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Review article

Patterns of cervical cancer care in Argentina: Applying ASCO recommendations adjusted by local resources

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ABSTRACT

Keywords: Cervical cancer Argentina ASCO resource-stratified practice guideline Pattern of care There are significant differences in cervical cancer incidence and mortality between low-middle and high-income countries. The American Society of Clinical Oncology (ASCO) resource-stratified clinical practice guideline was designed to provide an appropriate cervical cancer treatment based on the best available evidence in scenarios with different diagnostic and therapeutic resources. Argentina, a Latin American high middle income country, shows however, that cervical cancer rates are similar to those of low-income countries. In addition, significant disparities in incidence and mortality are described throughout the country. The present article describes the current pattern of care of cervical cancer in Argentina and establishes recommendations adjusted to local resources in different regions of the country according to the ASCO guideline.

1. Introduction

Cervical cancer is the third leading cause of cancer mortality in women. Interestingly, a significant difference in incidence and mortality is observed between low-middle income countries (LMICs) and high-income countries (HIC). (Chuang et al., 2016; Gelband et al., 2015; WHO, 2014; Randall and Ghebre, 2016).

Natural history of cervical cancer, as well as their effective prevention and treatment strategies are well known. Thus, each cervical cancer death should be considered a preventable and unnecessary death. Complete and comprehensive control of cervical cancer requires the coordinated effort of multiple specialists and hospitals in the context of a consolidated health system, which allows universal access. (Randall and Ghebre, 2016).

According to the World Health Organization (WHO), therapeutic options should be selected in agreement with international, national or institutional guidelines based on a combination of evidence, the availability of trained professionals and equipment/infrastructure. (WHO, 2014) To this regard, the American Society of Clinical Oncology (ASCO) has recently launched a resource-stratified clinical practice guideline. The objective is to provide an appropriate cervical cancer treatment based on the best available evidence in scenarios with different diagnostic and therapeutic resources. (Chuang et al., 2016).

According to the World Bank, Argentina belongs to the group of high middle-income countries. (United Nations Development Programme, n.d.; http://economy.blogs.ie.edu/archives/2009/10/ %C2%BFque-es-el-indice-de-desarrollo-humano-idh.php, 2017) However, according to official figures from the National Program for the Prevention of Cervical Cancer (PNPCCU), cervical cancer in Argentina has a similar incidence and mortality rate as low-income countries. (http://www.msal.gob.ar/cancer-cervico-uterino/index.php/equiposde-salud/datos-epidemiologicos, 2017; World bank data, n.d.) The standardized mortality rate per 100,000 in 2009 was 7.5, remaining almost unchanged since 1980. (http://www.msal.gob.ar/cancer-cervico-uterino/index.php/equipos-de-salud/datos-epidemiologicos, 2017; Murillo et al., 2016) In addition, significant differences are observed in different regions throughout the country in terms of treatment access, human development index (HDI), economic development, density of population, as well as incidence and mortality for cervical cancer. (United Nations Development Programme, n.d.; http://economy.blogs.ie.edu/archives/2009/10/%C2%BFque-es-el-indice-de-desarrollo-humano-idh.php, 2017; http://www.msal.gob.ar/cancer-cervico-uterino/index.php/equipos-de-salud/datos-epidemiologicos, 2017; Informe nacional sobre desarrollo humano, 2013; International Atomic Energy Agency, 2014) Therefore, the aim of the present review is to describe the current pattern of care of cervical cancer in Argentina and to establish recommendations adjusted to local resources in different regions of the country.

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2. Oncological control plans for cervical cancer in Latin America

The estimated worldwide annual incidence and mortality of cervical cancer in 2012 was 527,624 and 265,653, respectively. More than 80% of new cases and 88% of deaths occur in low and middle-income countries (LMIC). (Gelband et al., 2015; Gelband et al., 2016; Ferlay et al., 2015; Fitzmaurice et al., 2015; Soerjomataram et al., 2012) These differences are due to geographic, socioeconomic, and cultural variations that restrict access to preventive services in certain subgroups of population throughout the globe. Thus, conditioning differences in access to screening and treatment, represent a failure of the health system to implement a comprehensive preventive strategy. (Chuang et al., 2016; Gelband et al., 2015; WHO, 2014; Randall and Ghebre, 2016).

The treatment of cervical cancer can be complex, requiring the participation of multiple specialists from different areas. Both therapeutic resources and their access tend to vary between different countries and even within different regions of the same country. (Chuang et al., 2016) WHO recommends the development and implementation of population oncology control plans in each country, aimed to chart the necessary activities. In 2011, however, only 21% of Latin American countries had operational oncological population registries. Consequently, establishing precise estimates of needs and activities in these countries was not possible. (Gelband et al., 2015) The development of a cancer population registry cannot be an isolated effort but part of a set of policies to reduce health inequities, prioritize cancer control, and develop effective national plans. (Goss et al., 2013; Arrossi, 2015).

There is a current initiative in Latin America and the Caribbean to develop a unique network of national cancer institutes known as the Network of National Institutes of Cancer of Latin America (RINC). This network is expected to include 18 countries with the objective of developing oncological control activities, improve practices, exchange information and knowledge, and identify needs by promoting coordination among its members. (Gelband et al., 2015; http://www2.rinc-unasur.org/wps/wcm/connect/fa41dd8044a541a-b960ebe2537792882/INFORME_FINAL_Junio_+2012.pdf?MOD = A-JPERES & CACHEID = fa41dd8044a541ab960ebe2537792882, 2012).

3. Radiotherapy deficit in low and middle-income countries

Radiation therapy represents one of the three main cancer treatment strategies. It is estimated that radiotherapy could benefit between 48 and 62% of cancer patients in terms of cure and palliation of symptoms. (Rosenblatt, 2014) There is, however, a marked inequity in the availability and access to radiotherapy among low and middle-income countries around the world, and even within countries. Thus, in sub-Saharan African countries or some places in Latin America less than 4% of patients have access to radiation treatment. In contrast, access is around 59–79% in some middle-income countries in Europe or Asia. (Jaffray and Gospodarowicz, 2014; Zubizarreta et al., 2015).

In addition, special attention also needs to be paid to avoid waiting times longer than 14 days due to an increase in the risk of local recurrence. (Rosenblatt, 2014; Chen et al., 2008) Brachytherapy, moreover, poses an even greater access problem. (Rosenblatt, 2014) It is estimated that, in those patients who do not have access to this treatment, there is a negative impact on prognosis and a loss in 4-year specific cause survival of almost 13%. (Han et al., 2013) Therefore, national cancer plans should ideally define the required number of professionals, departments and equipment according to population density, and the actual and expected burden of cancer in certain geographic areas. (Gelband et al., 2015).

4. ASCO recommendations according to local resources

ASCO considerations regarding cervical cancer care according to the

different local resources, have introduced a series of treatment alternatives with respect to the traditional and universal guidelines of management of cervical cancer. Thus, ASCO guideline highlights relevant concepts in different fields. For example, the possibility of providing less radical surgeries in case of not having adequately trained surgical teams, or the option of using neoadjuvant chemotherapy as a resource to achieve greater operability and decrease the number of patients requiring radiotherapy. Other recommendations include new radiation treatment fractionation that could increase their availability. (Chuang et al., 2016).

5. Situation of cervical cancer in Argentina

According to the World Bank, Argentina belongs to the group of high middle-income countries. (World bank data, n.d.) In addition, the United Nations Development Program states that this country has evolved in terms of human development since 1990. At present, Argentina is among the countries with a very high HDI's of 0.836. Economic development among regions is, however, considerably different. This generates distinct scenarios with respect to cervical cancer within the country. (United Nations Development Programme, n.d.; http:// economy.blogs.ie.edu/archives/2009/10/%C2%BFque-es-el-indice-dedesarrollo-humano-idh.php, 2017) Thus, incidence and mortality rates in Argentina are more in accordance with high or even medium HDI countries rather than with very high HDI ones. (United Nations Development Programme, n.d.; Ferlay et al., 2015; Fidler et al., 2016).

The incidence of cervical cancer in Argentina had a crude rate of 18.4/100,000 and an age standardized ratio of 17.5/100,000 being the second most common cancer during 2003–2007. (Murillo et al., 2016; IARC, 1997) Nevertheless, Argentina, does not have a population-based cancer registry. The existing data come mainly from two cities in which cancer registries allow a rough estimation of the incidence and mortality of cervical cancer.

According to the PNPCCU, cervical cancer is the third cause of cancer mortality in Argentina. (http://www.msal.gob.ar/cancer-cer-vico-uterino/index.php/equipos-de-salud/datos-epidemiologicos, 2017; Murillo et al., 2016) The standardized mortality rate per 100,000 was 7.5 in 2009, ranging from 6.80 in 2005 to 8.23 in 1992. This rate, however, remained almost unchanged since 1980 but varies widely between regions within the country. The central region, including the City of Buenos Aires (CABA), has a rate of 6.0/100,000 versus 15.6 for the northeast region of the country. This diversity is due to the significant socio-economic differences among those regions. Thus, the HDI is 0.807 and 0.889 for the CABA and the northeast region, respectively. (http://www.msal.gob.ar/cancer-cervico-uterino/index.php/equipos-de-salud/datos-epidemiologicos, 2017; Informe nacional sobre de-sarrollo humano, 2013).

A retrospective cross-sectional survey among 120 patients with cervical cancer performed in Buenos Aires, demonstrated that this disease is associated with a considerable socio-economic impact and negative consequences on treatment compliance. (Arrossi et al., 2007).

6. Prevention resources for cervical cancer in Argentina

Cervical cancer prevention must be considered a public health priority in Argentina (Arrossi et al., 2007). Previous studies performed in urban areas have documented that factor such as poverty, single social status, unemployment or inactive, lower levels of education as well as reduced access to health care and women over the age of 65 were associated with lower probability of Pap smear coverage. The study also identified that, in the poorest regions there were 1.7 to 2.6 times more possibilities of having never been screened (Arrossi et al., 2008). Since 2011, PNPCCU is working in coordination with 14 provinces, including the province of Buenos Aires. It is focused on cervical cancer prevention including HPV vaccination and population-based screening in the public health care. Thus, the HPV test, as a



Fig. 1. Radiotherapy, brachytherapy equipment, members of the Argentine Gynecology Oncology Association (AAGO) and number of inhabitants according to regions. NOA: North-west Argentina; NEA: North-East Argentina (International Atomic Energy Agency, 2014; Okamoto et al., 2003).

complementary part of secondary prevention, is currently available in 5 provinces and it is in the process of being expanded to the rest of the country. (Programa Nacional de prevención del CCU, n.d.) To this regard, a recent study demonstrated a high level of HPV self-collection adoption among a community of health workers in the province of Jujuy, resulting in an increased screening participation among socially vulnerable under-screened women (Arrossi et al., 2017).

The HPV vaccine was introduced in the national immunization schedule in 2011 by the National Ministry of Health. To this regard, the result of a recent qualitative and quantitative study performed in a randomized sampling was published. The study, aimed to establish the level of acceptance of the HPV vaccine in 12 schools in Northeast Argentina, observed an HPV vaccination acceptance rate of 46.6% (95% confidence interval: 34.8–58.6). The authors, however, did not identify any association between sociodemographic and psychosocial factors and the decision to have girls vaccinated against the HPV (Chaparro et al., 2016). On the other hand, WHO estimate that two years after the introduction of vaccination in Argentina, the first dose has reached more than 80% of girls in the target age group, nearly 60% have received the second dose, and 50% have had the final third dose (World Organization of Health, n.d.).

7. Diagnostics resources for cervical cancer in Argentina

The public health care system in Argentina generally has basic diagnostic staging resources recommended by the International Federation of Societies of Gynecology and Obstetrics (FIGO). Nevertheless, the availability of more complex diagnostic imaging alternatives is less accessible within the country. New strategies to stage cervical cancer, however, allow a clearer knowledge of the disease in a non-invasive way. Magnetic resonance imaging is currently considered the best imaging study to assess tumor local extension, tumor size, as well as parametrial invasion. Although expensive, it often allows a complete image staging in a single evaluation, with logistical and economical advantages. (Gelband et al., 2015; Sala et al., 2013; Nicolet et al., 2000; Okamoto et al., 2003).

8. Therapeutic resources for cervical cancer in Argentina

The access and characteristics of oncological treatments, the

fragmentation of the health system as well as the lack of a populationbased oncological registry, make it impossible to obtain accurate data.

8.1. Surgical treatment

The Argentinian Association of Gynecology Oncology (AAGO) has already certified 71 gynecologic oncologists, some of them passed an oral-written exam and others were trained in one of the 11 specialized centers mainly distributed in CABA and in other big cities throughout the country such as Córdoba, Rosario and Neuquén. As with radiotherapy, 54% of the registered professionals in AAGO work in CABA, with little or no presence of members in the regions with the highest cervical cancer mortality rates. (AAGO, 2017) (Fig. 1 and Table 3).

8.2. Radiation treatment

The Directory of Radiotherapy Centers of the International Atomic Energy Agency (IAEA), to which Argentina is subscribed, constitutes an updated registry of hospitals and institutions regarding radiotherapy equipment. (International Atomic Energy Agency, 2014) Argentina, like other countries in the region, has coverage of 51–75% of the population if we consider that 62.5% of oncology patients will require radiation therapy and that a radiotherapy machine treats 450 patients a year. (International Atomic Energy Agency, 2014) (Table 1) In this sense, Argentina has 1 to 3 machines per million inhabitants, 83 radiotherapy centers, 82 linear accelerators and 36 cobalt therapy machines. This calculation is based on a population of 43,416,755 people and 115,162 new cancer cases. The situation in Argentina is similar to Chile and Brazil, but worse than Uruguay who presents 5 machines per million inhabitants. (International Atomic Energy Agency, 2014).

However, it is interesting to analyze the distribution of equipment within the country. Thus, 59 out of 117 (50.42%) machines registered are located in the province of Buenos Aires. Although this is the most densely populated district, it shows one of the lowest cervical cancer mortality rates in the country. Moreover, of these 59 machines, 31 (26.49% of the total and 52.54% of the district's equipment) are located in CABA, the smallest district in the country, with the highest HDI (0.889), and with half the mortality rate in comparison with the national average. (Table 2) (http://www.msal.gob.ar/cancer-cervicouterino/index.php/equipos-de-salud/datos-epidemiologicos, 2017: Informe nacional sobre desarrollo humano, 2013; International Atomic Energy Agency, 2014) On the other hand, other districts with greater territorial extension, lower HDI and higher mortality rate (up to two times the national averages) do not have radiotherapy equipment. As Table 2 shows, the province of Formosa is a good example in this sense http://www.msal.gob.ar/cancer-cervico-uterino/index.php/equiposde-salud/datos-epidemiologicos, 2017; Informe nacional sobre desarrollo humano, 2013; International Atomic Energy Agency, 2014) (Table 2).

Distances between radiotherapy equipment is also markedly different among regions of Argentina. Radiotherapy equipment is located at markedly different distances among regions of Argentina. This is a key point, as Argentina has a great territorial expansion (2.78 million Km²). (International Atomic Energy Agency, 2014) (Fig. 1 and Table 3) Unfortunately, something similar occurs with brachytherapy equipment. (Tables 2 and 3, Fig. 1) (Chuang et al., 2016; http://www.msal.gob.ar/cancer-cervico-uterino/index.php/equiposde-salud/datos-epidemiologicos, 2017; International Atomic Energy Agency, 2014).

8.3. Chemotherapy treatment

Chemotherapy treatments are generally guaranteed in the different oncology units of the main hospitals of the country. Chemotherapy regimens used in patients with cervical cancer are generally given in combination with radiation therapy. Cisplatin, the most common drug

Table 1

Selected region	Temperate South America									
Countries	RT centers	Clinical accel.	Co-60	CT	Simul	TPS	LDR manual	LDR remote	HDR Ir-192	HDR Co-60
Argentina Chile Uruguay Total	82 32 10 124	83 41 15 139	35 11 6 52	28 9 7 44	26 6 3 35	66 17 14 97	15 11 1 27	0 0 1 1	6 3 0 9	0 1 0 1

External beam radiotherapy and brachytherapy centers and equipment. Temperate South América. Available in: International Atomic Energy Agency (IAEA). Directory of Radiotherapy Centers (DIRAC): http://www-naweb.iaea.org/nahu/dirac/default.asp. (International Atomic Energy Agency, 2014).

used in cervical cancer is inexpensive, allowing full treatment compliance throughout the country. (Programa Nacional de Consensos Inter-Sociedades, 2015) On the other hand, Bevacizumab, a targeted therapy recently approved by the FDA in the USA and in certain countries in Europe to treat women with advanced or recurrent cervical cancer, was approved in Argentina since in 2015. The cost of these drugs will probably represent one of the main limitations for its implementation in Argentina.

9. Recommendations of management of cervical cancer in Argentina

The recent ASCO recommendations are perfectly applicable not only to Argentina itself, but also within regions through the county with different resources to treat women with cervical cancer. (Chuang et al., 2016).

9.1. Pathology diagnosis

It is necessary to unify criteria for the pathologic reports, including prognostic factors, and using immunohistochemistry techniques in certain cases. The application of this recommendation will better define the prognosis, and help oncologists decide the best treatment strategy for each patient. Specific training of general pathologists in gynecological tumors can also contribute to the development of this area.

9.2. Surgical treatment

Less radical surgical procedures can also be implemented in areas with limited resources. In patients with stages IA1 without lymphovascular space invasion, for example, a conization rather than a hysterectomy can be therapeutic as well.

Based on the ASCO recommendations, as well as on the strong surgical tradition in Argentina, it is necessary to strengthen surgical strategies to treat cervical cancer beyond early stages of the disease. Thus, women with locally advanced cervical cancer (FIGO stage IB2-IIB) could undergo neoadjuvant chemotherapy by using inexpensive drug regimens such as cisplatin/carboplatin and paclitaxel followed by radical hysterectomy. This may be considered as a reasonable alternative in areas with limited access to radiation treatment. In this sense, it will be also appropriate to investigate whether it is feasible or not to establish a policy of redistribution of gynecological surgeons in favor of those areas with high incidence of cervical cancer in Argentina.

It is essential to define the capacity of each region in the country and its institutions, to perform radical oncological procedures. Treatment centralization of gynecological cancer has shown an increase in survival rates in several areas through the globe, by an integrated management of patients with multidisciplinary expert teams. (Fung-Kee-Fung et al., 2015) Centralization of treatment could also increase the application of minimally-invasive surgery (MIS) for those women with surgical indication. Ideally, over 70–80% of women with cervical cancer, who are potential candidates for surgical treatment, should be operated by MIS. An interesting study calculated that if 90% of women with endometrial cancer were operated by MIS, there would be 8059 less complications, 127,257 fewer days of hospitalization, and 534 million dollars would be saved yearly. (Scalici et al., 2015) Therefore, employing MIS to treat women with gynecological cancers seems to be crucial to accomplish the best outcomes for patients, physicians, hospitals, and for those who cover health-related expenses. Additional benefits of centralization of cervical cancer might include the possibility to perform more radical surgical procedures when necessary. Thus, even though an extrafascial hysterectomy is proposed by ASCO as an alternative strategy in case of limited resources for FIGO stages IA2-IB1-IIA, radical hysterectomy could be performed if necessary.

9.3. Concurrent chemoradiation

Even though concurrent chemoradiation is the standard treatment for women with FIGO stage IB2 to IVA, it is recommended to avoid delays in starting the treatment. It is necessary to prioritize those patients with greater possibility of curative therapy when the number of patients to be treated exceeds the capacity of the radiotherapy equipment. As it has been previously described, the access to radiotherapy treatment is unbalanced through the country, with less equipment than the required for the current necessities. Thus, the Argentinian government should make an important investment in equipment and specialists in the near future.

The application of fractionation schemes of shorter duration, which means, fewer fractions with higher doses per fraction, can also be considered. (Chuang et al., 2016) Ideally, external radiotherapy should always be combined with brachytherapy. In cases where this alternative is not available, an external radiotherapy boost is an option, reaching a final dose of 68 to 70 Gy with fractions of 1.8 or 2.0 Gy. If residual disease persists 2 months after radiotherapy, extrafascial hysterectomy can be a valid option. (Chuang et al., 2016; Nagase et al., 2010; Cetina et al., 2013; Kokka et al., 2015; Censo Nacional de Población, 2010).

9.4. Fertility-sparing treatment

Selected cases that wish to retain their fertility need to be properly counseled regarding possible fertility-sparing strategies. In addition, physicians who initially evaluate and diagnose patients with cervical cancer should be aware of the indications and available options of treatment. Ideally, they should have the possibility to refer patients who require the most complex surgeries or treatments to centers with sufficient training that work with multidisciplinary teams to provide the best quality of care. (Chuang et al., 2016).

10. Conclusions

Argentina belongs to the group of countries with very high HDI. However, the cervical cancer incidence and death rates, largely unbalanced within the country, corresponds with those countries with minor HDI. This situation is mainly explained based on differences in economic development as well as on the unequal access to prevention and treatment among different regions throughout the country. The recent ASCO recommendations allow to adjust alternative strategies of treatment according to local resources that aim to provide the best

Table 2

Distribution of external beam radiotherapy and brachytherapy equipment, by districts and regions. Number of inhabitants, HDI, and district mortality rate. (http://www.msal.gob.ar/ cancer-cervico-uterino/index.php/equipos-de-salud/datos-epidemiologicos, 2017; Informe nacional sobre desarrollo humano, 2013; International Atomic Energy Agency, 2014; Kokka et al., 2015).

Region	Province	Inhabitants	HDI (2011)	Mortality/100,000 (2009-2011)	Radiotherapy equipment (%)	Brachytherapy equipment (%)
Pampeana	C.A.B.A.	2,890,151	0.889	3,8	31 (26.49)	9 (25.71)
	Prov. de Buenos Aires	15,625,084	0.838	6,2	28 (23.93)	4 (11.42)
	La Pampa	127,205	0.864	6,6	3 (2.56)	1 (2.85)
	Córdoba	3,308,876	0.862	4,8	12 (10.25)	3 (8.57)
	Santa Fe	3,194,537	0.846	7,2	11 (9.40)	8 (22.85)
	Entre Ríos	1,235,994	0.839	6,4	2 (1.70)	1(2.85)
Cuyo	Mendoza	1,738,929	0.852	6,9	6 (5.12)	3(8.57)
	San Luis	431,588	0.828	10	1 (0,85)	0 (0)
	San Juan	695,640	0.825	9,2	2 (1.70)	1(2.85)
Northwest	Jujuy	673,307	0.829	11,2	0 (0)	0(0)
	Salta	1,214,441	0.832	12,7	1 (0,85)	0(0)
	Tucuman	1,475,384	0.843	8,9	4 (3.41)	1(2.85)
	Santiago del Estero	874,006	0.807	8,2	1(0.85)	0(0)
	Catamarca	367,828	0.836	8,2	2(1.70)	0(0)
	La Rioja	333,642	0.834	7,9	0(0)	0(0)
Northeast	Chaco	1,055,259	0.807	13,5	2(1.70)	1(2.85)
	Formosa	539,883	0.806	15,5	0(0)	0(0)
	Corrientes	992,595	0.828	13,9	2(1.70)	0(0)
	Misiones	1,101,593	0.817	15,2	2(1.70)	0(0)
Patagonia	Neuquén	619,745	0.855	7,4	1(0.85)	0(0)
	Rio Negro	638,645	0.851	12,3	4(3.41)	2(5.71)
	Chubut	638,645	0.848	6,8	2(1.70)	1(2.85)
	Santa Cruz	273,964	0.873	9,7	0(0)	0(0)
	Tierra del Fuego	155,053	0.880	2,9	0(0)	0(0)
Total country		40,201,994	0.848	7,2	117 (100)	35 (100)

Table 3

Distribution of external radiotherapy and brachytherapy equipment, AAGO members, number of inhabitants and mortality rates, according to regions. (http://www.msal.gob.ar/cancercervico-uterino/index.php/equipos-de-salud/datos-epidemiologicos, 2017; Informe nacional sobre desarrollo humano, 2013; International Atomic Energy Agency, 2014; Okamoto et al., 2003; Kokka et al., 2015).

Regions	Inhabitants	Mortality rate/100,000 (2006-2008)	Radiotherapy equipment	Brachytherapy equipment	AAGO members
C.A.B.A.	2,890,151	6,0	31	9	78
Pampeana (without C.A.B.A.)	23,491,696		56	17	48
Patagónica	2,326,052	7,6	7	3	5
Сиуо	2,866,157	7,7	9	4	0
Northwest	4,938,608	11,4	8	1	4
Northeast	3,689,330	15,6	6	1	2
Total country	40,201,994	7,5	117	35	137

possible quality of care to women affected by cervical cancer in Argentina.

Conflict of interest

None of the authors have any conflict of interest; no other relationships or activities that could appear to have influenced the submitted work.

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