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Breastfeeding and Risk of Breast Cancer: Case-Control Study

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The aim of this study was to investigate a possible association of breast cancer occurrence in women with their breastfeeding experience. A matched case-control study was conducted in Kragujevac, Serbia. A total of 382 women (191 cases with breast cancer and 191 controls) were interviewed, but the data were explored on breastfeeding and breast cancer only among parous women (339 women). Logistic regression was used to calculate odds ratios (ORs) as estimates of the relative risk of breast cancer. Compared with controls, significantly more cases ever breastfed [adjusted OR (OR_{adj}) = 2.90, 95 percent confidence interval (95 percent CI) 1.02–8.22], breastfed all their children (OR_{adj} = 2.93; 95 percent CI 1.03–8.29), and had longer lifetime duration of breastfeeding (OR_{adj} = 3.44, 95 percent CI 1.15–10.24 for 13 or more months). In comparison with controls, significantly more cases breastfed at first birth (OR_{adj} = 3.17, 95 percent CI 1.36–7.37). Breast cancer risk increased if first breastfeeding occurred at an older age (p for trend = .042) and with longer duration of breastfeeding (p for trend = .037). Our study is one of the few in which breastfeeding was found to be a risk factor for breast cancer.

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association was observed among women without a family history of breast cancer (Stuebe et al. 2009). Compared with parous women who never breastfed (Beaber et al. 2008), those who breastfed had a reduced risk of ductal carcinoma, but not lobular or ductal-lobular carcinoma, which suggests that ductal carcinoma has distinct risk factors differing from lobular and ductal-lobular carcinoma.

Some authors (Becher, Schmidt, and Chang-Claude 2003; Coogan et al. 1999; Freudenheim et al. 1997; Kim et al. 2007; Lee et al. 2003; Nemesure et al. 2009; Okobia et al. 2005; Oran et al. 2004; Rao, Ganesh, and Desai 1994; Sezer et al. 2011; Xu et al. 2012; Yu et al. 2012; Zheng et al. 2001) have found no connection between breast cancer and history of breastfeeding. In some studies breastfeeding has been found to be a risk factor for breast cancer (Negri et al. 1996; Ulusoy et al. 2010).

The aim of this study was to investigate a possible association of breast cancer occurrence in women with their breastfeeding experience.

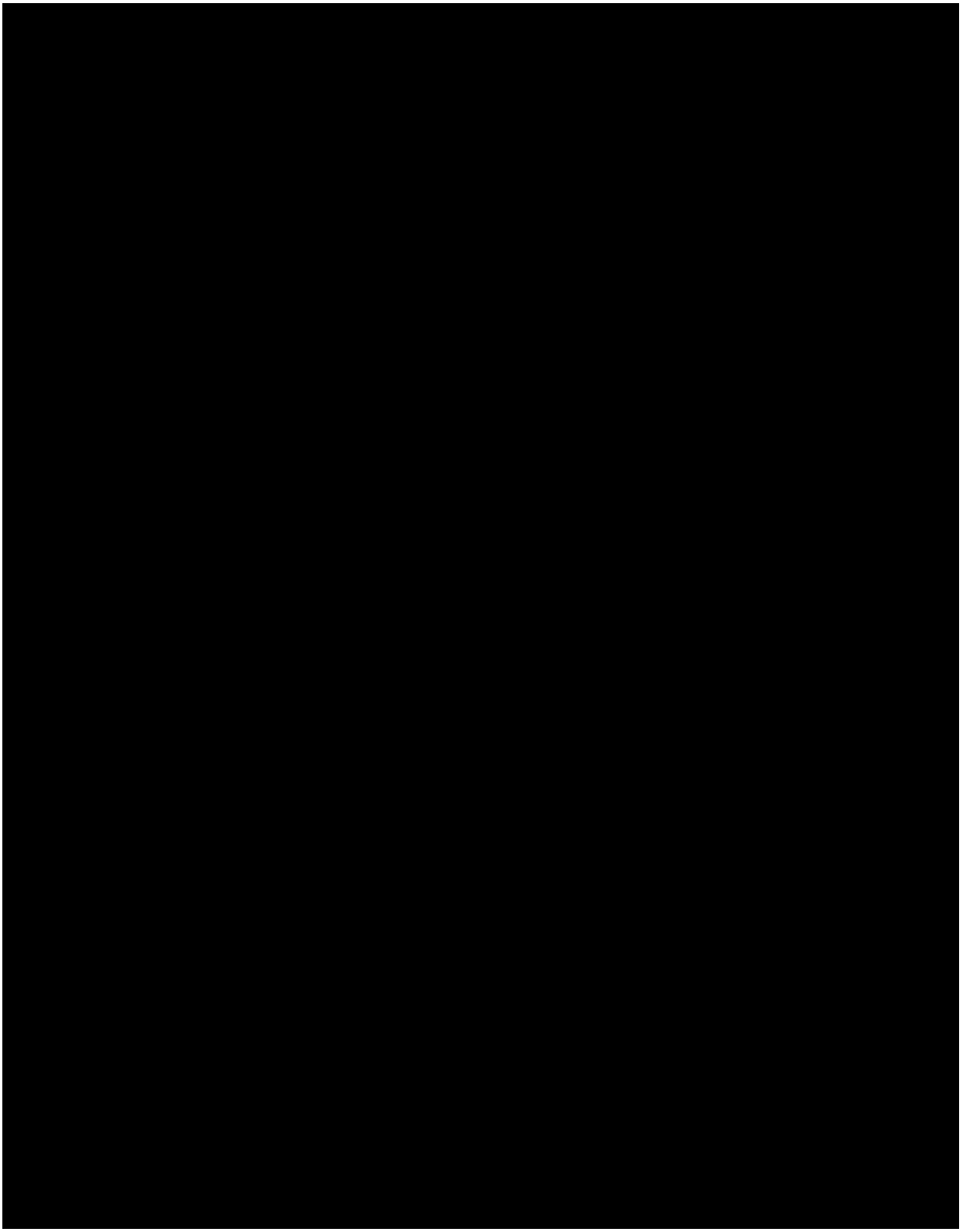
METHODS

Study Sample

This hospital-based case-control study was performed in Kragujevac (a city in Serbia with about 200,000 inhabitants) during the period January 2004–December 2005. The Clinical Center in Kragujevac, one of the four medical institutions in the country, provides tertiary health care.

A "case" of breast cancer (191 patients) was defined as a woman who had a newly diagnosed first primary breast cancer during the study period. The data were collected from all women with breast cancer in whom the diagnosis was evaluated by the Consilium for breast cancer at the Center for Oncology and Radiology in the Clinical Center in Kragujevac. During the period of our study, Serbia officially accepted recommendations similar to Minimal Clinical Recommendations proposed by the European Society for Medial Oncology (2001), which precisely proposed rules for standard diagnostics of breast cancer. To confirm the diagnosis of breast cancer, surgical biopsy of the breast and histopathologic examination of the sample were performed. The final pathological diagnosis was made according to the World Health Organization classifications (Tavassoli and Devilee 2003). The case group comprised women of all ages (because neither the number of pre- nor post-menopausal women was enough to allow separate analyses). The study group comprised all patients (191 cases) with histologically confirmed breast cancer in the study period (Ninkovic et al. 2012), the participation rate being 100 percent). No one refused to participate in the study.

The controls (191 participants) were individually matched to the respective case by age (±2 years), time of hospital admittance, and place of



Data Analyses

In the analysis of data, first descriptive statistics were computed to describe the sample, and in bivariate analyses chi-square tests were used to determine differences between cases and controls in key categorical characteristics and risk factors, and *t*-tests were used to determine differences in continuous measures. Multiple logistic regression was used to determine odds ratios (ORs) with 95 percent confidence intervals (CI) while adjusting for all variables that were related to breast cancer in bivariate analyses at a p value of <0.10 (menopausal status, abortion history, family history of breast cancer, body mass index, alcohol use). Adjustment was also made on some other variables, known from literature data as possible confounders for the association between breastfeeding and breast cancer, although they did not differ significantly between cases and controls in the present study (age, place of residence, educational level, employment, age at menarche, oral contraceptive use, number of pregnancies, number of live births, age at first birth, and tobacco use). Model fit was assessed by the Hosmer–Lemeshow test of goodness of fit and Cox and Snell's and Nagelkerke's Pseudo R square measures. Tests for trends were based on the logistic regression models. Statistical significance was considered when $p < .050$. All statistical analyses were conducted using the Statistical Package for Social Sciences software (version 19.0, SPSS Inc., Chicago, IL, USA).

RESULTS

The case group and control group each consisted of 191 women. More than 80 percent of cases and controls were ≥50 years old (Table 1). The median age of cases was 59 years (age range 35–80 years), and the median age of controls was 58 years (age range 35–80 years). A total of 60.7 percent of participants were from urban areas. About 60 percent had ≤8 years of school, and about 50 percent were employed. Age and place of residence were matched variables.

Cases and controls did not differ significantly in age at menarche, oral contraceptive use, pregnancy, parity, number of live births, age at first birth, menopausal status, tobacco use, and family history of breast cancer (Table 2). Breast cancer was positively related to age at menopause ($p = .0240$), body mass index ($p = .012$), and alcohol use ($p = .029$). History of abortions was more frequent among the controls ($p = .027$).

Compared to controls, significantly more cases ever breastfed ($p = .045$), breastfed all their children ($p = .043$), breastfed a greater number of children ($p < .05$), and had longer lifetime duration of breastfeeding ($p = .027$) (Table 3). In comparison with controls, significantly more cases breastfed their first birth ($p = 0.008$) and for a longer period of time ($p < .05$), p for

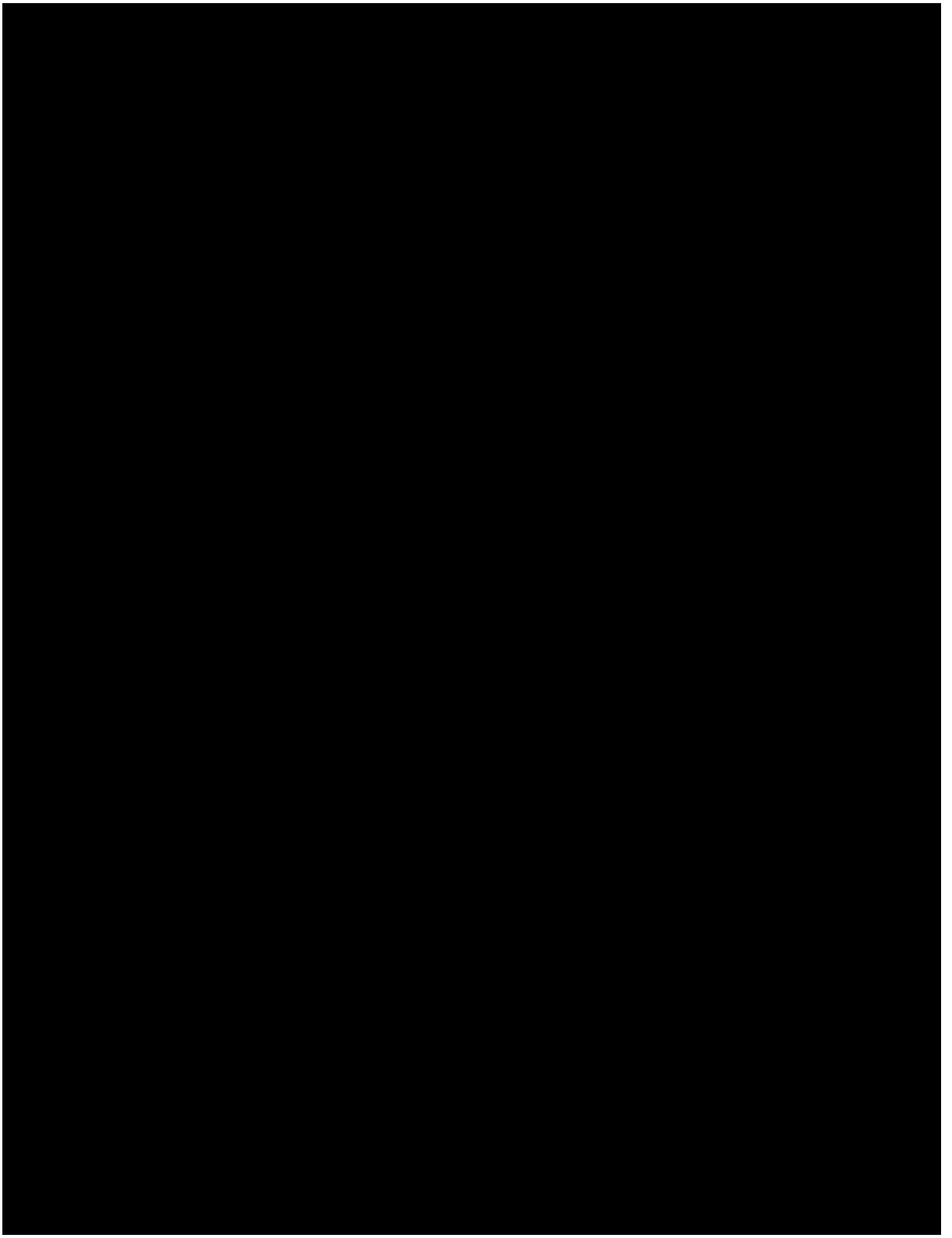


TABLE 2 Reproductive, Health, and Lifestyle Characteristics of Women With Breast Cancer and Controls

	Cases (n = 191) No. (%)	Controls (n = 191) No. (%)	OR*	95% CI†	p‡
Age at menarche					
<13 years	42 (22.0)	35 (18.3)	1.00#		
≥13 years	149 (78.0)	156 (81.7)	0.80	0.48–1.31	.373
Pregnancy[b]					
No	18 (9.4)	13 (6.8)	1.00#		
Yes	173 (90.6)	178 (93.2)	0.70	0.33–1.48	.351
Parity[c]					
Yes	168 (97.1)	171 (96.1)	1.00#		
No	5 (2.9)	7 (3.9)	0.73	0.23–2.34	.593
Number of live births[c,d]					
0	5 (2.9)	7 (3.9)	1.00#		
1	40 (23.1)	48 (27.0)	1.17	0.34–3.96	.805
2	97 (56.1)	95 (53.4)	1.43	0.44–4.66	.554
≥3	31 (17.9)	28 (15.7)	1.55	0.44–5.44	.494
Age at first birth (years)[c,d]					
Never	5 (9.7)	7 (3.9)	1.00#		
<25	132 (76.3)	134 (75.3)	1.38	0.43–4.45	.591
25–29	27 (15.6)	28 (15.7)	1.35	0.38–4.78	.642
≥30	9 (5.2)	9 (5.1)	1.40	0.32–6.11	.654
Menopausal status					
Pre-/perimenopausal	37 (19.4)	29 (15.2)	1.00#		
Postmenopausal	154 (80.6)	162 (84.8)	0.75	0.44–1.27	.280
Age at menopause[e]					
≤51 years	100 (64.9)	124 (76.5)	1.00#		
>51 years	54 (35.1)	38 (23.5)	1.76	1.08–2.88	.024
Abortion history[c,f]					
No	32 (18.5)	18 (10.1)	1.00#		
Yes	141 (81.5)	160 (89.9)	0.50	0.27–0.92	.027
Family history of breast cancer					
No	178 (93.2)	186 (97.4)	1.00#		
Yes	13 (6.8)	5 (2.6)	2.71	0.95–7.77	.063
Body mass index					
<25 kg/m^2	64 (33.5)	88 (46.1)	1.00#		
≥25 kg/m^2	127 (66.5)	103 (53.9)	1.70	1.12–2.56	.012
Alcohol use					
No	176 (92.1)	186 (97.4)	1.00#		
Yes	15 (7.9)	5 (2.6)	3.16	1.13–8.88	.029
Tobacco use					
Never	130 (68.1)	124 (64.9)	1.00#		
Ever	61 (31.9)	67 (35.1)	0.87	0.57–1.33	.516

Abbreviations: *OR: odds ratio; †95 percent CI: 95 percent confidence interval; ‡p: probability value (according to bivariate logistic regression analysis) indicates statistical significance of the difference between cases and controls; #Reference category.

[a]Three of the cases never had intercourse; [b]All pregnancies irrespective of their outcome; [c]Only for pregnant women; [d]Only the women who ever gave live/still birth; [e]Only for postmenopausal women; [f]Any abortion (induced and spontaneous).

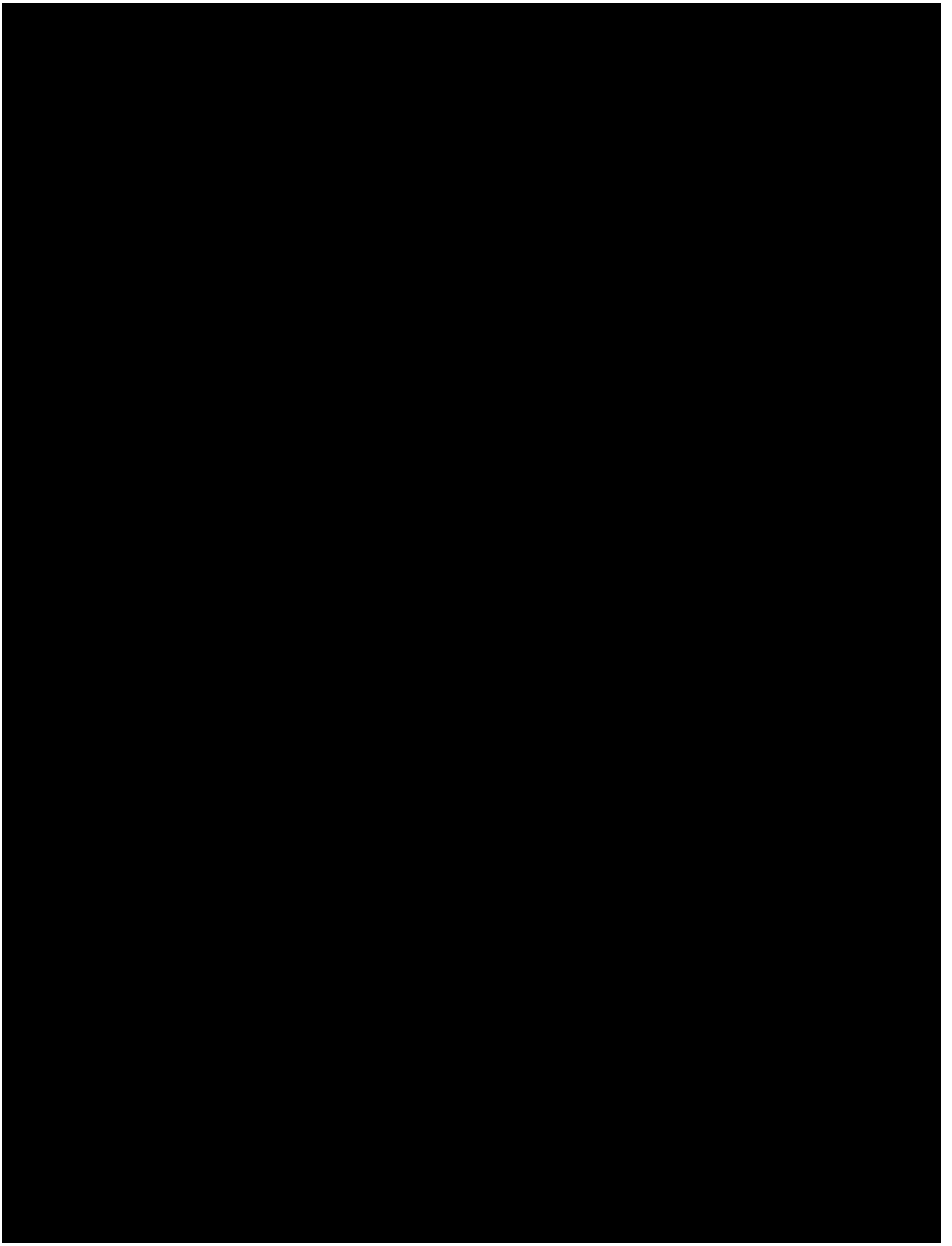
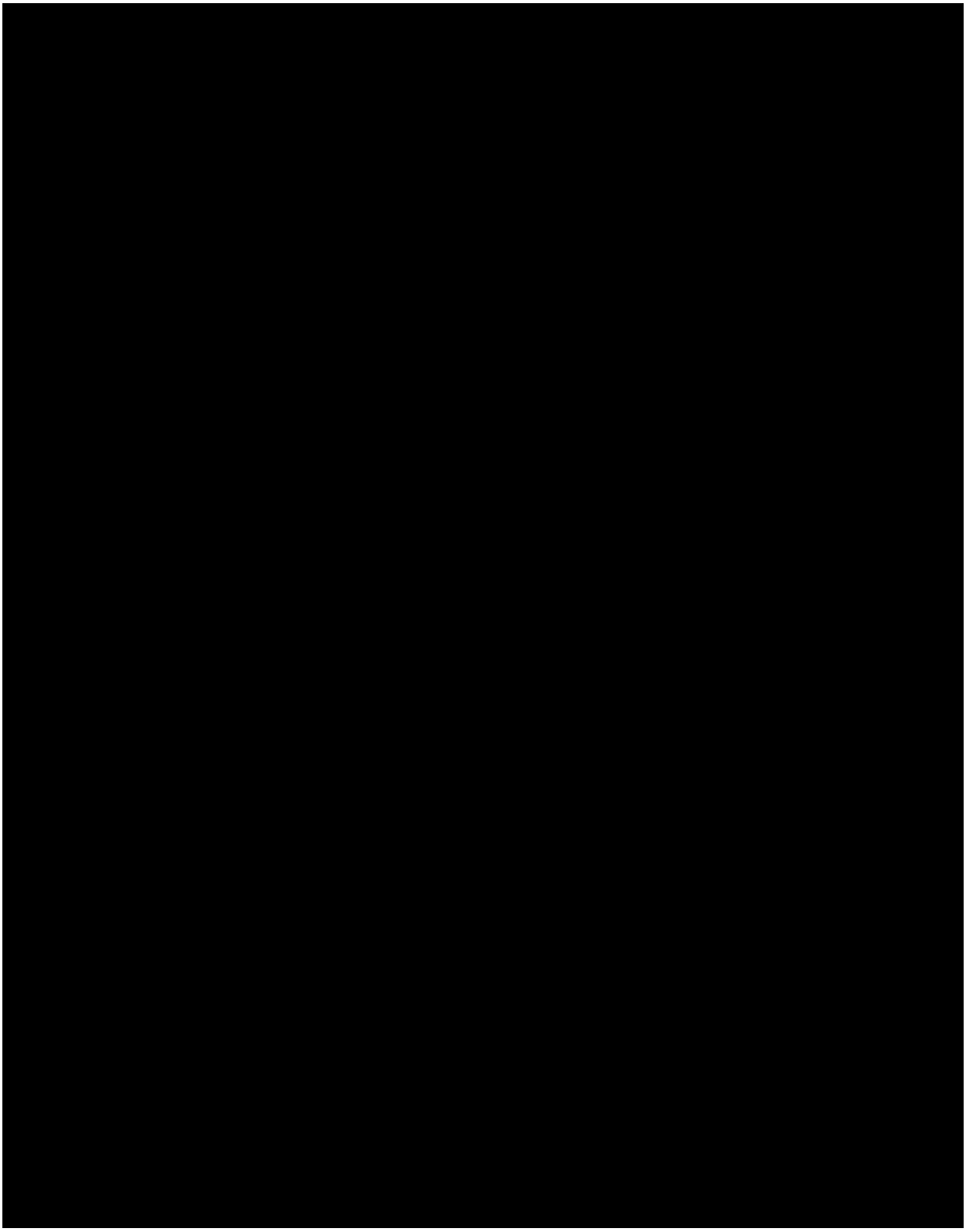


TABLE 3 Risk of Breast Cancer Associated With Breastfeeding Among Parous Women (*Continued*)

	Cases (n = 168)	Controls (n = 171)	Odds ratio (95% confidence intervals)					
Breastfeeding history*	No. (%)	No. (%)	Unadjusted			Adjusted**		
p_{trend}			0.036			0.037		
Age (years) at first breastfeeding								
Never	9 (5.4)	25 (14.6)	1.00†			1.00†		
<25	125 (74.4)	117 (68.4)	2.96	1.33–6.61	0.008	2.69	1.03–7.03	0.043
25–29	26 (15.5)	25 (14.6)	2.88	1.13–7.38	0.027	3.44	1.02–11.58	0.046
≥30	8 (4.8)	4 (2.3)	5.55	1.34–22.98	0.018	9.82	0.92–105.13	0.059
p_{trend}			0.038			0.042		
Breastfeeding in last birth‡								
No	8 (6.3)	13 (10.6)	1.00†			1.00†		
Yes	120 (93.8)	110 (89.4)	1.77	0.71–4.44	0.222	1.70	0.63–4.58	0.297
Duration of breastfeeding last birth‡								
0 months	8 (6.3)	13 (10.6)	1.00†			1.00†		
1–6 months	21 (16.4)	29 (23.6)	1.18	0.41–3.34	0.760	1.17	0.38–3.59	0.780
7–12 months	69 (53.9)	57 (46.3)	1.97	0.76–5.08	0.162	1.97	0.70–5.51	0.197
≥13 months	30 (23.4)	24 (19.5)	2.03	0.72–5.70	0.178	1.89	0.62–5.83	0.265
p_{trend}			0.248			0.378		
Age (years) at last breastfeeding‡								
Never	8 (6.3)	13 (10.6)	1.00†			1.00†		
<25	39 (30.4)	43 (35.0)	1.47	0.55–3.93	0.439	1.40	0.47–4.22	0.546
25–29	50 (39.1)	48 (39.0)	1.69	0.64–4.45	0.285	1.55	0.55–4.39	0.410
≥30	31 (24.2)	19 (15.4)	2.65	0.93–7.57	0.069	2.45	0.76–7.85	0.132
p_{trend}			0.247			0.476		

Abbreviations: *Nulliparous women were excluded from the analysis; **Adjusted for age, place of residence, educational level, employment, age at menarche, oral contraceptive use, number of pregnancies, number of live births, age at first birth, menopausal status, abortion history, family history of breast cancer, body mass index, alcohol use, tobacco use; †Reference category; ‡Only women who have had at least two children.



Although the biological mechanisms underlying the protective effect of the breastfeeding are still unknown, possible explanations are supported by a number of complex changes that occur during breastfeeding (Clevenger 2003; Faupel-Badger et al. 2010; Freudenheim et al. 1997; Gruenke et al. 1987; Henderson et al. 1985; Mannello, Tonti, and Canestrari 2008; Patton et al. 1990; Petrakis et al. 1987; Russo et al. 2005): changes in prolactin and estrogen levels during breastfeeding, differentiation of epithelial cells in the mammary gland making it more resistant to carcinogenesis, the breast milk may protect the breast tissue by excretion of fat-soluble carcinogens (e.g., toxic organochlorines, cholesterol/3-epoxide) and by greater exposure to potentially protective agents (e.g., carotenoids), the delayed onset of ovulation, reduced cumulative number of ovulatory menstrual cycles, an expression of transforming growth factor-β, and negative growth factor in human breast cancer cells.

A biologic rationale why breastfeeding might pose a risk for breast cancer is difficult to distinguish from the possible explanations for the protective role of breastfeeding (Albrektsen, Heuch, Thoresen, and Kvåle 2006; Butt et al. 2014). Some authors suggest that prolactin plays a role as a growth factor in the pathogenesis of breast cancer (Clevenger 2003). Today it is known that breast tissue, both normal and malignant, is a significant source of autocrine prolactin (Chen et al. 2012). Prolactin was higher in women who reported insufficient versus sufficient milk production (Hietala, Olsson, and Jernström 2008). Women who use medication to stop milk flow at the time of the birth of their infant are not at greater risk for breast cancer (Freudenheim et al. 1997). Also, certain kinds of breast cancer (i.e., hormone-independent tumors) may develop in an environment with low levels of estrogen/progesterone. The tumors with high proliferation and histological grade III were associated, but not strongly, with a relatively long duration of breastfeeding (Butt et al. 2014). Also, during breastfeeding an engorgement and excretory duct obstruction may occur, generating the structural changes in breast tissue, which may be '*locus minoris resistentiae*' over a lifetime.

Also, the question remains as to what period of a woman's life is breast tissue more susceptible to the influence of various endogenous and exogenous risk factors or protective factors: in utero, during puberty, during the first pregnancy, during the first breastfeeding, or before or after menopause (Bernstein 2002; Henderson et al. 1985; Tworoger et al. 2013). According to the literature, in comparison with nulliparous women, women who have pregnancies early have a decreased lifetime breast cancer risk (Kelsey, Gammon, and John 1993). However, lifetime risk for breast cancer is increased in women who had their first baby at the age of 30 years or later (Albrektsen et al. 2006; Britt, Ashworth, and Smalley 2007; Lambe et al. 1996; Trichopoulos et al. 1983). In women whose first full-term pregnancy was at age 30+ years, the transient increase of breast cancer risk was more pronounced and lasted for an additional 10 years (Rosner, Colditz, and Willett 1994; Schedin 2006). In a recent meta-analysis, Ma et al.

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