Eurasian J Med 2015; 47: 48-55 The Eurasian Journal of Medicine **Original Article**

Changing Trends in the Incidence of Ovarian Neoplasia and Its Relationship with the Risk Factors: A Report of 311 Cases from North-Eastern Anatolia Region

Ovarian Neoplazi İnsidansında Değişen Trendler ve Risk Faktörleri ile İlişkisi: Doğu Anadolu Bölgesi'nden 311 Olguluk bir Rapor

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Abstract

Objective: Ovarian cancer is one of the most common and lethal gynecologic malignancy. In Turkey, the 8th most commonly seen neoplasm is ovarian cancer. The risk factors of ovarian cancer are menstrual reproductive events including gravida, menarche and menopause status, and life style habits such as cigarette smoking and habitat. In this study we aimed to determine the risk factors leading to ovarian cancer in Turkish women population and show the tumor markers in this population.

Materials and Methods: This study included 311 ovarian neoplasia cases diagnosed at the Pathology Department of Ataturk University in Erzurum over last seven years extending from 2005 to 2013. This study is a retrospective analysis basing on the pathology reports and accesible patient files. Serum tumor markers of the patients were retrospectively reported from their records. Conventional stained preparations existing in our archive examined by two pathologists as well independent of each other, and histopathologic diagnosis and the distribution of the sub-group was revised.

Results: A total of 311 patients were included in this study in which patients were diagnosed at the Pathology Department of Ataturk University in Erzurum. Serous cystadenoma is the most common ovarian tumor followed by mucinous cystadenoma, germ cell tumors, and dysgerminoma. All of the tumor markers were significantly normal.

Conclusion: Upto our knowledge this was the first epidemiological study in Turkey. Analysis of each country's statistical information reflecting its own profile is also important. The relationship between the profiles of patients and types of ovarian neoplasia may give an idea about the risk factors of the disease in its region. Additionally, distribution of tumor markers might be considered for the discriminating of the benign or malign characters of the ovarian neoplasia.

Keywords: Ovarian neoplasia, epidemiology, histopathology, tumor markers

Özet

Amaç: Over kanseri, en yaygın ve ölümcül olarak izlenen jinekolojik malignensidir. Türkiye'de kanser sıklık sıralamasında 8. sıradadır. Over kanseri risk faktörleri arasında, gravida, menarş ve menopoz durumu, sigara içme ve yaşam tarzı alışkanlıkları, adet düzeni yer almaktadır. Bu çalışmada, Türk kadın nüfusunun over kanserine yol açan risk faktörlerinin belirlenmesini ve bu populasyondaki tümör belirteçleri göstermeyi amaçladık.

Gereç ve Yöntem: Bu çalışmaya, 2005-2013 yılları arasında Erzurum Atatürk Üniversitesi Patoloji Anabilim Dalı'nda tanılanan 311 over neoplazm olgusu dahil edildi. Patoloji raporları ve erişilebilir hasta dosyaları retrospektif bir analiz ile değerlendirildi. Hastaların serum tümör belirteçleri kendi kayıtlarından alındı. Arşiv preparatları birbirinden bağımsız iki patolog tarafından tekrar değerlendirildi ve histopatolojik tanıların subgruplardaki dağılımı gözden geçirildi.

Bulgular: Erzurum Atatürk Üniversitesi Patoloji Anabilim Dalı'nda tanı alan 311 hasta bu çalışmaya dahil edildi. Sıklık sırasına göre, seröz kistadenoma, müsinöz kistadenom, germ hücreli tümörler ve disgerminomun en sık izlenen over tümörleri olduğu saptandı. Tümör belirteçlerinin tümü normal olarak belirlendi.

Sonuç: Her ülkenin kendi profilini yansıtan istatistiki bilgilerinin analizi önemlidir. Bu bağlamda, elde edilen veriler doğrultusunda, bu çalışmanın, over neoplazmları konusunda, Türkiye'de yapılan kapsamlı ilk epidemiyolojik çalışma olduğu saptanmıştır. Hastaların ve over neoplazi türlerinin profilleri arasındaki ilişki, hastalığın kendi bölgesindeki risk faktörleri hakkında bir fikir verebilir. Buna ek olarak, tümör markerlerinin dağılımı over neoplazilerinin benign veya malign karakterlerin ayrıştırılması için kullanılabilir.

Anahtar Kelimeler: Over neoplazisi, epidemiyoloji, histopatoloji, tümör belirteçleri

Received: April 11, 2014 / **Accepted:** April 24, 2014 / **Available Online Date:** August 26, 2014

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DOI:10.5152/eajm.2014.40

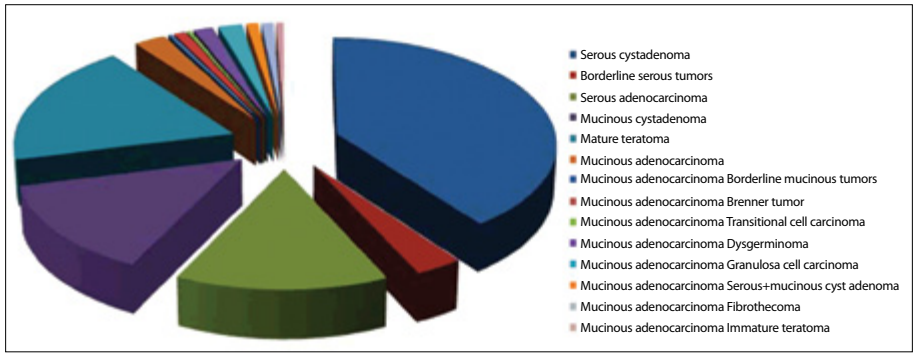

Figure 1. *The distrubition of histological subtypes of ovarian neoplasms.*

Introduction

Ovarian cancer is one of the most common and lethal gynecologic malignancy [1]. Ovarian cancer is the 7th most frequent neoplasm in developed countries [2]. The total number of ovarian cancer cases has been estimated to be around 238719 per year in 2012 and are approximately 3.6% of all cancers in women [3, 4] in the world. In Turkey, the 8th most commonly seen neoplasm was ovarian cancer and the incidence was estimated approximately 2400 per year (3.9%) in 2012 [3, 4]. However, the incidence in Turkey is hardly possible to access because of the insufficient statistical records.

The risk factors of ovarian cancer are menstrual reproductive events including gravida, menarche and menopause status, and life style habits such as cigarette smoking and habitat [5]. Additionally, age is pivotal for the types of ovarian cancer [6]. Early detection of ovarian cancer is much more important to improve outcomes of the disease. Epidemiological studies may support early detection and has supplied prevention, and screening methods for the ovarian cancer. Although many epidemiological studies were found in the literature about other countries, there has been no epidemiological study sited in our country.

The serum biomarkers CA-125, CA-199, CA-153 and CEA are the most widely used serum tumor markers for management of women with ovarian cancer [7]. The biological tumor markers are also used for screening, early detection, monitoring of ovarian cancer status [8]. These glycoproteins are mullerean epithelial origin that includes endosalpinx, endometrium, and endocervix. So, the benign conditions which are associated with epithelial tissues may affect these tumor markers. Additionally, there has been no consensus developed for these tumor markers.

In this study we aimed to determine the risk factors leading to ovarian cancer in Turkish women population and show the tumor markers in this population.

Materials and Methods

Current study included 311 ovarian neoplasia cases diagnosed at the Pathology Department of Ataturk University in Erzurum over last seven years extending from January 2005 to June 2013. This study is a retrospective analysis basing on the pathology reports and accesible patient files. Those cases are investigated according to their age, sex, hometown, smoking status, location of the lesion, tumor markers and histopathological diagnosis. The definition of non-smoker/never-smoker, ex smoker and smoker is designed as: never smoker/non smoker; as a person who had never smoked or had smoked <20 cigarettes in his or her lifetime, ex smoker; those who stopped smoking for more than ten years, and smoker; those who have smoked ever in their life more than just occasional smoking [9].

Serum tumor markers including CA-125, CA-199, CA-153, CEA of the patients were retrospectively reported from their records. The cut-off values were 35 U/mL for CA-125, 30 U/mL for CA-153, 37 U/Ml for CA-199, 6 for AFP, and 2.5 for CEA [10]. Serum CA-125 values were determined as normal lower than 35 U/mL and higher more than 35 U/mL. Other tumor markers were similarly evaluated normal or higher according to the cut-off values.

The ovarian tumors were classified according to histological classification of World Health Organization (WHO) [11]. Conventional stained preparations existing in our archive examined by two pathologists as well independent of each other and histopathologic diagnosis and the distribution of the sub-group was revised (Figure 1). SPSS 20.0 was used for statistical analysis. Percent of the variables were compared in the groups of ovarian neoplasms. p values <0.05 were accepted as statistically significant. If the letters used for intra- group comparision are different (eg. a, b, c) indicate statistically significant ($p<0.05$), the same letters (eg. a, a) indicate statistically no significant ($p>0.05$).

Results

A total of 311 patients were included in this study in which patients were diagnosed at the Pathology Department

Table 1. Distribution of patients with ovarian neoplasia according to various clinicopathological parameters

	Age		Gravida		Cigarette Smoking			First Menarche				Tumor Localization			Menstrual Cycles				Location	
	<45	≥45	0	≥1	No	Ex	Yes	09. Eki	11. Ara	13-14	15-16	Right	Left	Bila-teral	Irre-gular	Re-gular	Mena-pau-se	Ame-norr-hea	ur-ban	ru-ral
Serous cystadenoma (n=124)	54[a]	46[a]	18.5[a]	81.5[b]	91.1[a]	2.4[b]	6.5[b]	6.5[a]	53.2[b]	38.7[c]	1.6[a]	54.8[a]	36.3[b]	8.9[c]	43.5[a]	29[b]	27.4[b]	0	52.4[a]	47.6[a]
Borderline serous tumors (n=10)	80[a]	20[b]	20[a]	80[b]	90[a]	10[b]	0	10[a]	40[a]	40[a]	10[a]	30[a]	30[a]	40[a]	80[a]	10[b]	10[b]	0	30[a]	70[a]
Serous adenocarcinoma (n=44)	25[a]	75[b]	4.5[a]	95.5[b]	86.4[a]	11.4[b]	2.2	0	52.3[a]	40.9[a]	6.8[b]	29.5[a]	34.1[a]	36.4[a]	29.5[a]	11.4[a]	59.1[b]	0	59.1[a]	40.9[a]
Mucinous cystadenoma (n=43)	63[a]	37[b]	9.3[a]	90.7[b]	93[a]	4.7[b]	2.3	0	46.5[a]	48.8[a]	4.7[b]	44.2[a]	48.8[a]	7[b]	48.8[a]	30.2[a,b]	20.9[b]	0	55.8[a]	44.2[a]
Borderline mucinous tumors (n=1)	0	100	0	100	0	0	100	0	0	100	0	0	100	0	0	100	0	0	0	100
Mucinous adenocarcinoma (n=8)	50	50	0	100	87.5[a]	12.5[b]	0	0	62.5[a]	25[a]	12.5[a]	50[a]	12.5[a]	37.5[a]	50[a]	12.5[a]	37.5[a]	0	50	50
Brenner tumor (n=3)	33.3[a]	66.7[a]	0	100	66.7[a]	33.3[a]	0	0	66.7[a]	0	33.3[a]	33.3[a]	66.7[a]	0	33.3[a]	0	66.7[a]	0	33.3[a]	66.7[a]
Transitional cell carcinoma (n=1)	0	100	0	100	0	100	0	0	0	100	0	0	0	100	0	0	100	0	0	100
Dysgermi-noma (n=5)	100	0	80[a]	20[a]	100	0	0	0	60[a]	40[a]	0	60[a]	40[a]	0	80[a]	20[a]	0	0	60[a]	40a
Granulosa cell carcinoma (n=6)	33.3[a]	66.7[a]	0	100	83.3[a]	16.7[a]	0	0	66.7[a]	16.7[a]	16.7[a]	0	100	0	16.7[a]	33.3[a]	50[a]	0	50	50
Serous+ mucinous cystadenoma (n=3)	100	0	0	100	100	0	0	0	100	0	0	33.3[a]	66.7[a]	0	66.7[a]	33.3[a]	0	0	0	100
Fibrothe-coma (n=3)	33.3[a]	66.7[a]	0	100	100	0	0	0	100	0	0	66.7[a]	33.3[a]	0	33.3	0	66.7	0	66.7[a]	33.3[a]
Mature teratoma (n=58)	90[a]	10[b]	15.5[a]	84.5[b]	100	0	0	3.4[a]	13.8[a]	50[b]	32.8[b]	53.4[a]	41.4[a]	5.2[b]	63.8[a]	27.6[b]	5.2[c]	3.4[c]	44.8[a]	55.2[a]
Immature teratoma (n=2)	0	100	50	50	100	0	0	50	0	50	0	0	100	0	50	0	50	0	50	50

The different letters used for intra- group comparision (eg. a, b, c) indicate statistically significant ($p<0.05$), the same letters (eg. a, a) indicate statistically no significant ($p>0.05$).

of Ataturk University in Erzurum, between 31 June 2013 and 1 January 2006. Clinicopathological features of women with ovarian neoplasia were summarized in Table 1. The mean age of the patients were 41.5±16.3. Borderline serous tumors (80%), mucinous cystadenoma (63%), dysgerminoma (100%), and mature teratoma (90%) were significantly seen in patients younger than 45 whereas serous adenocarcinoma (75%), borderline mucinous (100%), transitional cell carcinoma (100%), and immature teratoma (100%) were significantly found in patients older than 45 (Figure 2). All cancers except dysgerminoma (20%) and mature teratoma (50%) were appeared in multigravida women. When the relationship between smoking status and tumor type was evaluated, ratio of nonsmokers were significantly higher in

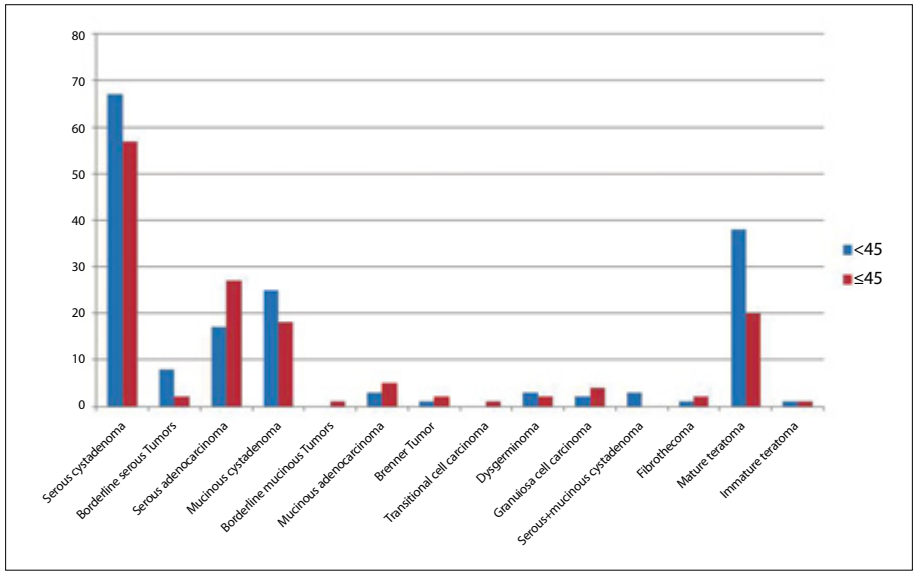

Figure 2. *Reported cancer among first-degree relatives of patients with ovarian neoplasms by histologic type of tumor and age at diagnosis.*

Table 2. Relative risk of ovarian neoplasia and major subtypes by smoking status

	Non Smoker	Ex smoker	Smoker
Serous cystadenoma	113	3	8
Borderline serous tumors	9	1	0
Serous adenocarcinoma	38	5	1
Mucinous cystadenoma	40	2	1
Borderline mucinous tumors	0	0	1
Mucinous adenocarcinoma	7	0	1
Brenner tumor	2	1	0
Transitional cell carcinoma	0	1	0
Dysgerminoma	5	0	0
Granulosa cell carcinoma	5	1	0
Serous+mucinous cystadenoma	3	0	0
Fibrothecoma	3	0	0
Mature teratoma	58	0	0
Immature teratoma	2	0	0

all groups (Table 2). According to the age of first menarche, serous cystadenoma were seen 6.5% in age 9-10, 53.2% in age 11-12, 38.7% in age 13-14, and 1.6% in age 15-16, respectively and there was statistically significant difference between the groups. Patients with borderline serous or serous adenocarcinoma were found significantly lower ratio in 15-16 age of first menarche. Menstrual cycle of the patients with serous cystadenoma (43.5% vs. 29%), borderline serous tumor (80% vs. 10%), and mature teratoma (63.8% vs. 27.6%) was irregular. Women with serous adenocarcinoma were significantly in menapause (59.1%) (Table 3). There has been no difference for the habitual status of the patients in all cancer groups, rural or urban. Although only serous cystadenoma were statistically significant seen in right ovary, tumors were mostly located in the right ovary (Figure 3). The association between tumor markers and types of ovarian neoplasia were

Table 3. Distribution of patients with ovarian neoplasia according to major subtypes of various clinical parameters

	First Menarche					Parite				Gravida			
	No Menarche	(9-10) Age	(11-12) Age	(13-14) Age	(15-16) Age	0	(1-5)	(6-9)	(10-)	0	(1-5)	(6-9)	(10-)
Serous cystadenoma	0	8	66	48	2	30	70	18	6	23	66	26	9
Borderline serous tumors	0	1	4	4	1	2	8	0	0	2	6	2	0
Serous adenocarcinoma	0	0	23	18	3	8	26	7	3	2	24	10	8
Mucinous cystadenoma	0	0	20	21	2	7	26	6	4	4	25	10	4
Borderline mucinous tumors	0	0	0	1	0	0	1	0	0	0	1	0	0
Mucinous adenocarcinoma	0	0	5	2	1	0	3	3	2	0	2	4	2
Brenner tumor	0	0	2	0	1	0	2	1	0	0	2	1	0
Transitional cell carcinoma	0	0	0	1	0	0	1	0	0	0	1	0	0
Dysgerminoma	0	0	3	2	0	4	1	0	0	4	1	0	0
Granulosa cell carcinoma	0	0	4	1	1	1	4	1	0	0	4	2	0
Serous+mucinous cystadenoma	0	0	3	0	0	0	3	0	0	0	3	0	0
Fibrothecoma	0	0	3	0	0	0	3	0	0	0	2	1	0
Mature teratoma	2	8	29	19	0	20	33	3	2	9	40	7	2
Immature teratoma	0	1	0	1	0	1	0	1	0	1	0	1	0

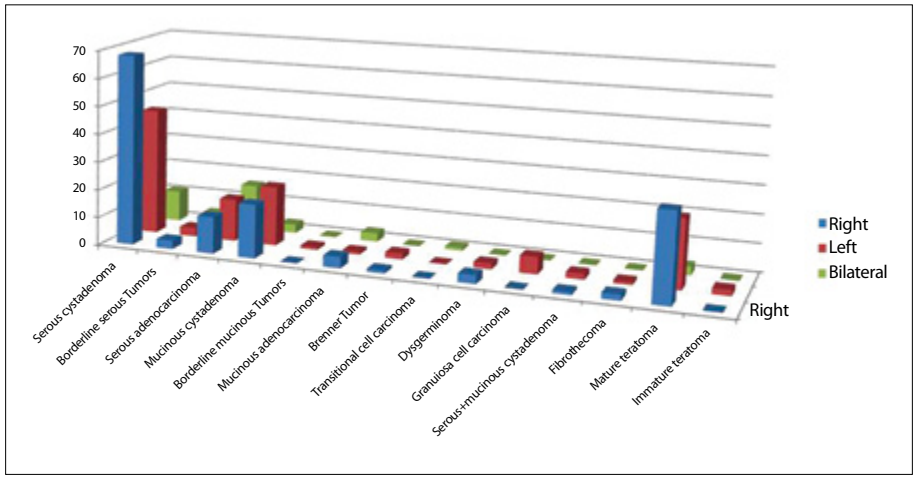

Figure 3. *The distrubition of histological subtypes of ovarian neoplasms according to localization.*

illustrated in (Table 4). In the all tumor groups, all of the tumor markers were significantly normal.

Discussion

One of the leading cause of cancer related death in women is ovarian cancer with 151905 deaths of world (4.3%) [3, 4]. The sub-group named as ovarian surface epithelial tumors are the most common lethal gynecologic neoplasms for women of reproductive age and older and these tumors display biological behaviors that follow their histopathological grading of malignant, borderline or low malignant potential, or benign [12] In Turkey, the number of mortality due to ovarian cancer was 1588 women (4.8%) [3, 4]. But there were conflicting data about the insidence in Turkey because of insufficient recording system. After the endometrium cancer, ovarian cancer is the second commonly seen malignancy in Turkey. Approximately 90% of ovarian cancers are derived from tissues that come from the coelomic epithelium or mesothelium [13]. Serous cystadenoma is the commonest ovarian tumor followed by mucinous, germ cell tumors, and dysgerminoma. In our study,

Table 4. Distribution of patients with ovarian neoplasia according to tumor markers

	CA-125		CA-153		CA-199		AFP		CEA	
	<35	≥35	<30	≥35	<37	≥37	<6	≥6	<2.5	≥2.5
Serous cystadenoma (n=124)	81.1[a]	18.9[b]	89.6[a]	10.4[b]	94.2[a]	5.8[b]	100	0	73.1[a]	26.9[b]
Borderline serous tumors (n=10)	50	50	100	0	100	0	100	0	62.5[a]	37.5[a]
Serous adenocarcinoma (n=44)	56.8[a]	43.2[a]	59.1[a]	40.9[a]	93.2[a]	6.8[b]	93[a]	7[b]	79.5[a]	20.5[b]
Mucinous cystadenoma (n=43)	76[a]	24[b]	80[a]	20[b]	96[a]	4[b]	100	0	80[a]	20[b]
Borderline mucinous tumors (n=1)	100	0	100	0	100	0	100	0	100	0
Mucinous adenocarcinoma (n=8)	50	50	66.7[a]	33.3[a]	33.3[a]	66.7[a]	100	0	33.3[a]	66.7[a]
Brenner tumor (n=3)	100	0	100	0	100	0	100	0	100	0
Transitional cell carcinoma (n=1)	0	100	0	100	100	0	100	0	100	0
Dysgerminoma (n=5)	75[a]	25[a]	75[a]	25[a]	100	0	75[a]	25[a]	50	50
Granulosa cell carcinoma (n=6)	100	0	100	0	100	0	100	0	100	0

The different letters used for intra-group comparision (eg. a, b, c) indicate statistically significant ($p<0.05$), the same letters (eg. a, a) indicate statistically no significant ($p>0.05$).

the commonly seen tumors are serous cystadenoma (40%), mature teratoma (18%), serous adenocarcinoma (14%), and mucinous cystadenoma (14%).

Most of the studies reported that the age of the women positively associated with ovarian cancer [14, 15]. Similarly, our fundings supported the other epidemiological studies. Comparison of the age distribution of ovarian neoplasia cases revealed that benign ovarian neoplasms were significantly found in women lower than 45 whereas malign neoplasms were accompanied with women higher than 45 in our study. More than 80% of epithelial ovarian cancers are found in postmenopausal women and the peak incidence of invasive epithelial ovarian cancer is at 56 to 60 years of age [13]. These cancers are relatively uncommon in women younger than age 45. Benign ovarian neoplasms and borderline tumors which are associated with a very good prognosis occur predominantly in premenopausal women [16].

Although most of studies in the literature claimed that cigarette smoking was associated with an incresed risk factor for ovarian cancers, especially mucinous epithelial ovarian cancer [17-19], Goodman and Tung reported that active tobacco smoking was not a risk factor for invasive ovarian cancer [20]. In a recent large population study, epithelial ovarian cancer did not observe an association with smoking [21] Our results confirm that smoking may not increase the risk of ovarian cancer. However, this study was not based on cigarette smoking and did not search the insidence of ovarian cancer in cigarette smoking women.

Early menarche and low parity were associated with increased risk of ovarian cancer [22]. In a population based case control study, ≤13 age at menarche was significantly related to the risk of ovarian cancer [23]. Although protective effect of parity is unclear, duration of menstrual cycle in life is inversely associted with ovarian cancer, having at least one child is protective of the disease, with a risk reduction of 0.3 to 0.4 [13]. The protection effect of oral contraceptives against epithelial ovarian cancer that was well established in the literature have the similar mechanism [24, 22]. In our study, epithelial ovarian neoplasms were mostly associated with early menarche whereas the ratios of all groups were higher according to the gravida.

Although several lifestyle factors affect a woman's risk of ovarian cancer, the most important risk factor, family history of disease, is unlikely to be related to socio-economic status. Urban areas had higher incidence rates, compared to rural areas, across all deprivation levels [25]. Similarly, our study showed that there was no difference for the insidence of habitual status, urban and rural.

Tung et al. [26] revealed that lifetime ovulation was significantly and positively associated with the risk of ovarian cancer. Their data provide the clear evidence for the hypothesis that ovulation is integral to the etiology of ovarian cancer. Therefore, factors that induced anovulation, including oral contraceptives, pregnancy, and breastfeeding, were associated with a reduced risk of ovarian cancer. Despite our study displayed that menstrual irregularity was frequent in the ovarian malignancy. An important limitation of this study is that we examined menstrual irregularity in the women with ovarian cancer.

The clinical diagnosis and following of ovarian cancer depends on the clinical findings and image examination, however, ovarian cancer can hardly be diagnosed at early stage and monitarization after first treatment is vital [27, 28]. Early diagnosis decrease the morbidity and mortality of ovarian cancer. However, most serum tumor markers are neither sensitive nor specific enough for cancer diagnosis. CA-125 is used to diagnose and follow up epithelial ovarian cancer especially serous adenocarcinoma. CA-199 is

another tumor marker that may be useful for the detection of mucinous adenocarcinoma. In this study, we looked over the positivity rates of tumor markers in the ovarian cancer groups. Indeed, benign conditions such as serous cystadenoma, mucinous cystadenoma, and mature teratoma had normal value of CA-125 in our study. In serous adenocarcinoma group, the proportions of the normal tumor markers were higher than elevated tumor markers; however there were no statistically significant difference. When we compared the serous cystadenoma, CA-125 ratios were higher in serous adenocarcinoma (18.9% vs. 43.2%). Although there were no significant difference in the same group, CA-199 ratios were higher in mucinous adenocarcinoma comparing to the other groups. Because of the limited number of the germ cell tumor, ratios of AFP which were useful for the diagnosis of germ cell tumors such as dysgerminoma did not show statistically significant within the group. However the highest ratios were in dysgerminoma group compared with other groups.

In conclusion, to our knowledge current study was the first epidemiological study in Turkey. Analysis of each country's statistical information reflecting its own profile is also important. The relationship between the profiles of patients and types of ovarian neoplasms may give an idea about the risk factors of the disease in its region. Additionally distribution of tumor markers might be considered for the discriminating of the benign or malign characters of the ovarian neoplasia.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ethic Committee of Ataturk University Faculty of Medicine (Date 10.10.2012 Decision No: B.30.2.ATA.0.01.00/111).

Informed Consent: Written informed consent was not obtained due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.D.; Design - E.D.; Supervision - E.D., S.Ş., M.Ç.; Funding - E.D., E.A.; Materials - F.T.D., B.B.; Data Collection and/or Processing - B.B., F.T.D.; Analysis and/or Interpretation - E.D., S.Ş.; Literature Review - M.Ç., F.T.D.; Writing - E.D.; Critical Review - S.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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