

Epidemiology of ovarian cancer in North Sardinia, Italy, during the period 1992-2010

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Summary

Introduction: The aim of this study was to analyze and describe the incidence and mortality trends of ovarian cancer in North Sardinia, Italy, in the period 1992–2010. **Materials and Methods:** Data were obtained from the tumor registry of Sassari province which makes part of a wider registry web, coordinated today by the Italian Association for Tumor Registries. **Results:** The overall number of ovarian cancer cases registered in the period under investigation was 600. The mean age of the patients was 62 years. The standardized incidence and mortality rates were 11.2/100,000 and 5.1/100,000 respectively. A substantially stable trend in incidence and mortality of ovarian cancer was evidenced. Relative survival at five years from diagnosis was 44.2%. **Conclusions:** The incidence and mortality trends of ovarian cancer in North Sardinia remained relatively stable in the last decades, while prognosis remains relatively poor.

Key words: Ovarian cancer; Incidence; Mortality; Sardinia, Italy.

Introduction

Ovarian cancer is one of the most common malignant neoplasias in women worldwide, with more than 238,000 new cases estimated in 2012; furthermore, more than 151,000 deaths estimated make ovarian cancer one of the most lethal gynecologic malignancies [1]. Large part of cases are registered in developed countries, except for Japan, with higher incidence rates in Northern Europe and United States, intermediate rates in western Europe, and lower rates in developing countries. In high incidence areas, the lifetime risk of ovarian cancer is 1-2% [2].

In spite of many therapeutic progresses obtained combining aggressive surgery and chemotherapy [3], the prognosis of ovarian cancer remains poor, with a mean five-year survival rate of about 40% [2]. Unfortunately, the majority of cases are diagnosed at an advanced stage, and the five-year survival in Stages III and IV drops to 30% and 20%, respectively [4]. The lack of a precise clinical manifestation, along with the absence of effective screening programs may explain the low number of cases diagnosed at an early stage.

Previous reports investigated the epidemiological characteristics of ovarian cancer in North Sardinia, Italy in the past [5-6]. The aim of this population-based study was to analyze and describe the incidence and mortality trends of ovarian cancer in the period 1992–2010, and to compare them with those of previous reports, in order to investigate the epidemiological evolution of the disease in the area.

Materials and Methods

The epidemiological data presented in this article were obtained from the “Cancer Registry of the Province of Sassari”. This registry was created in 1992 by the local health agency for the epidemiological surveillance of tumors in the province. In 1999, it became part of a wider web of tumor registries, coordinated by the Italian Association for Tumor Registries (Associazione Italiana Registri Tumori, AIRTUM). The association coordinates 34 registries in the country, collects and publishes data, and collaborates with international organizations in the field.

Every registry collects data on tumoral diseases affecting inhabitants in the territory of jurisdiction through the local hospitals and healthcare services, as with other registries (e.g., death registries). Demographic, clinical, pathological, and prognostic data are collected for each case of cancer and are registered in a digital database. This database was the data source for the present population-based report and for other reports published in the past, depicting the burden of the principal malignant tumors in the area [7-11].

The demographic characteristics of the patients affected by ovarian cancer were collected. Crude incidence and mortality rates per 100,000 inhabitants per year were calculated, as were standardized rates adjusted for European age-population standards. A comparison between incidence and mortality in the province of Sassari and those in other Italian provinces was performed. Additionally, the cumulative risk of developing the disease and of dying between zero and 74 years of age was estimated. The age-class distribution and time-trends of incidence, mortality and histology were evaluated. Finally, relative five-year survival was calculated with the Ederer method.

Revised manuscript accepted for publication June 9, 2014

Table 1. — Age-class incidence distribution of ovarian cancer in North Sardinia, 1992-2010.

Age class	% of cases
0-14	0
15-29	4
30-44	11.9
45-59	25
60-74	34.3
75+	24.8

Table 2. — Age-class incidence and mortality rates of ovarian cancer in North Sardinia, 1992-2010.

Age (years)	Incidence / 100,000	Mortality / 100,000
0-4	0	0.6
5-9	0	0
10-14	0	0
15-19	2.8	0
20-24	2.4	0.4
25-29	3.1	0
30-34	5.3	0.9
35-39	4.2	0.9
40-44	12.3	1.3
45-49	13.6	3.8
50-54	19.8	5.1
55-59	21.8	10.9
60-64	27.1	13.4
65-69	28.2	15.5
70-74	41.5	27.3
75-79	43.6	30.8
80-84	39.3	32.8
85+	45.5	46.5

Results

The overall number of cases of ovarian cancer registered in the period under investigation was 600. Diagnosis was obtained by histological or cytological reports in 501 cases (83.5%) and using other information sources (clinical reports, radiological referrals, death certifications, etc) in 93 cases (15.5%); in six cases (1%) the modality of diagnosis was not known. The mean age of the sufferers was 62 years. The cumulative risk of developing the disease between zero and 74 years of age was 0.91%.

Among the 501 tumors that had a histological or cytological diagnosis, 130 (25.9%) were serous carcinomas, 92 (18.4%) were mucinous carcinomas, 45 (18.4%) were endometrioid carcinomas, and 144 (28.8%) were other histotypes, while in the remaining 90 (18%) cases the exact histologic subtype was not specified.

The crude and standardized incidence rates of ovarian cancer in the period under investigation were 14.1/100,000 and 11.2/100,000, respectively. Table 1 shows the distribution of cases in percentages in relation to age, while Table 2 shows the distribution of incidence rates per age-class. Peak incidence occurred at 60-74 years. Figure 1 depicts the trend

Table 3. — Comparison of incidence and mortality rates of ovarian cancer in North Sardinia with those of other Italian provinces.

Province	Incidence / 100,000	Mortality / 100,000
Alto Adige	14.3	8.2
Biella	12.8	7.2
Ferrara	10.7	5.6
Firenze	13.4	6.7
Friuli V.G.	11.7	7.1
Genova	15	6.7
Macerata	12	7.3
Modena	12.9	6.5
Napoli	9.3	4.5
Parma	16.5	7.7
Ragusa	11.8	6.6
Reggio Emilia	12.4	6
Romagna	12.8	5.9
Salerno	11.3	6.2
Sassari	11.2	5.1
Torino	13.2	9.4
Trento	11.7	8.6
Umbria	13.5	5.6
Varese	17.8	5.3
Veneto	10.8	7.1

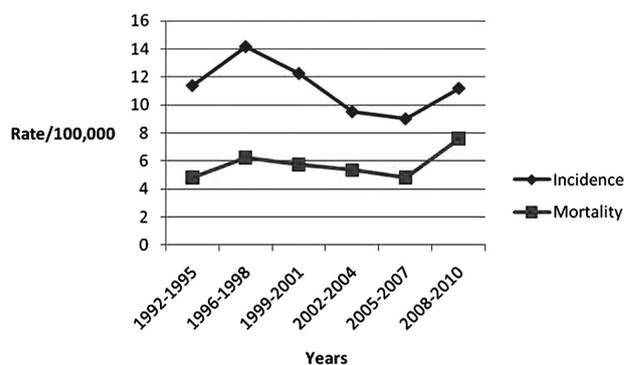


Figure 1. — Incidence and mortality rates trends of ovarian cancer in North Sardinia, 1992-2010.

of incidence rates in the period 1992–2010; there were no substantial modification registered, with incidence rates oscillating between 9.01/100,000 and 14.17/100,000. Analysis of the trend of mean age at disease onset for the same period of time did not reveal any relevant changes. Furthermore, no substantial modifications of the proportions of the histological types mentioned before were found. Table 3 shows the comparison of the incidence and mortality in the province of Sassari with those in other Italian provinces.

There were 307 deaths registered in the period under investigation. Crude overall mortality rate was 7.2/100,000, while standardized mortality rate was 5.1/100,000. Mean age at death was 69.9 years. The cumulative risk of death between zero and 74 years of age was 0.4%. Table 2 shows

the age-class distribution of mortality rates. There was a slight increase in mortality after the sixth decade of life. As shown in Figure 1, a substantially stable trend of mortality rates between 1992 and 2010 was reported, oscillating between 4.85/100,000 and 7.59/100,000, with a slight increase between 2008 and 2010. Finally, relative survival at five years from diagnosis was 44.21%.

Discussion

Ovarian cancer is one of the most incident cancer of the female reproductive tract. More than 238,000 new cases and more than 151,000 deaths were estimated in the world in 2012 [1]. Most of ovarian cancer cases are sporadic, and only 5% to 10% of ovarian cancers are familiar; mutations in the *BRCA1* and *BRCA2* genes are responsible for the majority of hereditary ovarian cancers. Epidemiologic and molecular-genetic studies have identified both risk and protective factors for the disease [12-15]. Increasing age, family history of breast or ovarian cancer, nulliparity, early menarche, and late menopause are known risk factors [16-18] for ovarian cancer, while the impact of tobacco and alcohol consumption are still under investigation [19-20]. On the other hand, oral contraceptives, pregnancy, multiparity, breastfeeding, hysterectomy, and tubal ligation appear to decrease ovarian cancer risk [16-18].

Ovarian cancer is considerably more common in developed areas of the globe; about 91% of the new cases and 89% of the deaths estimated in 2012 worldwide occurred in those areas. Most of the cases of ovarian cancer are diagnosed at a late stage, and this causes a higher mortality. However, when ovarian cancer is detected in an early stage, the survival at five years is quite good.

In Europe in 2012 there were estimated more than 44,577 new ovarian cancer cases and the standardized incidence rate of the disease was 9.4/100,000 [1]. High risk European regions include Northern countries (Scandinavia) and Eastern countries (e.g. Poland, Bulgaria) [1]. More than 30,079 deaths were estimated in 2012 in Europe (standardized mortality rate: 5.1/100,000) [1].

In Italy it has been estimated that approximately 5,911 new cases of ovarian cancer occurred in 2012 [1]. These figures make ovarian cancer the sixth most frequent malignancy in women and the second most frequent gynecological malignancy. Incidence rates showed a moderate reduction during the two last decades (-2.2% per year) in the country [21]. Furthermore, a decreasing trend in incidence rates is observed, moving from northern to southern Italian regions. The global mortality rate in Italy is 6.4%, and it shows a moderate reduction in recent years; the reduction of mortality rates is smaller than the one seen for the incidence rates (-1.3% per year) and a decreasing trend is observed from North to South. The five-year survival of patients with ovarian cancer has improved in Italy in the last decades, and it is currently estimated at approximately 38% [21].

Concerning Sardinia, estimated incidence rates were 4.27/100,000, 11.99/100,000, and 9.2/100,000 in the periods 1974-1985, 1992-2001, and 2005-2009, respectively [6, 21]. The standardized incidence rate the present authors calculated for the period 1992-2010 was 11.2/100,000, confirming the steady trend of incidence previously reported. Furthermore, this rate was inferior to those of several other Italian regions, especially the northern ones (Table 3).

Concerning mortality, standardized mortality rate in North Sardinia was 5.1/100,000, being one of the lowest in Italy; also the cumulative risk of death from the disease was extremely low (0.4%). With regards to survival, the relative five-year rate estimated in the present region was 44.21%. This figure was slightly superior to that estimated for the entire country.

From an etiologic point of view, a fraction of ovarian cancer cases recognizes genetic factors in their pathogenesis [22]. Germline mutations in either *BRCA1* or *BRCA2* genes occur in approximately 10% of unselected women with ovarian cancer and, on the other side of the coin, women with inherited *BRCA1/2* mutations are at significant risk of developing ovarian cancer [23]. The lifetime risk of developing ovarian cancer in women who carry a germline *BRCA* mutation has been estimated to be of 40-60% for *BRCA1* and 11-27% for *BRCA2* [24]. A meta-analysis of 22 studies with over 8,000 disease probands has defined the incidence for ovarian cancer to be approximately 39% for *BRCA1* and 11% for *BRCA2* [25]. In North Sardinia, less than 10% of breast cancer families presented an association with ovarian cancer (at least one affected family member) [26]. Nevertheless, presence of ovarian cancer was demonstrated to significantly increase the occurrence of *BRCA1/2* germline mutations in Sardinian breast cancer families [26-27]. Finally, *BRCA2* mutations were notably more recurrent than *BRCA1* mutations in breast cancer families from North Sardinia [26-27]. Gathering all these findings, one could speculate that: *a*) the poor association with ovarian cancer may explain the relatively low prevalence of *BRCA1/2* germline mutations in Sardinian population; and *b*) the very low proportion of *BRCA1* mutations may account for the very limited number of breast cancer families with association to ovarian cancer in such a population. As a confirmation of this, breast cancer families originating from South Sardinia, where *BRCA1* mutations were instead demonstrated to be much more prevalent, present markedly higher rates of association with ovarian cancer [28].

Conclusions

The incidence and mortality trends of ovarian cancer in North Sardinia remained relatively stable in the last decade. Mortality and cumulative risk of death from the disease were low. Furthermore, survival of patients with ovarian cancer was relatively good in the area, sanctioning the adequacy of the preventive and clinical measures employed in

the management of the disease. As for other malignancies, concurrence of different environmental factors and genetic backgrounds may determine the incidence of ovarian cancer. This is particularly true in Sardinia, whose population shows genetic peculiarity due to geographical isolation and strong genetic drift.

Acknowledgements

The Authors wish to thank all Sardinian clinicians and researchers who participated into this study. This work was partially supported by Italian Ministry of Health "Progetto Ricerca Finalizzata" and Sardinia Regional Government (Regione Autonoma della Sardegna).

References

- [1] World Health Organization: "Globocan 2012". Available at: <http://globocan.iarc.fr>
- [2] Pisani P., Bray F., Parkin D.M.: "Estimate of the worldwide prevalence of cancer for 25 sites in the adult population". *Int. J. Cancer*, 2002, 97, 72.
- [3] Miolo G., Bidoli E., Lombardi D., Santeufemia D.A., Capobianco G., Dessole F., et al.: "Weekly paclitaxel in heavily pretreated ovarian cancer patients: does this treatment still provide further advantages?" *Arch. Gynecol. Obstet.*, 2012, 285, 499.
- [4] Beard C.M., Hartmann L.C., Atkinson E.J., O'Brien P.C., Malkasian G.D., Keeney G.L., et al.: "The epidemiology of ovarian cancer: a population based study in Olmsted County, Minnesota. 1935-1991". *Ann. Epidemiol.*, 2000, 10, 14.
- [5] Cossu A., Budroni M., Capobianco G., Pirino D., Palmieri G., Dessole S., et al.: "The incidence of female genital tumors in the Province of Sassari in the period 1992-2000". *Eur. J. Gynaecol. Oncol.*, 2004, 25, 96.
- [6] Cossu A., Budroni M., Capobianco G., Pirino D., Palmieri G., Dessole S., et al.: "Epidemiological aspects of ovarian malignancies in North Sardinia in the period 1992-2001". *Eur. J. Gynaecol. Oncol.*, 2005, 26, 47.
- [7] Budroni M., Cossu A., Paliogiannis P., Palmieri G., Attene F., Cesaraccio R., et al.: "Epidemiology of malignant pleural mesothelioma in the province of Sassari (Sardinia, Italy). A population-based report". *Ann. Ital. Chir.*, 2013, 28, 84.
- [8] Paliogiannis P., Attene F., Cossu A., Budroni M., Cesaraccio R., Tanda F., et al.: "Lung cancer epidemiology in North Sardinia, Italy". *Multidiscip. Respir. Med.*, 2013, 12, 45.
- [9] Cossu A., Budroni M., Paliogiannis P., Palmieri G., Scognamillo F., Cesaraccio R., et al.: "Epidemiology of thyroid cancer in an area of epidemic thyroid goiter". *J. Cancer Epidemiol.*, 2013, 2013, 584768. doi: 10.1155/2013/584768. Epub 2013 Mar 4.
- [10] Palmieri G., Paliogiannis P., Scognamillo F., Budroni M., Cesaraccio R., Pulighe F., et al.: "Colorectal cancer epidemiology in an area with a spontaneous screening program". *Acta Medica Mediterr.*, 2013, 29, 231.
- [11] Cossu A., Paliogiannis P., Attene F., Palmieri G., Budroni M., Sechi O., et al.: "Breast cancer incidence and mortality in North sardinia in the period 1992 - 2010". *Acta Medica Mediterr.*, 2013, 29, 235.
- [12] Cherchi P.L., Marras V., Capobianco G., Ambrosini G., Piga M.D., Fadda G.M., et al.: "Immunohistochemical evaluation of a new epithelial antigen, Ber-Ep4 in ovarian cancer: preliminary results". *Eur. J. Gynaecol. Oncol.*, 2001, 22, 433.
- [13] Cherchi P.L., Capobianco G., Ambrosini G., Fadda G.M., Piga M.D., Ruiu G., et al.: "Intracystic evaluation of tumor markers in benign and malignant ovarian pathology". *Eur. J. Gynaecol. Oncol.*, 2002, 23, 163.
- [14] Capobianco G., Marras V., Meloni G.B., Dessole S., Ashqar N., Cherchi C., et al.: "Immunohistochemical evaluation of Ber-EP4 a new epithelial antigen in ovarian cancer: a propos of 62 cases". *Eur. J. Gynaecol. Oncol.*, 2012, 33, 90.
- [15] Lorenzato A., Biolatti M., Delogu G., Capobianco G., Farace C., Dessole S., et al.: "AKT activation drives the nuclear localization of CSE1L and a pro-oncogenic transcriptional activation in ovarian cancer cells". *Exp. Cell. Res.*, 2013, 319, 2627.
- [16] Hennessy B.T., Coleman R.L., Markman M.: "Ovarian cancer". *Lancet*, 2009, 374, 1371.
- [17] Riman T., Nilsson S., Persson I.R.: "Review of epidemiological evidence for reproductive and hormonal factors in relation to the risk of epithelial ovarian malignancies". *Acta Obstet. Gynecol. Scand.*, 2004, 83, 783.
- [18] Bertone-Johnson ER.: "Epidemiology of ovarian cancer: a status report". *Lancet*, 2005, 365, 101.
- [19] Rota M., Pasquali E., Scotti L., Pelucchi C., Tramacere I., Islami F., et al.: "Alcohol drinking and epithelial ovarian cancer risk. A systematic review and meta-analysis". *Gynecol. Oncol.*, 2012, 125, 758.
- [20] Jordan S.J., Whiteman D.C., Purdie D.M., Green A.C., Webb P.M.: "Does smoking increase risk of ovarian cancer? A systematic review". *Gynecol. Oncol.*, 2006, 103, 1122.
- [21] Italian Association for Tumor Registries (Associazione Italiana Registri Tumori, AIRTUM). Available at: <http://www.registri-tumori.it/cms/>
- [22] Easton D.: "Breast cancer genes—what are the real risks?" *Nat. Genet.*, 1997, 16, 210.
- [23] Risch H.A., McLaughlin J.R., Cole D.E.C., Rosen B., Bradley L., Fan L., et al.: "Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer". *Am. J. Hum. Genet.*, 2001, 68, 700.
- [24] King M.C., Marks J.H., Mandell J.B.: "Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2". *Science*, 2003, 302, 643.
- [25] Antoniou A., Pharoah P.D., Narod S., Risch H.A., Eyfjord J.E., Hopper J.L., et al.: "Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies". *Am. J. Hum. Genet.*, 2003, 72, 1117.
- [26] Palomba G., Pisano M., Cossu A., Budroni M., Dedola M.F., Farris A., et al.: "Spectrum and prevalence of BRCA1 and BRCA2 germline mutations in Sardinian breast cancer patients through a hospital-based screening". *Cancer*, 2005, 104, 1172.
- [27] Palmieri G., Palomba G., Cossu A., Pisano M., Dedola M.F., Sarobba M.G., et al.: "BRCA1 and BRCA2 germline mutations in Sardinian breast cancer families and their implications for genetic counseling". *Ann. Oncol.*, 2002, 13, 1899.
- [28] Palomba G., Loi A., Uras A., Fancello P., Piras G., Gabbas A., et al.: "A role of BRCA1 and BRCA2 germline mutations in breast cancer susceptibility within Sardinian population". *BMC Cancer*, 2009, 9, 245.

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