

Breast Cancer and Hormonal Intake among Egyptian Females



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In Egypt

Neoplasm account for
6.4% of all causes of death
in the young age group and
7.1% of all deaths

in the middle age group
as reported by

Ministry of Health and Population

Women Cancers

They form about **25% of all cancer cases** discovered in the period between 1999 & 2001 in Egypt.

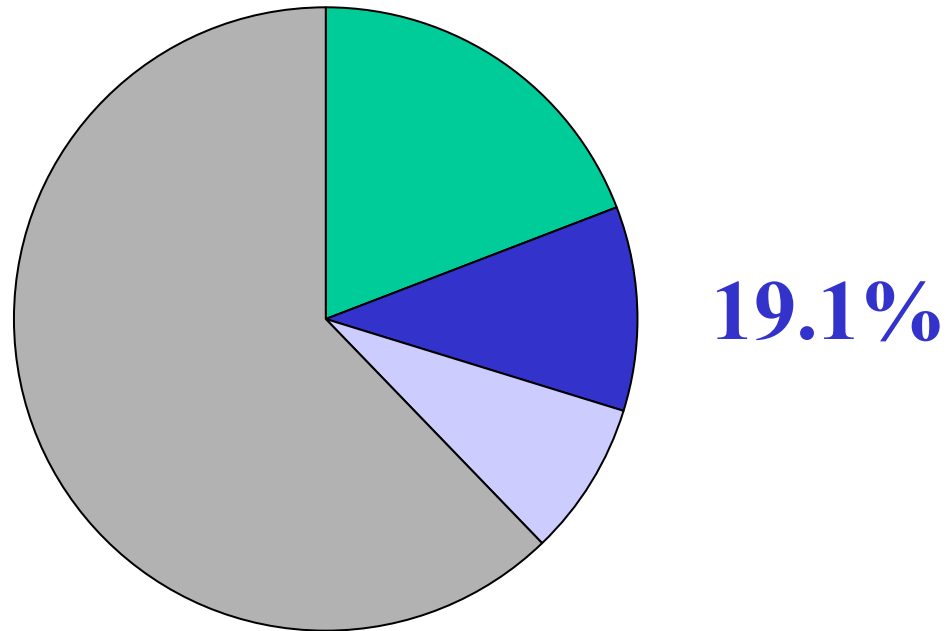
Carcinoma of the breast is the most prevalent cancer among Egyptian women and constitutes **29%** of National Institute of Cancer cases, and **33%** by the Alexandria Cancer Registry.

National Institute of Cancer (NIC)

The total **female cancers** that were admitted in 2001 were 2465 cancer cases.

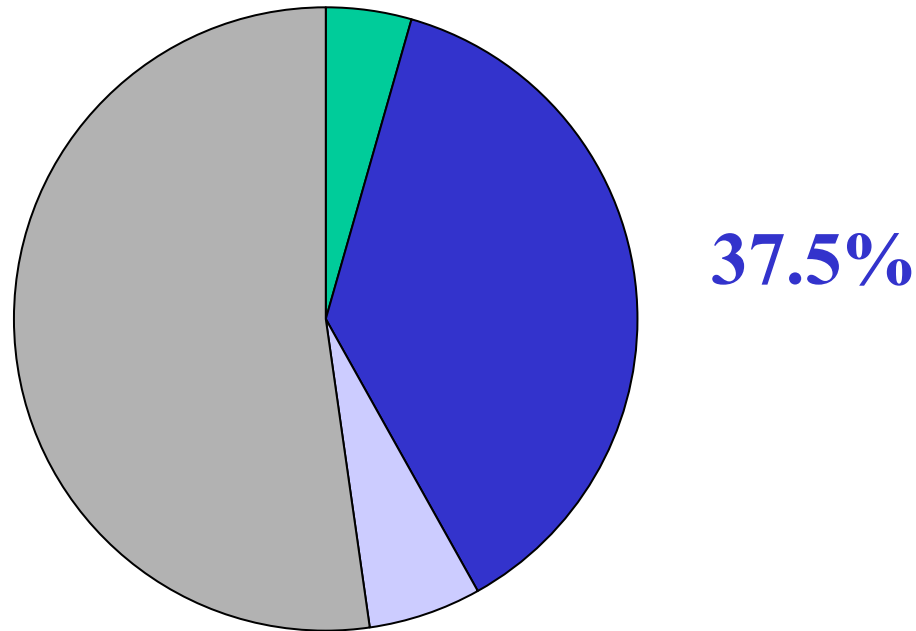
Admissions of breast cancer cases were the most frequent (81%), followed by ovarian cancer, (7.2%). Endometrial carcinoma constituted (4.6%).

Most Common Cancer Site (Male and Female), NCI, 2003



■ Urinary bladder ■ Breast ■ Lymphoma ■ Others

Most Common Cancer Site among Females, NCI, 2003



■ Urinary bladder ■ Breast ■ Lymphoma ■ Others

Cairo Breast Screening Trial (CBST)

Boulos et al, (2005) observed high rates of breast cancer among 4116 women who attended a Primary Health Centre for clinical breast examination (8 per 1000 at the first examination and nearly 2 per 1000 among those who attended for re-screening).

Omar et al, (2003) revealed that:

- The majority of breast tumors are **invasive duct subtype** and
- The profile of hormone receptors is positive for estrogen receptors and/or progesterone receptors in **less than half of cases.**

Women Cancer and Hormonal intake

- Women Cancers, as cancer of the breast, ovaries and endometrium are related to **hormonal intake**.
- Cancer of the breast could be enhanced by many factors; one of them is **estrogen**, whether endogenous or exogenous.
- It stimulates the growth of breast tumor cells with an increase in the levels of growth stimulatory factors like **transforming growth factor (TGF- alpha)**.

- Many studies have shown that **oral contraceptive (OC)** use is associated with an increase in a young woman's risk of breast cancer, although some studies suggest that the risk may be limited to recent use.
- There are data to suggest that **hormone replacement therapy (HRT)** with estrogen is associated with increased risk of developing breast cancer, which is proportionate to duration of use.

- A recent re-analysis of over 90% of breast cancer studies throughout the world showed an increased risk in breast cancer for women who used **post-menopausal hormones for 5 years or longer**.
- Most women using hormonal therapy (HT) for short-term treatment of vasomotor symptoms will not face measurable increases in their risk for breast cancer. That risk returns to baseline a few years after discontinuation of hormones (Nelson, 2003).

- Ross et al, (2000) provided a strong evidence in a case control study that the addition of a **progestin** to HRT **enhances** markedly the risk of breast cancer, OR= 1.24, relative to estrogen use alone OR= 1.1. These findings have important implications for the risk-benefit equation for HRT in women using combined hormonal replacement therapy (CHRT).
- **Endogenous estrogen and progesterone** could be assayed in blood while **exogenous hormonal intake** can only be assessed by thorough history intake.

Objective:

To study the association between breast cancer and history of intake of exogenous reproductive hormones (estrogen, progesterone and hormonal replacement therapy HRT) among Egyptian females.

Subjects and Methods

Study design

A case-control study was carried out at National Institute of Cancer (NIC) and Ain Shams University Hospitals during the period from October 2005 to October 2006.

Subjects

- **Breast cancer cases (198)** were recruited from Surgery unit of Faculty of Medicine in Ain Shams University hospitals and National Cancer Institute in Cairo.
- **Inclusion criteria** for selection of cases were age < 60 years, no family history of breast or ovarian cancer, no previous history of breast cancer, no previous benign breast disease, no occupational exposure to ionizing radiation. These criteria were included to control for all factors that would confound the role of exogenous hormones.
- All newly diagnosed cases fulfilling the inclusion criteria were surveyed on a daily basis during the estimated period of the execution phase, and included in the study after obtaining an informed consent.
- After a postoperative pathological examination, any case proven to be **benign** was excluded from the study.

Controls

They were defined as apparently healthy females (153) were selected from inpatients Department of Ophthalmology, Ain Shams University hospitals.

They were group matched for age with breast cancer cases. Inclusion criteria for selection of controls are the same as cases except for the presence of any breast lump.

Sample size

- Sample size was calculated taking into consideration the prevalence of the least prevalent risk factors in the general population, particularly the intake of hormonal contraceptives. Such figure was obtained after conduction of a pilot study that was conducted on females with and without breast cancer to estimate the extent of their use for exogenous estrogens (which was found to be 7 %).
- Assuming an association between female breast cancer and history of intake of reproductive hormones with an **Odds Ratio of 2**. The calculated sample size was **350**, for a 1:1 case-control study. All calculations were performed using the 6th version of Epi-Info statistical package.

Tools:

All cases and controls were subjected to the following:

I-Interview questionnaire:

It was designed to include questions about socioeconomic data, special habits as active and passive smoking, reproductive history, history of intake of reproductive hormones as contraceptive hormones, hormonal replacement therapy, and family history of the diseases.

II-Anthropometric measures:

Some anthropometric measurements were determined for both cases and controls. Measurements were done with privacy at the hospital ward by a female doctor.

Body weight: It was measured by a spring balance scale for the nearest 0.5 kg, with light clothing and no shoes and the balance was titrated regularly by known weights. (13)

Height: Standing height was measured to the nearest 0.5 cm while the subject is bare footed. (13)

BMI was calculated by dividing the body weight in kilograms by the square of the height in meters (kg/m^2). According to American Society of Nutrition 2002, normal weight is a BMI > 18.5 to <25 , overweight is a BMI of 25 to <30 and obesity is a BMI ≥ 30 . (14) (I am still saying it is low for our culture)

Waist Circumference: Was measured just superior to the iliac crest of the pelvis at the level of umbilicus anteriorly. (15)

Hip Circumference: Was measured at the maximal protrusion of the buttocks. (15)

Waist and hip circumferences were taken to the nearest cm with a flexible measuring tape and then waist/hip ratio (WHR) was obtained by dividing the waist circumference by the hip circumference. Women with a WHR 0.80-0.84 were classified as centrally overweight, whilst women with a WHR >0.85 were classified as centrally obese.

III - Laboratory Investigations:

- 1- A sample of the breast cancer tissue drawn by the surgeon (during the operation) after extraction to investigate the pathology staging and typing of the tumour.**
- 2-Immuno-histochemistry was done to detect the Estrogen and Progesterone receptors**

Statistical analysis:

All data was coded, tabulated and then statistical analysis was performed using computer programmes:

- Access Computer Package
- SPSS Package version 12
- Microsoft Word Document 2003

The difference between cases and control groups was assessed using t tests for quantitative data, and Chi square tests for qualitative data.

Ethical considerations:

Written informed consent was obtained from all the study subjects after explanation of the study objectives.

Special room was processed for anthropometric measurements to assure privacy of all subjects. Confidentiality of all data was kept for all subjects.

Results

Socio- demographic characteristics:

Mean age: Cases was 46.3 ± 8.3 years and control group was 45.9 ± 8.0 years. No statistical difference in the age between cases and controls as they were previously matched ($p > 0.05$).

level of education: No statistical difference between cases and controls as regards education as they were previously matched ($p > 0.05$).

Residence (rural/urban, living near high voltage power lines or a cell phone station): No statistical difference between cases and controls as regards, but more breast cancer cases were living near a factory (Type of factory as: **Cement, Aluminum, Iron,** Electric home appliances, and Textiles) than controls, ($p < 0.05$).

Marital status, number of children, employment: No statistical difference between cases and controls ($p > 0.05$), cases had late age at first marriage but not statistically significant.

Socio-Demographic Data Breast Cancer Cases and Controls

Variables	Controls n= 153	Cases n= 198	P value
Mean Age (years)	45.9 ± 8.0	46.3 ± 8.3	> 0.05
Level of Education	%	%	
-Illiterate to Prep. School	80.4	81.8	>0.05
-Secondary to University	19.6	18.2	
Residence			
Rural	31.4	35.4	> 0.05
Urban	68.6	64.6	
Living Near a factory			
No	88.0	79.3	0.032
Yes	12.0	20.7	
Living Near High Voltage Electric Cables			
No	82.4	88.4	> 0.05
Yes	17.6	11.6	
Living Near Cell Phone Station			
No	88.2	89.3	> 0.05
Yes	11.8	10.7	
Marital Status			
Non married	2.0	1.0	> 0.05
Married	73.9	75.3	
Widow	20.9	17.2	
Divorced & Separated	3.3	6.6	
Mean Duration of marriage (years)	25.0 ± 10.0	23.7 ± 10.6	> 0.05
Mean age at first marriage(years)	18.6 ± 4.6	20.6 ± 5.4	> 0.05
No of Children	n=145	n=187	
	4.1 ± 1.8	3.8 ± 1.6	0.07 NS
Employment			
Work	24.8	23.2	> 0.05
House wife	75.2	76.8	

Cigarette Smoking, Exposure to Radiation and Surgery in Breast Cancer Cases and Controls

The breast cancer cases showed a statistically significant higher rate of current or past exposure to passive smoking at home ($p < 0.001$), but the duration of exposure was insignificant.

Regarding the history of exposure to radiation and surgery, it shows no statistical difference between cases and controls.

Cases were more exposed to breast trauma ($p < 0.05$).

Cigarette Smoking, in Breast Cancer Cases and Controls

Variables	Controls n= 153	Cases n =208	P value
Cigarette Smoking	%	%	>0.05
Smoking Status:	98.0	96.5	
Non Smokers	0.0	1.5	
Current Smokers	2.0	2.0	
Ex-Smokers			
Mean age at start of smoking (years)	n=3 28.3 ± 8.3	n=5 22.0 ± 8.3	>0.05
Current Exposure to Passive smoking at home			<0.001
Yes	46.4	63.1	
No	53.6	39.9	
Mean age at start of Current Exposure (years)	n=73 26.4 ± 13.8	n=113 21.9 ± 11.6	0.02
Index Smoker	n=71	n=117	0.06 >0.05 0.016
Husband	66.2	78.6	
Son	44.3	48.5	
Other family members	2.9	14.0	
Past history of Exposure to Passive Smoking at home	n=149	n=193	<0.001
Yes	31.5 68.5	60.1 39.9	
No			
Mean duration of Exposure to Past passive smoking(years)	n=47 19.3 ± 8.2	n=105 21.1 ± 10.0	>0.05

Exposure to Radiation and Surgery in Breast Cancer Cases and Controls

Variables	Controls n= 153	Cases n =208	P value
History of Mammography	3.3	1.0	>0.05
Age at Mammography	35.6 ± 9.6	47.0 ± 4.2	>0.05
No of times of Mammogr.	1 ± 0	2 ± 1.4	>0.05
History of X-ray			>0.05
Chest X-ray	26.8	24.4	>0.05
Head & Neck	5.2	5.1	>0.05
Back	2.0	5.6	
History of Breast Trauma	2.6	7.6	0.042
History of Radiotherapy	0.0	0.5	>0.05
Surgery in breast	7.2	10.1	>0.05
Needle Biopsy	0.0	25.0	0.27
Partial Breast Excision	27.3	15.0	>0.05
Breast Benign tumour	18.2	21.1	>0.05
Breast Malignant Tumour	0.0	5.3	>0.05
Hysterectomy	7.8	3.5	>0.05
Age at hysterectomy (years)	n=12 42.8 ± 5.3	n=6 46.0 ± 1.4	0.013

Exposure to Environmental Chemicals and Insecticides in Breast Cancer Cases and Controls .

Breast cancer cases were more exposed to insecticides ($p < 0.05$) and domestic Chemicals ($p < 0.001$), such as (chlorine, phenol and benzene) than controls.

There was possibility of residence near-by a factory ($p < 0.05$),

Exposure to Environmental Chemicals and Insecticides in Breast Cancer Cases and Controls .

Variables	Controls n= 153	Cases n =208	P value
Current and past exposure to Chemicals as Chlorine, phenol, benzene	% 28.8	% 57.1	0.000
Site of exposure to insecticides and to chlorine phenol, benzene at home	95.3	96.5	>0.05
Duration of Exposure(years)	10.0 ± 6.2	18.5 ± 11.4	0.000
Rate of Exposure			
Once/wk	20.5	31.9	0.023
>once/wk	61.4	46.0	
Daily	15.9	7.1	
Exposure to Insecticides	15.7	27.8	0.007
Site of Exposure at home	100	94.5	0.005
Rate of Exposure			
Once/wk	16.7	21.8	0.005
>once/wk	16.7	12.7	
Daily	58.3	49.1	

How Tumour was Discovered and Previous Problems in the Same Breast

- **86.4%** of cases had no previous problems in the same breast.
- **Only 4.1%** had previous history of benign tumour in the same breast.
- **97.0%** of cases discovered the tumour due to present of symptoms.

How Tumour was Discovered and Previous Problems in the Same Breast

Variables	Cases n= 197
How Tumour was discovered	%
▪Physician	3.0
▪Symptoms	97.0
Previous Problems in the same breast:	
▪No problems	86.4
▪Benign Tumour	4.1
▪Fatty cyst	1.5
▪Inflammatory Disease	3.6
▪Yellowish discharge	1.5
▪Bloody discharge	0.0
▪Milk	2.5
▪Nipple changes	0.0

Reproductive History:

No statistical difference was found between cases and controls as regards **marital status**, the age of menarche, irregularity of menses, duration of menstrual cycle, **parity**, **age at first birth and lactation**, menopausal status and age at menopause.

No difference as regards the age at first or last pregnancy, mean duration of breast feeding.

Breast Cancer cases differed significantly in having menstrual irregularity early at the age of Menarche.

They used to focus breast feeding on one of the breasts (**left breast**) ($p < 0.05$).

Reproductive History in Breast Cancer Cases and Controls

“Menstrual History”

Reproductive History	Controls n=153 %	Cases n=198 %	P value
Age at Menarche Mean ±SD	11.5 ± 4.7	10.6 ± 5.1	>0.05
History of Irregular Menses	16.3	30 15.2%	>0.05
Duration of menstrual cycle (days) Mean ±SD	n=150 30.1 ± 10.3	n=193 28.5 ± 8.5	>0.05
duration of Menstruation (days) Mean ±SD	n=150 5.0 ± 1.8	n=194 5.1 ± 2.2	>0.05
Time of Irregularity: At start of Menarche	n=23 0.0	n=27 23.1	0.014
All life	39.1	25.9	>0.05
At start and before cessation	0.0	11.1	>0.05

Reproductive History in Breast Cancer Cases and Controls

“Menopausal History”

Reproductive History	Controls n=153 %	Cases n=198 %	P value
Menopausal status	n=67	n=82	
Post menopausal	45.8	43.9	>0.05
Pre menopausal	54.2	56.1	
Age at Menopause (years)			
Mean ±SD	46.4 ± 5.9	46.7 ± 5.9	>0.05
Causes of Menopause:			
1-Pregnancy & Breast feeding	2.9	2.3	>0.05
2-Age	67.1	74.7	
3-Surgery	17.1	6.9	
4-Medicine	5.7	11.5	
5-Others	7.1	4.5	
Age of first cause (years)			
Mean ±SD	25.5 ± 2.1	41.0 ± 1.4	

Reproductive History in Breast Cancer Cases and Controls

“Pregnancy and Breast feeding History”

Reproductive History	Controls n=153 %	Cases n=198 %	P value
Age at first Pregnancy (Years) Mean ±SD	20.7 ± 4.6	22.5 ± 5.1	>0.05
Age at last Pregnancy (years) Mean ±SD	32.9 ± 5.1	32.8 ± 5.3	>0.05
duration of breast feeding (months) Mean ±SD	75.5 ± 21.8	75.4 ± 24.2	>0.05
Breast Feeding > from Left breast	3.7	13.2	0.01

History of intake of hormonal treatment:

No statistical difference was observed among cases and controls as regards the intake of hormonal contraception, mean duration of intake, intake of Hormonal Replacement Therapy, but the breast Cancer cases showed significantly longer mean duration of hormonal treatment for menstrual irregularity ($p < 0.05$).

Intake of Reproductive Hormones in Breast Cancer Cases and Controls

“Hormonal Contraception”

Intake of Reproductive Hormones	Controls n=153	Cases n=198	P value
Intake of Hormonal Contraception	% 43.8	% 41.1	>0.05
Duration of Hormonal Contraception	n=67	n=82	
Mean ±SD	6.1 ± 4.5	5.7 ±5.4	>0.05
Median	5.0	4.0	
Duration of Intake of hormonal contraception (Risk Groups)			
< 5years	44.8	52.4	
≥ 5 years	55.2	47.6	>0.05

Intake of Reproductive Hormones in Breast Cancer Cases and Controls "Hormonal Treatment"

Intake of Reproductive Hormones	Controls n=153	Cases n=198	P value
No of Intake of Curative Hormones	10.5	16.2	>0.05
Duration of Hormonal treatment of menstrual irregularity (months)	n=5	n=4	0.03 >0.05
Mean ±SD	12.0 ± 11.0	33.5 ± 57.9	
Median	6.0	5.0	
Duration of treatment of stoppage of lactation(months)	n=2	n=10	
Mean ±SD	5.5 ± 0.7	6.0 ± 6.7	>0.05 >0.05
Median	5.5	2.5	
Age of treatment of stoppage lactation(years)			
Mean ±SD	38.5 ± 2.1	32.1 ± 7.8	0.59
Hormonal Replacement Therapy			
	1.4	3.2	>0.05
Cause of intake:			
Menopause	1	0.0	
Hysterectomy	0.0	3	0.046

Anthropometric measurements:

No statistical difference between cases and controls as regards:

- **body mass index grades,**
- **waist hip ratio.**

No difference was observed among pre and post-menopausal.

Anthropometric Measurements in Pre and Post Menopausal Women.

	Controls		Cases		P value
	%		%		
Body Mass Index Grade:	n=149		n=181		>0.05
I-	10.7		5.5		
II-Overweight	24.8		26.0		
III- Obesity	55.7		51.4		
IV- Massive Obesity	8.7		1.1		
Waist/Hip Ratio Grades	n=151		n=188		>0.05
< 0.8	5.3		6.4		
≥ 0.8	94.7		93.6		
	Pre-menopausal		Post-menopausal		
	Controls	Cases	Controls	Cases	
	%	%	No %	No %	
Body Mass Index Grade:	n=79	n=98	n=70	n=83	>0.05
I-	12.7	6.1	8.6	4.8	
II-Overweight	22.8	22.4	27.1	30.1	
III- Obesity	55.7	57.1	55.7	44.6	
IV- Massive Obesity	8.9	0.0	8.6	20.5	
Waist/Hip Ratio Grades	n=81	n=105	n=70	n=83	>0.05
< 0.8	8.6	9.5	1.4	2.4	
≥ 0.8	91.4	90.5	98.6	97.6	

Pathological Findings:

- **The majority of breast tumours were of the ductal type** as found in the whole epidemiological sample.

Regarding age distribution no difference between the pathological classifications as the 3 types increase as the age increases.

Type of Carcinoma According to Different Age Groups of Breast Cancer Cases

Age groups (Years)	Type of Breast Carcinoma		
	Ductal n=338 %	Lobular n=5 %	Mixed n=8 %
24 - < 35	8.3	0.0	25
35 - < 45	31.4	20.0	25.0
45 - < 59	60.4	80.0	50.0

Pathological Findings:

- The profile of hormone receptors is positive for estrogen receptors and/or progesterone receptors in less than half of cases.
- Estrogen and progesterone receptors **percentage** increase with increasing age groups, but no statistical difference was observed.

Grades of Immuno-reaction of Estrogen and Progesterone Receptors among different age groups

Age group (years)	Estrogen Receptors Grades of Immuno-reaction (n=121)		
	Mild	Moderate	Marked
24 - < 35	0	10.7%	6.3%
35 - < 45	32.7%	39.3%	37.5%
45 - < 59	67.3%	50%	56.3%
Total	40.5%	46.3%	13.2%
	Progesterone Receptors Grades of Immuno-reaction (n=115)		
	Mild	Moderate	Marked
24 - < 35	2.8%	9.7%	7.7%
35 - < 45	40.8%	35.5%	15.4%
45 - < 59	56.3%	54.8%	76.9%
Total	61.7%	27%	11.3%

Estrogen receptors:

46% of the studied cases showed moderate immuno-reaction, 40.5% showed mild immuno-reaction and 13.2% showed marked immuno-reaction.

Progesterone receptors:

61.7% of the studied cases showed mild immuno-reaction, 27% showed mild immuno-reaction and 11.3% showed marked immuno-reaction.

Both Estrogen and progesterone receptors percentage increase as the age group increases but no statistical difference was observed.

On applying the TNM classification, most of the cases had no metastasis.

Progesterone receptor was expressed mostly among the group having no lymph nodes and no metastasis and expression increases as the Tumour size increases.

Estrogen and progesterone receptors and TNM classification

Variables	Classification (M)			
	No Metastasis	Metastasis		
Estrogen Receptor	%	%		
Absent	30.6	0.0		
Present	69.4	100		
Progesterone Receptor				
Absent	34.1	0.0		
Present	65.9	100		
	Classification (N)			
	N0	N1	N2	
Estrogen Receptor	%	%	%	
Absent	26.7	21.4	36.8	
Present	73.3	78.6	63.2	
Progesterone Receptor				
Absent	24.4	26.2	42.5	
Present	75.6**	73.8	57.5	
	Classification (T)			
	T1	T2	T3	T4
Estrogen Receptor	%	%	%	%
Absent	26.5	28.7	39.3	66.7
Present	73.5	71.3	0.7	33.3
Progesterone Receptor				
Absent	35.3	30.6	39.3	100
Present	4.7	69.7*	60.7	0.0

No significant difference in the TNM classification of breast cancer between cases with history of intake of reproductive hormones and those who did not take hormones.

Association between Intake of Hormones and TNM Classification among Breast Cancer Cases.

TNM Classification	No history of Hormonal Intake %	History of Hormonal Intake %	Total n=175 %
M:Metastasis	99.0	100.0	99.4
Metastasis No	1.0	0.0	0.6
▪Metastasis			
Node (N):			
▪No Node: No	23.1	29.6	25.7
▪Mobile Nodes:N1	25.0	22.5	24.0
▪Fixed Nodes: N2	51.9	47.9	50.3
▪Ipsellateral: N3	0.0	0.0	0.0
T Classification:			
According to size			
▪T1	19.4	19.7	19.5
▪T2	65.0	59.2	62.6
▪T3	13.6	19.7	16.1
Involving Chest Wall/ Skin			
T4	1.9	1.4	1.7

No statistical difference regarding type of tumour between breast cancer cases with history of intake of reproductive hormones and those who did not take hormones.

- **No significant difference was found regarding the type of tumour and the TNM classification of breast cancer between cases with or without positive history of intake of reproductive hormones.**

Intake of Hormones and Type of Malignant Tumour among Breast Cancer Cases

Type of Malignant Tumour	No history of Hormonal Intake %	History of Hormonal Intake %	Total n=175
Special- Type	12.7	8.7	19
- No Special Type	87.3	91.3	152
Types of Tumour			
•Tubular	1.9	1.4	3
•Medullary	1.0	0.0	1
•Mucoïd	1.9	1.4	3
•Papillary	0.0	1.4	1
•Classic Lobular	6.7	2.8	9
•Pajet 's Disease	1.9	2.8	4

Conclusions:

Among all the epidemiological variables studied, passive smoking (current and past), exposure to insecticides and domestic chemicals and breast trauma, were the most significant factors associated with breast cancer.

No relation between Estrogen and Progesterone receptors and history of intake of exogenous reproductive hormones in breast cancer cases.