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Pregnancy related cancer in Apulia. A population based linkage study

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ABSTRACT

Objective: Despite a quite large number of papers in literature, the current incidence of pregnancy associated cancer still remains uncertain. Moreover, different inclusion criteria and time intervals considered after delivery make these data poorly comparable. The aim of this study was to investigate the incidence of PACs in Apulia, an Italian region, while stressing differences or similarities with other populations.

Study design: We collected 682,173 pregnancies from national discharge forms, regarding hospitals in Apulia from January 2003 to December 2015. Our aim was not only to obtain the raw incidence of PACs but also to estimate the odds ratio (OR) for some potential risk predictors such as calendar year, age, nationality and pregnancy outcome using a logistic model. Women were sorted into different groups by age (<30, 30–34, 35–39, >=40) and by nationality (Italian or foreign nationals). Each pregnancy had two possible outcomes: delivery or abortion.

Results: We achieved a final cohort of 867 PACs: therefore, the raw incidence is 127.1 per 100,000 pregnancies. Breast cancer was the most common cancer (37.7 cases per 100,000 pregnancies) and as a typical feature in our population thyroid cancers followed it by incidence (22.3 per 100,000 pregnancies). Cervical cancer is, as expected, the first gynaecological cancer by incidence (3.8 per 100,000). Younger women have the lowest risk for PACs (64.5 per 100,000, OR = 1) while the highest risk for PACs was for women aged >=40 years (OR = 4.29, p < 0.05). Considering calendar years, we observed an increased OR from 2006 to 2009 (OR = 1.39 and OR = 1.41 respectively) without spotting a trend throughout the whole decade.

Conclusions: The ranking of each tumour by incidence more or less reflects its demographics in reproductive age females in western countries and the incidence for any cancer is expected to grow as the rate of first deliveries in older women continues to rise. We reported noticeable differences regarding the incidence of some cancers (such as thyroid cancer) with previous literature, reflecting an epidemiologic feature of our cohort. Women older than 40 years have a more than fourfold risk for oncologic diagnosis during pregnancy, and this finding is of pivotal clinical and social importance because of the tendency of women living in developed countries to postpone childbearing.

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Introduction

Pregnancy associated cancer (PAC), although fairly uncommon, raises puzzling ethical, social, familial and religious issues. This situation also affects patients' physical and psychosocial health while threatening foetal integrity [1].

The incidence of cancer during or immediately after pregnancy has generally been reported to range between 0.09 and 0.14% [2–8]. However, despite a quite large number of papers in literature, the current incidence of PACs still remains uncertain. Indeed, available

data are poorly comparable due to different inclusion criteria (invasive and non invasive disease), incoherent time intervals (12 or 18 months) after delivery and finally dissimilar population references. Moreover, the incidence of different types of cancer in women shows a wide variation worldwide with many genetic and epigenetic influences. This implies that data from a certain geographical area cannot be generalized and as a matter of fact are nearly useless for public health purposes in cancer screening policies.

In 2017, Parazzini et al. reported the incidence of pregnancy associated cancers (PACs) in Lombardy (a region in northern Italy), based on data from regional hospital discharge forms from 2001 to 2012. Their study showed that the risk of PACs was 122.9 per 100,000 pregnancies with the most common cancers being breast,

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thyroid and blood cancers. Furthermore, the incidence increased significantly with age but it did not show any increase over time in the considered decade [3].

The aim of the present study was to investigate the incidence of pregnancy related cancers in Apulia, a region with 4 million inhabitants in the southern Italian peninsula from 2003 to 2015, and to compare the Apulian data with those reported from other geographical areas.

Materials and methods

We evaluated data from the National electronic database containing all the hospital discharge forms, in Italian "Scheda di Dimissione Ospedaliera (SDO)" regarding hospitals in Apulia from January 2003 to December 2015. In each SDO the patient is identified by a nationwide unique reference anonymous code and a series of clinical information is reported. More precisely, each SDO contains personal and demographic data (e.g. date of birth, nationality, qualification, job), patients' main complaint, a comprehensive provision of medical services during hospitalization, history of the present illness, remote pathological anamnesis, review of systems with principal vital parameters, regular and acute medications, allergies, discharge dates. The main diagnosis and 5 secondary diagnoses are coded according to the International Classification of Disease, Ninth Revision (ICD-9) while up to 5 interventions and hospitalization-related costs are encoded according to the national diagnosis-related group (DRG) system. The first step was to select all those SDOs reporting DRG codes 370-375 and 380-381 (regarding deliveries and abortions respectively), and to check for any possible lapse including only the SDOs reporting diagnoses or delivery/abortion-related interventions.

In this report we consider PAC as the diagnosis of malignancy occurring 9 or 3 months before delivery or abortion respectively, or within 12 months after the date of pregnancy outcome considered as the discharge date. Among those patients, we selected all SDOs reporting ICD codes 140.-208., which mean a diagnosis of malignant cancer among the main or secondary diagnoses. We excluded SDOs in which cancer was recorded as secondary diagnosis or if a previous SDO reported cancer as the main diagnosis because our aim was to obtain only incident neoplasms.

The date of admission was tabbed as the date of cancer diagnosis and for each woman we collected only the first discharge form reporting an oncologic diagnosis. We divided tumours by principal anatomic sites using the aforementioned ICD-9 codes: breast (174.), thyroid (193.), skin except melanoma (173.), lymphoma (200.-202.), melanoma (172.), cervix (180.), nervous system (191.-192.), leukaemia (204.-208.), colorectum (153.-154.), ovary (183.), head and neck (140.-149., 160.), skeletal or connective tissue (170.-171.), kidney (189.), urinary tract (188., 189.1-189.4, 189.8-189.9), lung (162.), other gastrointestinal (150., 152., 156., 158.-159.), stomach (151.), pancreas (157.), endometrium (182.), placenta (181.), other gynaecologic tract (184.), multiple myeloma (203.), other (164., 190., 194.-199.). The risk of PAC is the ratio between the whole number of PACs and all pregnancies occurring during the interval between January 1 st, 2003 and December 31 st, 2015.

As secondary endpoints we also expressed the odds ratio (OR) for some potential risk predictors using a logistic model and so we stratified the incidence rate of PACs by year, age, nationality, pregnancy outcome. Women were divided by age into 4 groups (<30, 30-34, 35-39, >=40) and by nationality between Italian women or foreign nationals. Each pregnancy had two possible outcomes: delivery or abortion. The effect of the above items as potential risk predictors was estimated as were the odds ratio (OR).

Results

From January 2003 to December 2015 we recorded a total number of 682,173 pregnancies in women residing in Apulia; as raw data, we obtained 1008 women with pregnancy associated cancer within 9 or 3 months before the date of the pregnancy outcome (delivery or abortion respectively) and within 12 months after the same outcome, but we must exclude several cases from the SDO database to achieve our aim.

We identified 876 women with cancer as main diagnosis and 132 with cancer as secondary diagnosis according to ICD-9 codes. Among the latter, we rejected 81 patients who had a non-cancer primary diagnosis and other 15 cases with cancer diagnosis before pregnancy, with a total of only 36 women with incident cancer as a secondary item in the SDO form. Thus the number of pregnancy associated cancers was 912 cases; a further 50 cases were excluded because of unclear cancer site or metastasis of unspecified origin.

Overall we achieved a final cohort of 867 women with incident cancer in pregnancy: thus, the risk for a PAC in our population was calculated as 127.1 per 100,000 pregnancies. Table 1 shows the incidence of cancer by anatomical region. Breast cancer was the most common pregnancy associated cancer (257 cases) with an incidence of 37.7 cancers per 100,000 pregnancies; 229 women were diagnosed in post-pregnancy while 28 during pregnancy. Thyroid cancers followed breast by incidence (22.3 per 100,000 pregnancies) with 133 malignancies in post-pregnancy (19.5 per 100,000) and 19 cancer in pregnancy (2.8 per 100,000 cases). The ranking goes as follows: skin except melanoma (89 cancers and 13.0 per 100,000 pregnancies), lymphoma (77 cases and 11.3 per 100,000 pregnancies), melanoma (6.2 per 100,000), cervical cancer and central nervous system (3.8 per 100,000), leukaemia (3.7 per 100,000).

According to the data 19.2 and 107.9 per 100,000 pregnancies were diagnosed with cancer during pregnancy and in post-pregnancy respectively. Table 2 shows distribution of pregnancies stratified by four items or potential risk predictors. Women younger than 30 years were about 1/5 (20.07%) of our cohort with the lowest risk for PACs (64.5 per 100,000, OR = 1) while one third

Table 1
Classification of pregnancy-associated cancer by site.

Cancer site	Pregnancy		Post-pregnancy		All	
	No	Risk	No	Risk	No	Risk
Breast	28	4.1	229	33.6	257	37.7
Thyroid	19	2.8	133	19.5	152	22.3
Skin excluding melanoma	15	2.2	74	10.8	89	13.0
Lymphoma	19	2.8	58	8.5	77	11.3
Melanoma	6	0.9	36	5.3	42	6.2
Cervix	3	0.4	23	3.4	26	3.8
Nervous system	2	0.3	24	3.5	26	3.8
Leukemia	6	0.9	19	2.8	25	3.7
Colorectum	4	0.6	20	2.9	24	3.5
Ovary	4	0.6	18	2.6	22	3.2
Head and neck	6	0.9	15	2.2	21	3.1
Other or ill defined	2	0.3	19	2.8	21	3.1
Connective tissue	6	0.9	11	1.6	17	2.5
Kidney	5	0.7	9	1.3	14	2.1
Urinary tract	3	0.4	8	1.2	11	1.6
Lung	1	0.1	7	1.0	8	1.2
Other gastrointestinal tract	0	0.0	8	1.2	8	1.2
Stomach	0	0.0	7	1.0	7	1.0
Pancreas	0	0.0	6	0.9	6	0.9
Endometrium	0	0.0	4	0.6	4	0.6
Uterus	0	0.0	3	0.4	3	0.4
Placenta	0	0.0	3	0.4	3	0.4
Other	1	0.1	1	0.1	2	0.3
Gynecological						
Multiple myeloma	1	0.1	1	0.1	2	0.3
All cancers	131	19.2	736	107.9	867	127.1

Table 2
Distribution, risks and OR for pregnancy-associated cancer and their relative p-value.

	Pregnancies	Pregnancy-associated cancer		Risk	OR	p-value
	Frequency (n.)	Frequency (n.)	%			
Age						
<30	269820	174	20,07	64,5	1	
30-34	215169	259	29,87	120,4	1,88	<0,05
35-39	147567	287	33,10	194,5	2,96	<0,05
>= 40	49617	147	16,96	296,3	4,29	<0,05
Nationality						
Foreign	111507	108	12,46	96,9	1	
Italian	570666	759	87,54	133,0	1,33	<0,05
Outcome						
Delivery	212924	334	38,52	156,9	1	
Abortion	469249	533	61,48	113,6	1,26	<0,05
Year of pregnancy						
2003	58901	60	6,92	101,9	1	
2004	59877	70	8,07	116,9	1,12	0,51
2005	56959	56	6,46	98,3	1,22	0,387
2006	56545	84	9,69	148,6	1,39	0,05
2007	55518	52	6,00	93,7	0,87	0,46
2008	54254	77	8,88	141,9	1,31	0,12
2009	54213	84	9,69	154,9	1,41	<0,05
2010	54100	57	6,57	105,4	0,95	0,78
2011	52180	78	9,00	149,5	1,34	0,09
2012	49546	76	8,77	153,4	1,32	0,11
2013	46790	71	8,19	151,7	1,33	0,1
2014	44510	58	6,69	130,3	1,13	0,49
2015	38780	44	5,07	113,5	0,99	0,97

(33.10%) of our cohort was made up of women ranging from 35 to 39 years and the highest risk for PACs was for women aged \geq 40 years (296.3 cancers per 100,000 pregnancies, OR = 4.29, $p < 0.05$).

Eighty-seven percent of women were Italian with 759 cancers versus 108 cancers (12.46%) in foreign pregnant women: being a foreigner did not increase the risk for PACs while being Italian or born in Italy meant higher association with cancer during pregnancy. More than 500 pregnancies out of 867 ended with abortion so we can conclude that the incidence rate of developing a pregnancy-associated cancer was higher for pregnancies resulting in miscarriage. Considering calendar years, we observed an increased OR from 2006 to 2009 (OR = 1,39 and OR = 1,41 respectively).

Comments

Benign neoplasms, such as leiomyomas or adnexal cysts are commonly found in pregnant women while data regarding malignancies are scarce [1,9,10]. Knowing the exact incidence and distribution of cancer in pregnancy in each geographical area represents a key point in the field of obstetrics and gynaecology.

In 2016, Parazzini et al. reported the incidence of pregnancy associated cancer in Lombardy (a region in northern Italy), based on data from regional hospital discharge forms and we decided to use the same system to collect data [3]. In the current study a raw incidence of 127.1 cancers per 100,000 pregnancies was similar to that reported in Lombardy (122.9 per 100,000 maternities), and in other geographical areas such as Australia (137 per 100,000 pregnancies), California (94 per 100,000 live births), Washington DC, Germany and other single centre and multicentric experiences from nearby or faraway Countries [2–8]. So we can assume that there is no critical geographical difference.

However, there are noticeable differences regarding each cancer in different regions: melanoma is the most common in Australia (45.7 per 100,000 maternities) [11] while it is the fifth cancer by frequency in our experience (6.2 per 100,000 maternities). In our study the ranking of each tumour during pregnancy reflects more or

less its demographics in reproductive age females in the so-called high-resource countries [15]: breast cancer is the most frequent PAC [12–14] and as for any other cancer, it is expected to become more frequent since first births in older women continue to rise [16]. The second most frequent cancer in our series is thyroid cancer: this result is specific for Italian population which shows an important increase in incidence for this neoplasm in both sexes compared to other countries worldwide [17]: it is the second neoplasm by incidence in women younger than 49 years old while it is the 18th by number of deaths from cancer in women. That means that the increasing incidence just relates to the milder histotypes and this goes along with the improving 5 years overall survival rate (2005–2009, 95%; 1990–1994, 86%) [18].

Notably, the incidence of pregnancy-associated thyroid cancer in our study was higher than that recorded in Lombardy. In fact there is a statistically significant discrepancy between its incidence in northern and southern Italy: contrary to almost all cancers, the incidence of thyroid cancer is higher in southern Italy (27.5 \times 100,000 inhabitants vs 23.5 in northern Italy) with a greater (+17%; \times 100,000 inhabitants) incidence rate standardized for geographical area and sex [18].

We also detected 77 cases per 100,000 women of lymphoma, which represents the most common haematological malignant disorder in pregnancy, followed by acute leukaemia. Approximately 3 every 100 women [19] with HL (Hodgkin lymphoma) receive the diagnosis during pregnancy, usually at the same stage as in non-pregnant counterparts. Melanoma is the fifth most frequent cancer in our series with special concerns about this PAC in literature: one of the features of melanoma is the risk for transplacental metastases, with newborns developing clinical evidence of metastases having a poor prognosis [20]. Cervical cancer is the most frequent gynaecologic cancer in both our and other series. As previously mentioned, it is reasonable to expect a rising incidence of PACs but, surprisingly, the trend in our series diverges from this expected corollary with a peak in 2009 and unexplained statistically noticeable spikes in 2006 and 2011 and 2012 without increase.

Italian women seem to have an increased risk for PACs (OR = 1,29) compared to other countries and in Apulia we find a greater proportion for miscarriage/abortion (200.4 every 100,000 pregnancies in our report) compared to our counterpart in Lombardy (116 per 100,000 pregnancies). Probably the main weaknesses of our study is inherent to the specific nature of our database which prevents us from obtaining any more data than those considered, thus we had no information on the gestational age at birth or on neonatal outcomes.

Finally, as expected, the incidence of tumours by age showed an increasing trend in older women compared to younger ones. In fact, in agreement with data from either far-away countries like Australia or nearby regions (e.g. Lombardy), age seems to be a major factor in the incidence of PACs: in fact being older than 40 years during childbearing increases the risk for oncologic diagnosis more than four-fold. This finding is of great clinical and social importance as in developed countries women tend to postpone childbearing because of socio-economic reasons. This study does not provide any information on clinical management and follow up of cancer during pregnancy. However, we believe that improved knowledge of the exact incidence of this rare condition might make a significant contribution for a better management and treatment.

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