

Original Article

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Incidence trends for epithelial peritoneal, ovarian, and fallopian tube cancer during 1999–2016: a retrospective study based on the Korean National Cancer Incidence Database

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ABSTRACT

Objective: Primary peritoneal cancer (PPC), ovarian cancer (OC), and fallopian tube cancer (FTC) are considered as a single disease group. As knowledge of the pathogenesis and clinical presentation of peritoneal, ovarian, and fallopian tube (POFT) cancer grows, the tendencies in OC diagnosis are changing. We investigate the incidence and clinical characteristics of epithelial POFT based on cancer site and histologic type.

Methods: Data from the Korea Central Cancer Registry for the period between 1999 and 2016 were analyzed. The incidence rates and annual percent changes (APCs) for each tumor site were reported.

Results: Among 27,768 women with cancer, 1,086 (3.91%) had PPC, 25,847 (93.08%) had OC, and 835 (3.01%) had FTC. Age-standardized rates increased from 0.05 to 0.24, 3.51 to 5.48, and 0.04 to 0.28 in PPC, OC, and FTC, respectively. The proportion of PPC and FTC among all the POFT cases increased consistently during the study period (from, respectively, 1.48 and 1.06 in 1999 to 4.52 and 4.76 in 2016). The APC of PPC, OC, and FTC during 1999–2016 was 9.3%, 2.7%, and 8.6%, respectively. The incidence of PPC, OC, and FTC was highest among patients in the 65–69, 50–54, and 55–59 years age group, respectively. **Conclusion:** The overall incidence of PPC, OC, and FTC cancer has steadily increased. The relative increase of PPC and FTC has been significant. In this study, OC incidence had a relatively young peak age, in contrast to FTC and PPC, which had an older peak age.

Keywords: Epithelial Ovarian Cancer; Fallopian Tube Cancer; Peritoneal Carcinomatosis; Incidence; Asians

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

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INTRODUCTION

Ovarian cancer (OC) ranks tenth on incidence and fifth on mortality, however, it is considered the most lethal gynecological malignancy [1]. Epithelial ovarian cancer (EOC) is the most common OC type, accounting for over 90% of cases. Although, the origin of EOC was considered ovarian epithelium, recent studies have shown that EOC originates in the ovary as well as other sites, such as the fallopian tube, peritoneum, and the gastrointestinal (GI) tract [2,3]. In addition, there are accumulative reports that fallopian tube was the origin of high grade serous tumor histology [4,5]. Identifying the origin of the tumor is the most basic and important task for diagnosis, treatment and prevention of diseases. Recently, riskreducing salpingo-oophorectomy was tried to patients who have genetic mutations such as BRCA, if the origin of EOC is correctly identified, risk reducing salpingectomy can prevent EOC. That can reduce the unnecessary ovarian removal, it can reduce the adverse effect caused by removing ovaries, surgical menopause [6-9].

In addition, rather than classifying primary peritoneal cancer (PPC), OC, and fallopian tube cancer (FTC) as types of EOC, OC and FTC tend to be grouped together as a type of carcinoma originating from the fallopian tube, while PPC tends to be classified as a type of carcinoma different than OC or FTC [10]. In fact, about 4% of patients develop PPC even after preventive salpingo-oophorectomy performed in patients with BRCA mutations [11].

Protocols for diagnosis and treatment of PPC, OC, and FTC are currently similar although evidence suggests these cancers are distinct in their clinical characteristics. Some reports have suggested there is a difference in prognosis between PPC, OC, and FTC. However, these previous reports have some limitations, including using only serous histology for diagnosis and considering disease-free survival as primary outcome of interest [12]. In addition, these studies have limitations regarding data quality, accounting for ethnicity, and potential differences in the classification of carcinoma by pathologists at various hospitals included in the North American Association of Central Cancer Registries [13]. Finally, studies differ in their comparison groups, with some reports focusing on the incidence of PPC, OC, FTC, and one other comparing the OC and FTC [14], and the remainder focusing exclusively on serous carcinoma [15].

In the present study, we used the national cancer registry data of Korea to estimate the incidence rates and the clinical characteristics of peritoneal, ovarian, and fallopian tube (POFT) cancers by tumor origin site and histologic type.

MATERIALS AND METHODS

OC incidence data from 1999 to 2016 were extracted from the Korean National Cancer Incidence Database (KNCI DB). KNCI DB collects information based on the primary tumor origin sites, all cancers in data are primary EOCs. The classification of PPC, OC, and FTC was based on the registered data. The crude rate was calculated as the total number of cases divided by the mid-year population of the particular year. Age-standardized incidence rates (ASRs) were calculated as the sum of the expected age-specific rate divided by the sum of the Segi's world standard population [16]. Age-specific rates were calculated by multiplying the ASR by the proportion of the population in the corresponding age-specific group within the standard population [17]. All rates were expressed per 100,000 individuals.



Trends in incidence rates were examined by the annual percentage change (APC), calculated as $[exp(\beta)-1]\times100$, where β was the slope of the regression line of the natural log transformed ASR for 1999–2016 [2]. Average annual percent change (AAPC) was used as a trend summary statistic over a pre-specified fixed interval, computed as a weighted average of the APCs, with the weights equal to the length of the APC interval [18,19].

Incidence rates and APC were analyzed according to the tumor site, categorized by histology results. SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and Joinpoint 4.7.0.0 (National Cancer Institute, Bethesda, MD, USA) were used for analysis.

This study was approved by the Institutional Review Board at the National Cancer Center, Korea (NCC2019-0237) and performed according to the principles of the Declaration of Helsinki.

RESULTS

Between January 1999 and December 2016, a total of 27,768 patients were diagnosed PPC, OC, or FTC (1,086, 25,847, and 835, respectively). Stage was categorized as localized (26.26%), regional (18.84%), distant (48.86%), unknown (3.99%), or missing (2.05%). The most common histologic type was serous (14,004, 50.43%), followed by mucinous (4,112, 14.81%), endometrioid (2,592, 9.33%), and clear cell (2,394, 8.62%) (**Table 1**).

In 1999, 944 patients were diagnosed with any of the POFT cancers. Among them were 14, 920, and 10 cases of PPC, OC, and FTC, respectively. The corresponding values for 2016 were 110, 2,209, and 116 (**Table 2**). The overall and cancer type-specific incidence increased during the study period. The PPC incidence has risen at the highest rate (AAPC 9.3% for 1999–2016). The incidence of PPC increased during 1999–2009 (APC 14.9%), however, its relative increase decreased during the following years (APC 1.8% for 2009–2016) (**Fig. 1**). Concurrently, the proportion of PPC and FTC among the POFT increased consistently during the study period (1.48% and 1.06% in 1999, 4.52% and 4.76% in 2016) (**Fig. 2**).

Characteristics	No. of patients (%)	ASR (W)*
Total	27,768 (100.00)	4.64
Peritoneal	1,086 (3.91)	0.18
Ovarian	25,847 (93.08)	4.33
Fallopian tubal	835 (3.01)	0.14
Stage [†]		
Localized	5,302 (26.26)	1.40
Regional	3,805 (18.84)	0.96
Distant	9,865 (48.86)	2.41
Unknown	806 (3.99)	0.19
Missing	414 (2.05)	0.10
Histology		
Serous	14,004 (50.43)	2.33
Mucinous	4,112 (14.81)	0.73
Endometrioid	2,592 (9.33)	0.43
Clear cell	2,394 (8.62)	0.40
Others	4,666 (16.80)	0.74

 Table 1. Baseline characteristics of patients with peritoneal, ovarian, and fallopian tube cancer

ASR, age-standardized incidence rate; SEER, Surveillance Epidemiology and End Results.

*Segi's world standard population was used as standard population, ASRs are expressed per 100,000 people; †The variable of the SEER summary stage has been available since 2006.



Table 2. CR and ASR per 100,000 people* of peritoneal, ovarian, and fallopian tube cancer

Characteristics										Year									
-	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	1999- 2016
Peritoneum																			
Cases	14	18	22	18	27	26	42	44	62	62	81	82	81	86	100	101	110	110	1,086
Percentage	1.48	1.84	2.25	1.71	2.37	2.19	3.23	3.23	3.98	4.06	5.12	4.73	4.61	4.46	5.06	4.71	5.04	4.52	3.91
CR	0.06	0.08	0.09	0.08	0.11	0.11	0.17	0.18	0.25	0.25	0.33	0.33	0.32	0.34	0.40	0.40	0.43	0.43	0.25
ASR (W)*	0.05	0.07	0.08	0.06	0.10	0.09	0.14	0.14	0.19	0.18	0.22	0.22	0.21	0.23	0.26	0.25	0.25	0.24	0.18
Ovary																			
Cases	920	942	942	1,009	1,094	1,134	1,215	1,285	1,454	1,427	1,449	1,596	1,625	1,790	1,815	1,968	1,973	2,209	25,847
Percentage	97.46	96.42	96.42	95.91	95.88	95.62	93.53	94.35	93.26	93.39	91.59	91.99	92.54	92.75	91.76	91.79	90.38	90.72	93.08
CR	3.92	3.98	3.95	4.21	4.54	4.69	5.01	5.27	5.93	5.79	5.85	6.41	6.49	7.12	7.18	7.75	7.74	8.63	5.84
ASR (W)*	3.51	3.48	3.39	3.53	3.78	3.77	3.93	4.04	4.46	4.21	4.15	4.56	4.52	4.83	4.74	5.11	4.99	5.48	4.33
Fallopian tube																			
Cases	10	17	13	25	20	26	42	33	43	39	52	57	50	54	63	75	100	116	835
Percentage	1.06	1.74	1.33	2.38	1.75	2.19	3.23	2.42	2.76	2.55	3.29	3.29	2.85	2.80	3.19	3.50	4.58	4.76	3.01
CR	0.04	0.07	0.05	0.09	0.07	0.09	0.14	0.11	0.13	0.12	0.14	0.16	0.13	0.14	0.16	0.18	0.24	0.27	0.14
ASR (W)*	0.04	0.07	0.05	0.10	0.07	0.09	0.14	0.11	0.14	0.12	0.14	0.17	0.14	0.14	0.17	0.19	0.24	0.28	0.14
Total																			
Cases	944	977	977	1,052	1,141	1,186	1,299	1,362	1,559	1,528	1,582	1,735	1,756	1,930	1,978	2,144	2,183	2,435	27,768
Percentage	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
CR	3.60	3.61	3.52	3.68	3.95	3.95	4.21	4.29	4.79	4.50	4.51	4.94	4.86	5.20	5.16	5.55	5.47	5.99	4.64
ASR (W)*	3.94	3.98	3.88	4.02	4.29	4.29	4.61	4.66	5.25	4.93	4.98	5.41	5.35	5.66	5.61	6.09	5.94	6.55	5.07

ASR, age-standardized incidence rate; CR, crude rate.

*Segi's world standard population was used as standard population, CRs and ASRs are expressed per 100,000 people.

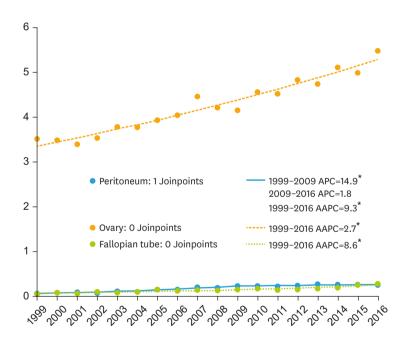


Fig. 1. Incidence trends for peritoneal, ovarian, and fallopian tube cancer. AAPC, average annual percent change; APC, annual percent change.

Age-specific incidence rate was calculated by tumor site. The peak incidence age of FTC was relatively younger than of PPC (55–59 for FTC, and 65–69 for PPC) (**Fig. 3**). Regarding age-specific incidence rate by tumor histology, serous tumors were mostly detected among patients in their sixties, while endometrioid and clear cell tumors were mostly detected among patients in their early fifties, and mucinous tumors were present among patients in their fifties and sixties (**Supplementary Fig. 1**).



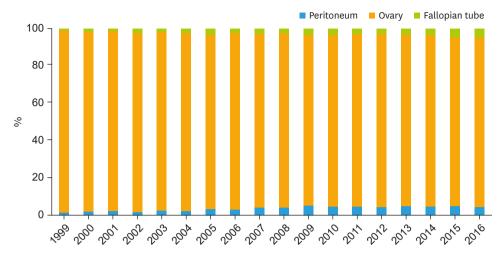
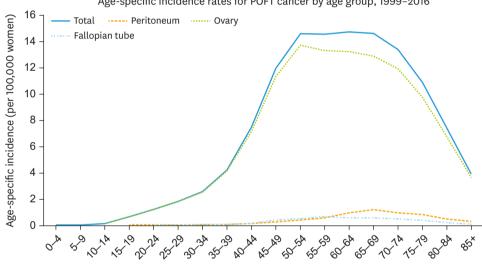


Fig. 2. Annual distribution of histology in peritoneal, ovarian, and fallopian tube cancer.



Age-specific incidence rates for POFT cancer by age group, 1999-2016

Fig. 3. Age-specific incidence rates for POFT cancer, 1999-2016. POFT, peritoneal, ovarian, and fallopian tube.

Table 3 shows the diagnostic proportion of PPC, OC, and FTC during 1999–2016. In mucinous, clear cell, and endometrioid types, there was no significant change in the PPC, OC, and FTC proportion between 1999 and 2016. In contrast, in serous histology, the proportion of FTC continuously increased.

DISCUSSION

The overall incidence of OC has increased between 1999 and 2016 in Korea. In other countries, OC has shown a decreasing tendency, while FTC has shown an increasing tendency. For example, in Denmark, the ASR of OC decreased overall from 19 in 1993-1994 to 14 in 2011–2013, while the incidence of FTC increased from 0.33 in 1993–1994 to 0.64 in 2001–2002 [14,15]. Moreover, the Liao group of the United States reported incidence trends of PPC, OC, and FTC based on the Surveillance Epidemiology and End Results (SEER) data.



Characteristics									Ye	ear								
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Serous																		
Peritoneum	0.00	0.84	2.57	0.90	2.40	2.14	2.99	4.02	5.25	4.95	5.96	4.91	5.29	5.72	5.60	5.60	6.75	5.30
Ovary	99.51	97.49	95.63	96.41	95.56	95.20	92.76	92.56	90.65	91.37	90.02	90.28	90.40	89.77	89.85	88.53	85.24	87.22
Fallopian tube	0.49	1.67	1.80	2.69	2.03	2.67	4.25	3.42	4.10	3.68	4.01	4.80	4.31	4.51	4.55	5.87	8.01	7.49
Mucinous																		
Peritoneum	1.03	0.87	0.97	0.51	0.43	1.45	0.46	0.98	0.83	1.11	3.74	1.83	1.63	0.79	3.13	0.68	0.71	1.09
Ovary	98.97	98.27	99.03	99.49	99.57	98.55	99.54	99.02	99.17	98.89	96.26	98.17	97.97	98.81	95.98	98.63	99.29	98.54
Fallopian tube	0.00	0.87	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.41	0.40	0.89	0.68	0.00	0.36
Endometrioid																		
Peritoneum	0.00	0.00	0.00	0.81	0.00	1.74	0.85	0.00	0.00	0.00	0.00	0.00	0.70	0.53	0.00	0.54	0.00	0.51
Ovary	100.00	100.00	98.97	97.56	98.23	95.65	94.92	96.55	98.54	97.44	97.83	97.59	97.18	98.40	97.70	98.39	98.96	97.95
Fallopian tube	0.00	0.00	1.03	1.63	1.77	2.61	4.24	3.45	1.46	2.56	2.17	2.41	2.11	1.06	2.30	1.08	1.04	1.54
Clear cell																		
Peritoneum	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.95	0.00	0.00	0.70	0.00	0.60	0.53	0.51	0.00	0.85	0.38
Ovary	100.00	100.00	100.00	98.57	100.00	100.00	98.84	99.05	99.11	100.00	98.60	99.37	99.40	98.93	98.98	100.00	99.15	99.62
Fallopian tube	0.00	0.00	0.00	1.43	0.00	0.00	1.16	0.00	0.89	0.00	0.70	0.63	0.00	0.53	0.51	0.00	0.00	0.00
Others																		
Peritoneum	1.48	1.84	2.25	1.71	2.37	2.19	3.23	3.23	3.98	4.06	5.12	4.73	4.61	4.46	5.06	4.71	5.04	4.52
Ovary	97.46	96.42	96.42	95.91	95.88	95.62	93.53	94.35	93.26	93.39	91.59	91.99	92.54	92.75	91.76	91.79	90.38	90.72
Fallopian tube	1.06	1.74	1.33	2.38	1.75	2.19	3.23	2.42	2.76	2.55	3.29	3.29	2.85	2.80	3.19	3.50	4.58	4.76

The ASR for FTC has increased from 0.19 in 2001–2005 to 0.63 in 2011–2014, while it has decreased for OC from 5.31 in 2001–2005 to 4.86 in 2011–2014 [15]. In the present study, based on Korean national cancer data, the increase of PPC was the most prominent; however, OC and FTC have also increased. The possible explanation of these results, first of all, the peak age is the highest among the PPC, OC, and FTC (**Supplementary Fig. 1**). And, as life expectancy is increased, the incidence of PPC can increase. And, PPC is diagnosed mainly as serous histology, PPC is almost high-grade serous carcinoma. Generally, PPC was diagnosed when little or no tumor involved in ovary [2]. Recently, neo-adjuvant chemotherapy followed by interval cytoreductive surgery was increased [20,21], it is possible that pathologic exam was performed after ovarian tumor was almost regressed due to neo-adjuvant chemotherapy, it can increase the PPC diagnosis. According to a report on the current state of histology [22], the proportion of serous histology is relatively low, however, the proportion of clear cell, endometrioid, and mucinous histology is relatively high in Asian populations. At the same time, pure mucinous OC of ovarian origin is considered rare [23], and a high proportion of patients diagnosed with mucinous type OC are likely to be cases of metastatic OC.

As a result of research, we currently know that POFT are cancers with not only ovarian epithelial origin, as previously believed, but can present with the fallopian tube, peritoneum, endometrium, and GI tract histology [3]. Recently, it has become recognized that serous histology originates from the fallopian tube, while clear cell and endometrioid histology originate from the endometrium. Concurrently, the mucinous type of cancer may originate from the GI tract, especially the appendix [10,24]. Given individual carcinoma tissue types, the FTC has had the largest relative increase within the serous histology category, despite limited increase in other histology. This suggests that the fallopian tube might be the origin site of high-grade serous OC. The increase in diagnoses of FTC has been interpreted as follows, according to the Liao group. First, pathologists have become



more interested in the fallopian tube, leading them to produce more tissue sections, resulting in an increase of recognized FTC. Second, FTC might be diagnosed incidentally through prophylactic salpingectomy performed on patients who had not been diagnosed with cancer ahead of surgery. However, according to Kurman [10,24], FTC and OC are the same type of cancer, while PPC is another type [25]. The fact that the number of PPC and FTC cases increases at a rate higher than the number of OC cases might not be clinically significant. However, what might be of significance in this context is the overall increase in cancer incidence, not the increase in incidence of a specific cancer type.

In the present study, OC was most common among women in their early fifties, while FTC and PPC were more common among women at an older age. These results are inconsistent with previous reports [15]. A previous study has reported FTC as the most common among women who were 70–74 years old, while PPC and OC have been shown to occur most commonly among women 75–79 years old. However, these discrepancies might have resulted from the between-study differences in populations. For example, the Liao group only analyzed data from serous histology; while our study included POFT cases of serous, mucinous, endometrioid, clear cell, as well as other types of histology (transitional cell, mixed, undifferentiated, among others). Our data has shown that serous tumors were most likely diagnosed among women in their sixties, while endometrioid and clear cell tumors were most likely diagnosed among women in the 50–60 years age group. These results support previous findings reported for Korean and Taiwanese populations [26-28].

The data used in this study, extracted from the KNCI DB, includes all of the Korean cases of epithelial POFT cancer. This is the first report on all epithelial POFT histologic types, including serous, mucinous, endometrioid, and clear cell cancer. This study has some limitations. First, this was a retrospective study, which likely makes it subject to bias inherent in this type of study design, including incomplete data on potentially relevant clinical factors. And, our data was based only on the registered by each institution, no central pathologic analysis lab, the exact number of each tumor can have biases. In addition, only the initial information after diagnosis was available, restricting the possibility of an elaborate analysis of survival.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Age-specific incidence rates for POFT cancer by histology, 1999-2016.

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