RESEARCH COMMUNICATION

Reproductive Variables and Risk of Breast Malignant and Benign Tumours in Yunnan Province, China

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Abstract

Introduction and aim: To compare reproductive factor influence on patients with pathological diagnosed malignant and benign tumor in the Breast Department, The First Peoples' Hospital of Kunming in Yunnan province, China. Methods: A hospital-based case-control study was conducted on 263 breast cancer (BC) cases and 457 non-breast cancer controls from 2009 to 2011. The cases and controls information on demographics, medical history, and reproductive characteristics variables were collected using a self-administered questionnaire and routine medical records. Histology of breast cancer tissue and benign breast lesion were documented by pathology reports. Since some variables in data analysis had zero count in at least one category, binomial-response GLM using the bias-reduction method was applied to estimate OR's and their 95% confidence intervals (95% CI). To adjust for age and menopause status, a compound variable comprising age and menopausal status was retained in the statistical models. Results: multivariate model analysis revealed significant independent positive associations of BC with short menstrual cycle, old age at first live birth, never breastfeeding, history of oral contraception experience, increased number of abortion, postmenopausal status, and nulliparity. Categorised by age and menopausal status, perimenopausal women had about 3-fold and postmenopausal women had more than 5-fold increased risk of BC compared to premenopausal women. Discussion and Conclusion: This study has confirmed the significant association of BC and estrogen related risk factors of breast cancer including longer menstrual cycle, older age of first live birth, never breastfeeding, nulliparity, and number of abortions more than one. The findings suggest that female hormonal factors, especially the trend of menopause status play a significant role in the development of BC in Yunnan women

Keywords: Risk factor - breast cancer - case control - Yunnan - China

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Introduction

Globally, cervix uteri and breast cancers (BC) in women were the commonest incident forms of cancer by a considerable margin. Breast cancer is now the most common cancer in both developed and developing countries. The range of mortality rates is much less (approximately 6-19 per 100,000) than that of incidence because of the more favorable survival of breast cancer in (high-incidence) developed regions. As a result, breast cancer ranks as the fifth cause of death from cancer overall (458,000 deaths), but it is still the most frequent cause of cancer death in women in both developing (269,000 deaths, 12.7% of total) and developed regions .

Although there are significant similarities across region of the world, they are also striking difference the peak age for breast cancer in Asian countries is between 40 and 50 years, whereas the peak age in the Western countries is between 60 and 70 years. Also, the incidence of breast cancer in Asia is rising and is associated with increased mortality. in the West, although the incidence is increasing, the mortality rate is definitely decreasing (2007). Data from Shanghai's Municipal Center for Disease Control and Prevention (CDCP) showed that in 2003, the peak age of breast cancer patients in China was 45–50 years old (Leong SP, Shen ZZ et al. 2010), which was around the stage of menopause for Chinese women (Loh et al., 2005; Chen et al., 2010).

Previous studies have identified several reproductive risk factors of breast cancer risk and reproductive factors, such as early age at menarche and later age menopause (Goldman & Hatch, 2000; Chantal et al. ,2008). Additionally, early first live birth and breastfeeding had a protective effect (Parker, 2001; Lee et al., 2004) while the risk of BC increases with use of oral contraceptives from appear to diminish once BC is stopped. All those

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factors suggest that estrogen influences breast cancer risk. These associations are generally believed to reflect the effects of exposure of the breast tissue to ovarian hormones, particularly estrogen and progesterone, during the reproductive years, and the effect of a first full-term pregnancy on the differentiation of the cells lining the milk ducts (Hankinson et al., 2004; Colditz et al., 2006).

One study recorded stronger associations in Asia-Pacific populations between increased BMI and premenopausal and postmenopausal breast cancers (Renehan et al., 2008). There was an increased risk of breast cancer associated with overweight or obesity in adulthood in Chinese women (Shi et al., 2010). Evidence for a risk reduction associated with increased physical activity was found in 47 (76%) of 62 studies included in a review paper add the risk decreased in a dose-dependent manner (Friedenreich & Cust, 2008).

Previews studies had identified the risk factors of BC by comparision with non-BC women. The current study, by contrast, compares patients with malignant with those with benign tumors. This study focused on reproductive factors and also included lifestyle, BMI, and demographic characteristics in Chinese women. It aims to provide evidence on risk factors of breast cancer for further biomedical study.

Materials and Methods

Study population and settings

This is a hospital-based case-control study to assess the risk factors related to breast cancer in female patients aged 20-75 years old diagnosed and treated at the Kunming breast disease center in Yunnan province, China, from 2009 to 2011. The study subjects compared 263 cases and 457 controls. Both case and control groups were classified based on pathological diagnosis as a gold standard. The case group consisted of patients with malignant breast tumors (ICD-10 categories "C50") and controls were benign breast disease patients (ICD-10 categories "N60-N64") (Table 1).

To illustrate the influence of hormonal factors on BC, age, menstrual status, pregnancy, contraception methods used and menopause status were measured by self-administered questionnaire. Demographic characteristics, BMI, family history, diet and exercise were also investigated.

Menstrual factors assessed were age at menarche, current menopause status, dysmenorrhea, menstrual cycle length. Age at menarche was classified (cut point based on the overall mean age at menarche) as not older than 13 years, older than 13 years old. Menopausal status was defined as the premenopausal, perimenopause and postmenopausal. A new variable was created from the patients' menopausal event and their current age. Since the minimum age at menopause was 35 years old, the new variable was categorized into current age less than 35 years and no menopause, current age great than 35 years and no menopause, current age great than 35 years and menopause, defined as premenopausal, perimenopausal and postmenopausal, respectively. To observe the effect and to control for each possible confounding effect on other variables has maintained in the model constantly. The body mass index was calculated based on height and weight as measured by the nursing staff. Based on the BMI (BMI = weight (kg)/height $(m)^2$), women were grouped into three categories as recommended by WHO for Asian populations: normal (BMI = 18.5-23.0 kg/m^2), overweight (BMI = 23.0-27.5 kg/m^2), and obese (BMI ≥ 27.5 kg/m^2) (2004). BMI was measured at the hospital visit. For cases, this was after the disease had occurred.

Table 1. Tumor Classification of BC and Benign Tumor

	Number	Percentage
Benign Tumor classification:		
Fibroadenoma	125	27.4
Fibrocystic disease	128	28.0
Other disease	157	34.4
Other inflammation disease	47	10.3
Malignant Tumor classification:		
DCIS	20	07.6
Invasive ductal carcinoma	203	77.2
Other malignant	33	12.5
Unspecified malignant	7	02.7

Data collection

A Self-administered questionnaire was used to collect information on demographics, menstrual and reproductive history, family history of cancer, diet and exercise. Data on other demographic variable, medical history and reproductive characteristics of breast cancer cases and controls were extracted from routine medical records. Histology of breast cancer tissue and benign breast lesion were verified by pathology reports.

Statistical analysis

After data exploration and cleaning, univariate analysis for association between outcome and potential risk and confounding factors was done using cross-tabulation and chi-square tests of association. Variables with P values less than 0.2 were selected to be included in a initial multivariate logistic regression model where the status of being BC or non-BC was the dependent variable and hormonal status variables and BMI were the exposure variables of main interest. Since some variables had zero count in at least one category leading to inability to get unbiased estimates the coefficient and standard errors, binomial-response GLM using the bias-reduction method described by David Firth (Ioannis ; Firth 1993) was applied to estimate OR's and their 95% confidence intervals (95% CI). Since cases and controls were not matched by age menopause status, the compound variable composes age and menopause was identified in the statistical model. All statistical analyses were conducted using R statistical software version 2 with Brglm (Ioannis) and Epicalc (Virasakdi) packages.

Results

A total of 720 inpatients (263 patients with breast cancer and 457 patients with benign breast lesion) from Kunming breast cancer center in Yunnan Province consented to this study. The mean age at recruitment was

48.6 years (S.D. = 10.2) with a range of 24-73 years in cases, and 39.9 years (S.D. = 10.0) with a range of 20-73 years in controls (Table 2). Almost all patients in the two groups were of Han nationality. The proportion of unmarried patients was higher in the benign group (10.3%) than in malignant group (1.5%). Other demographic and reproductive characteristics in cases and controls are summarized in Table 2.

As shown in Table 4, multivariate model analysis revealed the significant independent positive associations with BC of shorter menstrual cycle, older age at first live birth, never breastfeeding, history of oral contraception experience, increased number of abortion, menopause status, and nulliparities.

Menopause status showed significant association with BC (p for trend <0.001). After adjusted for other potential confounders in multivariate regression model, perimenopausal women compared to premenopausal women had about 3-fold risk of BC, postmenopausal women had more than 5-fold risk of BC.

Among other reproductive variable associated with breast cancer, older age of first full-term live birth, had a 1.82-fold risk of BC than women with older age (95%CI: 1.14-2.89). After birth without breastfeeding women had 3.26–fold (95%CI: 1.07-9.92) risk of BC compared with breastfeeding history. Number of abortion showed an increasing higher risk of BC. As far as women who

Table 2. Reproductive Factors of BC and Benign Tumor

		Cancer (N/P) 263 (36.5)	Benign (N/P) 457 (63.5)	P value
Ethnic:	Others	21 (08.0)	54 (11.8)	0.135
	Han	242 (92.0)	403 (88.2)	
Marital status:	unmarried	4 (01.5)	47 (10.3)	< 0.001
	married	248 (94.3)	401 (87.7)	
	divorced	11 (04.2)	9 (02.0)	
Eccupation:	works	73 (27.8)	57 (12.5)	< 0.001
	officers	56 (21.3)	133 (29.1)	
	others	134 (51.0)	267 (58.4)	
Education:	midschool	106 (40.3)	73 (16.0)	< 0.001
	highschool	95 (36.1)	252 (55.1)	
	college	62 (23.6)	132 (28.9)	
Age group:	(20,25]	4 (01.5)	46 (10.1)	< 0.001
	(25,30]	2 (00.8)	57 (12.5)	
	(30,35]	9 (03.4)	56 (12.3)	
	(35,40]	32 (12.2)	71 (15.5)	
	(40,45]	46 (17.5)	94 (20.6)	
	(45,50]	49 (18.6)	78 (17.1)	
	(50,55]	38 (14.4)	30 (06.6)	
	(55,60]	34 (12.9)	17 (03.7)	
	(60,65]	26 (09.9)	3 (00.7)	
	(65,70]	19 (07.2)	4 (00.9)	
	(70,75]	4 (01.5)	1 (00.2)	
Age at menarche:	≤ 13 year	107 (40.7)	219 (47.9)	0.072
	> 13 year	156 (59.3)	238 (52.1)	
Menstrual period:	< 5 days	175 (66.5)	224 (49.0)	< 0.001
	> 5 days	88 (33.5)	233 (51.0)	
Menstrual cycle:	≤ 29 days	101 (38.4)	98 (21.4)	< 0.001
	> 29 days	162 (61.6)	359 (78.6)	
Dysmenorrhea:	No	169 (64.3)	342 (74.8)	0.003
	Yes	94 (35.7)	115 (25.2)	
Pregnancy:	Yes	263 (100)	392 (85.8)	< 0.001
	No	0 (00.0)	65 (14.2)	
Number of pregnancy:	1	89 (33.8)	321 (70.2)	< 0.001
	2	74 (28.1)	58 (12.7)	
	>2	100 (38.0)	13 (02.8)	
	No	0 (00.0)	65 (14.2)	
Abortion:	Yes	120 (45.6)	76 (16.6)	< 0.001
	No	143 (54.4)	316 (69.1)	
	Missing	0 (00.0)	65 (14.2)	
Number of abortion:	1	60 (22.8)	62 (13.6)	< 0.001
	2	47 (17.9)	12 (02.6)	
	>2	13 (04.9)	2 (00.4)	
	No	143 (54.4)	381 (83.4)	
Age of first deliver:	≤ 24 y	130 (49.4)	212 (46.4)	< 0.001
	> 24 y	133 (50.6)	160 (35.0)	
	Missing	0 (00.0)	85 (18.6)	
Breastfeeding:	Yes	242 (92.0)	365 (79.9)	< 0.001
	No	21 (08.0)	7 (01.5)	
	Missing	0 (00.0)	85 (18.6)	
Time of breastfeeding:	≤ 10 m	84 (31.9)	264 (57.8)	< 0.001
	> 10 m	158 (60.1)	101 (22.1)	
	Missing	21 (08.0)	92 (20.1)	
Oral contracept:	No	167 (63.5)	433 (94.7)	< 0.001
	Yes	96 (36.5)	24 (05.3)	
Sterilization:	No	255 (97.0)	455 (99.6)	0.006
	Yes	8 (03.0)	2 (00.4)	
Menopause:	Yes	116 (44.1)	50 (10.9)	< 0.001
	No	147 (55.9)	407 (89.1)	
Menopause status	Premenopausal	12 (04.6)	149 (32.6)	< 0.001
	Perimenopause	135 (51.3)	258 (56.5)	
	Postmenopausal	116 (44.1)	50 (10.9)	

Table 3. Other Factors of BC and Benign Tumor

		Cancer (N/P) 263 (36.5)	Benign (N/P) 457 (63.5)	P value
Familyhistory:	No	250 (95.1)	456 (99.8)	< 0.001
	Yes	13 (04.9)	1 (00.2)	
BMI:	[14,23]	142 (54.0)	320 (70.0)	< 0.001
	(23,27.5]	97 (36.9)	117 (25.6)	
	(27.5,41]	24 (09.1)	20 (04.4)	
Diet:	Balance	189 (71.9)	355 (77.7)	00.223
	oil	24 (09.1)	36 (07.9)	
	vegeterian	31 (11.8)	47 (10.3)	
	Others	19 (07.2)	19 (04.2)	
Exercise:	No	26 (09.9)	196 (42.9)	< 0.001
	Yes	237 (90.1)	261 (57.1)	

Table 4. Multivariate Analysis of BC and Benign Tumor

		OR	95% CI	P value
Education:	highschool	Ref		
	College	1.87	1.05-3.34	0.033
	Midschool	1.69	0.97-2.97	0.065
Menstrual cycle:	≤29 d	Ref		
	>29 d	2.54	1.56-4.13	0.000
Age of first live birth:	<24 y	Ref		
	≥24 y	1.82	1.14-2.89	0.011
	Unknown	0.00	0.02	0.000
Breastfeeding:	Ever	Ref		
	Never	3.26	1.07-9.92	0.038
Oral contraception:	No	Ref		
	Yes	2.56	1.34-4.88	0.004
Sterilization:	No	Ref		
	Yes	5.98	0.86-41.76	0.071
Family history:	No	Ref		
	Yes	3.58	0.44-29.08	0.233
Exercise:	No	Ref		
	Yes	13.97	6.64-29.42	0.000
Number of abortion:	Never	Ref		
	One	2.50	1.38-4.52	0.002
	≥Two	12.31	5.02-30.20	0.000
Number of parity:	Nulliparous	Ref		
	One	0.09	0.04-0.2	0.000
BMI:	14-23	Ref		
	>23-27.5	1.13	0.69-1.85	0.620
	>27.5-41	1.71	0.71-4.14	0.236
Menopause status:	premenopause	Ref		
	perimenopause	2.55	1.19-5.5	0.016
	postmenopause	5.47	2.29-13.1	0.000

had once a live birth, it showed decreased the risk of BC compared to nulliparous (OR=0.09, 95%CI: 0.04-0.2). Shorter menstrual cycle had 2.54-fold (95%CI: 1.56-4.13) risk of BC compared to longer cycle. Those who had oral contraception experience women had 2.56-fold (95%CI: 1.34-4.88) risk of BC compared to never use. Compared with women who obtained high school education, college or above group increased 1.87-fold (95%CI: 1.05-3.34) risk of BC whereas lower education no associations (95%CI: 0.97-2.97). Women who engaged regular physical exercise had higher risk of BC. Those who had sterilization operation had no detectable association with risk of BC compared to never experience. The association between risk of BC and those women who had family history of cancer (95%CI: 0.44-29.08) was not been detected (Table 3). Women are engaged in an occupation and BMI showed no detectable association with risk of BC.

Discussion

The risk factors for malignancy among women who come to the clinic identified in this study included higher education and reproductive factors such as longer menstrual cycle, older age with first live birth, never breastfeeding, nulliparity, more than one time abortion, oral contraception experience and being peri and post menopausal.

To assess the association between menopause status and risk of breast cancer, we categorized menopause status and age into three groups. The result show that it had the trend increased risk of BC (p for trend <0.001). It hints that the risk of BC increased along with age a tendency to increase in addition to the state of menopause outside changed. A previous study similarly found that women with natural menopause at age 55 or older had twice the breast cancer risk of those whose menopause occurred before age 45 (Trichopoulos et al., 1972), however, it no suggested a trend of increase. Many studies only compared premenopause and post menopause, revealed that there was an increasing risk of breast cancer, include late age at menopause (< 50 year) (Liu et al., 2011).

Breast cancer risk increases with early menarche and late menopause probably due to increased exposure of the breasts to oestrogen and/or progesterone (Key, 1995).

The higher breast cancer risk in women with a late menopause is most likely explained by both the longer duration exposure to estrogen and progesterone experienced by these women and higher level of hormone (Goldman & Hatch, 2000). Patients with older age at first childbirth and lower parity had higher risk of BC in this study, consistent with the results of previous study (Britt et al., 2007). Women who had a late first full term pregnancy (after age of 35 years) was at an elevated risk of breast cancer, compared with women with first birth before age 25. A meta-analysis of eight case-control studies in Japan reported that late age at first delivery and early age at menarche were significantly associated with risk of breast cancer. They also found that number of parity is an independent risk factor of breast cancer (Nagata et al., 1995).

In this study age at menarche had no detected association with BC but longer menstrual cycle had higher risk of BC. Age at menarche is controversial in various studies. Some studies indicated that early age at menarche was associated with increasing risk of BC (Chantal et al., 2008; Shin et al., 2011) whereas other study failed to show any associated with risk (Kabat et al., 2011). The mean age at menarche has changed as a birth cohort effect. It proved by a study in the United States that the mean age at menarche declined over time from 13.3 years (95% CI: 13.2–13.5) in the oldest age group, those born prior to 1920, to 12.4 years (95% CI: 12.2–12.5 years) in the youngest group, born between 1980 and 1984 (Margaret et al., 2007). The age at menarche may also reflect external exposure to exogenous estrogenic stimuli. Hormones do not have marked direct effects on their epithelial cells, but hormones stimulate ovulation which is followed by cell division during repair of the epithelium (Key, 1995). It is not endogenous by itself. That is why it is hard to interpret as the risk of BC by itself.

In this study a lack of history of breastfeeding was associated with increased risk of BC, consistent with previous study (Liu et al., 2011). In a meta-analysis, mothers who breastfed for a total of one year were found to be slightly less likely to develop breast cancer than mothers who had not breastfed; those who breastfed for a total of two years had about twice the benefit of those who breastfed for a total of one year (2002).

An explanation for the protection afforded by lactation is that the cumulative number of ovulatory menstrual cycles a woman experiences will be lower among women substantial lactation experience because breast-feeding delays ovulation following a completed pregnancy. Breast-feeding is a potentially modifiable behavior, thus its impact on reducing risk of breast cancer is extremely important.

This study showed an increased risk of BC with times of abortion. The association between abortion and risk of BC in a study in China showed that the risk factors of female breast cancer included abortion times more than two (Li et al., 2006). Another study found that risk was raised among women reporting at least one abortion, but no trend was seen with number of abortions (Heuch et al., 2008). In a meta-analysis study, pooled odds ratio for number of abortions greater than and equal three was statistically significant (95%CI:1.68-5.36) (Tao et al., 2011).

Although some previous case–control studies found an increased risk of breast cancer in women who had an induced abortion, the evidence from prospective studies conducted in Shanghai of China suggested that induced abortions did not increase the risk of breast cancer (Rosenblatt et al., 2006).

A collaborative reanalysis of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries revealed the inconsistent findings across studies and difficulties in evaluation of these associations. They concluded that beast cancer risk did not appear to be associated with an increased number of either spontaneous or induced abortions (2004).

Case-control studies rely on the reporting of past behavior, with a sensitive topic like abortion, this can have

a significant impact on the precision of the information gathered. Cases with BC in these studies may link abortion to BC by themselves and are likely to provide more complete or even biased information about their abortion history than controls without BC. Such differences in the completeness of reporting can compromise the accuracy of the study results.

In this study, history of oral contraceptive was increased the risk of BC. This is consistent with a previous study (Lacey et al., 2009). A largest meta-analysis comprises a total of 54 epidemiologic studies (Collaborative Group on Hormonal Factors in Breast Cancer) and including 53,297 women with breast cancer and 100,239 controls did not reveal an elevated breast cancer risk in women taking contraceptives (Bjelic-Radisic & Petru, 2010). The finding in this study could be influenced by a recall bias, detection bias or could be due to the biologic effect of the pills.

In this study, we found that current BMI had no association with risk of BC. It is likely that cases with BC had weight loss to some extent before visiting the hospital and thus any effect of high BMI on BC may have been nullified.

A study conducted in China pointed out that there was an increased risk of breast cancer associated with overweight or obesity in adulthood. Compared with women who had never been overweight or obese in their adulthood, the adjusted OR of breast cancer was 1.99 (1.42-2.79) for those who had BMI ≥ 25.0 at age 21 and just before diagnosis and rose to 3.04 (1.18-7.86) for those whose BMI was ≥ 25.0 five years before diagnosis (Shi et al., 2010).

Compared with women who obtained high school education, those who reached college or higher education increased by 1.87-fold (95%CI: 1.05-3.34) the risk of BC whereas those who had lower education were not significantly different from reference group associations.

Previous study proved that higher education levels may be associated with health through different pathways because subjects with higher levels of education may be more receptive to prevention messages and may have a better ability to change their health behavior and to better use the health care system (Galobardes et al., 2006). However, in a recent study the authors found no association between education level and risk of invasive breast cancer after adjusting for all known risk factors (Menvielle et al., 2011). This study found higher education increasing risk of BC probably due to well-educated women usually neglecting their health because of busy work, when disease occurred symptom normally been found at the advanced stage, therefore, this group women had higher risk of BC. In western country, routine mammography is used for screening of BC and women with highly educated is more frequently done. Therefore, the higher education, the less risk of breast cancer.

In this study family history of cancer was not a risk factor of BC may likely because of the sample size was small to detect of family history of cancer. Another reason might be the fact that the incidence of BC and other cancers among Chinese women was low in the past, either by the detection facilities or the true low incidence rate. Finding an association of family history of cancer by a retrospective recall in a population where the cancer detection or incidence rate is rapidly rising is unlikely unless the effect is very strong.

Women who engaged in regular physical exercise had higher risk of BC in this study. The finding is not consistent with previous study (Joanna, 2007). The probable explanation is that the definition of exercise in the questionnaire was not clear and it caused misunderstanding in the interviewee. When women perceived that the question was about formal physical exercise and not including their working activities, those who did a lot of physical activities during their work might not undertake formal exercise such as Tai Chi. Therefore, the result was not unsatisfactory.

There was strong association between hormone related reproductive factors with BC risk in this study. Interpretation of associations of circulating estrogens with breast cancer risk had been discussed by many epidemiological studies. They show strong associations between circulating estrogen concentrations and breast cancer risk, but cannot directly establish whether the circulating oestrogens cause the increase in risk. Estrogens can be synthesized by aromatase in the breast tissue; the extent of synthesis is related to the breast stroma as well as the breast adipose tissue, and may be increased in proximity to a tumor (Bulun et al., 2009).

More researches is needed to better understand the relative importance of circulating and breast tissue accumulating estrogens and other hormones in relation to breast cancer risk. Over the next few years existing prospective studies will be able to provide much more data. It will be particularly important to use sensitive and specific assays. Developments in mass spectrometry methods now make this a feasible assay method in epidemiological studies (Ziegler et al., 2010).

Since this study is a case-control study, recall biases of some variable and other bias such as temporal sequence of current BMI and BC occurrence are unavoidable. Therefore it could not clearly elucidate the risk factor of BC. However, this study initiates a good baseline for BC studies in Yunnan where groups of minority population reside. Further studies will be conducted in the near future.

In conclusion, in this study the estrogen related risk factors of breast cancer included woman who had longer menstrual cycle, older age of first live birth, never breastfeeding, nulliparity, and number of abortions more than one. Therefore, it is recommended to women with these risk factors perform breast cancer screening tests earlier and regularly. These findings suggest that female hormonal factors, especially in the trend of menopause status play a significant role in the development of cancer in Yunnan women.

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