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Association of Dyslipidemia with Breast Cancer in Women

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Συσχέτιση Δυσλιπιδαιμίας με Καρκίνο Μαστού στις Γυναίκες

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Introduction: Dyslipidemia and increased cholesterol levels are showed to be positively associated with breast cancer risk. Due to population ageing, breast cancer is expanding at an alarming rate, globally. Therefore, efforts to minimize increased rates of breast cancer are targeting the modifiable risk factors, such as dyslipidemia through dietary and life style modification. The **purpose** of this study was to explore the relationship between dyslipidemia and breast cancer in pre and postmenopausal women. **Material and Method:** In the present epidemiological study, were enrolled 501 premenopausal and postmenopausal women with breast cancer in four public hospital in Athens. Data were collected by the completion of a specially designed questionnaire which included patients' characteristics. The level of statistical significance was set at $p<0.05$. **Results:** Of the 501 women enrolled in the study, 34% was over 60 years old. In terms of lipids profile, 50.3% had high total cholesterol levels (240+ mg/dl), 33.5% had high LDL levels (160+ mg/dl), 38.5% had high triglycerides levels (200+mg/dl) and 77.7% had moderate risk HDL levels (41–59 mg/dl). Regarding Body Mass Index, weight and overweight/obese was 59.4%. Concerning type of cancer, 52.5% had invasive ductal carcinoma, 32.1% had non-invasive non ductal, 8.6% had invasive lobular carcinoma and 6.8% had non-invasive lobular carcinoma. Women with non-invasive non-ductal carcinoma had higher abnormal values of total cholesterol, $p=0.006$, triglycerides, $p=0.009$, and lower HDL values, $p=0.005$. In terms of non-invasive non-ductal carcinoma, it was more common in women who increased their body weight over 10 kg after menopause, $p=0.026$, those of primary and secondary education, $p<0.001$, with comorbidity, $p<0.001$. Moreover, participants with non-invasive non ductal carcinoma had a larger waist and hip circumference, $p=0.007$ and $p<0.012$, respectively, and advanced menopausal age, $p=0.099$. Regarding, invasive ductal carcinoma, it was more common in smokers, $p=0.005$, who regularly consumed alcohol, $p=0.010$ and at younger ages, $p<0.001$. Concerning

lobular carcinoma, the invasive one was more common in women older than 61 years, p<0.001. Longer hospital stay was observed in women with invasive lobular carcinoma of the breast, p<0.008. Women who reported adenoma as a benign breast disease were more likely to develop non-invasive lobular carcinoma, p=0.002 while women with non-invasive lobular carcinoma had a shorter physical exercise time, p=0.039. Conclusions: Population-based epidemiological data are needed for a more accurate analysis of the association between dyslipidemia and breast cancer development with ultimate goal to provide directions for treatment and prevention of cancer.

Key-words: *Dyslipidemia, cholesterol, breast cancer, risk factors, women.*

Introduction

Breast cancer is the most common cancer in women worldwide, with about 2.3 million new cases each year, and is also the leading cause of cancer-related mortality, globally.[1,2] During last four decades, prevalence of breast cancer is increasing steadily, and is expected to further increase, .which is mainly attributed to the ageing population in Europe.[1,3,4] Among 40 European Countries in 2018, breast cancer was the leading cause of death from cancer in women (138.000, 16.2% of 850.000 cancer deaths).[3] According to breast cancer statistics, there were more than 2.26 million new cases of breast cancer in women in 2020 with Belgium to rank first in the list followed by Netherlands.[4] More recently, in 2022, breast cancer is estimated to account for one–third of all new cancer diagnoses in American females.[5]

Modifiable and non modifiable factors seem to increase the incidence of breast cancer which is higher in Western countries. Non–modifiable factors, include female gender, age and heredity while modifiable factors encompass eating habits, alcohol consumption, smoking, physical inactivity, duration of breastfeeding, advanced age in early pregnancy, reproductive factors, and obesity.[1,6]

Dyslipidemia and a diet high in saturated fat consist risk factors for breast cancer. More in detail, cancer cells show specific changes in various aspects of lipid metabolism, which may affect the availability of structural lipids for membrane synthesis, the contribution of lipids to energy homeostasis, and lipid signaling functions including activation of pathways related to inflammation.[7,8] The interaction between cholesterol, lipoproteins, proinflammatory signaling pathways and tumor growth has been studied in breast cancer cells and experimentally in vivo models. In humans, both benign and malignant breast tissue proliferation are associated with changes in plasma lipid and lipoprotein levels.[9,10–13] Epidemiological data regarding the relationship between lipoproteins and breast cancer, showed conflicting results.[9,10–13] It still remains unclear whether total, low or high density lipoprotein (LDL, HDL) contribute to disease manifestation.[13]

In terms of cholesterol, a recent prospective study, illustrated a link between total cholesterol and all cancers. Although researchers could not draw a conclusion about the role of total cholesterol in all cancers, they identified a positive relationship between total cholesterol and breast and prostate cancer risk. Women with total cholesterol levels above 240 mg/dL were at higher risk of developing breast cancer than women with cholesterol levels below 160 mg/dL.[14,15] However, recent and prior studies demonstrated vague results and limited data are proving a link between breast cancer risk and plasma cholesterol levels.[15,16]

It is already known that cholesterol maintains the stability of the cell membrane, regulate its' fluidity and has a vital effect on biogenesis and membrane proliferation.[16] During tumor growth, tumor cells synthesize cholesterol, which is further metabolized to the cell membrane and maintains rapid proliferation. In addition, the expression of high cholesterol and low–density lipoprotein (LDLR) receptors are believed to be risk factors and drivers of

tumor progression, involving in breast and colon cancer exarcebation.[17–19]

In general, cholesterol is involved in the formation of lipid tissue, which plays and essential role in several active signaling cataracts in cancer development. These signaling pathways are often associated with receptors that promote tumor proliferation and cell adhesion.[17,20–24] Additionally, cholesterol homeostasis is controlled by a detailed metabolic pathway in organisms, which includes biosynthesis, metabolism, uptake, and outflow. All of these processes are closely related to tumor growth.[17]

Purpose

The purpose of this study was to explore the relationship between dyslipidemia and breast cancer in pre– and post–menopausal women.

Research Hypothesis

H0. Dyslipidemia is not an independent risk factor for breast cancer

H1. Dyslipidemia is an independent risk factor for breast cancer

Material and Method

Sample of the study

In the present study were enrolled 501 premenopausal and postmenopausal women with breast cancer who were treated or followed up at four public hospital in Athens. The research was conducted between 2017–2020

Sample: inclusion and exclusion criteria

Inclusion criteria in the present study for participants were: a) to have primary breast cancer, b) to understand and speak the Greek language and c) collection of data immediately after diagnosis and before chemotherapy or surgery. Participants were excluded if they had a history of mental illness or were diagnosed with metastatic breast cancer (initial diagnosis or recurrence) during the study period. Women who met the above criteria were included in the sample.

Methodology

It was an epidemiological study with convenience sampling. Data were collected by the completion of a specially designed questionnaire either by patients or through an interview plus data from patients' files and laboratory tests. More in detail, this questionnaire included socio–demographic and clinical characteristics of participants, information regarding their way of living and individual and family history. In terms of lipid control, patient preparation for blood sampling were included in the pre–analysis factors that may affect serum lipid and lipoprotein values. Before blood sampling, a 12–14 hours fasting is necessary for triglycerides measurement, desirable for of HDL–cholesterol measurement if it is involved in the metabolism of triglycerides. Prolonged fasting or diet may alter the results.

Ethical considerations

The study was carried out after the approval of the research protocol by the Scientific Council of all participant–hospitals. Principles of the Helsinki Declaration were followed throughout the study. Written, informed consent for participation was obtained from all patients after explanation of the purpose of the study. Anonymity was preserved and participation was on a voluntary basis. Patients had the right to leave at any stage of the study.

Statistical analysis

Data of the questionnaire were coded and the SPSS statistical package was used for their analysis. (version 25.0). The significance level was set at 0.05. The statistical tests x^2–test, t–test and one way anova variance analysis were applied depending on the type of variables.

Results

Descriptive results

The sample of the study consisted of 501 women with breast cancer.

Regarding demographic characteristic, 30.7% of the sample was less than 50 years old, 35.3% were 51–60 years old, 21.6% were 61–70 and 12.4% were 71 years old and over. With respect to marital status, 66.2% of the sample were married, 16.4% were single, 10.8% were divorced and 6.6% were widowed. According to the level of education, 14.6% had primary education, 37.3% secondary education, 14.0% post–secondary education and 34.1% had higher education or postgraduate studies. Concerning profession, 22.8% were private employees, 22.0%

were civil servants, 21.8% were engaged in housework or were unemployed, 8.2% were retired, 18.2% were self-employed and workers were 6.8% of the sample. The largest percentage of the sample, 50.7%, lived in the greater Attica area, 24.8% lived in the prefecture capital, 17.0% in a small town and 7.6% in a village (table 1).

In terms of lipids profile, 50.3% had high total cholesterol levels (240+mg/dl), 33.5% had high LDL levels (160+mg/dl), 38,5% had high triglycerides levels (200+mg/dl) and 77.7% had moderate risk HDL levels (41–59 mg/dl). In regard to Body Mass Index, 40.6% had normal weight and overweight/obese was 59.4% (table 2)

Concerning type of cancer, 52.5% had invasive (infiltrating) ductal carcinoma (IDC), 32.1% had non–invasive non ductal, 8.6% had invasive lobular carcinoma (ILC), and 6.8% had non–invasive lobular carcinoma.

In terms of the waist / hip circumference index, 68.8% were at low risk, 22.8% at medium risk and 8.4% at high risk of cardiovascular disease (table 2).

Regarding other clinical characteristics, the age of menarche in 14.0% was eleven years and under, in 76.8% 12–14 years and over 15 years it was 9.2%. The menopausal age in 25.5% was below 45 years, in 36.0% 46–50 years and in 38.6% over 51 years. The gain of weight at menopause was 7–10 kg and 11+ in 26.2% and 9.7%, respectively. The age of first childbirth in 39.8% was 24 years and younger, in 45.1% it was 25–30 and over 31 it was in 15.1%. Furthermore, 24.8% of participants had no children, 13.2% have one child, 48.9% two and 13.2% more than two. Moreover, 66.1% of the sample breastfed their children and of these 48.3% for less than 3 months and 51.7% for three months and more. Of the sample–studied, 16.8% reported benign breast diseases, of which 87.0% had cysts and 13.0% had adenoma. In terms of medicine, 16.0% received oral contraceptives, 8.4% chronic hormonal replacement and 15.1% antibiotics. As far as medical history is concerned, 38.5% reported family history of breast cancer, 40.1% had comor-

Table 1. *Distribution of the sample according to demographic characteristics Index*

Demographic characteristics		**N**	**%**
Age	≤50	154	30,7
	51–60	177	35,3
	61–70	108	21,6
	71+	62	12,4
Marital status	Married / cohabitation	331	66,2
	Unmarried	82	16,4
	Divorced	54	10,8
	Widow	33	6,6
Educational level	Primary	73	14,6
	Secondary	187	37,3
	Post–secondary	70	14,0
	Tertiary / postgraduate studies	171	34,1
Occupation	Private employee	114	22,8
	Public employee	110	22,0
	Household / unemployed	100	21,8
	Retired	41	8,2
	Freelance	91	18,2
	Worker	34	6,8
Place of residence	Wider area of Attica	254	50,7
	Capital of the prefecture	124	24,8
	Small town	85	17,0
	Village	38	7,6

Table 2. Distribution of the sample according to the levels of blood lipids and Body Mass Index\

Lipids/ Body mass index–BMI		N	%
Total cholesterol	Normal (up to 199 mg/dl)	97	19,4
	Borderline high (200–239 mg/dl)	152	30,3
	High (240+ mg/dl)	252	50,3
LDL	Ideal (έως 100 mg/dl)	27	5,4
	Almost ideal (101–129 mg/dl)	149	29,7
	Borderline high (130–159 mg/dl)	157	31,3
	High (160+ mg/dl)	168	33,5
HDL	<40mg/dl	24	4,8
	Moderate risk (41–59mg/dl)	388	77,7
	Protective (60+mg/dl)	89	17,8
Triglycerides	Normal (up to 150mg/dl)	108	21,6
	Borderline high (151–199mg/dl)	200	39,9
	Increased values (200+mg/dl)	193	38,5
BMI	Normal weight (18,5–25 kg/m2)	202	40,6
	Overweight (25–30 kg/m2)	178	35,7
	Obese (>30 kg/m2)	118	23,7
Waist/hip circumference index	Low risk	172	68,8
	Medium risk	57	22,8
	High risk	21	8,4

bidity, of which 54.3% had cardiovascular disease, 18.3% diabetes mellitus and 27.7% thyroid or other diseases. Concerning the habits of women,15.5%used to smoke up to 15 cigarettes per day and 18% over 15 cigarettes per day. Alcohol consumption was accounting for 14.6%, with daily use or 2–3 times a week and 21.8% occasionally. Concerning physical exercise, 74.3% do not exercise at all or one hour a week, while 30.9% used to walk over 60 min per day (table 3).

Statistical results

From the statistical test x^2–test it was found that women with non-invasive non-ductal breast cancer had higher values of total cholesterol, p=0.020, and moderate risk HDL values, p<0.001, while no statistically significant differences were found in relation with LDL cholesterol and triglyceride levels, p>0.05 (table 4).

Invasive lobular carcinoma was more common in women older than 61 years, p<0.001. Comparing the incidence and type of cancer with other independent variables, marital status was not found to be related to the incidence and type of breast cancer, p=0.383, but it was found that non–invasive non–ductal breast cancer was more common in women with primary and secondary education, p<0.001 (table 5)

It was found that non–invasive non–ductal breast cancer was more common in women who have increased their body weight. weight over 10 kg after menopause, p=0.026. Women who reported adenoma as a benign breast disease were more likely to develop non-invasive lobular carcinoma, p=0.002. Non-invasive non-ductal breast cancer was more common in participants with comorbidity, p<0.001, and more often in those with cardiovascular disease and diabetes mellitus, p=0.057 and in women receiving medicine for cardiovascular disease, p=0.019 (table 6).

No statistically significant differences were found between the sample and body mass index, p=0.640 and with the waist/hip circumference index, p=0.138. No statistically significant differences were found in the type of cancer in relation to occupation, place of residence, age of menarche, age of menopause, age of first childbirth, number of children, breastfeeding and duration of breastfeeding, p>0.05 .

Table 3. *Distribution of the sample according to clinical characteristics.*

Clinical characteristics		**N**	**%**
Diagnosis	Invasive (infiltrating) ductal carcinoma (IDC)	263	52,5
	Non–invasive non–ductal carcinoma in situ	161	32,1
	Invasive lobular carcinoma	43	8,6
	Non–invasive lobular carcinoma	34	6,8
Menarche age	≤11	70	14,0
	12–14	385	76,8
	15+	46	9,2
Menopausal age	≤45	109	25,4
	46–50	154	36,0
	51+	165	38,6
Weight at Menopause	≤2	124	30,9
	3–6	133	33,2
	7–10	105	26,2
	11+	39	9,7
Age of first childbirth	≤24	150	39,8
	25–30	170	45,1
	31+	57	15,1
Number of children	None	124	24,8
	One	66	13,2
	Two	245	48,9
	More than two	66	13,2
Duration of breastfeeding	None /1–3 months	128	48,3
	>more than 3 months	137	51,7
Benign breast diseases	Yes	84	16,8
	No	417	83,2
Oral contraceptives	Yes	80	16,0
	No	420	84,0
Chronic hormonal replacement	Yes	42	8,4
	No	456	91,6
Administration of antibiotics	Yes	75	15,1
	No	422	84,9
Breast cancer family history	No–one	308	61,5
	Mother/Sister	137	27,3
	Grandmother /Aunt	56	11,2
Comorbidity	Cardiovascular disease	113	54,3
	Diabetes Mellitus	38	18,3
	Thyroid disease/ other	57	27,4
Smoking	Yes Up to 15 cigarettes/per day	78	15,5
	Yes >15	90	18,0
	No	333	66,5
Alcohol consumption	Daily / 2–3 times a week	73	14,6
	Occasionally	109	21,8
	None	319	63,6
Physical exercise	Not at all / up to one hour per week	372	74,3
	2–3 hours per week / 1 hour per day	129	25,7
Walking hours per day	None	133	26,7
	1–29′	126	25,3
	30–59′	86	17,2
	60′+	154	30,9

Table 4. *Comparison between the incidence of breast cancer in relation to BMI and blood lipid levels*

Clinical Characteristics		Type of breast cancer								P
		Invasive ductal carcinoma (IDC)		Non-invasive non-ductal carcinoma in situ		Invasive lobular carcinoma (ILC)		Non-Invasive lobular carcinoma (ILC)		
		n	%	n	%	n	%	n	%	
BMI	Normal weight	110	42,1	63	39,4	14	32,6	15	44,1	0,640
	Overweight/Obese	151	57,9	97	60,6	29	67,4	19	55,9	
Total Cholesterol	Normal	64	24,3	22	13,7	7	16,3	4	11,8	0,020
	Borderline high	77	29,3	44	27,3	15	34,9	16	47,1	
	High	122	46,4	95	59,0	21	48,8	14	41,2	
LDL	Ideal	13	4,9	7	4,3	4	9,3	3	8,8	0,298
	Almost ideal	85	32,3	45	28,0	12	27,9	7	20,6	
	Borderline high	70	26,6	56	34,8	17	39,5	14	41,2	
	High	95	36,1	53	32,9	10	23,3	10	29,4	
HDL	High	11	4,2	9	5,6	1	2,3	3	8,8	<0,001
	Moderate risk	185	70,3	140	87,0	36	83,7	27	79,4	
	Protective	67	25,5	12	7,5	6	14,0	4	11,8	
Triglycerides	Ideal	53	20,2	32	19,9	12	27,9	11	32,4	0,142
	Borderline high	115	43,7	55	34,2	16	37,2	14	41,2	
	Increased values	95	36,1	74	46,0	15	34,9	9	26,5	

From the statistical analysis, it was not found that the oral contraceptives, the chronic hormonal substitution and the frequent taking of antibiotics are responsible for the type of cancer, p>0.05. Family history of breast cancer was not found to be statistically significantly associated with any type of breast cancer, p=0.605

Invasive ductal breast cancer was more common in smokers, p=0.005, as well as in those who regularly consumed alcohol, p=0.010. No statistically significant differences were found with respect to exercise and walking hours per day, p>0.05 (table 5).

From the anova statistical test which was used to explore the type of breast cancer in relation to lipid levels, it was found that women with non–invasive non–ductal breast cancer had higher abnormal values of total cholesterol, p=0.006, triglycerides, p=0.009, and lower HDL values, p=0.005. In relation to socio–demographic characteristics, it was found that invasive ductal breast cancer was observed at younger ages of the sample, p <0.001, and individuals with non–invasive non–ductal breast cancer had a larger waist and hip circumference, p=0.007 and p<0.012, respectively, and an advanced menopausal age, p=0.099 and in particular differed in age statistically significantly only from those with invasive ductal breast cancer, p=0.014. Longer hospital stay from the disease onset was observed in women with invasive lobular carcinoma of the breast, p<0.008. It was also found that women with non–invasive lobular carcinoma had a shorter exercise time, p=0.039 (table 8).

Discussion

According to the descriptive results of the present study, 52.5% had invasive (infiltrating) ductal carcinoma (IDC), 32.1% non–invasive ductal carcinoma in situ, 8.6% had invasive lobular carcinoma (ILC) and 6.8% non–invasive lobular carcinoma. Ductal and lobular tumors are the two most frequently diagnosed subtypes of invasive breast carcinomas (75% and 15% of all malignant tumors, respectively).[25–27]

Noteworthy, differences are observed in types of breast cancer, worldwide. Histologically, ductal carcinoma is the commonest type of breast cancer among women in Africa and Europe with similar frequency. In

Table 5. *Comparison between the incidence of type breast cancer and socio-demographic characteristics*

Socio-demographic characteristics		Type of breast cancer								
		Invasive ductal carcinoma (IDC)		Non-invasive non-ductal carcinoma in situ		Invasive lobular carcinoma (ILC)		Non–Invasive lobular carcinoma (ILC)		
		n	%	n	%	n	%	n	%	P
Age	–50	92	35,0	32	19,9	13	30,2	17	50,0	<0,001
	51–60	128	48,7	32	19,9	10	23,3	7	20,6	
	61–70	36	13,7	50	31,1	19	44,2	3	8,8	
	71+	7	2,7	47	29,2	1	2,3	7	20,6	
Marital status	Married / cohabitation	174	66,4	106	65,8	30	69,8	21	61,8	0,383
	Unmarried	40	15,3	25	15,5	6	14,0	11	32,4	
	Divorced	31	11,8	17	10,6	5	11,6	1	2,9	
	Widow	17	6,5	13	8,1	2	4,7	1	2,9	
Education level	Primary	20	7,6	42	26,1	6	14,0	5	14,7	<0,001
	3 years	28	10,6	5	3,1	1	2,3	3	8,8	
	Secondary 6 years	82	31,2	50	31,1	13	30,2	5	14,7	
	Post–secondary	43	16,3	18	11,2	4	9,3	5	14,7	
	Tertiary / Postgraduate	90	34,2	46	28,6	19	44,2	16	47,1	
Occupation	Private employee	63	24,0	35	21,9	8	18,8	8	23,5	0,577
	Public employee	61	23,3	33	20,6	8	18,6	8	23,5	
	Household / Unemployed	49	18,7	40	25,0	11	25,6	9	26,5	
	Retired	25	9,5	9	5,6	6	14,0	1	2,9	
	Freelance	47	17,9	29	18,1	10	23,3	5	14,7	
	Worker	17	6,5	14	8,8	0	0,0	3	8,8	
Place of residency	Wider area of Attica	130	49,4	86	53,4	18	41,9	20	58,8	0,612
	Capital of the prefecture	65	24,7	36	22,4	15	34,9	8	23,5	
	Small town/Village	68	25,9	39	24,2	10	23,3	6	17,6	

addition, more women have grade 3 tumours in Africa than in Europe. In Tanzania, for example, 56.4% have tumours with histological grade 3, while, in Nigeria, 45.1% have grade 3 tumour. Most women in Europe present with a grade 1 or 2 tumour. African–American women are also considerably more likely to have grade 3 tumours, increased number of positive nodes, and more necrosis than white women. Black British women have been shown to have higher rates of grade 3 tumours and lymph–node–positive disease than white British women. This may explain why the progression of breast cancer is more aggressive in African women than in European women.[28] The most frequent type of breast cancer among Saudi women is ductal carcinoma (81.80%) followed by lobular carcinoma (3.40%).[27] Subtypes of breast cancer have different clinical, molecular, and pathologic features, thus involving different treatment modalities and prognosis.[27]

From statistical, it was found that women with non-invasive ductal carcinoma had higher abnormal values of total cholesterol, triglycerides, and lower HDL values. Dietary cholesterol represents a significant risk factor for breast cancer and genetically elevated plasma high–density lipoprotein (HDL) and low–density lipoprotein (LDL) levels appear to be associated with an increased risk.[5] A recent metanalysis by Li et al,[24] showed a nonlinear relationship between dietary cholesterol and breast cancer, but the association became statistically significant when

Table 6. *Comparison between the of type breast cancer and clinical characteristics.*

Clinical characteristics		Type of breast cancer								
		Invasive ductal carcinoma (IDC)		Non–invasive non–ductal carcinoma in situ		Invasive lobular carcinoma (ILC)		Non–Invasive lobular carcinoma (ILC)		
		n	%	n	%	n	%	n	%	P
Weight increase after menopause	Up to 2 Kgs	81	37,0	26	20,5	10	28,6	7	35,0	0,026
	3–6	71	32,4	46	36,2	10	28,6	6	30,0	
	7–10	54	24,7	37	29,1	8	22,9	6	30,0	
	11+	13	5,9	18	14,2	7	20,0	1	5,0	
Menarche age	–11	33	12,5	24	14,9	9	20,9	4	11,8	0,692
	12–14	20	77,2	124	77,0	32	74,4	26	76,5	
	15+	27	10,3	13	8,1	2	4,7	4	11,8	
Menopausal age	–45	68	29,3	28	20,1	8	22,2	5	23,8	0,300
	46–50	85	36,6	52	37,4	12	33,3	5	23,8	
	51+	79	34,1	59	42,4	16	44,4	11	52,4	
Age of first childbirth	–24	83	41,7	47	37,0	14	43,8	6	31,6	0.329
	25–30	81	40,7	66	52,0	12	37,5	11	57,9	
	31+	35	17,6	14	11,0	6	18,8	2	10,5	
Number of children	None	64	24,3	34	21,1	11	25,6	15	44,1	0,242
	One	38	14,4	21	13,0	5	11,6	2	5,9	
	Two	128	48,7	80	49,7	24	55,8	13	38,2	
	More than 2	33	12,5	26	16,1	3	7,0	4	11,8	
Breastfeeding duration	None/3 months	61	43,3	48	50,0	14	63,6	7	70,0	0,139
	>3 months	80	56,7	46	50,0	8	36,4	3	30,0	
Breast diseases	Cysts	22	91,7	14	93,3	4	80,0	0	0,0	0,002
	Adenoma	2	8,3	1	6,7	1	20,0	2	100,0	
Oral Contraceptives	Yes	46	17,5	24	15,0	7	16,3	3	8,8	0,602
	No	217	82,5	136	85,0	36	83,7	31	91,2	
Chr. hormone replacement	No	239	91,6	149	93,1	37	86,0	31	91,2	0,531
	Yes	22	8,4	11	6,9	6	14,0	3	8,8	
Breast cancer family history	No	160	60,8	101	62,7	29	67,4	18	52,9	0,825
	Mother/Sister	73	27,8	43	26,7	11	25,6	10	29,4	
	Grandmother/ Aunt	30	11,4	17	10,6	3	7,0	6	17,6	
Comorbidity	Yes	83	31,6	84	52,2	19	44,2	15	44,1	<0,001
	No	180	68,4	77	47,8	24	55,8	19	55,9	
Type of comorbidity	Cardiovascular	54	62,1	39	45,3	13	68,4	7	43,8	0,057
	Diabetes mellitus	10	11,5	24	27,9	1	5,3	3	18,8	
	Thyroid /other	23	26,4	23	26,7	5	26,3	6	37,5	

Table 7. *Comparison between the of type breast cancer and the way of living*

		Type of breast cancer								
		Invasive ductal carcinoma (IDC)		Non–invasive non–Ductal carcinoma in situ		Invasive lobular carcinoma (ILC)		Non-Invasive lobular carcinoma (ILC)		
Life style		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**P**
Smoking	Yes	104	39,7	39	24,2	17	39,5	8	23,5	0,005
	No	158	60,3	122	75,8	26	60,5	26	76,5	
Alcohol	Daily / 2–3 times a week	48	50,5	16	27,1	4	22,5	5	50,0	0,010
	Occasionally	47	49,5	43	72,9	14	77,8	5	50,0	
Physical exercise	Not at all /1 hour a week	193	73,4	121	75,2	34	79,1	24	70,6	0,817
	2–3 hours /week/1 hour a day	70	26,6	40	24,8	9	20,9	10	29,4	

Table 8. *Comparison between the of type breast cancer and mean values of demographic characteristics and level of lipids.*

	Type of breast cancer								
	Invasive ductal carcinoma (IDC)		Non-invasive non-Ductal carcinoma in situ		Invasive lobular carcinoma (ILC)		Non–Invasive lobular carcinoma (ILC)		
	n	**$\bar{X}$±SD**	**n**	**$\bar{X}$±SD**	**n**	**$\bar{X}$±SD**	**n**	**$\bar{X}$±SD**	**p**
Age	263	52,9±9,0	161	61,9±13,2	43	56,0±10,1	34	52,9±16,3	<0,001
BMI	263	26,6±4,9	161	27,3±5,0	43	28,5±5,7	34	26,9±5,5	0,122
Waist size	133	81,1±13,6	71	81,6±13,8	22	77,8±11,1	24	71,4±12,7	0,007
Hip circumference	133	105,3±14,7	71	106,6±15,6	22	100,9±11,0	24	96,5±13,9	0,012
Menarche age	263	12,8±1,3	161	12,7±1,3	43	12,5±1,3	34	13,1±1,4	0,370
Menopausal age	232	47,9±5,4	139	49,3±5,2	36	48,7±4,8	21	49,0±6,7	0,099
Age at 1st child	199	25,9±5,2	127	25,9±4,6	32	26,0±5,0	19	26,2±4,2	0,993
Number of children	263	1,5±0,1	161	1,6±0,1	43	1,4±1,0	34	1,2±1,1	0,136
Breast feeding duration	141	2,8±0,9	92	2,8±1,1	22	2,5±1,0	10	2,3±1,1	0,199
Relatives' age at breast cancer	92	54,8±12,2	54	56,3±13,0	13	54,5±6,6	15	55,1±7,4	0,898
Total cholesterol	263	231,0±40,4	161	245,0±41,6	43	233,8±36,4	34	231,2±32,1	0,006
Triglycerides	263	192,6±50,0	161	201,6±53,9	43	180,6±41,2	34	175,1±44,9	0,009
HDL	263	52,7±10,7	161	49,6±5,7	43	52,5±7,4	34	51,0±6,8	0,005
LDL	263	143,1±32,1	161	145,0±28,2	43	137,8±29,0	34	141,2±29,0	0,557
Walking hours per day	261	0,6±0,7	161	0,5±0,7	43	0,5±0,57	34	0,3±0,31	0,039

the cholesterol intake was greater than 370 mg/dl. Results from this meta-analysis indicated that dietary cholesterol was associated with an increased risk of breast cancer. Similarly Xiao et al,[29] in a metanalysis of 32 observational studies including 43.285 breast cancer cases showed a positive association of a Western dietary pattern and an inverse association of a prudent dietary pattern with the risk of breast cancer. Western dietary pattern was associated with a 14% increased risk whereas a prudent dietary pattern was associated with an 18% reduced risk of breast cancer. Etiology and risk factors of breast cancer differs by menopausal status. More in detail, Western dietary pat-

tern was associated with a 20% increased risk of breast cancer among postmenopausal but not among premenopausal ones. Contrariwise, the prudent dietary pattern was associated with a 23% reduction in breast cancer risk among premenopausal but not among postmenopausal women. Furthermore, high intakes of red meat, animal fats, and refined carbohydrates are associated with an increased breast cancer risk whereas intake of fruits, vegetables, whole grains, and dietary fiber with a reduced risk of breast cancer. Fruits and vegetables contain micronutrients with anti-cancer properties which may influence carcinogenic process by affecting the immune system and oxidative stress, altering hormonal status, modifying the structure and function of cell membranes, and modulating cell signaling transduction pathways and gene expression.[29]

LDL cholesterol levels at diagnosis was shown as a prognostic factor of breast tumor progression. A systemic LDL-C level above 117 mg dL-1 was found to be a predictive factor of tumor stage, and was positively associated with worse diagnosis because of more advanced clinical stage, of higher histological grade and elevated proliferative rate. Moreover, patients with LDL-C above 144 mg dL-1 were also prone to have lymph node metastasis. Patients with high levels of LDL-C at diagnosis had reduced disease free survival, even adjusting to tumor type, stage and BMI.[30] Preoperative lower levels of triglycerides and HDL-C level were risk factors of breast cancer patients. A decreased HDL-C level showed association with worse overall survival while decreased level of triglycerides showed a significant association with worse disease free survival.[31] Also, a correlation was found between metastasis and low density lipoprotein.[32] Statin use may reduce breast cancer risk, and cholesterol-lowering medications have been associated with improved outcomes in patients on hormonal therapy, suggesting an interaction of circulating cholesterol levels with estrogen–sensitive breast tissues.[33]

This study revealed that non–invasive ductal carcinoma was more common in women whose body weight increased over 10 kg after menopause. The biological association between obesity and disease risk may be related to circulating lipid levels and tissue lipid metabolism.[31] Patients with breast cancer and normal BMI had significantly better overall survival than obese patients.[34] Elevated cholesterol, low-and very density lipoprotein cholesterol are comorbidities of obesity and may be independent risk factors of breast cancer.[7]

The present results also demonstrated, that non-invasive ductal carcinoma in situ was more common women with primary and secondary education. A low level of education is a risk factor in the development of breast cancer since it is associated with poor lipid profile, obesity, smoking, and physical inactivity. Education increases the risk of ER-positive breast cancer due to alterations in high–density lipoprotein level, triglyceride level, height, waist-to-hip ratio, body mass index, and smoking status. Other mediators including low–density lipoprotein, hip circumference, number of cigarettes smoked per day, time spent performing light physical activity, and vigorous physical activity for >10 minutes explain a small part of the causal effect of education on the risk of developing breast cancer. Compared to women who completed less than 9 years of education, university graduates had a higher probability of being diagnosed with in situ and invasive breast cancer.[35] Socio–cultural factors may lead to delays in the diagnosis and treatment of invasive lobular carcinoma. The outcome would have been better if the patient sought for medical care sooner at an earlier stage.[36]

Non–invasive ductal carcinoma in situ was more common in participants with comorbidity, mainly cardiovascular disease and diabetes mellitus. Similarly Wijeratne et al,[37] showed among 5100 women diagnosed with breast cancer (mean age 56±12 years) that the most common co–morbidities were hypertension (n=1566, 30%) and diabetes mellitus (n=1196, 23%).

In terms of life style, invasive ductal carcinoma was more common in smokers as well as in those who regularly consumed alcohol. Consuming at least one alcoholic drink per day on average is positively associated with invasive breast cancer for women with a diagnosis of prior ductal carcinoma in situ. If confirmed, modulating alcohol consumption could be one strategy for women with a history of ductal carcinoma.[38]

It was also found that women with non–invasive lobular carcinoma devoted a shorter time to exercise. In a relevant study conducted by Katuwal et al,[39] increased occupational physical activity was associated with lower breast cancer risk with the modest protective effect observed for lobular subtype and smaller

effect for ductal subtype. Breast cancer risk in both pre and postmenopausal group was significantly reduced among women who were economically inactive. Physical activity reduces the levels of circulating sex steroids that increases the risk of breast cancer among pre and postmenopausal women. Other mechanisms of breast cancer risk reduction through physical activity are via reduction in fat, boosting of immune system, and decreased insulin levels.

Several lifestyle-related factors, including obesity (postmenopausal women only), excess alcohol consumption, physical inactivity, smoking and an unhealthy dietary pattern, have also been positively associated with breast cancer. Existing evidence suggests that up to 50% of breast cancer cases may be preventable by adherence to healthy lifestyle practices.[40] Having a genetic predisposition increases a woman's lifetime risk of breast cancer, and this risk may be increased or decreased according to individual's lifestyle.[40]

Invasive lobular carcinoma was more common in women older than 61 years while invasive ductal carcinoma, was more common at younger ages. Age has a significant association with breast cancer development. As the women's' age is advancing, damages occur to the ductal epithelial cells of mammary glands, thus increasing the chance for neoplastic transformation. A possible explanation could be a prolonged exposure to estrogen which is an independent risk factor for breast cancer development. Moreover, with aging, depending on lifestyle, the possibility of sustaining cellular damage via exposure to radiation and other environmental oncogenic risk factors can also affect the genomic machinery.[41]

However, geographical variations are observed in terms of age at presentation between Africa and Europe. In Africa, the mean age is 48 years and almost two–thirds are premenopausal contrary to Europe where the majority present at post menopause. In the United Kingdom, the median age at presentation for Black women is similar to African women at 46 years compared to 67 years in white British women. African-American women have been found to present at a significantly younger age than their Caucasian counterparts.[28]

In the present study, no statistically significant differences were found in the type of cancer in relation to occupation, place of residence, age of menarche, age of menopause, age of first childbirth, number of children, breastfeeding and duration of breastfeeding. Age at first delivery and breastfeeding were significantly associated with invasive ductal carcinoma but not with Invasive lobular carcinoma. Deliberate weight loss and age at menarche were significantly associated with Invasive lobular carcinoma. Smoking, history of benign breast disease and BMI were associated with both subtypes.41 Age at menarche, and age at first baby birth, illiteracy, smoking and family history of cancer were risk factors associated with breast cancer development among women in Afghanistan.[42]

Conclusions

The results of the present study showed the following:

Non-invasive breast cancer was more common in women who have gained more than 10 kg after menopause and in women in primary and secondary education. Women with non–invasive breast cancer had higher abnormal levels of total cholesterol and moderate risk of HDL. Non-invasive breast cancer was more common in participants with comorbidity and specifically with cardiovascular disease and diabetes mellitus. Participants with non–invasive breast cancer had a larger waist and hip circumference, a longer menopausal age, and in particular differ in age statistically significantly only from those with invasive disease.

Invasive breast cancer was more common in smokers and those who regularly used to drink alcohol. In relation to demographic characteristics, invasive ductal cancer was observed at younger ages while invasive lobular carcinoma was more common in women older than 61 years.

Women with invasive lobular breast cancer had a longer hospital stay from disease onset and a shorter physical exercise time. Women who reported adenoma as a benign breast disease were more likely to develop non-invasive lobular breast cancer.

Provision of health education to women are valuable in decreasing the burden of breast cancer and its' impact on the healthcare system, globally.

Additional studies are required to address the relationship between breast cancer and cholesterol, with the goal to develop potential therapeutic strategies and minimize the cholesterol effect on breast cancer risk.

ABSTRACT

Συσχέτιση Δυσλιπιδαιμίας με Καρκίνο Μαστού στις Γυναίκες

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Εισαγωγή: Η δυσλιπιδαιμία και τα αυξημένα επίπεδα χοληστερόλης φαίνεται να συνδέονται θετικά με τον κίνδυνο καρκίνου του μαστού. Λόγω της γήρανσης του πληθυσμού, ο καρκίνος του μαστού επεκτείνεται με ανησυχητικό ρυθμό, παγκοσμίως. Ως εκ τούτου, οι προσπάθειες για την ελαχιστοποίηση των αυξημένων ποσοστών καρκίνου του μαστού στοχεύουν στους τροποποιήσιμους παράγοντες κινδύνου, όπως η δυσλιπιδαιμία μέσω της τροποποίησης της διατροφής και του τρόπου ζωής. **Σκοπός** αυτής της μελέτης ήταν η διερεύνηση της σχέσης μεταξύ δυσλιπιδαιμίας και καρκίνου του μαστού σε προ και μετεμμηνοπαυσιακές γυναίκες. **Υλικό και Μέθοδος:** Στην παρούσα επιδημιολογική μελέτη συμμετείχαν 501 προ και μετεμμηνοπαυσιακές γυναίκες με καρκίνο του μαστού σε τέσσερα δημόσια νοσοκομεία της Αθήνας. Τα δεδομένα συλλέχθηκαν με τη συμπλήρωση ενός ειδικά σχεδιασμένου ερωτηματολογίου, το οποίο περιλάμβανε τα χαρακτηριστικά των ασθενών. Το επίπεδο στατιστικής σημαντικότητας ορίστηκε στο p<0,05. **Αποτελέσματα:** Από τις 501 γυναίκες που συμμετείχαν στη μελέτη, το 34% ήταν άνω των 60 ετών. Όσον αφορά το λιπιδαιμικό προφίλ, το 50,3% είχε υψηλά επίπεδα ολικής χοληστερόλης (240+ mg/dl), το 33,5% είχε υψηλά επίπεδα LDL (160+ mg/dl), το 38,5% είχε υψηλά επίπεδα τριγλυκεριδίων (200+mg/dl) και το 77,7 % είχε επίπεδα HDL μέτριου κινδύνου (41-59 mg/dl). Όσον αφορά στον Δείκτη Μάζας Σώματος, το 59,4% ήταν υπέρβαρες/παχύσαρκες. Σχετικά με τον τύπο του καρκίνου, το 52,5% είχε πορογενές διηθητικό καρκίνωμα, το 32,1% είχε πορογενές μη διηθητικό καρκίνωμα, το 8,6% είχε διηθητικό λοβιακό καρκίνωμα και το 6,8% είχε μη διηθητικό λοβιακό καρκίνωμα. Οι γυναίκες με πορογενές μη διηθητικό καρκίνωμα, είχαν υψηλότερες μη φυσιολογικές τιμές ολικής χοληστερόλης, p=0,006, τριγλυκεριδίων, p=0,009 και χαμηλότερες τιμές HDL, p=0,005.Το πορογενές μη διηθητικό καρκίνωμα, ήταν συχνότερο σε γυναίκες που αύξησαν το σωματικό τους βάρος περισσότερο από 10 kg μετά την εμμηνόπαυση, p=0,026, εκείνες της πρωτοβάθμιας και δευτεροβάθμιας εκπαίδευσης, p <0,001 και με συννοσηρότητα, p<0,001. Επιπλέον, οι συμμετέχοντες με πορογενές μη διηθητικό καρκίνωμα είχαν μεγαλύτερη περιφέρεια μέσης και ισχίου p=0,007 και p<0,012, αντίστοιχα, και προχωρημένη ηλικία στην εμμηνόπαυση, p=0,099. Όσον αφορά στο πορογενές διηθητικό καρκίνωμα, ήταν συχνότερο στις καπνίστριες, p=0,005, σε όσες κατανάλωναν τακτικά αλκοόλ, p=0,010 και στις μικρότερες ηλικίες, p<0,001. Όσον αφορά στο λοβιακό καρκίνωμα, το διηθητικό ήταν πιο συχνό σε γυναίκες άνω των 61 ετών, p<0,001. Παρατηρήθηκε μεγαλύτερη παραμονή στο νοσοκομείο σε γυναίκες με διηθητικό λοβιακό καρκίνωμα του μαστού, p <0,008. Οι γυναίκες που ανέφεραν το αδένωμα ως καλοήθη νόσο του μαστού είχαν περισσότερες πιθανότητες να αναπτύξουν μη διηθητικό λοβιακό καρκίνωμα, p=0,002 ενώ οι γυναίκες με μη διηθητικό λοβιακό καρκίνωμα είχαν μικρότερο χρόνο σωματικής άσκησης, p=0,039. **Συμπεράσματα:** Απαιτούνται επιδημιολογικά δεδομένα με βάση τον πληθυσμό για ακριβή ανάλυση της συσχέτισης μεταξύ δυσλιπιδαιμίας και ανάπτυξης καρκίνου του μαστού με απώτερο στόχο την παροχή κατευθύνσεων για τη θεραπεία και την πρόληψη του καρκίνου.

Λέξεις-ευρετηρίου: *Δυσλιπιδαιμία, χοληστερόλη, καρκίνος μαστού, παράγοντες κινδύνου, γυναίκες.*

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