EJGO European Journal of Gynaecological Oncology

World trends of incidence of gynecologic malignancies in young women

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Summary

Although cervical, ovarian, and uterine cancers are rare in young women, they may cause symptoms and physical disability, and the cancer treatment may also result in psychological stress, infertility, and iatrogenic menopause. While the incidence of cervical cancer appears to be decreasing, the incidences of ovarian and uterine cancers are increasing in young women. A thorough knowledge of the epidemiology of these cancers is important to help clinicians to understand the cost-effectiveness and outcomes of the screening and treatment strategies, and to help the policy makers to have a more accurate prediction of the disease load for better allocation of health resources. A more structured and detailed data collection system is needed so that the epidemiologic characteristics of these cancers can be better studied across different countries and age groups.

Key words: Cervical; Ovarian; Uterine; Cancers; Young women.

Introduction

In 2012, there were more than 6.6 million new cancer cases in women and more than 1.1 million (17.4%) were below the age of 45 [1]. Overall speaking, cervical, uterine, and ovarian cancers were the fourth, sixth and seventh most common female cancers. However, the actual incidence varied between different geographic areas and age groups due to the presence of different risk factors. Female genital tract cancer is of particular concern to young women because the cancer treatment may potentially result in a loss of fertility with or without iatrogenic menopause. Furthermore, these cancers may pose psychological stress, poor-self image, stigmatization, and sexual disturbance to this group of women, affecting their quality of life.

Cancer registry is important because it can allow physicians and policy makers to monitor the cancer distribution pattern, identify new etiological factors, evaluate the treatment outcomes and preventive measures. It was estimated that less than 20% of the world population were included in their respective cancer registry, 35% were covered by the death statistics in 2000, and the coverage was even worse in some areas in Asia and Africa [2]. Globocan, a project launched by the International Agency for Research on Cancer (IARC), the World Health Organization, provides an estimation of the incidence, mortality, and prevalence rates of 28 cancers for 184 countries [1]. The IARC also coordinates with the International Association of Cancer Registries and compiles the actual incidence of different cancers recorded by various regional and national cancer registries globally in the Cancer Incidence in Five Continents (CI5) database [3]. Time trend analysis, extracted from 118 selected populations from 102 cancer registries, is allowed for 27 major cancers up to the year 2007. On the other hand, the International Federation of Gynecology and Obstetrics (FIGO) had been publishing a three-yearly statistical report since 1937. It provided a useful overview on the epidemiology and survival data of different gynaecological cancers with respect to different stages, demographic factors, histology, and treatment modality of the tumour. Unfortunately, the data collection had ceased from 2009 onwards due to some logistic problems [4].

This article aims to provide a glimpse at the trend of cervical, ovarian, and uterine cancers, the three most common gynaecological cancers, in young women, based on the largest databases from the IARC with supplement from different registries or articles as appropriate. However, it is noteworthy that the data may not reflect the whole situation, as some countries are not covered by a comprehensive registry system and some data may be out-dated.

Cervical cancer

In many developed countries, the age-adjusted incidence rate (ASR) of cervical cancer has dropped dramatically from 14–5 per 100, 000 women in 1970–80s, to 6–8 per 100,000 in 2015s [5-8]. This was largely attributed to the implementation of national cervical screening programme and early treatment of pre-invasive diseases. Nowadays, about 85% of cervical cancer occurred in the developing countries, with the highest incidence in Eastern Africa

Revised manuscript accepted for publication June 5, 2017

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXIX, n. 6, 2018
doi: 10.12892/ejgo4234.2018

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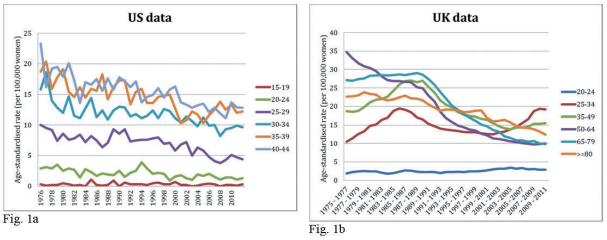
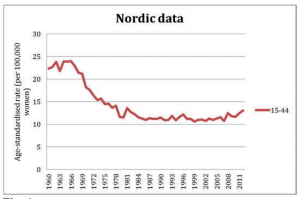


Fig. 1a

Fig. 1b



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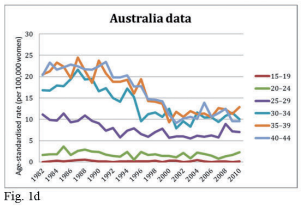

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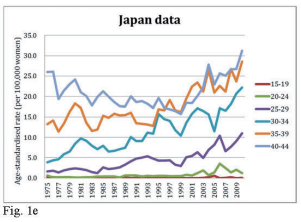

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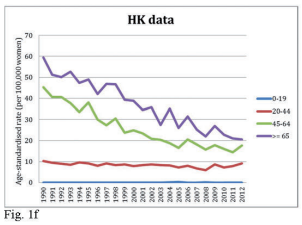


Fig. 1f

Figure 1. — Incidence rate of cervical cancer in different countries: (a) the United States [7], (b) the United Kingdom [5], (c) Nordic countries [8], (d) Australia [11], (e) Japan [14], and (f) Hong Kong [12].

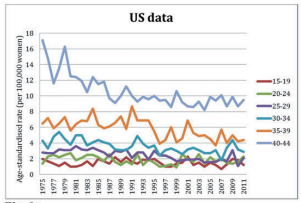
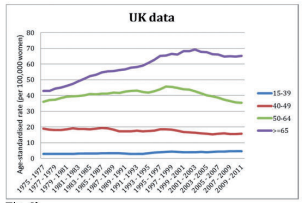


Fig. 2a



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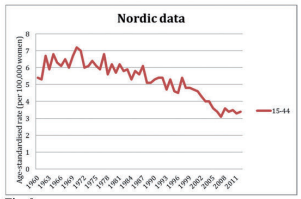

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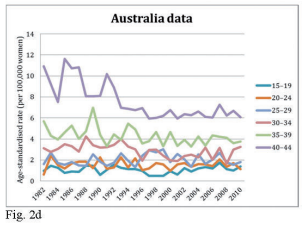

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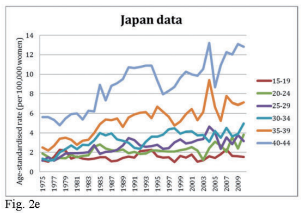

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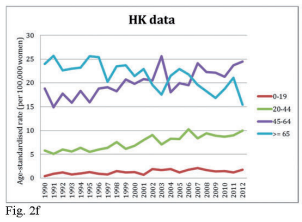

Fig. 2f

Figure 2. — Incidence rate of ovarian cancer in different countries: (a) the United States [7], (b) the United Kingdom [5] (c) Nordic countries [8]. (d) Australia [11] (e) Japan [14], and (f) Hong Kong [12].

where the ASR was up to 42.7 per 100,000 women [1]. The mean age of cervical cancer is 49–52 years [9-11]. In some places like the United Kingdom, there were two peaks in the age-specific incidence rates where the first occurred at age 30–34 years with 20 per 100,000 women, and the second at the age 80–84 years with 13 per 100,000 women in 2009-2011 [5]. This might be due to the early sexual exposure and hence human papillomavirus (HPV) infection in these younger women. Similar age distribution was also observed in the northern European countries in 2008-2012 [8]. For women under 45 years, cervical cancer was the second commonest cancer according to Globocan, with 177,976 new cases in 2012, constituting 33.7% of all cervical cancer cases among all age groups [1]. In the United States, 26.4% were younger than 45 years, whereas in Australia 40.2% and 31.1% were under the age of 45 and 40 years, respectively [6, 7], demonstrating that the burden of cervical cancer is not negligible in young women.

It should be pointed out that while the trend of the incidence in women younger than 45 years was either decreasing or static in countries like the United States, Australia, and Hong Kong [6, 7, 12], the incidence was increasing in some populations (Figure 1). In the United Kingdom, the incidence rates for women aged 25–34 years initially decreased by 34% between 1985–1987 and 2000–2002, but it rose by 54% again in recent years [5], and the average rise was 10.3 per year in those aged 20–29 years between 2000 and 2009 [13]. The ASR based on Nordic population decreased by almost a half from 1960s to 1990s, but it also appeared to rise slightly in the recent years [8]. A rise in incidence of cervical cancer was also observed for women aged 25–44 years in Japan from 1975 to 2010 [14]. According to the CI5 plus database, young women in certain developed countries, such as Finland (25–29 years), Italy (25–29 years), Norway (25–29 years), Spain (20–39 years), and Switzerland (20–24 years), also revealed an increasing trend between 1993 and 2007 [3]. However, newer online data were not available.

The rise of incidence of cervical cancers among young women in some countries was unexpected and the reason was not known. The Cancer Research UK speculated that it might be due to the increase in public awareness of the disease, leading to higher attendance rate to cervical screening programme, increased HPV infection, and increased smoking prevalence [15, 16]. High-risk HPV is a causative agent for cervical cancer. There have been multiple phase

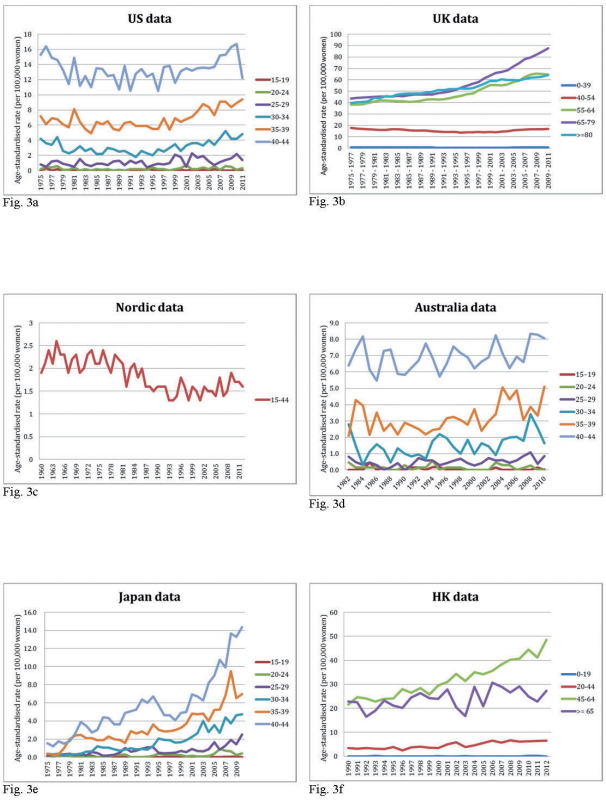

Fig. 3a Fig. 3b Fig. 3c Fig. 3d Fig. 3e Fig. 3f

Figure 3. — Incidence rate of uterine cancer in different countries: (a) the United States [7], (b) the United Kingdom [5], (c) Nordic countries [8], (d) Australia [11], (e) Japan [14], and (f) Hong Kong [12].

III trials proving the efficacy of HPV vaccines in preventing cervical pre-invasive diseases [17-20]. With the introduction of national vaccination programme, the incidence of cervical cancer is anticipated to fall in the near future although longer follow-up studies, including studies on cost-effectiveness, acceptability, and social uptake pattern, are definitely essential.

Ovarian cancer

Ovarian cancer, regardless of the histological subtypes, was the seventh commonest cancer among all women and were the fifth commonest cancer in those younger than 45 [1]. There were 52,119 new cases in this age group accounting for 21.8% of all cases of ovarian cancer. The estimated ASR was higher in developed countries (9.1 per 100, 000) compared to less developed countries (5 per 100, 000). This may be due to the presence of risk factors like infertility and low parity in more affluent countries, although the difference in the quality of data collection might also play a role [5].

Ovarian cancer is predominant in older women. For example in the United Kingdom, three-quarters were diagnosed in women aged 55 or above, and the peak age was at 80– 4 years [5]. The overall incidence rate of ovarian cancer fluctuated between 10 and 20 per 100, 000 women in many developed countries and a decreasing trend was observed in some of them [5, 8, 21]. Nevertheless, this is not a universal phenomenon. For example, an increase in incidence rate was observed in Singapore over the last 40 years, where it rose from 6.7 per 100, 000 person-years in 1974 – 78 to 12.5 in 2009–13 [22].

For women younger that 45 years, the trend of incidence varies in different geographical areas (Figure 2). In Nordic countries, the ASR fell between 1960 and 2012 [8]. In United States and Australia, the incidence rate of those at 40–45 years fell from the peak of 12–17 per 100,000 women from 1970–80s, to 6–10 per 100,000 women in 2010s [7, 23]. The European ASR decreased in women of 40–49 years in the United Kingdom from 19 per 100,000 women from 1975–77 to 15.7 from 2009–11, but increased slowly from 2.9 to 4.5 per 100,000 women during the same period in those aged 15– 39 years. It was postulated that the decrease in the 40–49 age group of women was due to the popularity of oral contraceptive pills, and the increase among 15–39 year women might partly be due to a rise in the incidence of germ cell tumours [5, 24, 25]. In Japan, apart from those from 15–19 years, all groups from 20–44 years demonstrated an increasing trend of ovarian cancer from 1975 to 2010 and the rise was more obvious in those from 40–44 years [14]. In Hong Kong, the incidence rose from the nadir of about 5 to 10 per 100, 000 women for those at 20–44 years between 1990 and 2012 [12]. The reason was not addressed but reduced numbers of birth or subfertility might partly contribute to this phenomenon.

There is no proven benefit of routine screening programme against ovarian cancer in asymptomatic women [26], and most of these studies were performed in postmenopausal women [27-31], making its role even more controversial in young women. The United Kingdom Familial Ovarian Cancer Screening Study (UK FOCSS) is a study examining the role of regular ultrasound and CA 125 in high-risk women, aged 35 or above, who had a strong family history of breast or ovarian cancer, or had an mutation in a gene such as BRCA 1 or 2 [32]. Phase I results showed that those women diagnosed with cancer whose screening interval was longer than a year were more likely to be diagnosed at an advanced stage. The result of the Phase II study, using four-monthly instead of yearly screening interval, is not available yet. Some have also advocated salpingectomy at the same setting of sterilization or hysterectomy as a means to prevent ovarian cancer [33-36], as the fimbrial ends are now considered to be the origin of certain epithelial ovarian cancers such as the high-grade serous carcinoma [37]. Preliminary data showed that this was a safe approach without major perioperative complications and harmful effect on the ovarian function in premenopausal women. However, this strategy would proba-

bly benefit less in young women who still wish to retain their fertility potential.

Uterine cancer

Uterine cancer was the sixth commonest female cancer. Similar to ovarian cancer, it was more common in developed countries, ranking the fourth among all female cancers affecting about 14.7 per 100, 000 women in 2012, in comparison to the developing countries where the estimated ASR was only 5.0 per 100, 000 women, ranking the eighth [1]. The overall incidence rate is rising in many developed countries, from about 1.5–12 per 100,000 women in 1970s to 14–20 per 100,000 women in recent years, which was related to the problem of obesity, the use of hormonal replacement therapy and nulliparity [5, 12, 14, 22, 38]. The incidence in Italy appeared rather static at about 18 per 100, 000 from 1990 to 2000 [21]. The overall incidence in Canada dropped from about 20 per 100,000 women in 1980s to about 18 per 100,000 women in 1990s, but increased again to 23.3 per 100,000 women in 2014, with an average 2.6% rise per year since 2004 [39]. In the Untied Kingdom, the incidence rose in women after 40 years and was peak at 70–74 years of age [5]. The median age was younger at 50–60 years in Japan, Singapore, and Hong Kong [14, 22, 40].

For women under 45 years, uterine cancer was the eighth commonest female cancer according to Globocan [1]; 34,980 new patients were identified in this age group in 2012 comprising of 10.9% of all cases of uterine cancer. Most places demonstrated a static or increasing trend in its incidence in young women (Figure 3). In the United States, the ASR of those at 25–39 years which has been increasing since 1970s, and the rise was more obvious in those aged 35–39 years [7]. A slow falling trend had been observed in those at 40–45 years from about 16 per 100,000 women in the 1970s to about 12 per 100, 000 women in the 1980s, but the incidence rate rose again afterwards to a figure similar to that in 1970s. Similar pattern was observed in Australia, where there was a rising trend in age groups between 25 and 44 years especially those at 30–39 years [41]. The rise in Japan was quite drastic in the 35–44-year-old women and was more than double from less than two to 7–14 per 100,000 women from 1975 to 2009 [14]. In the United Kingdom, the incidence rate in those younger than 55 was rather stable, in comparison to the older age group in which the rise was more than double in those aged 65–69 between 1975–77 and 2009–11 [5, 42]. The incidence rate among those at 15–44 years in the Nordic countries decreased from 2.5 to 1.5 per 100,000 women from 1960s to 1990s, but had a slow increasing trend again in 2010s [8].

Currently there is no proven evidence to support a screening strategy for endometrial malignancy even in high-risk patients, such as those with Lynch Syndrome. Some centers have implemented immunochemistry (IHC) and/or microsatellite instability (MSI) screening for inherited mismatch repair gene mutation in all colorectal and endometrial cancer patients younger than 50–60 years and some have also evaluated the role of universal screening regardless of family history, which might help to identify those carriers so that second malignancy may be prevented and genetic counselling can be offered to their family members [43-46]. Ultrasound [47, 48] and endometrial biopsy [49, 50] had also been implicated in endometrial surveillance but their roles are still not clear. Recently, short-term use of depo-provera and progestagen-containing oral contraceptive pills had been shown to reduce endometrial proliferation and induce progestagen-related microscopic changes in a group of 25–50 year-old Lynch syndrome patients [51]. Again, although risk-reducing surgery in terms of hysterectomy and bilateral salpingo-oophorectomy can effectively reduce the risk of endometrial as well as ovarian cancer [52], this approach can only be reserved for those who are post-menopausal and those who have no wish of fertility.

Conclusion

From the data above, it appears that in some developed countries, the incidence of cervical cancer is decreasing, although the rate has increased slowly among young women in the recent few years, implying that cervical cytology screening programme alone is not sufficient enough in preventing cervical cancer. The incidence of ovarian cancer in young women is low in general but an increasing trend is observed in some places like Japan and Hong Kong. Uterine cancer is becoming more common in young women in many parts of the world and this is possibly due to the problem with obesity. Nonetheless, the entire global picture may not be revealed by the existing databases because some countries, especially those developing countries, lack a comprehensive cancer data collection network and the detailed epidemiology information of different cancers is not known. Currently, the University of Oxford is assisting the African Cancer Registry Network, supported by the International Network for Cancer Treatment and Research (INCTR), to launch a study on the burden and trends in cancers of the breast and female genital tract in sub-Saharan Africa. Another intrinsic problem with most available online databases is that the coding method, using International Classification of Diseases (ICD) classification, encompasses different subtypes. For instance, both epithelial and non-epithelial ovarian cancers are grouped under C56, and uterine carcinoma and sarcoma are under C54 and C55. These different malignant diseases have different risk factors, pathological features, clinical behaviors, and treatment modalities. Pooling them up in epidemiological database cannot reflect the genuine trend of the individual disease entity. Previously the FIGO committee had computed the demographic data and clinical outcomes according to dif-

ferent stages and histological subtypes of each gynecological cancer. It is hoped that the data collection can be soon resumed because such valuable information is essential to help the clinicians and health policy makers to understand the disease pattern and treatment outcomes, and to determine a better way to detect and prevent the diseases.

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