



Comparison of Age- Standard Incidence Rate Trends of Gynecologic and Breast Cancer in Iran and Other Countries

**Maliheh ARAB¹, Giti NOGHABAEI²*

1. Dept. of Gynecology-Oncology, Shabid Beheshti University of Medical Sciences, Tehran, Iran

2. Imam Hossein Medical Center, Shabid Beheshti University of Medical Sciences, Tehran, Iran

***Corresponding Author:** Email: drmarab@yahoo.com

(Received 10 Apr 2014; accepted 25 July 2014)

Abstract

Background: Female cancer, especially breast and gynecologic cancers are considered multistage disease, highly influenced by risk and protective factors and/or screening preventive modalities. Consequences of all these factors result in the trend of change over time.

Methods: In this comparative study, based on data of national cancer registry of Iran 2004 published by Iranian Ministry of Health, age – standard incidence rate (ASR) according to the world population was calculated in all reported gynecologic and breast cancers. Source of all subjects are pathologic based. In the next step, the calculated ASR of Iran and those of the other countries in 2004 were compared to GLOBOCAN ASR reports of 2008.

Results: In Iran ASR of breast cancer 2004 (24.93) changed to 18.4 in 2008. Ovarian cancer ASR of 2004, 3.07 was 3.1 in 2008. Endometrial cancer ASR in 2004 (2.29) was 1.7 in 2008. Cervical cancer ASR of 1.71 in 2004 was 2.2 in 2008.

Conclusions: In Iran incidence trend of breast and endometrium are decreasing in the same direction of USA and Australia. Increasing trend of ovary and cervix ASR in Iran is in the inverse direction of USA and Australia which are decreasing. Future studies to find out the same trend or any changes, might develop these findings and improve consequent practical decisions based on results of this study and complementary future studies.

Keywords: Ovarian cancer, Cervical cancer, Breast cancer, Gynecologic malignancies, Iran

Introduction

Cancer occurrence is highly influenced by environment, genetic, gender, age, race, socioeconomic status, education, culture, obesity, and all life style related factors which might result in incidence rate change of these cancers in every population (1, 2). Main gynecologic cancers (ovary, endometrium and cervix) besides breast cancer are responsible for 1.6% of total human cancers in the world (3).

Breast, endometrium and ovary are cancers with high incidence in the developed and western countries, North Europe and North America. Lower incidence in the less developed regions in-

cluding Asian countries is observed (3-5). There are suggestions regarding different survival of ovarian cancer, adjusted by available diagnostic and therapeutic modalities. More attention to confounding factors are needed, for instance undiagnosed late stage ovarian cancer cases leading to dead affect involved diagnosed cancer population into more early stage and lower age population (6). Cervical cancer incidence is among the 3 most common female cancers in 90% of the countries in the world (7).

Breast and gynecologic cancer incidence rates are the consequence of many factors. A common well

known etiology for breast, ovarian and endometrial cancer is parity, with lower incidence in multiparous women (8-11). Ovarian cancer risk is less in multiparous and oral contraceptive user females. Risk factors of ovarian cancer include age, white race, nulliparity, positive family history of ovarian, endometrial and breast cancer (12-14).

Cervical cancer is more common in the regions with low socioeconomic status (15).

Study of incidence trend might clarify epidemiologic and clinical points to be studied more and used as and documented background for decision making and necessary interventions. In the present study change of incidence rate in breast, ovarian, endometrial and cervical cancer in a 4-5 year period of time in different countries including Iran is compared.

Materials and Methods

Data of 2004 national cancer registry of Iran, published by the Iranian Ministry of Health regarding all reported breast, ovarian, endometrial and cervical cancers were included in this comparative study (16). Iranian national cancer registry report, as pathology based registry has presented crude incidence rates.

These data are not standardized by population in 2004, so comparing it with those of the other countries is not possible. From 2008, age standard data of Iran is presented in GLOBOCAN database.

So, in the first step, results of breast, ovarian, endometrial and cervical cancer patients were standardized with standard world population. All reported female cancers of breast, cervix, ovary, and endometrium were included in the analysis. Since other gynecologic cancers are rare their crude incidence rates were not included in the study. Data of each of cancers in 2004 was separately proceeded to age- standard incidence rate according to the world standard population of the same year. In the second step, results of Age- standard incidence rates (ASR) of the 4 above mentioned can-

cers in Iran, 2004 besides ASR of 6 other countries including USA, Australia, Japan, India, Africa and Thailand, 2004 were compared to ASR reports of all above mentioned cancers in 2008, GLOBOCAN database.

The main variables are ASR of breast, ovarian, endometrial and cervical cancer cases in different countries which are presented in two time cutoff (2004 and 2008), in order to clarify the trend of disease in these time periods in different regions. Cancer registry data of Iran is pathology based which include 80% of cancer cases (16).

This 80% coverage might make results biased. Published data of the Iranian ministry of health and care is ethically available for study and private data of patients is not included.

Results

About 24498 female cancer patients were reported in 2004 Iran, including 1923 (7.8%) gynecologic cancer patients (ovary, endometrium, uterus, cervix, vagina, vulva, placenta and other female genital organ), 16310 (66.6%) non-gynecologic patients and 6265 (25.6%) breast cancer cases. That is, breast and gynecologic cancer patients cover 33.42% of all site female cancer cases in 2004. Age groups of patients (all female) are shown in table 1 as demographic picture.

The percentages of cancer patients in Iran 2008 was 8.1% gynecologic, 69.9% non-gynecologic, 22% breast cancer based on GLOBOCAN, 2008 database (17).

The depiction of comparing Iranian female cancers 2004 and 2008 percentage in non-gynecologic, breast, ovarian, cervix and endometrial subgroups are presented in Fig.1.

Compared ASR of Iranian female gynecologic and breast cancer cases in 2004 and 2008 trend are presented in Table 2.

Comparison of the 4 mentioned cancers and ASR trends of each cancer between Iran and 6 other countries, in 2004 and 2008 are presented in Table 3.

Table 1: The Number and frequency of breast and gynecologic female cancer patients according to age-groups in Iran, 2004

Age group (yr)	breast	Female gynecologic cancers	Breast + Gyn. Cancer of all site female cancers (%)
0-9	0 (0)	8 (0.03)	8 (0.03)
10-19	0 (0)	43 (0.18)	43 (0.18)
20-29	164 (0.67)	127 (0.52)	291 (1.19)
30-39	1111 (4.53)	214 (0.87)	1325 (5.41)
40-49	2001 (8.17)	402 (1.64)	2403 (9.81)
50-59	1535 (6.26)	472 (1.93)	2007 (8.19)
60-69	814 (3.32)	387 (1.58)	1201 (4.90)
70-79	389 (1.59)	200 (0.82)	589 (2.40)
80+	100 (0.41)	42 (0.17)	142 (0.58)
Unknown	151 (0.62)	28 (0.11)	179 (0.73)
Total	6265 (25.57)	1923 (7.85)	8188 (33.42)

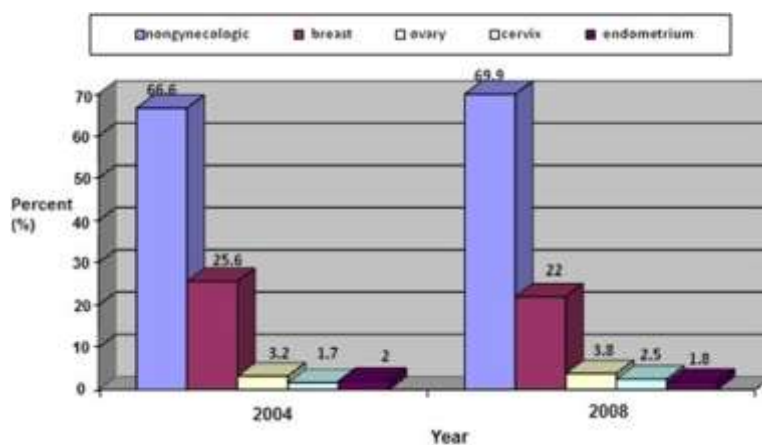


Fig. 1: Percentage of female cancer cases (categorized based on gynecologic, non-gynecologic and breast) in Iran, 2004 and 2008

Table 2: ASR trend of gynecologic and breast cancer cases in Iran, 2004 and 2008

Cancer site	2004	2008
Breast	23.94	18.4
Ovary	3.07	3.1
Cervix	1.71	2.2
Endometrium	2.29	1.7
Total	31	25.4

Table 3: Comparison of standard incidence rate and its trend (2004 to 2008), in breast, cervical, endometrial and ovarian cancer patients in different countries

Country region	Breast		Ovary		Endometrium		Cervix	
	2004	2008	2004	2008	2004	2008	2004	2008
USA (34, 35)	101.7	76	10.6	8.8	18.7	16.5	7	5.7
Australia (34, 36)	119.5	85.5	11.6	7.8	16.6	11.5	6.9	5
Japan (34, 37)	48.1	42.7	8.1	7.6	6.5	7.6	9	9.8
India (34, 35)	19.1	22.9	4.9	5.7	1.7	1.9	30.7	27
Uganda (34, 38)	30	27.8	—	—	—	—	45	47.5
Africa (34)	—	28	3.3	4.2	—	2.5	—	25.2
Thailand (34, 39)	26.7	30.7	—	6.8	—	4.3	20	24.5
Iran	24.93	18.4	3	3.1	2.29	1.7	1.71	2.2
World (5, 34)	—	38.9	6.6	6.3	—	8.2	—	15.2

All the sums are presented as standard rates according to the world population per 100,000

Discussion

We noticed in this study that in Iran the incidence trend of breast and endometrium are decreasing, besides increasing trend of ovary and cervix. Most of breast and gynecologic female cancer patients occur in 40-59 age group (Table 1). This distinct the disease burden in terms of considering the high probable diagnosis and anticipating therapy for this age group. The frequency of occurrence for different cancers in Iran has been shown in Fig. 1 through the percentages of non gynecologic cancers and gynecologic cancers along with breast cancer in 2004 and 2008. As it is shown, breast cancer is the most common female cancers among Iranian women. Among the gynecologic cancer cases, ovary is the most common. This marks the burden of gynecologic cancer in Iranian female population through 2004-2008 (Fig.1). Compared ASR of Iranian female gynecologic and breast cancer cases, 2004-2008 shows that the incidence of ovarian, cervical and endometrial cancer has not changed significantly, although the ASR of breast cancer has decreased from 24.93 in 100,000 population in 2004 to 18.4 in 100,000 population in 2008 (Table 2). This decreasing trend needs more evaluation. The lower occurrence and the younger age population in Iran might explain the mentioned trend (17). A brief comparison of breast and gynecologic cancer ASR of Iran and those of the other countries are presented below.

Breast cancer

The most common cancer in the world among 4 under study cancers is breast cancer followed by cervix, endometium and ovary (Table 2). Breast cancer in all of the compared six countries revealed the highest incidence rate cancer. The highest age standard incidence rate (ASR) of breast cancer is observed in USA and Australia with a decreasing trend. In Iran and Uganda ASR is lower with a decreasing trend between 2004 and 2008. In Japan there is a higher ASR in comparison to Iran, Thailand and Uganda and lower in comparison to western countries, decreasing trend is like Iran. In India and Thailand, ASR is lower with a rising trend (Table 3).

Several risk factors are associated with breast cancer including smoking, late child bearing, nulliparity, early menarche and late menopause, low breast-feeding, post-menopausal estrogen- progesterone replacement therapy, low physical activity, high BMI in older age, alcohol consumption, diet and the old age (18-20). These risk factors are an area of more study in the future to clarify causes of any increasing or decreasing trends in each country. Iran is a low incidence area of breast cancer like other Asian countries and inverse to western countries (17). In Iran in older age and after menopause slope of increasing breast cancer incidence by age exhibit slow rise in contrast to USA with continuous increase after menopause (21). Trend of breast cancer in USA has increased 26% within 1980s and with lower speed within 1990s

(22). A 3.5% decrease in breast cancer ASR is observed from 2001 to 2004 which might be due to decreasing practice of hormone replacement therapy (23). As observed in Table 3 trend of breast cancer ASR from 2004 to 2008 in USA has been decreasing.

Increase of breast cancer incidence rate observed in the data of the present study, in Thailand and India might be the result of adoption of some aspects of western life style such as lower activity, more fast food usage, trend to obesity, later marriage, lower parity and so on.

Cervical cancer

The most common gynecologic cancer in the world is cervical cancer (Table 3). In Africa the most common cancer in women is cervical cancer (24). The most common gynecologic cancer in Japan, India, Uganda, Africa and Thailand is cervical cancer, as well. Cervical cancer incidence in USA and Australia is relatively low and trend is in favor of decrease. In countries such as Uganda, Africa and Thailand incidence is high and trend is increasing (Table 3). In Iran, ASR of cervical cancer is low (the lowest ASR of cervical cancer among the compared countries) but trend is increasing (Table 2).

HPV infection as a sexually transmitted infection is regarded as the main factor influencing cervical cancer development (25). Other risk factors are as follows: multiple partners, early age intercourse, smoking, socioeconomic status, and multiparity (26, 27). Proper screening (Pap smear and HPV testing) results in cervical cancer ASR decrease, which is observed in developed countries (28-30). This matter might explain the observed decreasing trend of cervical cancer ASR in USA and Australia from 2004- 2008 (Table 3). Regarding increases trend of cervical cancer in Iran, more HPV infection are considered.

Ovarian cancer

The most common gynecologic cancer in Iran is ovary, although ASR of ovarian cancer is lower in comparison to other countries (Table 3). Ovarian cancer ASR of Iran is lower than the world that is decreasing. Trend of ovarian cancer ASR in Iran is

increasing such as Africa and India which are increasing, as well. In western countries such as USA and Australia, ovarian cancer ASR is higher with a decreasing trend.

Other studies report high rates of ovarian cancer in developed and western countries with a plateau in ASR and a lower rate in developing and Asian countries including Iran with increasing trend as observed in the present cancer data (4, 5). Main risk factors of ovarian cancer are nulliparity, low parity, obesity, white race, high fat diet and inactivity. In contrast breast feeding, multiparity and oral contraceptive pill consumption are protective factors (5, 31, 32). It seems reasonable that a trend to western lifestyle, that influence diet, obesity and lower parity is lead to increase in trend of ovarian cancer ASR which is observed in the present data (Table 3). Epidemiologic trends are important to prevent improper changes in ovarian cancer trend.

Endometrial cancer

The most common gynecologic cancer in USA and Australia is endometrial cancer (Table 3). Endometrial cancer ASR in these countries is high but decreasing. In contrast to Japan and India where endometrial cancer incidence is lower with increasing trend, in Iran Endometrial cancer ASR is low and the trend is decreasing (Table 2)

One of the main limitations of comparative ASR studies is different management of data gatherings. More careful organized cancer registry may simulate higher ASR, and vice versa is true as well. Data of Iranian cancer registry might be in improvement curve and not in maximum clarify specially due to its pathologic basis.

Main risk factors of endometrial cancer are old age, nulliparity, early menarche, late menopause and obesity (33). Trend of developing countries to obesity and higher life expectancy might explain the increasing trend of endometrial cancer incidence in these countries. Probable causes of the decreasing trend in endometrial cancer in developed countries might be studied more in the future.

Two main limitations of the study are as follows. At first, underestimate of cancer incidence especially in 2004 is probable due to new organization

of cancer registry and pathology based method. Second point is the wide range of causes, risk factors, epidemiologic parameters in different regions and for each of 4 studied gynecologic cancers. So, authors seriously feel the need of several step by step studies for more definite clinical discussion followed by decision in practice.

Conclusion

In countries such as USA and Australia ASR of breast, ovary and endometrium are higher in comparison with other countries including Iran and the trend is decreasing. The incidence of cervical cancer is lower and trend is in favor of more decrease. In contrast in countries, such as Africa, Thailand, India and Iran, although ASR of breast, ovary and endometrium is lower in comparison with western countries, the trend is in favor of increase, except of breast in Iran with a decreasing trend. Changes in lifestyle towards western pattern might explain increase trend of breast, ovary and endometrial cancer in the globe. The trend of cervical cancer incidence in these countries is in favor of increase. The first one probable reason is change of sexual behavior towards western lifestyle and the second, is lack of organized preventative screening programs resulting in increase in cervical cancer ASR. More studies focusing on epidemiologic patterns and the causes including risk factors for each cancer besides more attention to continuation of the present study trend in the future might clarify and suggest preventative interventions in public health planning and clinical decision making regarding cancer.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgement

All employees of the Ministry of Health are appreciated for gathering and organizing the raw data. Dr. Parvin Esfahani, expert in social medicine, is appreciated for help in adjusting data and ASR. This study is approved and supported by Clinical Research Development Unit, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences. The authors declare that there is no conflict of interests.

References

1. Taheri NS, Bakhshandehnosrat S, Tabiei M, Kashani E, Rajaei S, Besharat S, et al. (2012). Epidemiological pattern of breast cancer in Iranian women: is there an ethnic disparity. *Asian Pac J Cancer Prev*,13:4517-20
2. Stewart BW, Kleihues P (2003). *World cancer report*. IARC press Lyon.
3. WHO methods and data sources for global burden of disease estimates 2000-2011 (2013). Global Health Estimates Technical Paper WHO/HIS/HSI/GHE/2013.4. Available from: http://www.who.int/healthinfo/statistics/GBD_method.
4. Shin HR, Carlos MC, Varghese C (2012). Cancer control in the Asia Pacific region: current status and concerns. *Jpn J Clin Oncol*, 42(10):867-81.
5. Arab M, Khayamzadeh M, Tehranian A, Tabatabaefar M, Hosseini M, Anbiaee R, et al. (2010). Incidence rate of ovarian cancer in Iran in comparison with developed countries. *Indian journal of cancer*, 47(3):322-7.
6. Arab M, Khayamzadeh M, Mohit M, Hosseini M, Anbiaee R, Tabatabaefar M, et al. (2009). Survival of ovarian cancer in Iran: 2000-2004. *Asian Pac J Cancer Prev*, 10(4):555-8.
7. Xavier Bosch F (2013). The Path to Eliminate Cervical Cancer in the World and the Challenges of Professional Education. *Vaccine*, 31 (5):11-12.
8. Horn J, Opdahl S, Engström MJ, Romundstad PR, Tretli S, Haugen OA, et al. (2014). Reproductive history and the risk of molecular breast cancer subtypes in a prospective study

- of Norwegian women. *Cancer Causes Control*, 25(7):881-9.
9. Doufekas K, Olaitan A (2014). Clinical epidemiology of epithelial ovarian cancer in the UK. *Int J Womens Health*, 23;6:537-545.
 10. Butt S, Harlid S, Borgquist S, Ivarsson M, Landberg G, Dillner J, et al. (2012). Genetic predisposition, parity, age at first childbirth and risk for breast cancer. *BMC Res Notes*, 7;5:414.
 11. Schonfeld SJ, Hartge P, Pfeiffer RM, Freedman DM, Greenlee RT, Linet MS, et al. (2013). An aggregated analysis of hormonal factors and endometrial cancer risk by parity. *Cancer*, 119(7):1393-401.
 12. Zhang M, Lee AH, Binns CW (2004). Reproductive and dietary risk factors for epithelial ovarian cancer in China. *Gynecol Oncol*, 92(1):320-6.
 13. Tomao F, Lo Russo G, Spinelli GP, Stati V, Prete AA, Prinzi N, et al. (2014). Fertility drugs, reproductive strategies and ovarian cancer risk. *J Ovarian Res*, 8;7:51.
 14. Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT (2004). Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol*, 191(3):733-40.
 15. Grunewald T, Davies E, Mak V, Russell-Jones R, Acland K, Moller H (2007). Does deprivation of area of residence influence the incidence, tumour site or T stage of cutaneous malignant melanoma? A population-based and clinical database study. *Clin Exp Dermatol*, 32(5):574-7.
 16. Table of numbers and percentages of cancers according to histology result (2006). *Iranian Annual of National Cancer Registration Report*. 1st ed. Cancer office, Health Deputy, Iran, pp.: 241-3.
 17. Hosseini MS, Arab M, Nemati Honar B, Noghabaei G, Ghasemi T, Safae N, et al. (2013). Comparison of Age-specific and Age-standard Female Breast Cancer in Iran and Western Countries. *J Basic Appl Sci Res*, 3(6):558-61.
 18. Hortobagyi GN, de la Garza Salazar J, Pritchard K, Amadori D, Haidinger R, Hudis CA, et al. (2005). The global breast cancer burden: variations in epidemiology and survival. *Clin Breast Cancer*, 6(5):391-401.
 19. Liu TJ (2007). Validity of sentinel lymph node biopsy in Taiwanese breast cancer patients. *J Formos Med Assoc*, 106(2):126-33.
 20. Morabia A, Costanza MC (2005). The obesity epidemic as harbinger of a metabolic disorder epidemic: trends in overweight, hypercholesterolemia, and diabetes treatment in Geneva, Switzerland, 1993-2003. *Am J Public Health*, 95(4):632-5.
 21. Hosseini MS, Arab M, Nematihonar B, Noghabaei G, Safaei N, Ghasemi T (2013). Age-specific incidence rate change at breast cancer and its different histopathologic subtypes in Iran and Western countries. *Pak J Med Sci*, 29(6):1354-57
 22. Jemal A, Thomas A, Murray T, Thun M (2002). Cancer statistics. *CA Cancer J Clin*, 52(1):23-47.
 23. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. (2008). Cancer statistics. *CA Cancer J Clin*, 58(2):71-96.
 24. Hovland S, Arbyn M, Lie AK, Ryd W, Borge B, Berle EJ, et al. (2010). A comprehensive evaluation of the accuracy of cervical pre-cancer detection methods in a high-risk area in East Congo. *Br J Cancer*, 102(6):957-65.
 25. Bosch FX, de Sanjose S (2003). Chapter 1: Human papillomavirus and cervical cancer--burden and assessment of causality. *J Natl Cancer Inst Monogr*, 3-13.
 26. International Collaboration of Epidemiological Studies of Cervical Cancer (2006). Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. *Int J Cancer*, 119(5):1108-24.
 27. Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, Goodill A, et al. (2006). Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *Int J Cancer*, 118(6):1481-95.
 28. Moyer VA (2012). Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*, 156(12):880-91.
 29. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. (2012).

- American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin*, 62(3):147-72.
30. Campbell CMP, Menezes LJ, Paskett ED, Giuliano AR (2012). Prevention of invasive cervical cancer in the United States: past, present, and future. *Cancer Epidemiol Biomarkers Prev*, 21(9):1402-8.
 31. Arab M, Khayamzadeh M, Hashemi M, Hosseini M, Tabatabaeefar M, Anbiaee R, et al. (2010). Crude and age-specific incidence rate patterns for histopathologic subtypes of ovarian cancer in Iran. *Arch Iran Med*, 13(3):203-8.
 32. Arab M, Noghabaei G (2013). Ovarian cancer incidence in Iran and the world. *Reports of Radiotherapy and Oncology*, 1(2): 69-72.
 33. Myung SK, Ju W, Choi HJ, Kim SC (2009). Soy intake and risk of endocrine-related gynaecological cancer: a meta-analysis. *BJOG*, 116(13):1697-705.
 34. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, 127(12):2893-917.
 35. Rastogi T, Devesa S, Mangtani P, Mathew A, Cooper N, Kao R, et al. (2008). Cancer incidence rates among South Asians in four geographic regions: India, Singapore, UK and US. *Int J Epidemiol*, 37(1):147-60.
 36. AIHW, Cancer Australia (2012). *Gynaecological cancers in Australia: an overview*. Cancer series no. 70. Cat. no. CAN 66. Canberra, AIHW.
 37. Matsuda T, Marugame T, Kamo K-i, Katanoda K, Ajiki W, Sobue T (2010). Cancer incidence and incidence rates in Japan in 2004: based on data from 14 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project. *Jpn J Clin Oncol*, 40(12):1192-200.
 38. Parkin DM, Namboozee S, Wabwire-Mangen F, Wabinga HR (2010). Changing cancer incidence in Kampala, Uganda, 1991–2006. *Int J Cancer*, 126(5):1187-95.
 39. Sriplung H, Wiangnon S, Sontipong S, Sumitsawan Y, Martin N (2006). Cancer incidence trends in Thailand, 1989-2000. *Asian Pac J Cancer Prev*, 7(2):239-44.