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OCCUPATIONAL EXPOSURE AND LIFESTYLE FACTORS AND RISK OF BREAST CANCER IN THE CENTRAL REGION OF TUNISIA: A CASE-CONTROL STUDY

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ABSTRACT

Known risk factors of breast cancer only explain a minority of cases. Other environmental, occupational and lifestyle-related risk factors have also been suggested to play a role. The aim of our study was to assess the relationship between lifestyle and occupational factors and breast cancer risk. In order to do this, a case-control study was conducted on 110 women with histological confirmed breast cancer during the 2013–2016 period at Farhat Hached University Hospital, Sousse, Tunisia, and 150 cancer-free controls matched by age (within 5-year intervals). A semi-quantitative estimate of exposure to self-reported occupational risk factors taking into account the daily exposure frequency (H), the exposure duration in years (D) and the exposure level (N) was recorded. One occupational condition, pesticide exposure, was independently associated with breast cancer (pa=0.003; ORa=8.68 95%CI [2.11-35.55]). Being overweight and dairy product consumption were also factors independently associated with breast cancer (pa=0.000; ORa =3.44 95% CI = [1.82,6.52] and pa=0.001, ORa= 6.74 95%CI = [2.13-21.27] respectively). Our results suggest a role for lifestyle and work-related factors in increasing the risk of developing breast cancer.

1. Introduction

Breast cancer is a common and serious condition. It represents the leading cause of cancer mortality and morbidity in women in all age groups [1]. As a result, the World Health Organization (WHO) considers breast cancer a public health priority and a major problem for women around the world [2].

In 2014, breast cancer ranked as the most common cancer in Tunisia with an incidence rate of 18.26 / 100 000 F / year for women. This has a significant impact on female mortality as 22 % of 2800 women diagnosed with breast cancer died [3].

Although the association of breast cancer risk with environmental or occupational exposures remains unknown or disputed [4 ,5], there is a growing understanding of the complexity of the disease mechanism and the diversity of potential etiological agents [6].

Overall, the known risk factors, mainly related to hormonal and reproductive life (age at first menses, parity, age at full term first pregnancy, age at last menstruation, etc ...) weight gain after menopause, and/or Hormone Replacement Therapy, which results in prolonged and increased exposure to estrogen, explain only a minority of cases [7].

As for the susceptibility genes known to date, they only explain about a third of the genetic share in breast cancers [8].

Other environmental, occupational and lifestyle-related risk factors have so far been little explored in the genesis of breast cancer [4].

With the exception of ionizing radiation, none of them has been clearly identified so far in epidemiological studies as being at the origin of an increased risk [9].

No studies to our knowledge have been made to this effect in Tunisia. The objective of our study was to identify the professional and lifestyle factors associated with breast cancer among women in the Tunisian center.

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2. Material and methods

To meet our objective, we conducted a case-control study at Farhat Hached University Hospital in Sousse, Tunisia after gaining hospital approvals.

The cases were breast cancer patients, confirmed by an anatomopathological examination, and followed either at the outpatient clinic and / or at the carcinology ward of Farhat Hached University Hospital of Sousse during the period between January 01, 2013 and December 31, 2016.

The inclusion criteria were patients who had been working at the time of the first symptoms of the disease or who had previously worked and who had consented to the questionnaire. Patients who did not engage in work and who did not consent to participate in the study were excluded.

The controls were recruited at random and during the same period and were women consulting and/or hospitalized at the different departments of Farhat Hached University Hospital: occupational medicine, dermatology, internal medicine, rheumatology, gynecology, general surgery and who voluntarily agreed to participate in our study. These patients must be free from self-reported breast carcinological pathology or other carcinological pathology. Controls were matched to cases by age ± 5 years.

Data collection

A questionnaire was conducted by direct contact with the patients after consent to participation. Data collection and interviews were conducted by the same investigator. Information on socio-demographic characteristics, medical-surgical history, family history of cancer, hormonal and reproductive life, alcohol and tobacco use, recreational activities and eating habits were collected. The BMI calculation was based on weight and height at the time of cancer diagnosis.

All lifestyle and habit-related factors prior to breast cancer diagnosis were collected by self-report. Frequency of consumption of vegetables, red meat, fat and consumption of dairy products was considered low if weekly consumption ≤1, average if consumption is between 2 and 3 and frequent if consumption is greater than 4 times a week [10]. For physical activity, we mainly considered the practice or not of a regular physical activity of at least 30 minutes at least 4 times a week [11]. Information also on the frequency of the use of dyeing for hair, the use of deodorants and armpit shaving as well as the duration of external sunshine was collected.

The detailed and exhaustive professional curriculum has been completed. The search for a possible exposure to the occupational risk factors implicated in the literature in the occurrence of breast cancer and a semi-quantitative estimate of the exposure to these factors (self reported) taking into account the daily exposure frequency (H), duration of exposure in years (D) and exposure level (N) was achieved. For the exposure level, it was evaluated as follows: baseline normal exposure: 0, light exposure: 1, moderate exposure: 2 (direct contact with the product) and significant exposure: 3 (very close handling).

An exposure index (I) for each product was calculated to approximate the intensity of exposure to the product. For this, we used the duration of exposure in years (D), the number of hours of daily exposure (H) and the level of exposure (N). This index (I) was the product of the multiplication of the number of hours per day (H), the duration of exposure (D) and the exposure level (N) as follows: I = H x D x N [12].

The possible exposure to an exhaustive list of the products incriminated in the literature was sought, such as pesticides, organic solvents, detergents, paints, polycyclic aliphatic hydrocarbons (PAHs), incinerator discharges, ethylene oxide, metal dust, textile dusts, as well as exposure to ionizing radiation and magnetic fields.

Statistical analysis

For data analysis, variable differences between the patients and controls were assessed by Chi-square test. Logistic regression model was used to calculate the Odds Ratio (OR) and 95% confidence intervals (95% CI). The associations between cancer and risk factors were shown by Odds Ratio. Data were analyzed using SPSS software version 18. Level of significance was considered at $P < 0.05$.

3. Results

The mean and standard deviation of dimensional change, flow and gelation time of irreversible hydrocolloid impression material modified with distilled water and 1.0% of chitosan solution are given in Table 1. The chitosan-modified group exhibited slightly more dimensional changes and flow characteristics compared to the control group. However, statistically, no significant differences were observed between the groups (Table 1). More gelation time was demonstrated by 1.0% chitosan solution modified irreversible impression materials compared to the control group. A significant difference (p=0.01) in gelation time was observed between the two groups (Table 1).

Variables	Case		Controls		P value	OR (95% CI)
	N	%	N	%		
Education:						
Illiterate	12	10,9	25	16,6	0,12	0,86[0,36-2,03]
Elementary school	40	36,4	41	16		1
Secondary school	31	28 ,2	52	34,6		1[0,8-1,3]
Higher education	27	24,5	32	21,3		1,27 [0,79-2,01]
Marital status						
Never married	13	11,8	14	9,3	0,36	1
Married	91	82,7	124	82,7		0,79 [0,35-1,76]
Widowed	5	4,5	5	3,3		1,07 [0,25-4,59]
Divorced	1	0,9	7	4,7		1,1 [0,9-1,5]
Age at menarche (years):						
≤13	73	66,4	106	70,7	0,07	1
14-15	33	30	36	24		1,33[0,67-2,32]
≥16	4	3,6	8	5,3		0,72[0,21-2,50]
Age at last menstruation (years)						
<45	22	47,8	33	57,9	0,25	1
45-50	14	30,4	18	31,6		0,40[0,12-1,25]
≥51	10	21,7	6	10,5		0,46[0,13-1,59]
Age at first full-term pregnancy						
<22	31	34	20	15,6	0,69	1
22-24	14	15,2	34	26,6		0,69 [0,33-1,44]
25-27	23	25	43	33,6		1,16 [0,62-2,15]
>27	24	26,1	31	24,2		2 [0,92-4,34]
Pregnancy number						
0	18	16,4	26	17,3	0,23	1
1	15	13,6	22	14,7		0,63[0,31-1,20]
2	19	17,3	49	32,7		0,62[0,29-1,32]
≥3	58	52,7	53	35,3		0,35[0,18-0,67]
Oral contraceptive use						
Never	87	79,1	119	79,3	0,82	1
Ever	23	20,9	31	20,7		1,07[0,58-1,95]
Family breast cancer history:						
No	92	83,6	139	92,7	0,03	1
Yes	18	16,4	11	7, 3		2,25 [1,03-4,89]

Table 1. Selected demographic characteristics of breast cancer cases and controls in Tunisia.

At the univariate analysis, a statistically significant increase in the risk of breast cancer occurrence was observed in overweight and obese OR= 2.83 95%CI [1.65-4.85], p <10 ⁻³. This risk is all the more important in women aged 50 and over OR = 3.90 95%CI [1.46-10.45], p = 0.007. A statistically significant association was also found in cases of heavy weekly dairy product consumption; OR = 3.32 95%CI [1.46-7.54], p = 0.003 and frequent fat consumption OR = 3.97 95%CI [1.58-9.97], p = 0.02 (Table 2). No correlation was found with other lifestyle factors namely, the use of hair dye, armpit shaving and the use of deodorants as well as external sunlight.

Variables	Case		Controls		p value	OR (95% CI)
	N	%	N	%		
Body mass index (kg/m2)						
≤25	45	36,3	101	61,7	10^{-3}	1
>25	65	63,7	49	38,3		2,83 [1,65-4,85]
Vegetables and fruit consumption frequency						
Rare/no	0	0	0	0		-
Moderate	11	10	20	13,3	0,41	1
Frequent	99	90	130	70,7		0,82 [1,49-1,35]
Red meat consumption frequency						
Rare/no	17	15,5	12	8		1
Moderate	34	30,9	64	42,7		1,77[0,78-4,01]
Frequent	59	53,6	74	49,3	0,28	0,66[0,38-1,14]
Dairy products consumption frequency						
Rare/no	8	7,3	31	20,7	0,003	1
Moderate	34	30,9	13	8,7		0,40[0,17-0,92]
Frequent	68	61,8	106	70,7		4,07[2-8,27]
Fat products consumption frequency						
Rare/no	6	5,5	28	18,7		1
Moderate	73	66,4	110	73,3	0,03	1,16 [0,62-2,15]
Frequent	31	28,2	12	8		2 [0,92-4,34]
Regular Physical activity						
No	99	90	110	73,3		1
Yes	11	10	40	26,7	0,001	0,35[0,18-0,67]
Hair dye use						
Moderate	67	60,9	111	74		1
Frequent	43	39,1	39	26		0,54[0,32 -0,92]
Deodorants use						
Moderate	39	35,5	50	33,3		1
Frequent	71	64,5	100	66,7	0,25	0,54[0,32 -0,92]
Sun exposure duration						
<1hour/day	36	49, 3	37	50,7	0,15	1
≥1hour /day	74	39,6	113	60,4		0,67 [0,39-1,16]

Table 2. Association of lifestyle factors and breast cancer

The different sectors in which our participants were assigned during their professional activity are shown in Table 3 below. On average and regardless of their case-control status, women had only one job and remained around 16 ± 9 ,03 years in their respective jobs. By grouping the current and past business sector, it was noted that the majority of the cases surveyed in the textile sector (20.9%) and majority of controls in the administrative sector (29.3%). The factors significantly associated with breast cancer were the agriculture sector OR= 3.22 95%CI [1.26-8.20], p = 0.01 and seniority in the electronic industry OR = 1.41 95%CI [1.02-1.99], p = 0.04. In contrast, the administration sector was associated with a risk reduction OR = 0.21 95%CI [0.10-0.46], p. $<10^{-3}$.

Professional activitysector		**Type**		Pvalue	OR (95%CI)
		Cases	Controls		
Agriculture	Number n (%)	15 (13,6)	7(4,7)	**0,010**	3,22[1,26-8,20]
	Senioritym±SD	19,93±11,31	18,86± 7,47	0,82	1,01 [0,92-1,10]
Education	Number n (%)	19(17,3)	22(14,7)	0,56	1,21 [0,62-2,37]
	Senioritym±SD	20,84±8,01	19,09±12,21	0,59	1,01[0,95-1,08]
Health	Number n (%)	11(10)	11(7,3)	0,44	1,40[0,58-3,36]
	Senioritym±SD	21,64±9,71	14,55±7,42	0,082	1,10[0,98-1,23]
Electronicindustry	Number n (%)	8(7,3)	10(6,7)	0,84	1,09[0,41-2,87]
	Senioritym±SD	20,75±7,81	8,80±3,88	**0,045**	1,41[1,02-1,99]
Plastic industry	Number n (%)	7(6,4)	4(2,7)	0,21	2,48[0,70-8,69]
	Senioritym±SD	14,29±6,21	16,25±10,30	0,66	0,96[0,80-1,14]
Textile	Number n (%)	23(20,9)	27(18)	0,55	1,20[0,64-2,23]
	Senioritym±SD	13,39±8,70	13,74±7,37	0,87	0,99[0,92-1,06]
Hotel and catering trades	Number n (%)	7(6,4)	4(2,7)	0,21	2,48[0,70-8,69]
	Senioritym±SD	11,29±5,46	7±2,16	0,12	1,85[0,83-4,13]
Administration	Number n (%)	9(8,2)	44(29,3)	**0,000**	0,21[0,10-0,46]
	Senioritym±SD	17±7,93	15,57±9,97	0,68	1,01[0,94-1,09]
Leather and shoesindustry	Number n (%)	4(3,6)	6(4)	1	0,90[0,24-3,28]
	Senioritym±SD	14,25±8,50	16,33±8,45	0,67	0,96[0,81-1,14]
Hairdressingsector	Number n (%)	2(1,8)	4(2,7)	1	0,67[0,12-3,15]
	Senioritym±SD	16±5,65	8,25±2,87	-	-
Others	Number n (%)	5(4,5)	11(7,6)	0,12	0,29[0,061-1,37]
	Senioritym±SD	9±5,32	9,56±10,58	0,22	1,1[0,94-1,28]

m :meanvalue/SD:standard deviation

Table 3. Odds Ratios by Industry and by Duration of Employment in an Industry

As for the evaluation of the occupational exposure to the detailed products, the factor significantly associated with breast cancer was exposure to pesticides (OR = 3.22 95%CI [1.22-8.20], p = 0,01). Table 4 below summarizes the characteristics of the exposures found in cases and controls.

Exposure		Cases	Controls	Pvalue	OR (95%CI)
Pesticides	frequency n (%)	15(13,6)	7(4,7)	**0,010**	3,22 [1,22-8,20]
	EI : m±SD	117,47±87,67	102,14±43,38	0,65	1[0,99-1,01]
Plastics	frequency n (%)	7(6,4)	4(2,7)	0,21	2,50[0,71-8,7]
	EI : m±SD	218±133,55	265±161,14	0,57	0,99[0,98-1]
Organic solvents	frequency n (%)	16(14,5)	13(8,7)	0,13	1,79[0,82-3,90]
	EI : m±SD	282,75±194,75	196,46±119,27	0,18	1[0,99-1]
Detergents	frequency n (%)	6(5,5)	9(6)	0,86	0,91[0,31-2,64]
	EI : m±SD	132,33±117,86	80,67±49,58	0,29	1[0,99-1]
Textile dusts	frequency n (%)	21(19,1)	25(16,7)	0,61	1,18[0,62-2,23]
	EI : m±SD	216,24±175,61	215,56±162,83	0,98	1[0,99-1]
Ionizing radiation	frequency n (%)	1(0,9)	0	-	-
	EI : m±SD	56	0	-	-
Magnetic fields	frequency n (%)	4(3,6)	6(4)	1	0,90[0,24-3,28]
	EI : m±SD	132±93,48	115±83,61	0,7 3	1[0,98-1,01]

EI :exposure index /m :mean value/SD:standard deviation

Table 4. Table summarizing the frequency and intensity of occupational exposures of cases and controls.

After multivariate analysis by binary logistic regression, the lifestyle factors independently associated with breast cancer were: overweight (ORa = 3.44 95%CI [1.82-6.52], pa $<10^{-3}$) and frequent dairy product consumption (ORa= 6.74 95%CI [2.13-21.27], pa $<10^{-3}$). Pesticide exposure was also independently associated with an increased risk of breast cancer in our study population (ORa = 8, 68 95%CI [2.11-35.55], pa $<10^{-3}$). A summary of variables independently associated with the risk of breast cancer occurrence after binary logistical regression is presented in Table 5.

	Cases Number (%)	Controls Number (%)	Pb	ORb CI	Pa	Ora CI
Overweight and obesity	65(63,7)	49(38,3)	0,000	2,83 [1,65-4,85]	0,000	3,44 [1,82, 6,52]
Dairy products consumption	102(92,7)	119(78,7)	0,003	3,32 [1,45-7,54]	0,001	6,74 [2,13-21,27]
Family history of breast cancer	18(16,4)	11(7,3)	0,003	2,25 [1,03-4,89]	0,035	3,13 [1,08-9,05]
Pesticides	15(13,6)	7(4,7)	0,010	3,22 [1,22-8,20]	0,003	8,68 [2,11-35,55]

Table 5. Summary of variables independently associated with the risk of breast cancer occurrence after binary logistic regression

4. Discussion

This study illustrated the role of lifestyle and occupation-related factors in the etiopathogeny of breast cancer. This case-control study showed that overweight, frequent consumption of dairy products and occupational exposure to pesticides were associated with the risk of breast cancer. In our series, there is no difference in the age, geographical origin and study period minimizing selection bias.

In Tunisia, no epidemiological study has been carried out to date on the possible occupational origin of breast cancer, with the same assessment of occupational exposures for cases and controls, also taking into account past exposure.

Consideration of some non-occupational factors such as history of breast pathology, diet and lifestyle is one of the advantages of our study that allowed the analysis with the control of confounding variables. However, the study encountered some limitations such as the low proportion of women in professional roles explaining the sample size and the retrospective nature making it difficult to establish causal links. Another limitation of the study is the possible memory bias; cases would be more likely to remember exposures.

The causes of the occurrence of breast cancer are multiple and incompletely understood, whether they are environmental, occupational or lifestyle factors, factors of genetic susceptibility or interactions between genes and the environment [13].

Our results are in agreement with the data in the literature. Indeed, the relationship between BMI and the risk of breast cancer is complex.

The different epidemiological studies had observed a variable association according to the menopausal status of women [14,15].

A case-control study conducted in central Tunisia by Msolly A et al, involving 400 cases and controls, showed that BMI at the time of diagnosis was positively correlated with the risk of breast cancer in postmenopausal women with OR = 1.7 95% CI [1.1-2.9] and OR = 2.1 95% CI [1.1-3.9] for women with a BMI between 23-27 and 27-31, respectively compared with women with BMI <19 and without risk association in pre-menopausal women [16]. It has also been shown in some studies that excessive fat leads to increased production and increased time exposure to steroid hormones; adipose tissue is also a storage site and metabolism of sex steroids. After menopause, the aromatization of androgens in adipose tissue is one of the most important sources of circulating estrogen [17].

As for the role of food, the association between the risk of breast cancer and the main components of human nutrition including fruits and vegetables, dairy products, and meat has been the subject of many studies. The hypothesis of the role of fat in increasing the risk of breast cancer is linked to the fact that there is a correlation between national fat consumption per individual and breast cancer mortality found in a few studies [18]. Dairy products were often incriminated in the genesis of breast cancer. High consumption was correlated with high consumption of fat; dairy products contain pesticides that could act as xenoestrogens, but also growth factors (IGF1) that can promote tumor growth. In contrast, calcium, vitamin D and linoleic acid could have anti-carcinogenic effects [19]. Since the late 1970s, the incidence of breast cancer has risen sharply and coincides with increasing access of women to work. It therefore seems interesting to study occupational risk factors for breast cancer. The evaluation of occupational exposures among our participants according to the nature of the professional activity revealed an exposure to different products that have been suggested in the literature in the past as increasing the risk for developing breast cancer, including pesticides. Several studies have found that women farmers exposed to pesticides have an increased risk of breast cancer. The US study conducted by Duell EJ et al in 2002 with 862 cases and 790 controls had shown a significant risk in women farmers with OR = 1.2 95% CI [0.8-1.7], also an OR high in those who reported being in the field during or shortly after pesticide application (OR = 1.8, 95% CI = 1.1-2.8) and for those who reported not wearing protective garments (OR = 2.0, 95% CI = 1.0-4.3) [20]. The pesticides that have been implicated in the increased risk of breast cancer are mainly organochlorine is the most prominent of which is “dichlorodiphenyltrichloroethane” (or DDT), which was used in developed countries until the 1960s as an insecticide and has a half-life greater than 60 years. It is currently banned in most Western countries but continues to be widely used in developing countries. Several of its active isomers including pp'DDT and p, p'-DDE (dichlorodiphenyldichloroethylene) are estrogenic and bind to estrogen receptors [20]. In the Canadian study by Band et al, a significant association was found in pre- and post-menopausal women and the risk of breast cancer among those working in the fruit and vegetable culture who frequently handle pesticides (OR = 1.35IC95 % [1.00-1.82]) [22].

Indeed, rural farm workers and their families who may be exposed to higher doses of polychlorinated pesticides, such as DDT, compared to the general population, have been reported to have a higher incidence of breast cancer compared to unexposed populations [23]. However, retrospective studies have produced conflicting results due to limitations such as small sample size, difficulty in measuring exposure to pesticides

and to estimate the correlation between blood pesticide concentrations and breast cancer progression [23].

Thus, the agriculture sector with exposure to pesticides deserves particular attention, especially since it is often a sector that escapes medical surveillance most often in Tunisia and subscribes to the anarchic use of pesticides which most often have dangerous effects on the health of the exposed. Poisoning by these pesticides sometimes results from poor work practices or neglect; in order to minimize pesticide exposure levels, a number of often simple and inexpensive rules must be followed.

5. Conclusions

Our results thus supported the role of lifestyle and work-related factors in increasing the risk of developing breast cancer. Other more in-depth, prospective, large-scale studies using objective biometrological tests (aimed at assessing exposures) are needed to better elucidate the risk factors for this cancer in Tunisia. Breast cancer thus appears as a multi-factorial disease. Knowing the full career history of women also allows for the evaluation of occupational exposures in an integrated way over time, or at different points in their lives, taking into account periods of vulnerability or latency. Improved methods of characterization of exposures will provide major elements for further investigation. An identification of the risk factors for breast cancer that can be acted upon, and a better understanding of the biological mechanisms involved, should facilitate implementation of effective prevention strategies associated with close monitoring of potentially exposed employees.

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