RESEARCH COMMUNICATION

A Nested Case-Control Study of Female Breast Cancer in Karunagappally Cohort in Kerala, India

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Abstract

Lifestyle factors related to breast cancer risk were examined in a case-control study nested in a cohort in Karunagappally, Kerala, South India. We sought interviews with all the residents in Karunagappally with the population of 385,103 (191,149 males and 193,954 females) in the 1991 census and established a cohort of 359,619 (93% of the population in 1991) in 1990. For analysis 264 breast cancer cases with age ≥20 years were selected from 438 breast cancer cases reported during the period 1990-2004 and for each case 3 non-cancer controls were randomly selected matched for age, religion and place of residence through the Cancer Registry, Karunagappally. Conditional logistic regression was used for the analysis. In the present study, in addition to a low number of pregnancies (P <0.001 and P for trend <0.001), more frequent intake of roots and tubers except tapioca (cassava) (OR for ≥ 5 times =1.56, 95% CI=1.09, 3.09, P for trend <0.05), milk drinking (OR=1.78, 95% CI=1.17-2.69, P<0.01) and consumption of chicken meat (OR=1.84, 95%CI=1.09-3.09, P<0.05) were found to increase breast cancer risk. The present study further showed that consumption of tapioca which is a commonly used food item in South India, particularly in Kerala, reduced breast cancer risk (OR=0.55, 95%CI=0.37-0.83, P<0.01). Risk analysis was attempted among pre- and post-menopausal women separately and similar odds ratio were obtained. Consumption of tapioca (cassava) decreased risk of developing breast cancer among pre-menopausal women (P<0.001 and OR=0.35, 95%CI=0.18, 0.65) and a low number of pregnancies (P<0.01), consumption of roots & tubers (P<0.05), usage of chicken meat (P=0.05) increased the risk of breast cancer among post-menopausal women. Further studies seem warranted to confirm the possible protective effect of tapioca consumption. There is an increasing need of breast cancer prevention programs responsive to the cultural practices of the people and the study results should provide leads to cancer control programs especially in rural areas.

Key Words: Breast cancer - nested case-control study - risk factors - Karunagappally, Kerala, India

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Introduction

Breast cancer has emerged as the leading cancer in women in India and more than 80,000 cases are diagnosed annually (Globocan 2002). In the state of Kerala, South India also this cancer is the leading cancer in women with an age standardized incidence rates Urban (29.4/1, 00,000) and rural (19.6 per 1, 00, 000) (PBCR two year report 2003-2006, RCC,Trivandrum; Jayalekshmi et al., 2006). Rapid industrialization and urbanization in Kerala in the last few decades have significantly influenced the life style of women. High education level, a life expectation at birth of more than 76 years, low birth and death rates, and minimal urban and rural differences in lifestyle mark the state population (www.keralawomen.org). The emerging trend of breast cancer incidence is alarming, with a significant impact on women and their families through young age mortality, disability and distress to patients and care givers and their families. The present study was conducted to identify risk factors for breast cancer among the rural population in South Kerala, India.

Subjects and Methods

Regional Cancer Centre, Trivandrum initiated a population based cancer study in 1990 in Karunagappally Taluk, Kollam district, Kerala, South India, in order to examine the cancer incidence in relation to natural radiation present in the sea coast of Karunagappally Taluk. As part of the study we collected data for various factors

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causing cancer other than radiation such as socio-demographic and lifestyle related factors. Karunagappally Taluk consists of 12 panchayats with an area of 192 Sq. km and had a population of 385,103 (191,149 males and 193,954 females) according to the 1991 census. To establish the cohort, 12-14 trained field enumerators visited all 71,674 households in the entire Karunagappally Taluk and collected data using a structured questionnaire from 359,619 residents by face to face interview. This corresponds to 93% of the Karunagappally population in 1991 (Nair et al., 2004). Cancer cases among cohort were ascertained by cancer registration methodology. Karunagappally Cancer Registry was initiated in 1/1/1990 and reports have been presented in "Cancer Incidence in Five Continents" vol. VII (Nair et al., 1997), vol. VIII (Nair et al., 2002) and vol. IX (Jayalekshmi and Rajan, 2007).

We identified the women with breast cancer from the records of cancer registry and compared with matched population controls obtained from the socio demographic survey of cohort members. 264 breast cancer cases aged ≥20 years and having sociodemographic data were selected for study out of a total of 438 breast cancer cases recorded by cancer registry during the period 1990-2004. A nested case control study in the cohort was conducted by selecting 3 non- cancer controls for each case. Controls were randomly selected after exactly matching with age, religion and place of residence. Socio demographic variables included in the analysis were education levels, marital status, income and occupation. Reproductive variables included were age at marriage, age at first and last pregnancy, number of pregnancies, age at puberty and type of menopause. Dietary variables considered were vegetarian use, non-vegetarian use, and consumption of roots and tubers, tapioca, chicken meat and milk.

The data were analyzed using univariate and multivariate conditional logistic regression. Associated risk was calculated using odds ratios (ORs) and 95% confidence intervals (CIs). Significant variables P <0.05 identified from univarite analysis were included in the multivariate model.

Results

The average age of the breast cancer cases at diagnosis was 46.4 years. Table 1 summarizes the results obtained from univariate conditional logistic regression analysis of breast cancer risk in relation to socio-economic factors. Women having higher levels of education had higher risk of breast cancer than less educated group (P<0.01). Occupation status shows marginal significance. Marital status and income level were not significantly related to breast cancer risk.

Table 2 shows the results of univariate conditional logistic regression analysis in relation to variables related to reproductive history. Breast cancer risk ratios were higher for those with older ages at marriage (P for trend <0.05), with older ages at first pregnancy (P for trend <0.001), and with less number of pregnancies (P for trend <0.001). Age at puberty, age at last pregnancy, menopausal characteristics were not significant in the analysis.

Table 1. Risk of Breast Cancer Associated with Socio-Demographic Characteristics

Variables	Cases (n=264)	Controls (n=792)	OR (95% CI)	P
Education				0.004
Illiterate	32 (12.1)	105 (13.3)	1 Reference group	
Primary	60 (22.7)	236 (29.8)	1.04 (0.52, 1.51)	
Middle	57 (21.6)	200 (25.2)	0.99 (0.59, 1.82)	
High	94 (35.6)	202 (25.5)	1.79 (1.04, 3.10)	
College	21 (7.9)	49 (6.2)	1.71 (0.83, 3.53)	
Marital Status				0.826
Single	8 (3.0)	26 (3.3)	1 Reference group	
Married	256 (97.0)	766 (96.7)	1.10 (0.46, 2.63)	
Income/ Year (Indian Rupees)				0.773
< 1200	90 (34.1)	290 (36.6)	1 Reference group	
≥-2500	92 (34.8)	277 (35.0)	1.09 (0.77, 1.57)	
-3500	52 (19.7)	146 (18.4)	1.19 (0.77, 1.84)	
>3500	30 (11.4)	79 (10.0)	1.29 (0.75, 2.21)	
Occupation*				0.058
0	44 (16.7)	133 (16.8)	1 Reference group	
1	42 (15.9)	169 (21.3)	0.68 (0.41, 1.15)	
2	28 (10.6)	55 (6.9)	1.57 (0.88, 2.82)	
3	150 (56.8)	435 (54.9)	1.03 (0.69, 1.55)	

*0-farm labours, cashew workers, mat making, beedi making etc.1- Husk processing, coir spinning, fish peeling etc. 2 Office work, business etc. 3- House wives

The results of univariate conditional logistic regression analysis of breast cancer risk in relation to dietary habits are summarized in Table 3. Breast cancer risk was increased among those who eat roots and tubers (excluding

Table 2. Risk of Breast Cancer Associated with Reproductive Characteristics

Variables	Cases	Controls	OR (95% CI)	P Trend/Heterogeneity
Age at marriage				0.019/0.038
12-18	86 (32.6)	321 (40.5)	1 Reference	
19-24	139 (52.6)	386 (48.7)	1.37 (0.99, 1.88)	
≥ 25	31 (11.7)	59 (7.4)	2.02 (1.22, 3.36)	
Single	8 (3.0)	26 (3.3)	1.16 (0.48, 2.84)	
Age at I st Pregnancy				0.000/0.002
≤ 20	100 (37.9)	402 (50.8)	1 Reference	
21-25	111 (42.0)	277 (35.0)	1.66 (1.20, 2.29)	
≥ 26	36 (13.6)	74 (9.3)	2.01 (1.25, 3.22)	
No Preg.	17 (6.4)	39 (4.9)	1.82 (0.94, 3.44)	
Number of Pregnancies				0.000/0.000
5+	57 (21.6)	267 (33.7)	1 Reference	
4	35 (13.3)	126 (15.9)	1.61 (0.97, 2.67)	
3	66 (25.0)	177 (22.3)	2.69 (1.65, 4.42)	
2	67 (25.4)	140 (17.7)	3.62 (2.17, 6.04)	
1	22 (8.3)	43 (5.4)	3.68 (1.91, 7.10)	
No Preg.	17 (6.4)	39 (4.9)	3.08 (1.53, 6.23)	
Age at Last Pregnancy				0.826/0.077
17-25	69 (26.1)	217 (27.4)	1 Reference	
26-35	145 (54.9)	394 (49.7)	1.09 (0.77, 1.54)	
≥ 36	33 (12.5)	142 (17.9)	0.62 (0.36, 1.07)	
No Preg.	17 (6.4)	39 (4.9)	1.34 (0.69, 2.60)	
Age at puberty				0.192
14-17	168 (63.6)	539 (68.1)	1 Reference	
11-13	96 (36.4)	253 (31.9)	1.23 (0.91, 1.65)	
Type of Menopause				0.135
None	136 (51.5)	406 (51.3)	1 Reference	
Natural	106 (40.2)	346 (43.7)	0.87 (0.52, 1.45)	
Artificial	22 (8.3)	40 (5.0)	1.59 (0.83, 3.01)	

Table 3. Risk of Breast Cancer Associated with the Dietary Variables

Variables	Cases	Controls	OR (95% CI)	P Trend/Heterogeneity
Vegetable use				0.100
Regular	44 (16.7)	100 (12.6)	1 Reference group	
Occasional	220 (83.3)	692 (87.4)	0.71 (0.49, 1.06)	
Non Vegetable use				0.201
Occasional	32 (12.1)	74 (9.3)	1 Reference group	
Regular	232 (87.9)	718 (90.7)	0.75 (0.48, 1.16)	
Roots/tubers/week (Except Tapioca)				0.008/0.027
< 2 times	99 (37.5)	365 (46.1)	1 Reference group	
2-4 times	112 (42.4)	306 (38.6)	1.38 (1.01, 1.89)	
≥ 5 times	53 (20.1)	121 (15.3)	1.66 (1.11, 2.48)	
Chicken use				0.012
No	25 (9.5)	118 (14.9)	1 Reference group	
Yes	239 (90.5)	674 (85.1)	1.82 (1.11, 2.98)	
Milk Drink				0.001
Occasional	209 (79.2)	691 (87.2)	1 Reference group	
Regular	55 (20.8)	101 (12.7)	1.92 (1.30, 2.84)	
Tapioca use/week				0.005
≤ 2 times	226 (85.6)	617 (77.9)	1 Reference group	
>3 times	38 (14.4)	175 (22.1)	0.59 (0.40, 0.86)	

tapioca) relatively frequently (P for trend<0.01), and those who eat chicken meat (P<0.05) and drink milk (P<0.01). Consumption of tapioca (cassava) resulted in a decreased risk of breast cancer risk (P<0.01). Regular vegetable use and occasional vegetable use were not statistically significant in the analysis. The variables were measured for controls up to the date of interview and for cases up to the date of diagnosis.

Table 4 shows results of multivariate conditional logistic regression analysis. There was no significant difference in risk of breast cancer noted among women with various education levels when the number of pregnancies and other factors were taken in to account. The less number of pregnancies, dietary habits such as usage of roots & tubers (except tapioca or cassava), usage of chicken meat, drinking milk increased the breast cancer risk and usage of tapioca (Cassava) decreased the risk among women. Risk analysis was attempted among pre and post menopausal women separately and similar odds ratios were obtained. Consumption of tapioca (cassava) decreased risk of developing breast cancer among pre-menopausal women and less number of pregnancies, consumption of roots & tubers, usage of chicken meat increased the risk of breast cancer among postmenopausal women.

Table 4. The Results of Multivariate Analysis

Variables	Cases	Controls	OR (95% CI)	P Trend/Heterogeneity
Number of Pregnancies				0.000/0.000
≥ 5	57 (21.6)	267 (33.7)	1 Reference group	
4	35 (13.3)	126 (15.9)	1.51 (0.89, 2.54)	
3	66 (25.0)	177 (22.3)	2.39 (1.43, 4.01)	
2	67 (25.4)	140 (17.7)	3.14 (1.80, 5.47)	
1	22 (8.3)	43 (5.4)	3.63 (1.79, 7.34)	
No Preg	17 (6.4)	39 (4.9)	4.65 (1.73, 12.5)	
Roots & tubers/week (ExceptTapioca)				0.016/0.025
< 2 times	99 (37.5)	365 (46.1)	1 Reference group	
2-4 times	112 (42.4)	306 (38.6)	1.53 (1.09, 2.15)	
≥ 5 times	53 (20.1)	121 (15.3)	1.56 (1.01, 2.41)	
Chicken use				0.016
No	25 (9.5)	118 (14.9)	1 Reference group	
Yes	239 (90.5)	674 (85.1)	1.84 (1.09, 3.09)	
Milk Drink				0.006
Occasional	209 (79.2)	691 (87.2)	1 Reference group	
Regular	55 (20.8)	101 (12.7)	1.78 (1.17, 2.69)	
Tapioca use/week				0.002
≤ 2 times	226 (85.6)	617 (77.9)	1 Reference group	
>3 times	38 (14.4)	175 (22.1)	0.55 (0.37, 0.83)	

Discussion

In the present study, in addition to the less number of pregnancies, consumption of roots and tubers (except tapioca or cassava), milk drinking, consuming chicken meat were found to be related to breast cancer risk. Interestingly in the present study, consumption of tapioca was found to be a protective factor against breast cancer. Although the association was observed both in pre- and post-menopausal breast cancer risk, only pre-menopausal breast cancer risk was statistically significantly related to tapioca consumption. There are several possible explanations for this finding. Dietary fiber is derived from the tapioca pulp fiber that is a by-product of tapioca starch milling operations. The tapioca fiber may be refined through an enzymatic destarching step to provide a fiber comprising at least 70% total dietary fiber, of which at least 12% is soluble dietary fiber (www.freepatentsonline.com). Regarding the effect of dietary fiber on risk of breast cancer, earlier studies are inconsistent. Recently, however, the UK Women's Cohort Study (UKWCS), which followed 35,792 women including 17,781 postmenopausal women and 15,951 pre-menopausal women during the period between 1995 and 1998, reported that consumption of fiber-rich vegetables is suspected to reduce risk of breast cancer in pre-menopausal women by 50%, but not in postmenopausal women (Cade et al., 2007). Secondly, thiocyanate (SCN), which is known to be anticarcinogenic (Hayes et al., 2008), may come into the body by eating Tapioca. Cassava, from which tapioca is produced, contains cyanogenic glucosides. Although cooking detoxifies them, thiocyanate is produced from residual cyanide (Padmaja, 1995). Another possible explanation is that frequent tapioca consumption is a surrogate parameter related to ethnic backgrounds of Kerala people since tapioca is a traditional food item in Kerala (Edison et al., 2006). In other words, frequent tapioca consumption may be related to lifestyles and genetic backgrounds prevalent in “native” Kerala people.

High fat intake is suspected to be related to breast cancer (Rozanim et al., 2004). Dinavahi et al. reported that increased risk of breast cancer is solely dependent on total fat intake (2001). The notion is likely to be explained by the strong relationship between breast cancer risk and obesity among postmenopausal women (WCRF/AICR report), whose major source of estrogen is male hormones transformed into estrogen in lipid tissue (www.aicr.org). The consumption of chicken meat was reported to be associated with risk of breast cancer (Dinavahi et al., 2001) and higher consumption of fried food items was associated

with increased risk of breast cancer (Jarvinen et al., 1997). The association of breast cancer risk with drinking milk everyday in the present study may also related to high calorie intake and resultant obesity. It is of note, however, that increased consumption of dairy products like whole milk are also known factors to increase the risk of breast cancer (Toniolo et al., 1994; Hjartkar et al., 2001).

Known risk factors of breast cancer include mainly reproductive factors. Increased risk is correlated with early menarche, nully parity, late aged first birth, late menopause and hormonal factors (Stewart and Kleihues, 2003). Breast cancer risk has been reported to increase with decreasing number of pregnancies and high parity by many studies, including those conducted in Asian countries (Rao et al., 1999; Yavari et al., 2004). The association with the number of pregnancies was confirmed in the present study as well. In the present study the lowest breast cancer risk was observed among those with 5 or more pregnancies. McCredie et al. (1998) reported that the lowest risk of among women with at least 4 children.

Older age at any delivery may confer an increased risk (Yavari et al., 2004; Hirose et al., 1999). In our study, the age at last pregnancy was not significantly related to breast cancer risk. On the other hand, age at marriage and age at first pregnancy was a significant risk factor for breast cancer only in univariate analysis. However, once the effect of the number of pregnancies was taken into account, the association was not significant. The age at first full term pregnancy, which is known to be strongly related to breast cancer risk, was not available in this study. Early ages at menarche was shown to increase breast cancer risk. In the current study, we did not find any statistical significance between age at menarche and risk of breast cancer. It was reported that the association of breast cancer risk with early age at menarche was particularly evident among women with a positive family history and genetic susceptibility (Becher et al., 2003; Hirose et al., 1999). However, we did not have information on family history in the present study. The risk for breast cancer increases significantly with increasing concentrations of both oestrogens and androgens (Key et al., 2002).

The WCRF/AICR report concluded that increased physical activity reduces breast cancer risk. In the present study, however, information on physical activity was not collected. The risk of breast cancer has been reported to be associated with socio economic status (Dinavahi et al. 2001; Yavari et al., 2004; Finny et al., 2003). In the present study, breast cancer risk was significantly higher among women with higher educational levels. However, the association became non-significant once the number of pregnancies and other factors were taken into account using multivariate analysis.

The present study showed that less number of pregnancies and dietary habits such as consumption of roots & tubers (except tapioca), usage of chicken meat, milk drinking increased the breast cancer risk. But usage of tapioca decreased the breast cancer risk. The association with education level was not significant after taking into account other risk factors. The increase of breast cancer risk by usage of chicken meat and drinking milk in the present study may be explained by resultant higher calorie intake. The associations of breast cancer risk with higher dietary consumption of roots and tubers (except tapioca) and lower intake of tapioca are of interest. Separate analyses were done in both pre and post-menopausal breast cancer women but statistical significance was not uniformly seen. Consumption of tapioca (cassava) decreased risk of developing breast cancer among pre-menopausal women. Less number of pregnancies, consumption of roots & tubers, usage of chicken meat increased the risk among post-menopausal women. The present study highlights the need of awareness on the association of breast cancer risk with dietary and reproductive factors. The increasing need of breast cancer prevention program responsive to the cultural practices of the people are highly warranted as such study results may be used as leads of cancer control programs especially in a rural area.

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