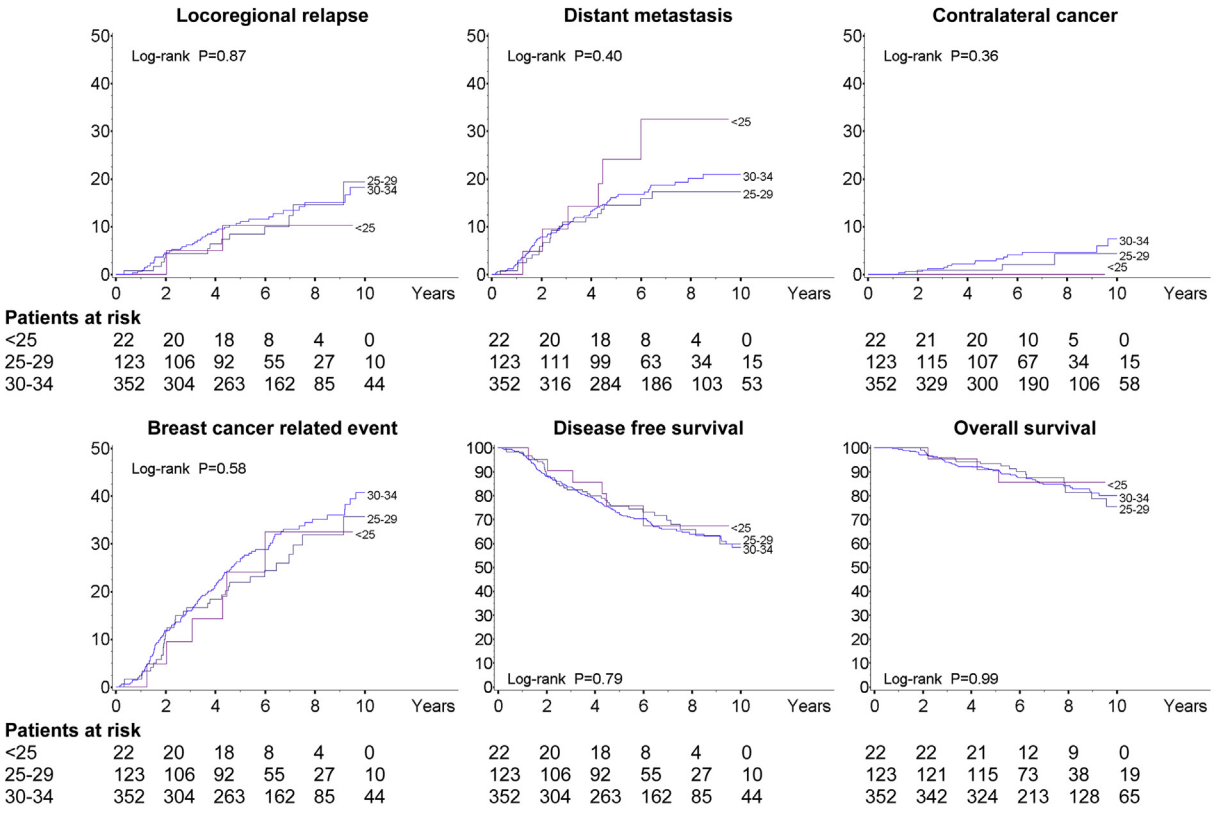
Discussion

A lot of studies evaluated biological behavior and risk of relapse and death in young breast cancer patients. Nonetheless no studies

Table 2b
Adjuvant treatment modalities in breast cancer patients according to age at diagnosis and IHC classification.

	HER2				Triple negative			
	<25	25–29	30–34	*P*-value[a]	<25	25–29	30–34	*P*-value[a]
ALL	0	11	18		3	29	62	
Hormonotherapy	*N* (%)	*N* (%)	*N* (%)	0.25	*N* (%)	*N* (%)	*N* (%)	0.62
None	–	11	16		3	22	55	
TAM alone	–	0	0		0	1	1	
LHRH alone	–	0	0		0	6	5	
TAM + LHRH	–	0	2		0	0	0	
Other/NOS	–	0	0		0	0	1	
Chemiotherapy								
None	–	1	1	0.68	0	2	2	0.80
Antracycline	–	6	8		2	17	33	
CMF	–	0	2		1	9	19	
Other/NOS	–	4	7		0	1	8	

[a] Fisher's exact test; NOS: Not otherwise specified; IHC: immunohistochemical.



Age group	Patients	Locoregional relapse	Distant metastasis	Contralateral cancer	Breast cancer related event	Disease free survival	Overall survival
Years	N	N (rate/100-yr)	N (rate/100-yr)	N (rate/100-yr)	N (rate/100-yr)	N (rate/100-yr)	N (rate/100-yr)
<25	22	2 (1.6)	6 (4.9)	0 (0.0)	6 (4.9)	6 (4.9)	3 (2.0)
25-29	123	13 (1.8)	19 (2.4)	3 (0.4)	33 (4.6)	37 (5.2)	19 (2.2)
30-34	352	43 (2.1)	63 (2.8)	17 (0.7)	116 (5.6)	119 (5.7)	56 (2.2)

Fig. 1. Survivals and cumulative incidence of local and distant recurrences of young patients (below 35 years) according to different age-strata.

have evaluated both the clinical/biological features and relapse and survival of different strata of very young women with early breast cancer.

One old study evaluated biological and clinical features of a small sample of young patients, considering for analysis different age strata between 26 and 44 years compared with a control group of carcinomas from women in the 50–67 years age group [3]. Authors didn't find any difference in distribution of biological markers, including grade of differentiation, proliferation, oestrogen/progesterone and c-erbB2 status, between the groups of 26–29 and 30–34 years. The work of Walker et al. didn't consider the age-strata of patients less than 25 years [3].

In a smaller recent study Collins et al. evaluated the distribution of some biological features and immunophenotypes among the three age groups (≤30, 31–35, and 36–40 years) of breast cancer patients. There were no significant differences in molecular phenotype, tumor stage or grade among the different age groups of young women; so authors conclude that the very youngs (≤30 years) do not appear to have poorer prognostic features compared to young women ≤40 years with breast cancer [24].

At variance with these data, our analysis carried out in a larger patients' cohort showed that the group of youngest patients, aged below 25 years, were characterized by a higher prevalence of poorly differentiated and highly proliferating tumors. Interestingly, these unfavorable markers also showed a linear correlation with younger age in the groups analyzed. However, no significant difference was found among the three age-strata in the distribution of ki-67 when the cut-off of 14% was considered.

In a previous recent publication we evaluated and compared two large groups of young patients, the group of 35–50 years and the group below 35 years. We showed that, according to the immunohistochemical classification, in the group of patients aged <35 years there were less tumors identified as Luminal A (9.2% vs.21.2%) and more Triple Negative tumors (16.2% vs. 7.5%; $p < 0.0001$) than in older patients [12].

In the present analysis instead, we didn't showed a significant different distribution of immunohistochemical subtypes of breast cancer between the three age groups; also if the number are low to definitive conclusions about the prevalence of IHC subtypes, these results are consistent with the same distribution of ER and PgR status and HER2 expression among the three age-strata.

In the work of Collins et al. the most frequent subtype in all age subgroups was the Luminal B (ranging from 32 to 41%). In our work the proportion of Luminal B subtypes was more higher than in the work of Collins, ranging from 65% to 77%; these our data are in line with the previous our publication [12] in which we found the same proportion of Luminal B subtype both in the group <35 years and in the older group aged 35–50 years, about 69 and 67% of cases,

respectively. The apparent discrepancy between the work of Collins and this our analysis could be partially explained with the different definition of Luminal B used in the two works. Collins et al. used grade and not Ki-67 as factor to differentiate Luminal A from Luminal B.

More in general, the proportion of ER+ tumors in our series is apparently higher than the percentage reported in published literature (ranging from 44% to about 60–65%) [9,11,13,22]; however the relevant data is the comparison with the percentage reported for patients age >35 years. In this our analysis the percentage of ER+ tumors (74%) is in line to data reported in our previous analysis; in our previous work [10] in fact, the percentage of ER + tumors (77%) in patients <35 years was statistically significant different from the 87% found in patients aged 35–50.

One of the first and large published studies focused on young breast cancer patients showed that younger patients had significantly lower survival rates and higher local and distant relapse rates than older patients. Moreover the study found that the hazard rate of relapse decreased over time in the youngest age group (≤33) to reach that of older patients after 5 years and the relation between the hazard of recurrence and age was continuous indicating a 4% decrease in recurrence for every year of age [14].

Recent large Korean series analyzed data on breast cancer patients aged <50 years who entered the Korean Breast Cancer Society Registration Program between 1992 and 2001. The authors compared OS among four age groups. In the Korean analysis patients in the group of age <30 years showed a worse survival outcome than patients aged 30–34; former group showed a reduced survival compared to group of 35–39 years but the survival rates of 35–39 group and 40–50 years patients did not differ significantly. In patients aged <35 years, the risk of death rose by 5% for every 1-year reduction in age, whereas there was no significant change in death risk with age in patients aged 35–50 years [15]. These results are in contrast with the study of de la Rochefordiere [14], in which authors showed that the relationship between recurrence hazard and age was continuous for every year of increase in age.

Our results are not completely overlapping with the results of Korean analysis. We didn't found in fact a significant difference in pattern of recurrence and survival decreasing the age of patients below 35 years, when the sample was divided in three age-groups but also when we considered age as a continuous variable instead of a categorical variable. So, even if the number of patients and events are low, in particular in the group of youngest women, our data question on the continuous reduction of survival with the progressive diminution of age. In addition these data would indicate that the group of very young patients (aged <35 years) is essentially a homogenous group, according to clinical and immunohistochemical parameters.

Anders et al. evaluated prognosis, clinicpathologic variables and performed mRNA and gene set analysis in two age-cohorts (≤45years ≥ 65 years). They found that age younger than 40 years conferred an inferior DFS when compared with age of 40–45 years at breast cancer diagnosis Further exploration of prognosis among patients age younger than 40 years revealed no significant differences in DFS between age groups younger than 30, 30–34, and 35–39 years. However in this study, the few numbers of cases in the subgroups age less than 40 years without any reference to adjuvant treatment received from different institution, reduce the reliability of survival results. Interestingly, in the same study the Authors founded 367 significant gene sets among young women's tumors that specifically distinguished them from tumors arising in older women, so concluding that breast cancer arising in young women is a unique biologic entity driven by unifying oncogenic signaling pathways [25].

However after some years same authors chose to reanalyze their previous data set to evaluate the relationship between age and breast cancer subtype, and to account for potential confounding variables not previously included. When correcting for significant clinic-pathologic features (i.e. subtypes, sample source, histologic grade) no gene differences were retained between age-defined groups in two different data sets [26].

More recently, a comprehensive analysis was conducted to clarify the relevance of several published prognostic gene signatures in young women (≤40) and to determine whether young age is truly associated with unique disease biology. Authors identified a total of 41 genes and 13 gene sets as potential candidate age-related genes and pathways aberrations reported in previous literature data. Within a cohort, of untreated patients the expression of 16 genes and gene sets were found to be significantly age dependent after adjustment. The common themes associated with young age were enrichment of biological processes related to immature mammary cell populations (RANKL, c-kit, BRCA1-mutated phenotype, mammary stem cells, and luminal progenitors cells), and growth factor signaling [mitogen—activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)-related] [27].

However the gene-signature analyses showed contradictory results, on the one hand showing that age alone does not appear to provide an additional layer of biologic complexity above that of breast cancer subtype and grade, on the other hand suggesting that breast cancer arising at a young age is biologically distinct beyond subtype distribution and is enriched with unique molecular processes [26,27]. Our study have some limitations typical of the retrospective character of the analysis, apart from a limited number of cases in the group of the youngest patients. Nevertheless the data were stored in an only one institution with a homogenous testing of biological markers and collection of clinical information, so increasing the reliability of comparison of clinical and biological features and of pattern of recurrence and survival.

Conclusion

In conclusion, our study showed that distinct age-strata of patients below 35 years didn't differ for pattern of recurrence and survival; no difference in the distribution of clinical and biological features were found in the various age subgroups, apart from tumor grade.

Our data indicate that the group of patients with breast cancer below 35 years is essentially a homogenous group when classical clinical and immunohistochemical features were considered.

Nevertheless the biology driving the disease process in young women has still largely unknown. The subset of very young patients merit further studies to better understand the biologic complexity driving breast cancer arising at a young age so to provide superior and tailored therapeutic options.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.breast.2013.08.006.

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