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Original Article

Ovarian Cancer in Iran: National Based Study

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Abstract

Background: Ovarian cancer (OC) is the 7th most common cancer, with 239,000 new cases per year. In Iran, it is the 8th most common cancer, with an ASIR of 3.9/100,000 women. The 5-year overall survival in Iran based on previous studies is about 61% which in comparison with eastern countries has better survival.

Methods: The study included patients from the Iran National Cancer Registry from 2009-2014. Several steps were taken to control data quality. This study used a Kaplan-Meier survival curve to compare OC survival rates across geographical, pathological, and other variables. All analyses were done in R (4.02) and SPSS (26), with a 0.05 *P*-value considered statistically significant.

Results: The study enrolled 7977 cases of OC. OC's ASIR was 4.10/100,000. In epithelial and non-specific OC, ASIR was >0.5. Five-year survival was 55% and 10-year survival was 45%.

Conclusion: OC is the 8th most common cancer in Iran, with lower age-specific incidence and better overall survival than East Asia and North America. In Iran, as in Eastern Europe, OC incidence correlated with reduced total fertility rate and population aging. Five and 10-year overall survival rates were 55% and 44%, respectively, higher than the West. This may be because late stage OC patients are excluded from pathology and classified as "undiagnosed" in death certificates or hospitalization files.

Keywords: Ovarian cancer; Epidemiology; Iran

Introduction

Ovarian cancer (OC) is the 7th most frequent cancer, with 239,000 new cases each year (1). The incidence rate is varied between 1/100,000 women in Africa to 17/100,000 in northern Europe (2). In Iran OC is the 8th most frequent cancer (3) with a 3.9/ 100,000 age-standardized incidence (4). Mean age of OC in the USA and Europe is above 60, but in Iran it is 49(1, 5-7).

The pathology of malignant ovarian tumors includes epithelial (80%-90%), stromal, and germ cell pathology. Non-epithelial OC such germ-cell, sex cord tumors, and metastatic encompass just 10% of cases. Unlike epithelial forms, non-epithelial OC occurs predominantly in reproductive age(8).

One in 75 women will acquire OC, and 1 in 100 will die from it (9). In prior research, Iran's 5-year overall survival was at 61%, better than Australia (34%), the USA (52%), and Japan (36.4%) (6, 10, 11). Serosal type has the lowest 5-year survival rate (41%) while Endometrioid and clear cell type has the highest rate (61% and 76% respectively). Germ cell tumors in comparison with epithelial

types has better survival rate (5- year survival rate 85% versus 59%)(8).
Hormones and reproduction have a role in OC pathogenesis. Obesity, early menarche, late menopause, positive family history, and early pregnancy age all increase the risk of OC (1, 12-14).
The current study is the first comprehensive epidemiologic investigation on OC in the eastern Mediterranean region, examining the incidence rate, age specific rate, and 5 and 10-year survival rate of OC in Iran from 2009-14.

Material and Methods

Study population

In this population-based cohort analysis, patients with OC recorded in the Iran National Cancer Registry (INCR) between 2009 and 2014 were included.
INCR, a Ministry of Health and Medical Education subsidiary, collected all cancer cases from hospitals, clinics, pathologies, and death certificates. IR. SBMU.CRC.1398.029.
INCR took many procedures to control data quality. First, the topography and morphology of tumors were examined for consistency with age. The next stage was to check patients' ages and rectify records whose ages deviated from their birth dates. Duplicate instances were removed from the research if their first names, surnames, and ages matched across all data.

Data variables

The ICD-O-3 was used to classify OC patients with a behavior code of three. In addition, the topography code of C56.9 was considered as OC (15). According to prior research, six histological categories were used: type I epithelial, type II epithelial, germ cell, sex cord-stromal, non-specific. Type I epithelial had five subtypes: clear cell, endometrioid, mucinous, squamous, and transitional cell or Brenner. Serous carcinoma, mixed epithelial-stromal carcinoma, and undifferentiated or other epithelial were histological subtypes of type II epithelial (16).

Data Cleansing

Data quality was evaluated in stages. Duplicate instances were detected by first name, surname, gender, and national ID number. INCR evaluated and validated data completeness and validity (17).

Statistical Analysis

Descriptive statistics were expressed as a number of cases for each histology groups and subgroups. The crude incidence rate (per 100,000 person years) and 95% confidence interval (CI) were calculated for all histological subtypes and age categories. The age-standardized incidence rates (ASIRs) per 100,000 were calculated according to year of diagnosis and histology groups using new World Health Organization (WHO) standard population and the direct standardization method (18). In addition, the 95% confidence interval (95% CI) of ASIRs were expressed using direct method (19). Moreover, the standardized rate ratio (SRR) with 95% CI was reported for histological groups (20). The one-, three-, five-, and ten-survival rates with mean survival time (years) were expressed for all age groups, histological groups and interaction of them. The Kaplan-Meier survival curve was also used to compare the survival rates of OC in different categories. All analysis was performed in R (version 4.0.2) and SPSS (ver. 26, IBM Corp., Armonk, NY, USA) and *P*-value of less than 0.05 were regarded as statistically significant.

Results

Between 2009 and 2014, the study included 8702 OC patients with a mean (SD) age of 51.0 (17.3) years. Incorrect data (108 instances), non-Iranian records (23 cases), and duplicate cases (584 cases) were eliminated from the analysis, leaving 7977 cases.
The incidence rate (per 100,000 person-years) of OC by histological groups and histological subtypes are shown in Table 1. The overall ASIR of OC had the negatively skewed distribution and the incidence rate of patients older than 45 yr were higher than 6 per 100,000 person-years. The

highest incidence rate of OC was observed in age of 60-79 yr with the rate of higher than 12 per 100,000 person-years (Fig. 1.A). The ASIR of OC (with 95% CI) had an upward trend during 2009-2014 (Fig. 1.B). In the next step, the distribution of age-specific incidence rate was showed for all histological groups. Accordingly, type I and II epithelial, sex cord-stromal, other specific non-epithelial, and non-specific OC had highest incidence rates in older ages, however, the germ cell OC was more occurred in lower age groups (Fig. 2).

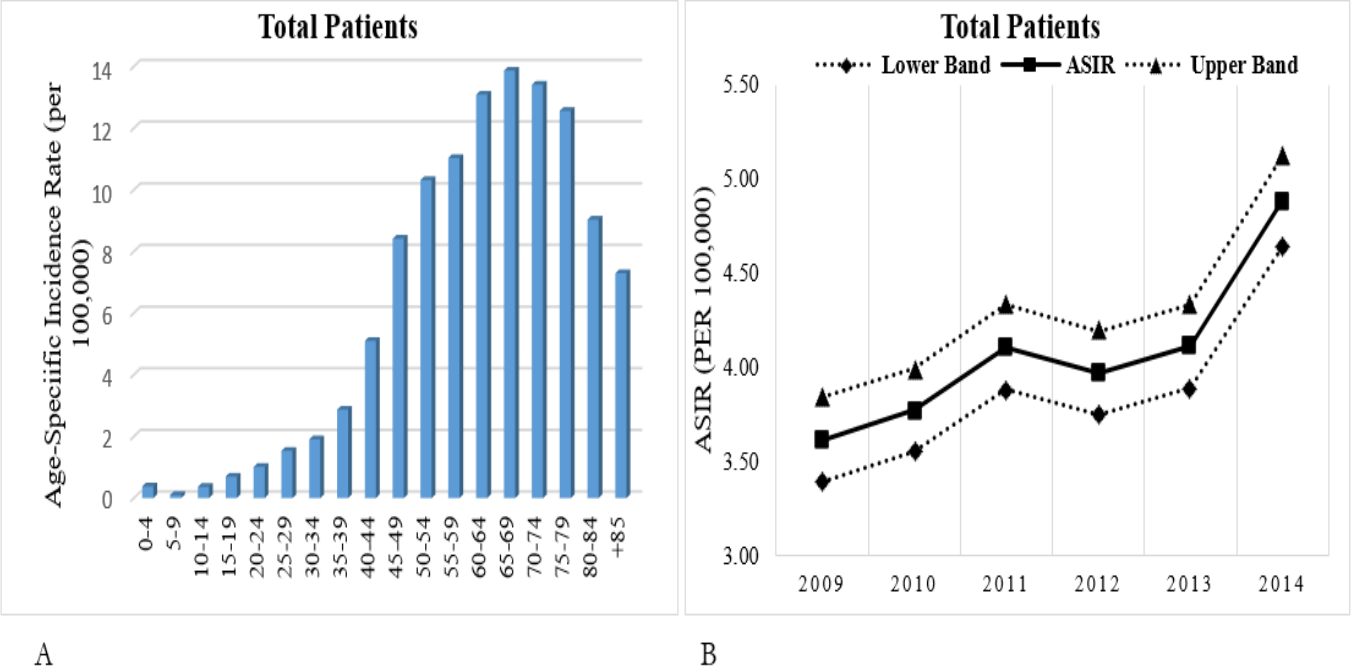

Fig. 1: A) Ovarian Cancer Incidence Rates by Age, Iran, 2009–2014 and B) Trend of Ovarian Cancer Incidence with 95% CI, Iran, 2009-2014

Overall, 2837 cases were included to the study. Accordingly, the ratio of new cases in type II to type I was about three in both incidence and survival analysis (Table 1 and 2). Moreover, the mean survival time of patients younger than 50 yr was 2.4 times of that in patients older than 70 yr. The survival rate of different histological groups was also reported in age categories (Table 2). The Kaplan-Meier survival curve of total ovarian patients are shown in Fig. 3.A. Besides, the Kaplan Meier was curved by histology subtypes (Fig. 3.B), age groups (Fig. 3.C), histology group in patients younger than 50 yr (Fig. 3.D), histology group in age higher than 50 and less than 70 yr (Fig. 3.E), and histology group in patients older than 70 yr (Fig. 3.F).

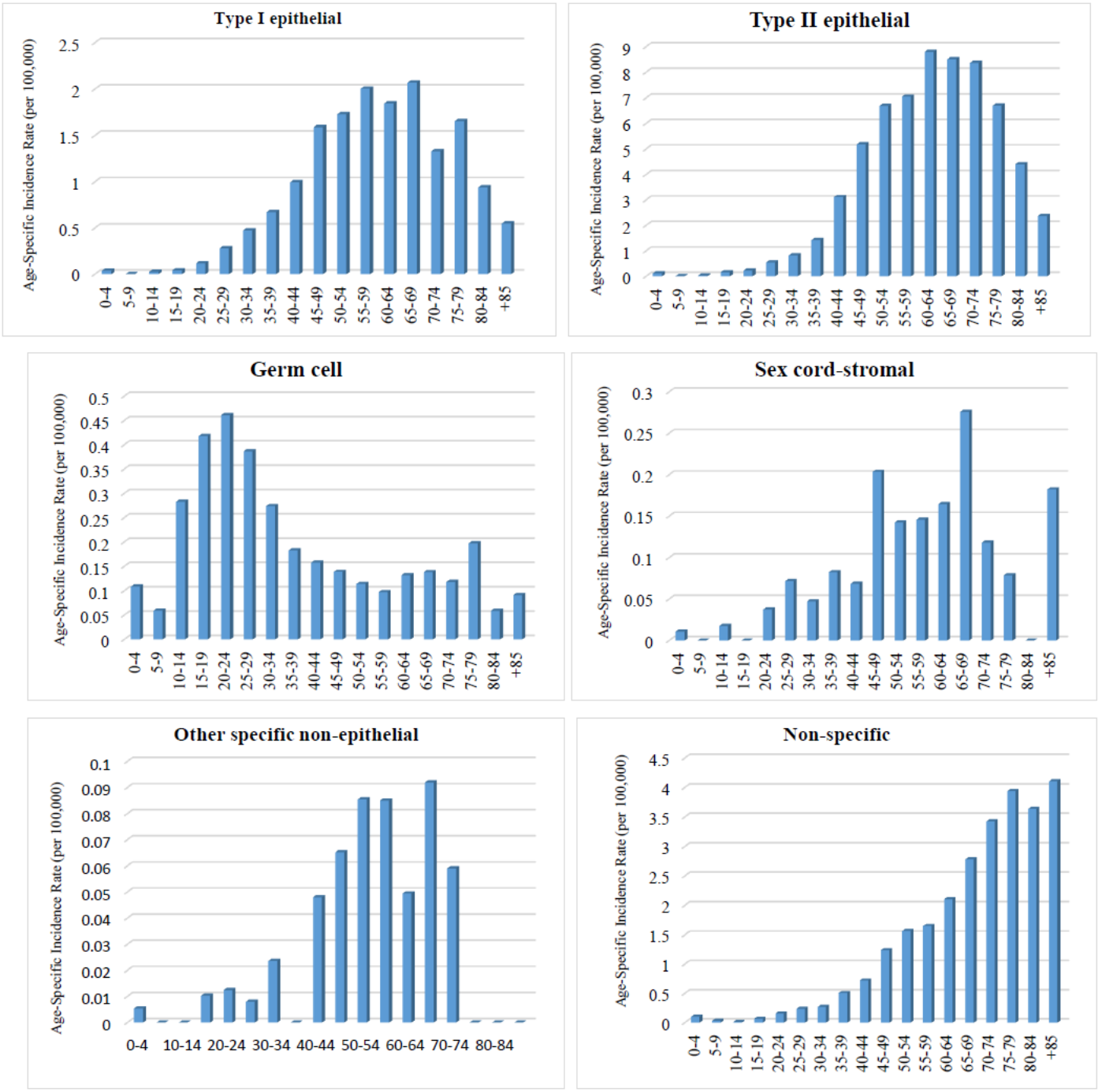

Fig. 2: Ovarian Cancer Incidence Rates by, and Histology Group, Iran, 2009–2014

Table 1: The incidence rate (per 100,000 person-years) of ovarian cancer by histological groups and histological subtypes

Histological Group	*Histological Subtype*	*No. of cases*	*Crude (95% CI)**	*ASIR (95% CI)***	*SRR (95% CI)****
Type I epithelial		1329	0.59 (0.56-0.63)	0.67 (0.63-0.70)	1.00 (0.90-1.12)
	Clear cell carcinoma	142	0.06 (0.05-0.07)	0.07 (0.06-0.08)	1.21 (0.86-1.69)
	Endometrioid carcinoma	456	0.20 (0.19-0.22)	0.23 (0.21-0.25)	1.00 (0.83-1.21)
	Mucinous carcinoma	611	0.27 (0.25-0.29)	0.30 (0.27-0.32)	1.02 (0.87-1.20)
	Squamous carcinoma	60	0.03 (0.02-0.03)	0.03 (0.02-0.04)	0.72 (0.43-1.21)
	Transitional cell or Brenner carcinoma	60	0.03 (0.02-0.03)	0.03 (0.02-0.04)	0.78 (0.46-1.30)
Type II epithelial		4495	2.01 (1.95-2.07)	2.37 (2.30-2.44)	1.04 (0.98-1.11)
	Serous carcinoma	3119	1.39 (1.34-1.44)	1.64 (1.58-1.70)	0.98 (0.91-1.05)
	Mixed epithelial-stromal carcinoma	66	0.03 (0.02-0.04)	0.04 (0.03-0.04)	1.27 (0.78-2.08)
	Undifferentiated or other epithelial	1310	0.59 (0.55-0.62)	0.69 (0.65-0.73)	1.21 (1.08-1.35)
Germ cell	Germ cell	541	0.24 (0.22-0.26)	0.22 (0.20-0.24)	0.86 (0.72-1.02)
Sex cord-stromal	Sex cord-stromal	148	0.07 (0.06-0.08)	0.07 (0.06-0.08)	0.79 (0.56-1.10)
Other specific non-epithelial	Other specific non-epithelial	53	0.02 (0.02-0.03)	0.03 (0.02-0.03)	1.16 (0.67-2.02)
Non-specific	Non-specific	1411	0.63 (0.60-0.66)	0.74 (0.70-0.78)	1.86 (1.66-2.07)
	Total	7977	3.56 (3.49-3.64)	4.10 (4.01-4.19)	1.13 (1.08-1.18)

* Crude Incidence Rate (95% CI) per 100,000 person-years of ovarian cancer.
** The Age-Standardized Incidence Rate (95% CI) per 100,000 person-years using new WHO standard population.
*** The Standardized Rate Ratio (95% CI) of period 2012-2014 to 2009-2011

Table 2: The one to ten-years survival rate (95% CI) of ovarian cancer by histological groups and histological subtypes

Variable		*No. of cases*	*1-Year Survival Rate (95% CI)*	*3-Years Survival Rate (95% CI)*	*5-Years Survival Rate (95% CI)*	*10-Years Survival Rate (95% CI)*	*Mean Survival Time (95% CI)*
Histological Group	Histological Subtype						
Type I epithelial		499	90.0 (87.0-92.0)	73.0 (69.0-77.0)	65.0 (61.0-69.0)	55.0 (50.0-61.0)	7.4 (7.0-7.7)
	Clear cell carcinoma	61	90.0 (83.0-98.0)	69.0 (58.0-82.0)	61.0 (50.0-74.0)	58.0 (46.0-72.0)	7.0 (5.9-8.2)
	Endometrioid carci-	169	92.0 (88.0-	81.0 (75.0-	73.0 (66.0-	60.0 (52.0-	8.0 (7.4-

	noma		96.0)	87.0)	80.0)	70.0)	8.6)
	Mucinous carcinoma	225	88.0 (84.0-92.0)	69.0 (63.0-75.0)	62.0 (56.0-69.0)	54.0 (46.0-62.0)	7.1 (6.5-7.7)
	Squamous carcinoma	15	93.0 (82.0-100.0)	60.0 (40.0-91.0)	47.0 (27.0-80.0)		5.2 (3.4-7.0)
	Transitional cell or Brenner carcinoma	29	90.0 (79.0-100.0)	69.0 (54.0-88.0)	59.0 (43.0-80.0)		6.1 (4.8-7.4)
Type II epithelial		1550	84.0 (83.0-86.0)	65.0 (63.0-67.0)	50.0 (48.0-53.0)	38.0 (35.0-41.0)	6.0 (5.8-6.2)
	Serous carcinoma	1084	88.0 (86.0-90.0)	68.0 (66.0-71.0)	53.0 (50.0-56.0)	40.0 (36.0-43.0)	6.3 (6.0-6.5)
	Mixed epithelial-stromal carcinoma	20	80.0 (64.0-100.0)	70.0 (53.0-93.0)	70.0 (53.0-93.0)	65.0 (47.0-90.0)	7.6 (5.6-9.6)
	Undifferentiated or other epithelial	446	77.0 (73.0-81.0)	56.0 (52.0-61.0)	42.0 (38.0-47.0)	34.0 (29.0-40.0)	5.3 (4.9-5.7)
Germ cell	Germ cell	210	94.0 (91.0-97.0)	90.0 (85.0-94.0)	88.0 (83.0-92.0)	86.0 (81.0-91.0)	9.6 (9.2-10.1)
Sex cord-stromal	Sex cord-stromal	70	91.0 (85.0-98.0)	86.0 (78.0-94.0)	84.0 (76.0-93.0)	79.0 (70.0-90.0)	8.8 (8.0-9.6)
Other specific non-epithelial	Other specific non-epithelial	18	83.0 (68.0-100.0)	67.0 (48.0-92.0)	56.0 (37.0-84.0)	33.0 (13.0-84.0)	5.8 (3.9-7.7)
Non-specific	Non-specific	490	69.0 (65.0-73.0)	49.0 (45.0-54.0)	43.0 (39.0-48.0)	37.0 (33.0-43.0)	5.1 (4.7-5.6)
Age Group	Levels						
	<50	1320	90.0 (88.0-92.0)	78.0 (76.0-80.0)	70.0 (67.0-72.0)	62.0 (59.0-65.0)	7.9 (7.6-8.1)
	50-69	1167	82.0 (80.0-84.0)	61.0 (58.0-64.0)	49.0 (46.0-52.0)	36.0 (33.0-40.0)	5.8 (5.5-6.0)
	≥70	350	64.0 (59.0-69.0)	37.0 (32.0-42.0)	23.0 (19.0-27.0)	14.0 (9.0-19.0)	3.3 (2.9-3.7)
Histology in Age groups	Levels						
<50							
	Type I epithelial	252	92.0 (89.0-96.0)	82.0 (77.0-87.0)	77.0 (72.0-83.0)	70.0 (63.0-77.0)	8.5 (8.1-9.0)
	Type II epithelial	618	90.0 (87.0-92.0)	75.0 (72.0-79.0)	61.0 (58.0-65.0)	50.0 (46.0-55.0)	7.1 (6.7-7.4)

	Germ cell	195	97.0 (95.0-99.0)	93.0 (89.0-97.0)	91.0 (87.0-95.0)	90.0 (86.0-94.0)	10.0 (9.7-10.4)
	Sex cord-stromal	42	93.0 (85.0-100.0)	88.0 (79.0-98.0)	86.0 (76.0-97.0)	86.0 (76.0-97.0)	9.3 (8.3-10.2)
	Other specific non-epithelial	7	100.0 (100.0-100.0)	71.0 (45.0-100.0)	57.0 (30.0-100.0)		5.5 (3.3-7.7)
	Non-specific	206	80.0 (74.0-85.0)	66.0 (60.0-73.0)	62.0 (56.0-69.0)	56.0 (50.0-64.0)	6.9 (6.3-7.6)
50-69							
	Type I epithelial	203	89.0 (84.0-93.0)	66.0 (60.0-73.0)	56.0 (50.0-64.0)	43.0 (36.0-53.0)	6.5 (5.9-7.1)
	Type II epithelial	723	85.0 (82.0-88.0)	63.0 (60.0-67.0)	49.0 (45.0-52.0)	35.0 (30.0-39.0)	5.8 (5.4-6.1)
	Germ cell	13	62.0 (40.0-95.0)	54.0 (33.0-89.0)	46.0 (26.0-83.0)		3.7 (1.9-5.4)
	Sex cord-stromal	23	91.0 (80.0-100.0)	87.0 (74.0-100.0)	87.0 (74.0-100.0)	76.0 (60.0-97.0)	8.7 (7.2-10.1)
	Other specific non-epithelial	10	80.0 (59.0-100.0)	70.0 (47.0-100.0)	60.0 (36.0-100.0)	50.0 (27.0-93.0)	6.2 (3.6-8.9)
	Non-specific	195	65.0 (59.0-72.0)	44.0 (37.0-51.0)	37.0 (31.0-45.0)	31.0 (25.0-40.0)	4.6 (3.9-5.2)
≥70							
	Type I epithelial	44	80.0 (68.0-92.0)	52.0 (39.0-69.0)	32.0 (21.0-49.0)		4.3 (3.2-5.4)
	Type II epithelial	209	67.0 (61.0-74.0)	40.0 (34.0-47.0)	24.0 (19.0-30.0)	15.0 (10.0-22.0)	3.5 (3.0-4.0)
	Germ cell	2					0.4 (0.1-0.8)
	Sex cord-stromal	5	80.0 (52.0-100.0)	60.0 (29.0-100.0)	60.0 (29.0-100.0)		5.1 (2.1-8.2)
	Other specific non-epithelial	1					0.9 (----)
	Non-specific	89	51.0 (41.0-62.0)	22.0 (15.0-33.0)	13.0 (8.0-23.0)		1.9 (1.4-2.4)
Total		2837	84.0 (82.0-85.0)	66.0 (64.0-68.0)	55.0 (54.0-57.0)	45.0 (43.0-48.0)	6.8 (6.2-8.0)

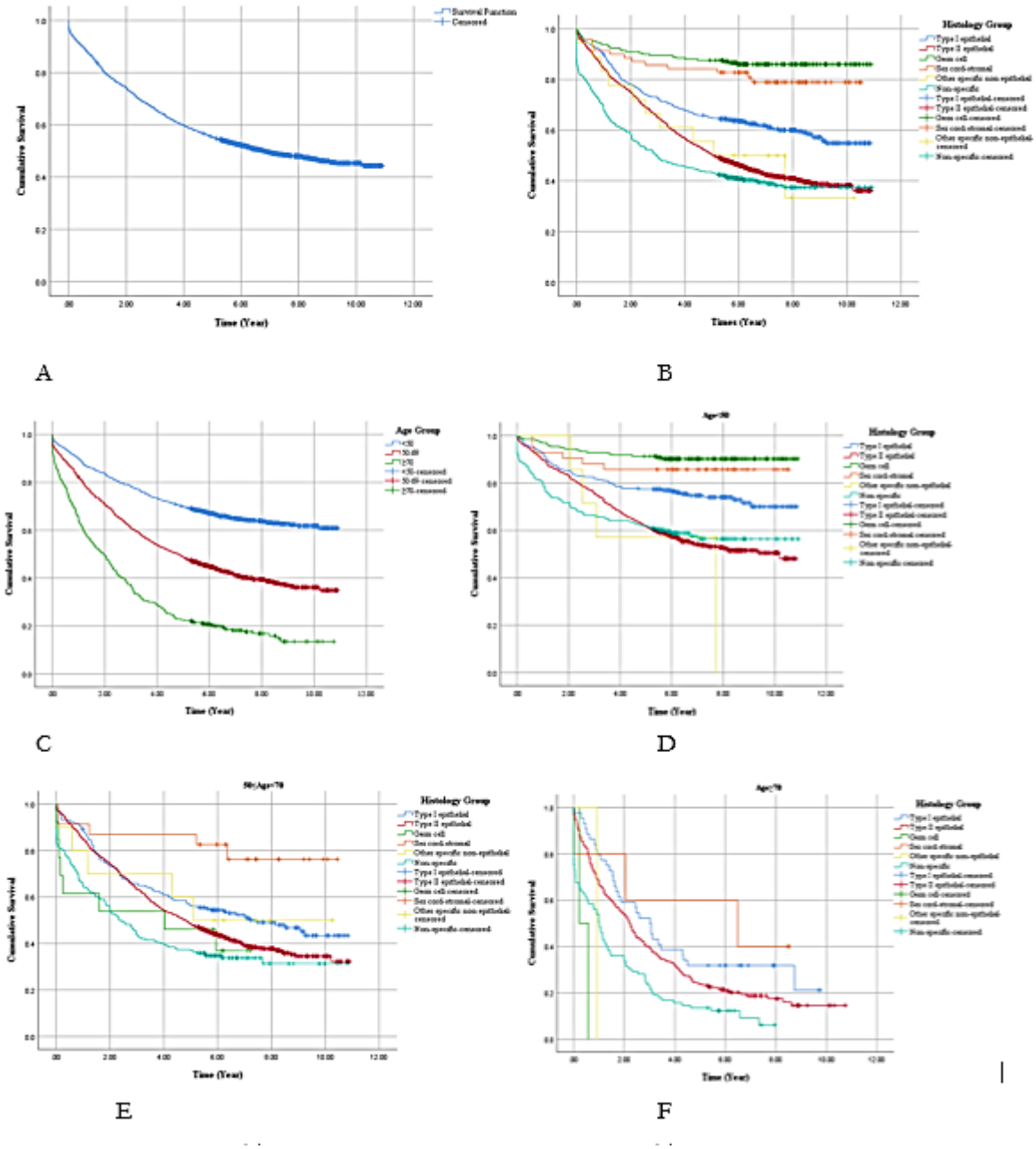

Fig.3: A) The overall Kaplan-Meier Survival Curve, The Kaplan-Meier Survival Curve by B) Histology Group, C) Age, D) Histology Groups in Age<50, E) Histology Groups in 50≤Age<70, F) Histology Groups in Age≥70, Iran, 2009-2014

Discussion

OC is the 7th most frequent cancer worldwide and the 8th in Iran. It is the 2nd reproductive system cancer in women after breast cancer and the 9th cause of cancer death in Iranian women (3, 21).

OC ASIR in Iran is 4.10 per 100,000 women. The highest incidence rates are in Central and Eastern Europe, North and South America (6.0, 11.4, 16.2, and 5.8 per 100,000 women), and the lowest are in Asia and Africa (3 or less per 100,000 women) (1). One reason for the low incidence is the Iranian population's youth (22).

An ASIR of 7.1 per 100,000 persons is considered high in industrialized countries, but only 5.8 in underdeveloped nations (23). In Asia, a substantial link was found between Human Development Index (HDI), life expectancy and ASIR of OC. Depopulation and long life expectancy lead to an aging population, increasing the risk of malignancies like OC (24). A high rate of ASIR has been seen in Japan and South Korea, both with high HDI and life expectancy over 80 yr (8.4 and 6.8 per 100,000 populations respectively (22). As we all know, HDI measures three basic dimensions: birth expectancy, educational achievement, and income (6, 25).

Iran's mean and median OC incidence age was 50 yr, with Germ cell and MESC (Type II) having the lowest and greatest mean age. An Iranian study also found that the median age of OC was 49 yr, with the lowest age (23 yr) in germ cell histology and the highest age in clear cell tumors (57 yr) (4). Iran's median age was lower than Australia's and Sweden's (63 and 61 respectively) (4). One cause might be the huge number of young people in these nations and Iran.

OC was more common in the 60-79 age range (27.2%). The greatest incidence rate was 45-65 yr in India (5) and 45-54 yr in Indonesia (5, 26). In England, the majority of cases were >65 yr old, while in the US, the greatest OC incidence rate was recorded among women aged 80-84 (26). In 2018, the age distribution of new cases in Iran was 35-59, compared to 60 in the USA. Given our aging population, this increase in age is predicted. Despite improving life expectancy, declining birth rate and an elderly population result in rising OC rate (4).

Our study's ASIR of type II epithelial OC was 2.37 per 100,000 participants, with serous carcinoma and undifferentiated OC being the most common similar to northern America, Europe and Oceania (1.64 and 0.69 per 100,000 populations respectively) (27, 28). Despite recent research, type II epithelial OC is rare in Thailand and Hong Kong (27). In 2018, serous carcinoma (type II epithelial) incidence rate was 4.9/100000, type 1 epithelial was 2.2/100000, while sex-cord and germ cell cancers were 0.3 and 0.4/100000 population correspondingly (29). While type I epithelial OC was the third most prevalent kind between 2005 and 2009, the Concord 2 research found it to be the second most common form between 2005 and 2009 with variable ratios from 32.5% in Asia to 19.4% in northern America (27). Type I epithelial tumors account for 41.3% and type II for 47.5% of Japan's. Endometriosis, the precursor of clear cell and endometrioid tumors, is more prevalent in Asia, which may explain why type I is more common (25, 29, 30). Type I mucinous carcinomas were the most common (0.3/100,000), like in other Asian nations (27). One reason for the high frequency is metastatic ovarian cancers, especially stomach tumors, which are common in Asian nations (31, 32).

Fig.1-B shows an increasing OC incidence trend from 2009-14. This rising tendency is also found in Asia, Central and Eastern Europe. (33). Parity in several Asian and Latin American nations fell from 6 live births in 1965 to 3 in 2000 due to family planning and western culture (34). Because of encouraging parity policies in northern European nations like Norway and Finland, the OC incidence trend is declining or steady (14, 35). Total Fertility Rate (TFR) fell from 2.05 in 2011 to 2.01 in 2016 in Iran, while OC prevalence increased (36, 37). As we know, pregnancy lowers ovulatory cycles and gonadotropin releases, lowering the risk of OC (33, 38).

Except for germ cells, all diseased groups with inclination for type II were menopausal. Asia and Central and South America have a younger population; hence, germ cell cancers are more common. As in other countries, our study found that sex cord cancers are rare (0.07(CI: 0.06-0.08)) (27, 39). Nonspecific tumors accounted for 17.5% of all proportions, far higher than other nations. Nonspecific cancers found in advanced stages require tissue biopsy or surgical excision to be

classified as type I, II, etc., hence we cannot categorize advanced stage tumors into specific subtypes (27).

Five and 10-year overall survival was 55% and 45% in this research. In a prior Iranian study, 61% of 451 OC patients survived 5 years, with younger patients (<45 yr) surviving longer than older patients (63% compared to 53%)(7). Figure 2-C shows that 5-year survival for women under 50 yr is 73% higher than for women over 50. Younger individuals may require extensive debulking due to nonmedical comorbidities, while elderly patients may require gentler chemotherapy (24, 40). The 5-year survival of OC patients in Iran is like Indonesia (54.8%) and more than Australia (34%), Japan (43.8%) and America (52%-based on SEER study) (41, 42). Undiagnosed instances in death certificates or hospitalization files might be one cause for Iran's high survival rate (7). This allows greater survival by eliminating high levels. The youthful population of Asian races also helps them survive (43).

The 5-year survival of germ cell and sex cord tumors is higher than type I and II epithelial malignancies (88 to 65 and 50 respectively) (7, 11, 27, 44). Patients with germ cell cancers tend to be young and respond well to treatment, which may explain their higher survival. Like earlier studies in Japan and Australia, clear cell and mucinous OC had greater survival than serous epithelial type (7, 11, 27, 45). The incidence of OC is higher in high HDI nations, whereas the survival rate is lower in low HDI countries. The relationship between socioeconomic position and OC survival is predicted by access to medical services, patient knowledge of symptoms, lifestyle, underlying condition, and atypical insurance status (24, 40). Moreover, early diagnosis by a gynecologic oncology team increases survival rates (24).

In the current study, the completeness and validity of data were assessed by INCR. Thus, two-source capture-recapture and Peterson-Chapman approaches were used to estimate completeness in cancer registry data (17). Moradian et al. studied the impact of data quality in Iranian cancer registry data. They defined data quality as the comparability, completeness, validity, and timeliness of recorded data. Incidence and survival studies require high-quality data (46).

Limitation

Since the patients' stages were not recorded, it was not able to write about death and survival link with different stages. We couldn't discuss the quality of patient care throughout diagnosis and management.

Conclusion

Compared to East Asia and North America, OC is the 8th most frequent cancer in Iran, with lower age-specific incidence and higher overall survival. The study is based on a national registry data after cleaning of that with completeness, comparability, validity and timeliness. Interesting result was the relation of rising OC incidence with reduction of TFR and population aging in Iran.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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