て．第56回日本婦人科腫瘍学会学術講演会（宇都宮），2014年7月

10) 青木大輔：特別講演：子宮頸がん検診の課題とHPV検査の有効性評価．第57回徳島婦人科腫瘍研究会（徳島），2014年5月

11) 青木大輔（講師）：【実践】日常業務でご留意いただきたい点．がん検診受診向上指導事業全国がん検診従事者研修会（東京），2014年5月

12) 青木大輔（講師）：【理論】各精度管理指標（チェックリスト・プロセス指標）の読み方．がん検診受診向上指導事業全国がん検診従事者研修会（東京），2014年5月

研究分担者：伊藤潔

1) 及川洋恵，田勢亨，藤原しのぶ，渡辺康子，佐藤朋晴，小澤信義，伊藤潔，八重樫伸生：シンポジウム：　宮城県における現状と展望．第23回日本婦人科がん検診学会総会・学術集会(大阪)，2014年11月

2) 伊藤潔，及川洋恵，田勢亨：シンポジウム：細胞採取法の変化と精度、そして注意点．第53回日本臨床細胞学会秋期大会（下関），2014年11月

3) 永井智之，新倉仁，海法道子，徳永英樹，伸生：安全な縮小手術を目指した子宮体癌リンパ節郭清の検討．第56回日本婦人科腫瘍学会学術講演会(宇都宮)，2014年7月

4) 橋本千明，永井智之，徳永英樹，海法道子，永瀬智，高野忠夫，新倉仁，伊藤潔，渡部洋，八重樫伸生：当院におけるロボット支援腹腔鏡下子宮体癌手術の検討．第56回日本婦人科腫瘍学会学術講演会(宇都宮)，2014年7月

5) 伊藤潔：震災時ストレスとその後の生活環境変化が婦人科疾患に及ぼす影響の解析．東北大学災害科学国際研究所平成25年度特定プロジェクト研究成果報告会(仙台)，2014年7月

6) 田勢亨，伊藤潔，及川洋恵，小澤信義，八重樫伸生：宮城県の子宮がん検診の将来像．第55回日本臨床細胞学会総会（春期大会）(横浜)，2014年6月

7) 佐藤いずみ，永瀬智，鈴木史彦，永井智之，田中創太，海法道子，徳永英樹，高野忠夫，新倉仁，伊藤潔，渡部洋，八重樫伸生：子宮体部漿液性腺癌薬剤耐性株におけるマイクロRNAの網羅的発現解析およびmiR-200 familyの発現解析．日本産婦人科学会第66回学術講演会(東京)，2014年4月

8) 鈴木史彦，永瀬智，佐藤いずみ，宇都宮裕貴，海法道子，徳永英樹，伊藤潔，新倉仁，高野忠夫，渡部洋，笹野公伸，八重樫伸生：ABCトランスポーターからみた子宮体部漿液性腺癌の薬剤獲得耐性メカニズム．日本産婦人科学会第66回学術講演会(東京)，2014年4月

研究分担者：宮城悦子

1) Konno R, Hanley JBS, Miyagi E：HPV vaccine concerns in Japan - social and political background. EUROGIN2015 (European Research Organization on Genital Infection and Neoplasia) . February 2015,Sevilla,Spain

2) Konno R, Hanley JBS, Miyagi E：HPV vaccine concerns in Japan - public health and scientific background. EUROGIN 2015 (European Research Organization on Genital Infection and Neoplasia). February 2015, Sevilla, Spain

3) Asai-Sato M, Maruyama Y, Kawano A, Mogami T, Matsunaga T, Hirahara F, Miyagi E：Metastatic site predicts prognosis of FIGO stage IV epithelial ovarian carcinoma. 15th Biennial Meeting of the International Gynecologic Cancer Society (IGCS). November 2014, Melbourne, Australia.

4) 宮城悦子: シンポジウム 2 ホルモン治療と内膜細胞診—良性疾患から内膜癌治療後まで—. 第 55 回日本臨床細胞学会春期大会（横浜）,2014 年 6 月

研究分担者：齊藤英子

1) 齊藤英子：女性労働者の健康管理の実際. 東京都医師会産業医研修会 (東京), 2015 年 3 月
2) 齊藤英子：子宮頸がん検診チェックリストの内容について. 全国がん検診指導者講習会（東京）,2015 年 3 月
3) 齊藤英子：女性労働者の健康管理. 中央区医師会産業医研修会 (東京), 2014 年 7 月

研究分担者：斎藤　博

1) Saito H：　Screening for Colorectal Cancer.　The 6th National Conference on Health Management of the Chinese Medical Assosiation. November 2014, Beijing, China.
2) 斎藤　博：基調講演：がん検診の有効性評価と推奨作成の方法. 日本消化器がん検診学会近畿支部第 24 回保健衛生研修会 (大阪), 2015 年 2 月
3) 斎藤　博：免疫法便潜血検査（FIT）による大腸がん検診. 第 14 回大腸画像アカデミー（CIA）（東京）,2015 年 1 月
4) 斎藤　博：がん検診からみたがん登録資料の活用. がん登録推進法に関するシンポジウム(東京) ,2014 年 12 月
5) 斎藤　博：特別講演：がん対策としてのがん検診のあり方-成果をあげるために. 中国四国産業衛生学会(広島) , 2014 年 11 月
6) 斎藤　博：特別講演：消化器がん検診の世界の動向と我が国における展望. 第 22 回日本消化器関連学会週間(神戸) , 2014 年 10 月
7) 斎藤　博：乳がん検診の有効性評価. 第 15 回よこはま乳癌シンポジウム(横浜), 2014 年 9 月
8) 斎藤　博：特別講演：新しい検診技術の評価法方法—その原則と道筋. 第 43 回日本消化器がん検診学会近畿地方会(和歌山) , 2014 年 7 月
9) 斎藤　博：教育講演：受診者のための消化器がん検診とは？～組織型検診の必要性～. 第 53 回日本消化器がん検診学会総会(福井), 2014 年 6 月
10) 斎藤　博：特別発言：個別検診の現状とあるべき姿シンポジウム. 第 53 回日本消化器がん検診学会総会(福井) ,2014 年 6 月

研究分担者：渋谷大助

1) 渋谷大助：ABC 分類に分類に基づく胃がん検診・内視鏡検診について. 第 52 回日本消化器がん検診学会東北地方会（秋田）, 2014 年 7 月
2) 島田剛延, 千葉隆士, 加藤勝章, 渋谷大助：大腸がん検診における中間期癌の検討. 第 52 回日本消化器がん検診学会東北地方会（秋田）, 2014 年 7 月
3) 千葉隆士, 加藤勝章, 島田剛延, 渋谷大助：当センターで発見された胃底腺型胃癌 13 例の臨床病理学的特徴. 第 87 回日本消化器内視鏡学会総会（福岡）, 2014 年 5 月

研究分担者：濱島ちさと

1) Hamashima C: Breast cancer screening guideline development in Japan. The Symposium on Stomach Cancer Screening Revised Guideline. December 2014, Goyang, South Korea
2) Hamashima C: Stomach cancer screening guideline development in Japan. The Symposium on Stomach Cancer Screening Revised Guideline. December 2014, Seoul, South Korea
3) Hamashima C : Sensitivities of endoscopic

Screening for gastric cancer by the incidence method. The 2014 Preventing Overdiagnosis Conference. September 2014, Oxford, UK.

4) Hamashima C :How should we resolve local problems in the guidelines for cancer screening programs. Guidelines International Network Conference 2014. August 2014,Melbourne, Australia
5) Hamashima C, Rossi PG:Types of outcomes (Intermediate / Disease-oriented vs. Patient-oriented) used in guideline development by various guideline-making bodies around the world various guideline-making bodies around the world.Health Technology Assessment International 11th Annual Meeting. June 2014, Washington DC, USA.
6) Hamashima C, Shabana M, Okamoto M, Osaki Y, Kishimoto T: Comparison of survival between patients with screen-detected and interval gastric cancer related to endoscopic screening. Health Technology Assessment International 11th Annual Meeting. June 2014,Washington DC, USA.
7) Hamashima C: Survival analysis for gastric cancer detected by endoscopic screening. International Society for Pharmacoeconomics and Outcomes Research. June 2014, Montreal, Canada
8) 謝花典子, 濱島ちさと, 吉中正人：鳥取県, 米子市における胃内視鏡検診の現状と問題点［パネルディスカッション 10 対策型内視鏡検診の現状と問題点］. 第 52 回日本消化器がん検診学会大会（JDDW 2014 Kobe）(神戸), 2014 年 10 月
9) 岸知輝, 濱島ちさと：胃がん・大腸がん・肺がん検診における高齢者高受診率への影響要因に関する検討. 第 52 回日本医療・病院管理学会学術総会(東京), 2014 年 9 月
10) 岸知輝, 濱島ちさと：がん検診における女性高齢者高受診率への影響要因に関する検討. 第 73 回日本公衆衛生学会総会(栃木), 2014 年 7 月
11) 濱島ちさと：特別講演「胃がん内視鏡検査のエビデンス」. 第 43 回日本消化器がん検診学会近畿地方会(和歌山), 2014 年 7 月

研究分担者：雑賀公美子

1) 雑賀公美子:シンポジウム：肺がん死亡と罹患の動向.第 55 回日本肺癌学会学術集会　第 29 回肺がん集検セミナー（京都）, 2014 年 11 月

H. 知的財産権の出願・登録状況

1. 特許取得
   なし
2. 実用新案登録
   なし
3. その他
   なし

Ⅲ. 学会等発表実績

委託業務題目「子宮頸がん検診における細胞診とHPV検査併用の有用性に関する研究」

1．学会等における口頭・ポスター発表

発表した成果(発表題目、口頭・ポスター発表の別)	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
子宮頸がん検診チェックリストの遵守向上にむけて（講演）	青木大輔	全国がん検診指導者講習会	2015年3月	国内
子宮頸がん検診　HPV検診について/HPV検診の全国の実態について（講演）	青木大輔	全国がん検診指導者講習会	2015年3月	国内
子宮頸がん検診と精度管理（共催セミナー）	青木大輔	第29回宮城県臨床細胞学会共催 セミナー	2015年2月	国内
子宮頸がん検診の課題とHPV検査の有効性評価（特別講演）	青木大輔	子宮がん検診従事者講習会	2015年1月	国内
子宮頸がん検診の課題とHPV検査の有効性評価（特別講演）	青木大輔	岡山県産婦人科専門医会	2015年1月	国内
子宮頸がん検診の課題とHPV検査の有効性評価（特別講演）	青木大輔	第3回滋賀県産科婦人科医会総会	2014年12月	国内
子宮頸がん検診と精度管理のあり方（特別講演）	青木大輔	第31回日本臨床細胞学会北陸支部連合学術集会	2014年9月	国内
子宮頸がん検診はなぜ受けた方が良いのか．子宮頸がん予防のための市民公開シンポジウム(特別講演)	青木大輔	日本臨床細胞学会石川県支部主催	2014年9月	国内
子宮頸がん検診における細胞診とHPV検査併用の有用性に関する研究」を開始して(シンポジウム)	青木大輔	第56回日本婦人科腫瘍学会学術講演会	2014年7月	国内
子宮頸がん検診の課題とHPV検査の有効性評価（特別講演）	青木大輔	第57回徳島婦人科腫瘍研究会	2014年5月	国内
【実践】日常業務でご留意いただきたい点（講師）	青木大輔	全国がん検診従事者研修会	2014年5月	国内
【理論】各精度管理指標（チェックリスト・プロセス指標）の読み方（講師）	青木大輔	全国がん検診従事者研修会	2014年5月	国内
宮城県における現状と展望（口頭）	及川洋恵,田勢亨,藤原しのぶ,渡辺康子,佐藤朋晴,小澤信義,伊藤潔,八重樫伸生	第23回日本婦人科がん検診学会 総会・学術集会	2014年11月	国内
HPV vaccine concerns in Japan－social and political back ground（口頭）	Konno R, Hanley JBS, Miyagi E	EUROGIN 2015 (European Research Organization on Genital Infection and Neoplasia)	2015年2月	国外
HPV vaccine concerns in Japan－public health and scientific background（口頭）	Konno R, Hanley JBS, Miyagi E	EUROGIN 2015 (European Research Organization on Genital Infection and Neoplasia)	2015年2月	国外
Metastatic site predicts prognosis of FIGO stage IV epithelial ovarian carcinoma（ポスター）	Asai-Sato M, Maruyama Y, Kawano A, Mogami T, Matsunaga T, Hirahara F, Miyagi E	15th Biennial Meeting of the International Gynecologic Cancer Society (IGCS)	2014年11月	国外

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Usefulness of a novel biomarker based on plasma amino acid profile for early detection of ovarian cancer（ポスター）	Maruyama Y, Miyagi E, Numazaki R, Nakanishi T, Kataoka F, Saruki N, Yamamoto H, Shinhara A, Muramatsu T, Takasu M, Ito N, Yoshida N, Yamakado M, Aoki D, Hirahara F	15th Biennial Meeting of the International Gynecologic Cancer Society (IGCS)	2014年11月	国外
ホルモン治療と内膜細胞診—良性疾患から内膜癌治療後まで—（シンポジウム）	宮城悦子	第55回日本臨床細胞学会春期大会	2014年6月	国内
女性労働者の健康管理の実際（口頭）	齊藤英子	東京都医師会産業医研修会	2015年3月	国内
子宮頸がん検診チェックリストの内容について（口頭）	齊藤英子	全国がん検診指導者講習会	2015年3月	国内
「女性労働者の健康管理」（口頭）	齊藤英子	中央区医師会産業医研修会	2014年7月	国内
がん検診の有効性評価と推奨作成の方法（基調講演）	斎藤　博	日本消化器がん検診学会近畿支部第24回保健衛生研修会	2015年2月	国内
免疫法便潜血検査（FIT）による大腸がん検診	斎藤　博	第14回大腸画像アカデミー（CIA）	2015年1月	国内
がん検診からみたがん登録資料の活用	斎藤　博	がん登録推進法に関するシンポジウム	2014年12月	国内
がん対策としてのがん検診のあり方成果をあげるために（特別講演）	斎藤　博	中国四国産業衛生学会	2014年11月	国内
Screening for Colorectal Cancer.	斎藤　博	The 6th National Conference on Health Management of the Chinese Medical Assosiation	2014年11月	国内
消化器がん検診の世界の動向と我が国における展望（特別講演）	斎藤　博	第22回日本消化器関連学会週間	2014年10月	国内
乳がん検診の有効性評価（口頭）	斎藤　博	第15回よこはま乳癌シンポジウム	2014年9月	国内
新しい検診技術の評価法方法—その原則と道筋（特別講演）	斎藤　博	第43回日本消化器がん検診学会 近畿地方会	2014年7月	国内
受診者のための消化器がん検診とは？～組織型検診の必要性～（教育講演）	斎藤　博	第53回日本消化器がん検診学会 総会	2014年6月	国内
個別検診の現状とあるべき姿シンポジウム（特別発言）	斎藤　博	第53回日本消化器がん検診学会 総会	2014年6月	国内
Types of outcomes (Intermediate / Disease-oriented vs. Patient-oriented) used in guideline development by various guideline-making bodies around the world various guideline-making bodies around the world（口頭）	Hamashima C, Rossi PG	Health Technology Assessment International 11th Annual Meeting	2014年6月	国外

2．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Trends in gynecologic cancer mortality in East Asian regions.	Lee JY, Kim EY, Jung KW, Shin A, Chan KK, Aoki D, Kim JW, Low JJ, Won YJ	J GynecolOncol.	2014年7月	国外
Human papillomavirus genotype distribution in cervical intraepithelial neoplasia grade 2/3 and invasive cervical cancer in Japanese women.	Azuma Y, Kusumoto-Matsuo R, Takeuchi F, Uenoyama A, Kondo K, Tsunoda H, Nagasaka K, Kawana K, Morisada T, Iwata T, Aoki D, Kukimoto I	Japanese journal of clinical oncology	2014年8月	国内
わが国の子宮頸がん罹患の実態－子宮頸がん罹患は“若年化”しているのか？	齊藤英子，青木大輔	医学のあゆみ	2014年11月	国内
What is the most effective strategy for improving the cancer screening rate in Japan?	Sano H, Goto R, Hamashima C	Asian Pac J Cancer Prev.	2014年5月	国外

Ⅳ. 研究成果の刊行物別冊

Original Article

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Trends in gynecologic cancer mortality in East Asian regions

Jung-Yun Lee[1], Eun-Yang Kim[2], Kyu-Won Jung[2], Aesun Shin[2,3], Karen K. L. Chan[4], Daisuke Aoki[5], Jae-Weon Kim[1], Jeffrey J. H. Low[6], Young-Joo Won[2]

[1]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul; [2]Cancer Registration and Statistics Branch and [3]Molecular Epidemiology Branch, National Cancer Center, Goyang, Korea; [4]Department of Obstetrics and Gynecology, University of Hong Kong, Hong Kong; [5]Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan; [6]Department of Obstetrics and Gynecology, National University Hospital, Singapore

Objective: To evaluate uterine and ovarian cancer mortality trends in East Asian countries.

Methods: For three Asian countries and one region (Japan, Korea, Singapore, and Hong Kong), we extracted number of deaths for each year from the World Health Organization (WHO) mortality database, focusing on women ≥20 years old. The WHO population data were used to estimate person-years at risk for women. The annual age-standardized, truncated rates were evaluated for four age groups. We also compared age-specific mortality rates during three calendar periods (1979 to 1988, 1989 to 1998, and 1999 to 2010). Joinpoint regression was used to determine secular trends in mortality. To obtain cervical and uterine corpus cancer mortality rates in Korea, we re-allocated the cases with uterine cancer of unspecified subsite according to the proportion in the National Cancer Incidence Databases.

Results: Overall, uterine cancer mortality has decreased in each of the Asian regions. In Korea, corrected cervical cancer mortality has declined since 1993, at an annual percentage change (APC) of −4.8% (95% confidence interval [CI], −5.3 to −4.4). On the other hand, corrected uterine corpus cancer mortality has abruptly increased since 1995 (APC, 6.7; 95% CI, 5.4 to 8.0). Ovarian cancer mortality was stable, except in Korea, where mortality rates steadily increased at an APC of 6.2% (95% CI, 3.4 to 9.0) during 1995 to 2000, and subsequently stabilized.

Conclusion: Although uterine cancer mortality rates are declining in East Asia, additional effort is warranted to reduce the burden of gynecologic cancer in the future, through the implementation of early detection programs and the use of optimal therapeutic strategies.

Keywords: Mortality, Ovarian neoplasms, Time trends, Uterine neoplasms

INTRODUCTION

Uterine and ovarian cancers are responsible for 10% and 2% of all cancer deaths worldwide, respectively, causing an estimated 489,000 deaths annually. Indeed, cancers of the cervix and ovary are respectively the fifth and seventh most common causes of death from cancer in Asia [1]. It has been estimated that the number of deaths due to uterine and ovarian cancer will reach approximately 347,100 by 2020 in Asia alone [1].

Mortality from cancers of the uterus and ovaries has been declining in Western countries for decades [2-5]. The incidence and mortality rates of gynecologic cancers in Asian countries differ from those in Western countries. Cervical cancer remains a major health problem in East Asia, although incidence rates have been decreasing [6,7]. In recent decades, East Asia has experienced rapid economic growth and social transformation. These socioeconomic changes have resulted in improved treatments and advances in screening. In particular, cervical

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Supplementary material for this article can be found at www.ejgo.org.

Correspondence to Young-Joo Won
Cancer Registration and Statistics Branch, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 410-769, Korea. E-mail: astra67@ncc.re.kr

cancer screening programs were introduced as early as the 1980s, and routine gynecologic examination has become popular in East Asian countries. In addition, behavioral factors such as delayed and reduced childbearing, use of hormone-replacement therapy, and reduced physical activity have also become more prevalent among East Asian women. These reproductive and lifestyle changes are associated with higher incidences of uterine corpus and ovarian cancer [8,9]. However, there are few studies on temporal trend in gynecologic cancer mortality in East Asian regions.

Specific trends in gynecologic cancer mortality differ widely by geographic region, age group, and time period. The aim of this study was to report and compare secular trends of uterine and ovarian cancer in Hong Kong, Japan, Korea, and Singapore. We designed our study to fully investigate the different cancer trends that are present in different regions, age groups, and time periods. In addition, we used national cancer incidence data from Korea to correct cervical and uterine corpus cancer mortality rates, which are otherwise substantially biased by missing cancer subsite information in mortality databases.

MATERIALS AND METHODS

1. Data source

The World Health Organization (WHO) obtains data on deaths by age, sex, and cause of death, as reported annually by member states based on their civil registration systems. WHO compiles these data in the WHO mortality database. The 4 East Asian regions with data available for longest period were Japan, Singapore, Korea, and Hong Kong. The coverage of cause of death in the registration systems had increased over 85% since 1990. We extracted annual uterine cancer mortality data for women aged ≥20 years in Hong Kong (1966 to 2009), Japan (1955 to 2010), Korea (1985 to 2010), and Singapore (1966 to 2009) from the WHO mortality database [10]. Ovarian cancer mortality data were also extracted from the same database for Hong Kong (2001 to 2009), Japan (1979 to 2010), Korea (1985 to 2010), and Singapore (1979 to 2009). To obtain estimates of person-years at risk, we used WHO population data [10].

Uterine cancer mortality was defined as deaths in the WHO mortality database that were coded as C53 (uterine cervical cancer), C54 (uterine corpus cancer), or C55 (unspecified uterine cancer), according to the International Statistical Classification of Disease and Related Health Problems, 10th revision (ICD-10) [11]. Assessment of ovarian cancer mortality was based on the ICD-10 code C56. Uterine cervical cancer and uterine corpus cancer have different etiologies and prognoses, and the ICD-10 code C55 (which is, "uterus, unspecified site") makes it difficult to determine the exact cervical and uterine corpus cancer mortality trends [12-15]. To solve this problem, we corrected the number of cervical cancer and uterine corpus cancer deaths using death certificate data during 1993 to 2010 from the Statistics Korea and data on cases of unspecified uterine cancer from the National Cancer Incidence Databases (NCIDB) of Korea [16]. To obtain a corrected count of cervical cancer deaths, we multiplied the total number of registered unspecified uterine cancer deaths (ICD-10: C55) by the proportion of registered, incident uterine cancer cases that were specifically coded as cervical cancer (ICD-10: C53). We then added the result to the deaths known to cause cervical cancer, thereby achieving at a corrected total of cervical cancer deaths. Analogous methods were applied to obtain a corrected estimate of uterine corpus deaths. The details of this correction procedure have been described in a previous report [17]. As the personal identification number used for data was deleted, this study did not require the ethical approval of the Institutional Review Board.

2. Statistical analysis

Annual age-standardized mortality rates were estimated using the world standard population [18]. Rates were age-standardized to the Segi's 1960 world standard, using the direct method. Annual percentage change (APC) was used to compare changes in gynecologic cancer mortality by age group within each time period. We also compared age-specific mortality rates across three calendar periods (1979 to 1988, 1989 to 1998, and 1999 to 2010). Trends in gynecologic cancer mortality were assessed using joinpoint regression model. This analysis was performed using the Joinpoint software ver. 3.5.3 from the Surveillance Research Program of the US National Cancer Institute (Bethesda, MD, USA) [19]. The joinpoint method identifies the best-fit lines through several years of data. The method proceeds by fitting a series of joined lines, which are straight on a logarithmic scale, to trends in the annual age-adjusted cancer mortality rates. The line segments are joined at points called joinpoints, each of which indicates a statistically significant change in trend.

RESULTS

1. Uterine and ovarian cancer mortality rates

Table 1 presents age-standardized uterine and ovarian cancer mortality rates per 100,000 women for each region. In general, mortality rates due to uterine cancer are higher than those due to ovarian cancer. During 1966 to 2009, Singapore

experienced the highest uterine cancer mortality rates among the four regions. In 2009, Korea had the lowest uterine cancer mortality rates among these regions. Between 2000 and 2009, Singapore had the highest ovarian cancer mortality rates. Furthermore, Korea and Hong Kong had the lowest ovarian cancer mortality rates.

2. Trends in uterine cancer mortality rates

Fig. 1A presents overall trends in uterine cancer mortality rates for each of the four East Asian regions. When certified uterine cancer deaths (ICD-10: C53, C54, and C55) are plotted, a significantly decreasing trend is evident throughout the entire study period.

Indeed, overall, uterine cancer mortality rates significantly declined across the study period for each of the four regions (**Table 2**, **Fig. 1A**). During the entire study period, Singapore had the highest uterine cancer mortality of the four regions, although there has been a trend of decreasing uterine cancer mortality in Singapore since 1966 (APC, −2.3%; 95% confidence interval [CI], −2.6 to −2.1). In Hong Kong, there was an overall trend of decrease of uterine cancer mortality since at least 1966 (APC, −4.0%; 95% CI, −4.6 to −3.5). More rapid reductions in uterine cancer mortality occurred in Japan between 1970 and 1990 (APC, −4.9%; 95% CI, −5.1 to −4.8) and in Korea between 1994 and 2010 (APC, −4.4%; 95% CI, −4.8 to −4.0). After 1990, however, the trend of decreased mortality began to slow in Japan. In the three Asian countries and Hong Kong, uterine cancer mortality rates have been declining significantly in almost all age groups. **Fig. 2A** presents changes in mortality rates by age group. Interestingly, the uterine cancer mortality rates tended to increase among women 20 to 34 years of age in Japan and among women over 70 years of age in Korea.

3. Trends in ovarian cancer mortality rate

Overall, no significant changes in ovarian cancer mortality were observed, except in Korea and Japan (**Table 2**). In Korea, ovarian cancer mortality rates significantly increased (APC,

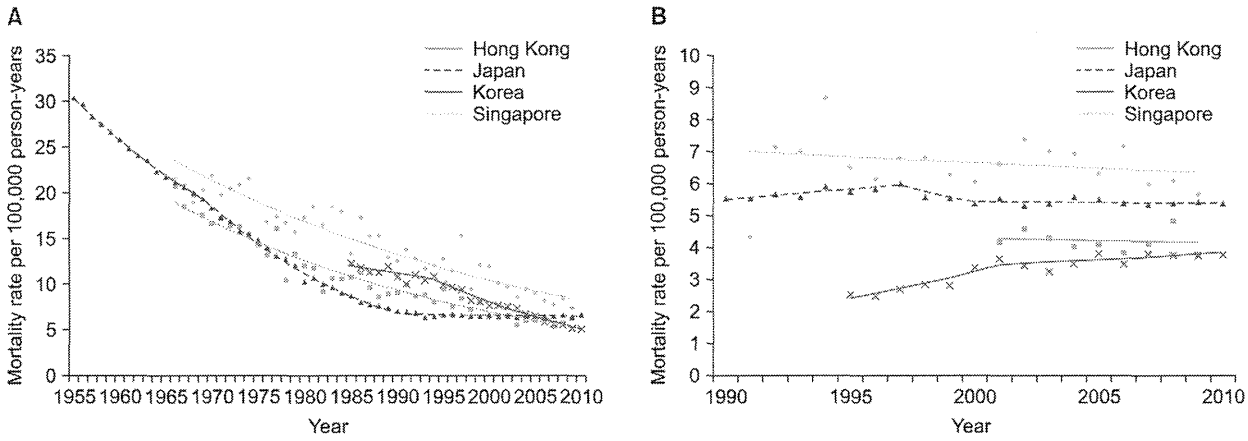

Fig. 1. Trends in uterine* and ovarian cancer mortality rates (age-standardized, women ≥20 years) obtained by joinpoint regression for 4 female Asian populations. (A) Uterine cancer. (B) Ovarian cancer. *Uterine cancer includes cervix uteri (International Statistical Classification of Disease and Related Health Problems, 10th revision [ICD-10] code C53); corpus uteri (ICD-10 code C54); and uterus, unspecified (ICD-10 code C55).

Table 1. Gynecologic cancer deaths and age-adjusted mortality rates among women ≥20 years according to region and calendar year

Country	Period	Age-adjusted uterine cancer* death rate (≥20 yr) per 100,000 women					Period	Age-adjusted ovarian cancer death rate (≥20 yr) per 100,000 women			
		1970	1980	1990	2000	2009		1980	1990	2000	2009
Hong Kong	1966–2009	16.7	12.1	9.0	6.3	6.0	2001–2009	–	–	–	3.8
Japan	1955–2010	18.4	11.3	6.9	6.5	6.2	1979–2010	4.6	5.5	5.3	5.3
Korea	1985–2010	–	–	10.9	7.8	5.3	1985–2010	–	–	3.4	3.8
Singapore	1966–2009	21.7	17.1	12.5	11.9	7.2	1979–2009	–	–	6.1	5.7

*Uterine cancer includes cervix uteri (International Statistical Classification of Disease and Related Health Problems, 10th revision [ICD-10] code C53); corpus uteri (ICD-10 code C54); and uterus, unspecified (ICD-10 code C55).

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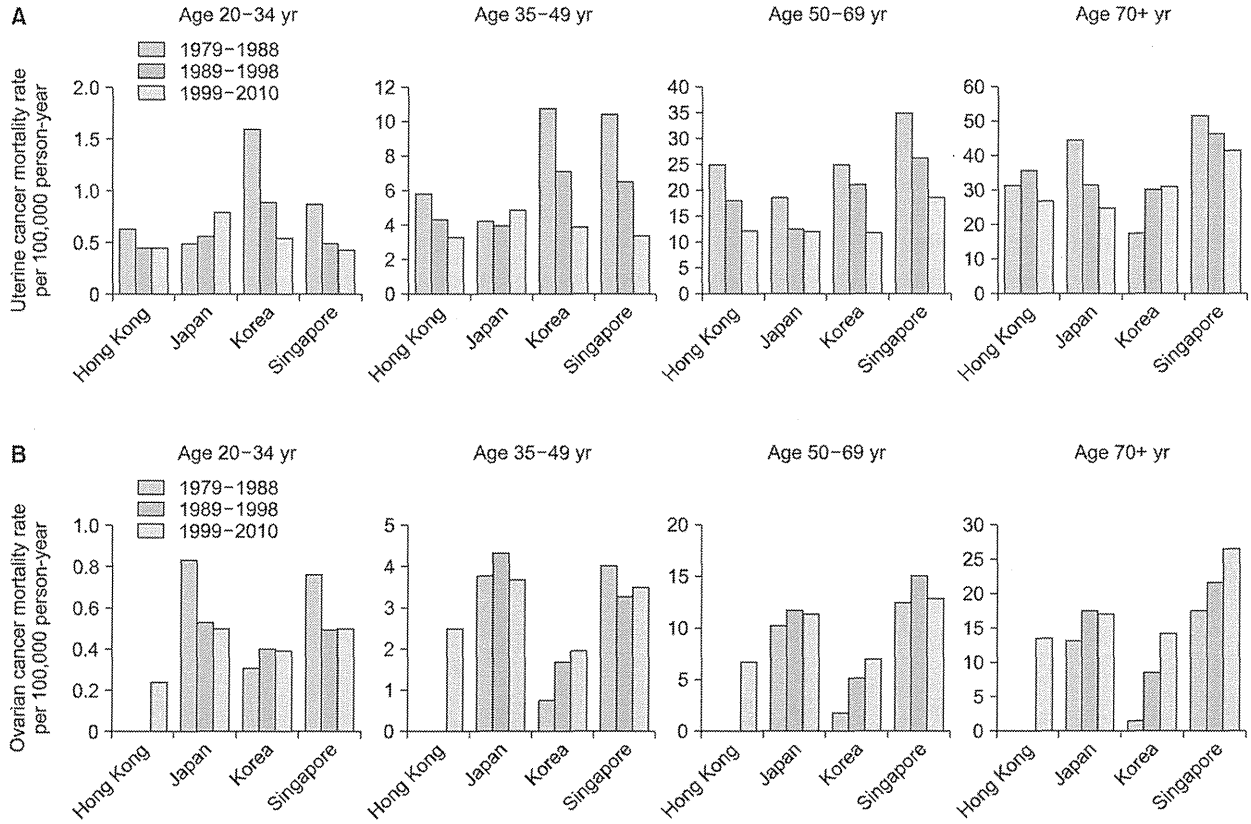

Fig. 2. Uterine and ovarian cancer mortality by age group, period, and region. (A) Uterine cancer. (B) Ovarian cancer. *Uterine cancer includes cervix uteri (International Statistical Classification of Disease and Related Health Problems, 10th revision [ICD-10] code C53); corpus uteri (ICD-10 code C54); and uterus, unspecified (ICD-10 code C55).

Table 2. Estimated annual percentage change of gynecologic cancer death rates, with 95% CIs

	Trend 1			Trend 2			Trend 3		
	Year	APC	95% CI	Year	APC	95% CI	Year	APC	95% CI
Uterine cancer*									
Hong Kong	1966–2009	−4.0†	−4.6, −3.5						
Japan	1955–1970	−3.2†	−3.4, −3.0	1970–1990	−4.9†	−5.1, −4.8	1990–2010	−0.2†	−0.4, −0.1
Korea	1985–1994	−1.4†	−2.3, −0.5	1994–2010	−4.4†	−4.8, −4.0			
Singapore	1966–2009	−2.3†	−2.6, −2.1						
Ovarian cancer									
Hong Kong	2001–2009	−0.4	−3.1, 2.3						
Japan	1990–1997	1.1†	0.4, 1.8	1997–2000	−3.1	−7.9, 2.0	2000–2010	0.0	−0.4, 0.4
Korea	1995–2000	6.2†	3.4, 9.0	2000–2010	1.1	0.0, 2.3			
Singapore	1991–2009	−0.5	−1.6, 0.5						

APC, annual percentage change; CI, confidence interval.
*Uterine cancer includes cervix uteri (International Statistical Classification of Disease and Related Health Problems, 10th revision [ICD-10] code C53); corpus uteri (ICD-10 code C54); and uterus, unspecified (ICD-10 code C55). †The APC is significantly different from zero ($p<0.05$).

Table 3. Calculation of the corrected cervical cancer and uterine corpus cancer deaths in Korea (1993 to 2010)

Year	No. of deaths by cause of death*						Proportion among all cancer (%)		Corrected deaths	
	Uterine, cervix (C53) (A)	Uterine, corpus (C54) (a)	Uterine, unspecified (C55)							
			Uterine, unspecified (C55) (B)	Registered as cancer incidence cases†						
				Registered as cancer of all sites (C)*	Uterine, cervix (C53) (D)	Uterine, corpus (C54) (d)	Uterine, cervix (E)=(D)/(C)×100	Uterine, corpus (e)=(d)/(C)×100	Uterine, cervix (G)=(A)+(B)×(E)/100	Uterine, corpus (g)=(a)+(B)×(e)/100
1993	416	4	944	542	419	22	77.3	4.1	1,125	50
1994	548	8	925	575	450	27	78.3	4.7	1,268	55
1995	544	29	839	576	448	26	77.8	4.5	1,192	69
1996	656	29	714	483	382	26	79.1	5.4	1,213	65
1997	680	30	709	507	384	28	75.7	5.5	1,216	67
1998	606	37	665	511	395	31	77.3	6.1	1,116	78
1999	690	38	593	476	345	40	72.5	8.4	1,118	85
2000	726	50	534	431	328	33	76.1	7.7	1,134	87
2001	807	56	495	419	313	37	74.7	8.8	1,177	96
2002	1,009	120	252	166	104	17	62.7	10.2	1,168	143
2003	1,111	146	140	94	54	9	57.4	9.6	1,192	157
2004	1,078	125	122	72	28	14	38.9	19.4	1,135	144
2005	1,066	151	128	84	42	22	50.0	26.2	1,133	183
2006	1,002	146	92	60	28	11	46.7	18.3	1,045	163
2007	987	165	89	63	22	21	34.9	33.3	1,019	195
2008	954	210	97	77	41	21	53.2	27.3	1,007	236
2009	949	221	87	66	24	13	36.4	19.7	982	238
2010	956	222	94	67	25	23	37.3	34.3	995	249
Total	14,785	1,787	7,519	5,269	3,832	421	61.5	14.1	20,235	2,360

*National death certificate data, Statistics Korea. †Korea National Cancer Incidence Databases.

2.6%; 95% CI, 1.8 to 3.5) across the entire period (1995 to 2010). Especially, rapid increase in ovarian cancer mortality occurred during 1995 to 2000 (APC, 6.2%; 95% CI, 3.4 to 9.0). In Japan, ovarian cancer mortality rates began to increase during 1990 to 1997 (APC, 1.1%; 95% CI, 0.4 to 1.8). Subsequently, the mortality rates appeared to decline, but the reduction was not statistically significant. **Fig. 1B** presents overall trends in ovarian cancer mortality rates for the four regions that were investigated in the current study. **Fig. 2B** presents ovarian cancer mortality by age group, again for each of these four regions. Among women older than 70 years, prominent increasing trends were found in Japan, Korea, and Singapore.

4. Corrected trends in uterine cervix and corpus mortality rates in Korea

Table 3 presents our method of correcting the number of annual deaths due to uterine cervix and uterine corpus cancer, based on the NCIDB in Korea. The proportion of all uterine cancer deaths with unspecified subtype was the highest in 1993 (69.2%) and gradually diminished until 2010 (7.4%), which suggest significant improvement of quality of the death certificate over the past two decades.

Fig. 3 presents the overall trends in cervical and uterine corpus cancer mortality rates in Korea, using the corrected estimates of mortality. After corrections, it was evident that overall age-standardized cervical cancer mortality rates significantly declined during 1993 to 2010 (APC, −4.8%; 95% CI, −5.3 to −4.4). On the other hand, increase in corrected uterine corpus mortality rates were observed during 1995 to 2010 (APC, 6.7%; 95% CI, 5.4 to 8.0). **Suppl. Table 1** and **Fig. 1** present changes in mortality rates by age group. Whereas cervical cancer mortality rates have been declining significantly in almost all age groups, a nonsignificant trend of increasing mortality rates was found among women 20 to 34 years of age after 2004 (APC, 6.4%; 95% CI, −2.6 to 16.2).

DISCUSSION

In the present study, we compared and assessed secular

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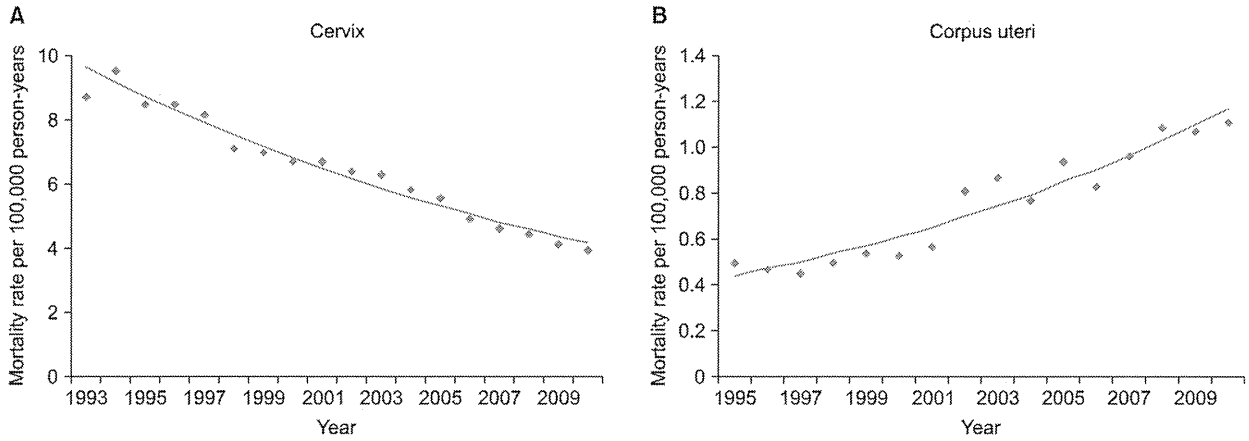

Fig. 3. Corrected trends in cervical and uterine corpus cancer mortality in Korea (age-standardized, women ≥20 years) obtained by joinpoint regression. (A) Cervix. (B) Corpus uteri.

trends of gynecologic cancer mortality among four East Asian female populations, including specific examinations of age-specific mortality. In some European countries, over 70% of deaths from uterine cancer were allotted to "uterus unspecified" during 1960; however, this proportion had reduced to 30% by around 1995 [14]. In Korea, a proportion of classification of "uterus, unspecified" has decreased from 69.1% of uterine cancer deaths in 1993 to 18.4% of uterine cancer deaths in 2002 [17]. We corrected the counts of cervical cancer and uterine corpus cancer deaths by referencing NCIDB in Korea. Our correction procedure allowed us to estimate separate mortality rates for cervical and uterine corpus cancer. After correcting the WHO mortality data, we found that cervical cancer mortality rates had decreased since at least 1993. On the other hand, the corrected data also revealed a trend of increasing uterine corpus cancer mortality rates, which began during or before 1995.

Considering the similar cancer mortality patterns that we observed across the four Asian regions, it is likely that the majority of deaths registered as "uterus, unspecified site" are the result of cervical cancer, as we found in Korea. Therefore, the overall trend of declining uterine cancer mortality might be attributed to the specific decline in cervical cancer mortality. This finding is also confirmed by gynecologic cancer mortality statistics from the Singapore Cancer Registry (**Suppl. Fig. 2**) [20].

Cervical cancer mortality has been decreasing in most developed countries, possibly as a result of early diagnosis and improved treatments [12,21-23]. Two causes likely explain the majority of the trend of decreasing cervical cancer mortality that we found in the four East Asian regions. First, mortality reductions have resulted from trends of decreasing incidence. Particularly, cervical cancer incidence has decreased as lesions have been detected increasingly early, when they are precancerous. The value of cervical cancer screening programs is widely accepted, and national screening programs for cervical cancer have been introduced in Japan (1983), Korea (1988), Taiwan (1995), and Hong Kong (2004). Cervical cancer screening programs have led to decreases in the incidence of invasive cervical cancer in Japan [7], Korea [24], and Taiwan [25]. Further, successful treatment of precancerous lesions (such as intraepithelial neoplasm and carcinoma *in situ*) has resulted in a decreasing trend of invasive cervical cancer. Second, mortality reductions have resulted from advances in cervical cancer therapy, particularly the introduction of concurrent chemoradiation. In 1999, Keys et al. [26] demonstrated that concurrent chemoradiation is associated with better outcomes than radiation alone. Since then, concurrent chemoradiation has been accepted as a standard treatment in the form of either a primary treatment or adjuvant treatment after surgery.

A worrying finding of our study was that uterine cancer mortality rates appeared to be increasing among women <50 years in Japan. Most deaths from uterine cancer among women <50 years can be attributed to cervical cancers [14]. Accordingly, the trend of increasing uterine cancer among younger women in Japan may reflect the trend of increasing cervical cancer incidence in this same population [27-29]. In Korea, cervical cancer mortality rates tended to increase among women 20 to 34 years of age after 2004. Although this increase was not statistically significant (APC, 6.4%; 95% CI, −2.6 to 16.2), further efforts are required to improve the outcomes in this young age group.

Despite decreasing trends of cervical cancer mortality in

Asian countries, cervical cancer still has the second greatest incidence of all cancers among young women in East Asian countries [30]. Because cervical cancer has been demonstrated to be a preventable disease, additional efforts are warranted in East Asia. Specific strategies to prevent cervical cancer are required, including both primary and secondary preventive measures, such as human papillomavirus vaccination and national cervical cytology screening.

Although the trends of decreasing cervical cancer mortality are promising, our results show an abrupt increase in uterine corpus cancer mortality in Korea. This finding should be interpreted in the context of the abruptly increasing incidence of endometrial cancer in East Asia [7,31]. Uterine cancer is mainly diagnosed among postmenopausal women. Endometrial cancer constitutes the majority of cases, while uterine sarcoma is a rare malignancy that accounts for approximately 3% of all uterine cancers [32]. Although endometrial cancer is the most common malignancy of the female genital tract in Western countries, its incidence is rather low in East Asia [33]. Changes in risk factors, especially those associated with lifestyle, have been suggested as the principal cause of the increasing endometrial cancer incidence in East Asia [31]. In particular, one of the established risk factors for endometrial cancer is an increase in unopposed estrogen, which can result from obesity or diabetes mellitus. Based on the trend of increasing uterine corpus cancer incidence that has been reported [34], we suggest that the burden of mortality from uterine corpus cancer will also increase in East Asia within the near future.

A troubling finding of the present study was the persistently high pattern of ovarian cancer mortality rates in Hong Kong, Japan, and Singapore, along with the trend of increased mortality in Korea. In Korea, increases in ovarian cancer mortality rates were found for all age groups, except women 20 to 34 years of age. In Japan and Singapore, it appeared that past age-specific decreases ovarian cancer mortality were reversing.

In the United States, ovarian cancer mortality rates leveled off during the 1980s and declined during the 1990s, with an annual average change of 0.9% [35]. Three or more years of oral contraceptive use reduces the risk of ovarian cancer, and consequently, widespread use of oral contraceptives has contributed to the trend of declining mortality [36]. Although oral contraceptives have long been the most common method of contraception for women in the United States and European countries, the rate of contraceptive use in East Asia has been substantially lower. The proportion of the Chinese women who used pills was only 2.1% in 2006 [37], while approximately 30% of European women used oral contraceptives in 2003 [38]. Therefore, the protective effects of oral contraceptives only contribute minimally to population cancer rates in Korea. In addition, early age at menarche, late age at menopause, lower fertility rates, and other reproductive factors are also risk factors for ovarian cancer. Korea and Japan are among the countries that have the lowest total fertility rates. Indeed, the total fertility rate has remained below 1.3 in Korea since 2005 [39]. East Asia underwent rapid industrialization during the 1960s, and Asian women born after the 1960s have tended to undergo menarche at earlier, delay childbirth, and have reduced fertility rates. The very low fertility rate and the low use of oral contraceptives will presumably sustain the trend of increasing ovarian cancer rates in East Asia [40]. Considering that epithelial ovarian cancer is mostly found at an advanced stage, and has low survival rates, we expect the burden from ovarian cancer to increase in Asian countries. Therefore, improvements to optimal cytoreductive surgery and new therapeutic modalities are urgently required for ovarian cancer.

In the current study, most of the deaths due to ovarian cancer occurred in women older than 50 years. Mortality rates for women over 70 years of age showed an increasing trend in Asian countries, while rates for women younger than 35 years remained stable or decreased. The present study shows that mortality rates for women over 70 years of age have doubled in past 20 years in Korea and Singapore. Considering that ovarian cancer incidence has not increased abruptly during the same period (and indeed has remained stable) [34], the increasing trend of mortality in old age groups could be the result of under treatment of ovarian cancer [41]. Elderly patients have been less likely to undergo standard treatments for ovarian cancer, such as optimal debulking surgery, and have been less likely to complete chemotherapy. Indeed, it has been reported that, among patients who do receive optimal treatment, old age is not an independent poor prognostic factor [42].

The main limitation to this study is the presence of "uterus, unspecified site" as the cause of death on many death certificates. This made it impossible to evaluate cervical and uterine corpus cancer trends separately, based on the WHO mortality database alone. We corrected Korean cervical and uterine corpus cancer mortality rates using Korea NCIDB. However, we were unable to correct the mortality rates for other regions. In addition, this study is limited by several problems that are inherent to the WHO mortality database. Specifically, some mortality data are incomplete and the database does not include full coverage of all deaths in every region. Inaccuracies in death registration coverage and cross-national differences in coding practices should be considered when applying the results of this study.

In conclusion, uterine cancer mortality has decreased in Hong Kong, Japan, Korea, and Singapore. After correcting the

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cervical and uterine corpus mortality rates in Korea, a significant trend of decreasing mortality was found for cervical cancer, and a trend of rapidly increasing mortality was observed for uterine corpus cancer. The most important contributor to declines in cervical cancer mortality has been the early diagnosis and improved treatments. Overall, ovarian cancer mortality was stable in East Asia, with the exception of Korea. A continuing increase in ovarian cancer mortality should be expected because of trend of increasing incidence in East Asia. Preventive measures, early detection programs, and standard use of optimal therapeutic strategies are urgently required, particularly for older age groups. Such improvements could include obesity control programs, increases in fertility, wider oral contraceptive use, optimal cytoreductive surgery, and novel target agents.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

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SUPPLEMETARY MATERIALS

Visit the following URLs for supplementary materials.

Supplementary Table 1.
http://ejgo.org/src/sm/jgo-25-174-s001.pdf

Supplementary Figure 1.
http://ejgo.org/src/sm/jgo-25-174-s002.pdf

Supplementary Figure 2.
http://ejgo.org/src/sm/jgo-25-174-s003.pdf

REFERENCES

1. Felay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. GLOBOCAN 2008: cancer incidence and mortality worldwide: IARC CancerBase No. 10. Lyon: IARC Press; 2010.
2. Akhtar-Danesh N, Elit L, Lytwyn A. Temporal trends in the relative survival among women with cervical cancer in Canada: a population-based study. Int J Gynecol Cancer 2012;22:1208-13.
3. Bray F, Loos AH, Tognazzo S, La Vecchia C. Ovarian cancer in Europe: cross-sectional trends in incidence and mortality in 28 countries, 1953-2000. Int J Cancer 2005;113:977-90.
4. Gonzalez-Diego P, Lopez-Abente G, Pollan M, Ruiz M. Time trends in ovarian cancer mortality in Europe (1955-1993): effect of age, birth cohort and period of death. Eur J Cancer 2000;36:1816-24.
5. Hannibal CG, Cortes R, Engholm G, Kjaer SK. Survival of ovarian cancer patients in Denmark: excess mortality risk analysis of five-year relative survival in the period 1978-2002. Acta Obstet Gynecol Scand 2008;87:1353-60.
6. Chung HH, Jang MJ, Jung KW, Won YJ, Shin HR, Kim JW, et al. Cervical cancer incidence and survival in Korea: 1993-2002. Int J Gynecol Cancer 2006;16:1833-8.
7. Katanoda K, Matsuda T, Matsuda A, Shibata A, Nishino Y, Fujita M, et al. An updated report of the trends in cancer incidence and mortality in Japan. Jpn J Clin Oncol 2013;43:492-507.
8. Cramer DW. The epidemiology of endometrial and ovarian cancer. Hematol Oncol Clin North Am 2012;26:1-12.
9. Pasalich M, Su D, Binns CW, Lee AH. Reproductive factors for ovarian cancer in southern Chinese women. J Gynecol Oncol 2013; 24:135-40.
10. World Health Organization Statistical Information System. WHO mortality database [Internet]. Geneva; World Health Organization; c2014 [cited 2013 Jul 29]. Available from: http://www.who.int/healthinfo/mortality_data/en/.
11. World Health Organization. International statistical classification of idseases and related health problems. Geneva: World Health Organization; 1994.
12. Arbyn M, Geys H. Trend of cervical cancer mortality in Belgium (1954-1994): tentative solution for the certification problem of unspecified uterine cancer. Int J Cancer 2002;102:649-54.
13. Bosch FX. Trends in cervical cancer mortality. J Epidemiol Community Health 1999;53:392.
14. Levi F, Lucchini F, Negri E, Franceschi S, la Vecchia C. Cervical cancer mortality in young women in Europe: patterns and trends. Eur J Cancer 2000;36:2266-71.
15. Loos AH, Bray F, McCarron P, Weiderpass E, Hakama M, Parkin DM. Sheep and goats: separating cervix and corpus uteri from imprecisely coded uterine cancer deaths, for studies of geographical and temporal variations in mortality. Eur J Cancer 2004;40:2794-803.
16. Shin HR, Won YJ, Jung KW, Kong HJ, Yim SH, Lee JK, et al. Nationwide cancer incidence in Korea, 1999-2001: first result using the national cancer incidence database. Cancer Res Treat 2005;37:325-31.
17. Shin HR, Park S, Hwang SY, Kim JE, Jung KW, Won YJ, et al. Trends in cervical cancer mortality in Korea 1993-2002: corrected mortality using national death certification data and national cancer incidence data. Int J Cancer 2008;122:393-7.
18. Segi M, Fujisaku S. Cancer mortality for selected sites in 24 countries (1950-1957). Sendai: Department of Public Health, Tohoku University School of Medicine; 1960.
19. Joinpoint Regression Program version 3.5.3 [Internet]. 2012 ed.

Bethesda, MD: National Cancer Institute; 2012 [cited 2012 Aug 5]. Available from: http://surveillance.cancer.gov/joinpoint/.
20. Ministry of Health. National Registry of Disease Office [Interent]. Singapore: Ministry of Health; c2013 [cited 2013 Nov 3]. Available from: https://www.nrdo.gov.sg/page.aspx?id=76.
21. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.
22. Minelli L, Stracci F, Prandini S, Moffa IF, La Rosa F. Gynaecological cancers in Umbria (Italy): trends of incidence, mortality and survival, 1978-1998. Eur J Obstet Gynecol Reprod Biol 2004;115:59-65.
23. Remontet L, Esteve J, Bouvier AM, Grosclaude P, Launoy G, Menegoz F, et al. Cancer incidence and mortality in France over the period 1978-2000. Rev Epidemiol Sante Publique 2003;51(1 Pt 1):3-30.
24. Jung KW, Won YJ, Kong HJ, Oh CM, Seo HG, Lee JS. Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2010. Cancer Res Treat 2013;45:1-14.
25. Chen YY, You SL, Chen CA, Shih LY, Koong SL, Chao KY, et al. Effectiveness of national cervical cancer screening programme in Taiwan: 12-year experiences. Br J Cancer 2009;101:174-7.
26. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154-61.
27. Kokawa K, Takekida S, Kamiura S, Kita M, Enomoto T, Kawaguchi R, et al. The incidence, treatment and prognosis of cervical carcinoma in young women: a retrospective analysis of 4,975 cases in Japan. Eur J Gynaecol Oncol 2010;31:37-43.
28. Banzai C, Yahata T, Tanaka K. Trends in the incidence of uterine cancer in Niigata, Japan: a population-based study from 1982 to 2007. Eur J Gynaecol Oncol 2011;32:521-4.
29. Yang L, Fujimoto J, Qiu D, Sakamoto N. Trends in cancer mortality in Japanese adolescents and young adults aged 15-29 years, 1970-2006. Ann Oncol 2009;20:758-66.
30. Arbyn M, Castellsague X, de Sanjose S, Bruni L, Saraiya M, Bray F, et al. Worldwide burden of cervical cancer in 2008. Ann Oncol 2011;22:2675-86.
31. Huang CY, Chen CA, Chen YL, Chiang CJ, Hsu TH, Lin MC, et al. Nationwide surveillance in uterine cancer: survival analysis and the importance of birth cohort: 30-year population-based registry in Taiwan. PLoS One 2012;7:e51372.
32. D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol 2010;116:131-9.
33. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
34. Lim MC, Moon EK, Shin A, Jung KW, Won YJ, Seo SS, et al. Incidence of cervical, endometrial, and ovarian cancer in Korea, 1999-2010. J Gynecol Oncol 2013;24:298-302.
35. Wingo PA, Cardinez CJ, Landis SH, Greenlee RT, Ries LA, Anderson RN, et al. Long-term trends in cancer mortality in the United States, 1930-1998. Cancer 2003;97(12 Suppl):3133-275.
36. Mant JW, Vessey MP. Ovarian and endometrial cancers. Cancer Surv 1994;19-20:287-307.
37. Zheng X, Tan L, Ren Q, Cui Z, Wu J, Lin T, et al. Trends in contraceptive patterns and behaviors during a period of fertility transition in China: 1988-2006. Contraception 2012;86:204-13.
38. Skouby SO. Contraceptive use and behavior in the 21st century: a comprehensive study across five European countries. Eur J Contracept Reprod Health Care 2010;15 Suppl 2:S42-53.
39. Central Intelligence Agency. CIA world factbook [Internet]. Washington, DC: Central Intelligence Agency; c2013 [cited 2013 Nov 3]. Available from: https://www.cia.gov/library/publications/the-world-factbook/.
40. Wong KH, Mang OW, Au KH, Law SC. Incidence, mortality, and survival trends of ovarian cancer in Hong Kong, 1997 to 2006: a population-based study. Hong Kong Med J 2012;18:466-74.
41. Bouchardy C, Rapiti E, Blagojevic S, Vlastos AT, Vlastos G. Older female cancer patients: importance, causes, and consequences of undertreatment. J Clin Oncol 2007;25:1858-69.
42. Jorgensen TL, Teiblum S, Paludan M, Poulsen LO, Jorgensen AY, Bruun KH, et al. Significance of age and comorbidity on treatment modality, treatment adherence, and prognosis in elderly ovarian cancer patients. Gynecol Oncol 2012;127:367-74.

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Human Papillomavirus Genotype Distribution in Cervical Intraepithelial Neoplasia Grade 2/3 and Invasive Cervical Cancer in Japanese Women

Yukari Azuma[1], Rika Kusumoto-Matsuo[1], Fumihiko Takeuchi[1], Asami Uenoyama[2], Kazunari Kondo[2], Hajime Tsunoda[2], Kazunori Nagasaka[3], Kei Kawana[3], Tohru Morisada[4], Takashi Iwata[4], Daisuke Aoki[4] and Iwao Kukimoto[1,*]

[1]WHO HPV LabNet Regional Reference Laboratory, WHO Western Pacific Region, Pathogen Genomics Center, National Institute of Infectious Diseases, Tokyo, [2]Department of Obstetrics and Gynecology, NTT Medical Center Tokyo, Tokyo, [3]Department of Obstetrics and Gynecology, Graduate School of Medicine, The University of Tokyo, Tokyo and [4]Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan

*For reprints and all correspondence: I. Kukimoto, Pathogen Genomics Center, National Institute of Infectious Diseases, 4-7-1 Gakuen, Musashi-murayama, Tokyo 208-0011, Japan. E-mail: ikuki@nih.go.jp

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Objective: Human papillomavirus vaccines are being introduced worldwide and are expected to reduce the incidence of cervical cancer. Here we report a cross-sectional study using a validated human papillomavirus genotyping method to reveal the human papillomavirus prevalence and genotype distribution in Japanese women with cervical intraepithelial neoplasia Grade 2/3 and invasive cervical cancer.

Methods: Cervical exfoliated cells were collected from 647 patients with abnormal cervical histology (cervical intraepithelial neoplasia Grade 2, $n = 164$; cervical intraepithelial neoplasia Grade 3, $n = 334$; and invasive cervical cancer, $n = 149$), and subjected to the PGMY-PCR-based genotyping assay. The association between human papillomavirus infection and lesion severity was calculated using a prevalence ratio.

Results: Overall, the prevalence of human papillomavirus deoxyribonucleic acid was 96.3% in cervical intraepithelial neoplasia Grade 2, 98.8% in cervical intraepithelial neoplasia Grade 3 and 88.0% in invasive cervical cancer (97.8% in squamous cell carcinoma and 71.4% in adenocarcinoma). The three most prevalent types were as follows: human papillomavirus 16 (29.3%), human papillomavirus 52 (27.4%) and human papillomavirus 58 (22.0%) in cervical intraepithelial neoplasia Grade 2; human papillomavirus 16 (44.9%), human papillomavirus 52 (26.0%) and human papillomavirus 58 (17.4%) in cervical intraepithelial neoplasia Grade 3; and human papillomavirus 16 (47.7%), human papillomavirus 18 (23.5%) and human papillomavirus 52 (8.7%) in invasive cervical cancer. The prevalence ratio of human papillomavirus 16 was significantly higher in cervical intraepithelial neoplasia Grade 3 compared with cervical intraepithelial neoplasia Grade 2 (prevalence ratio, 1.62; 95% confidence interval, 1.26–2.13) and in squamous cell carcinoma compared with cervical intraepithelial neoplasia Grade 3 (prevalence ratio, 1.55; 95% confidence interval, 1.25–1.87). Multiple infections decreased from cervical intraepithelial neoplasia Grade 2/3 (38.4/29.6%) to invasive cervical cancer (14.1%), whereas co-infections with human papillomavirus 16/52/58 were found in cervical intraepithelial neoplasia Grade 2/3.

Conclusions: The results of this study provide pre-vaccination era baseline data on human papillomavirus type distribution in Japanese women and serve as a reliable basis for monitoring the future impact of human papillomavirus vaccination in Japan.

Key words: human papillomavirus – genotyping – cervical cancer – prevalence ratio

INTRODUCTION

Persistent infection with a subset of human papillomaviruses (HPVs), known as high-risk HPVs, is a primary cause of the development of cervical precancerous lesions and invasive cervical cancer (ICC) (1). At least 15 genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) are recognized as high-risk HPVs (2), among which HPV16 is most frequently detected in ICC cases worldwide, followed by HPV18. Recent worldwide introduction of HPV vaccines targeting HPV16/18 (Cervarix® and Gardasil®) is expected to prevent incident HPV16/18 infection, thereby reducing cervical cancer cases (3). However, clinical trials on HPV vaccines have so far only evaluated its efficacy in preventing precancerous lesions, including cervical intraepithelial neoplasia (CIN) Grades 2 and 3, as a surrogate clinical endpoint, and its final effect on reducing ICC cases is not yet proven. Because the progression into ICC generally requires >10 years of persistent HPV infection, HPV type distribution in CIN2/3 lesions in the general population provides an early indicator to assess the effectiveness of HPV vaccination and thus to estimate any subsequent reduction in ICC cases.

East Asian countries including China, Korea and Japan show region-specific variation in HPV type distribution in ICC cases (4). In particular, HPV52 and HPV58 are more prevalent in these countries compared with Europe, North America and Africa (5, 6). Previous studies report that HPV16/18 cause the majority of ICC cases in Japan (7–10), ranging from 50 to 70%, whereas HPV52/58 are individually detected in ~7% of Japanese ICC cases. Since the HPV vaccines against HPV16/18 infection have exhibited only a limited efficacy for cross protection against other high-risk HPVs (11) it is important to monitor the prevalence of HPV52/58 in CIN2/3 and ICC cases in order to evaluate whether type-replacement occurs in post-vaccination era Japan.

In this study, we used a validated HPV genotyping method (12) to record the most recent data on the prevalence and type distribution of high-risk HPVs in Japanese women with CIN2/3 lesions and ICC. The results provide reliable baseline data on the HPV type distribution in Japanese women with precancerous lesions and cervical cancer that will enable accurate assessment of any future impact from HPV vaccination in Japan.

PATIENTS AND METHODS

Study Subjects and Specimen Collection

We enrolled 647 Japanese women who were histologically diagnosed with CIN2/3 or ICC by punch biopsy or cervical conization (CIN2, $n = 164$; CIN3, $n = 334$; and ICC, $n = 149$) at three hospitals in the Tokyo metropolitan area (NTT Medical Center Tokyo, Keio University Hospital, and The University of Tokyo Hospital) from September 2009 to December 2013. Histological diagnosis was made using hematoxylin–eosin-stained sections according to the World Health Organization (WHO) classification by experienced pathologists at each hospital. When diagnoses between punch biopsy and cervical conization were discordant, a higher grade of histology was taken as final diagnosis. The mean age ± standard deviation and age range in each histological grade was as follows: CIN2, 36.4 ± 7.7 years (21–62 years); CIN3, 38.9 ± 8.0 years (21–67 years); ICC, 48.0 ± 14.9 years (27–88 years). In Japan, Cervarix® and Gardasil® were approved for use in 2009 and 2011, respectively, but all the study participants reported no history of HPV vaccination except for one CIN2 case that had recently been administered with Gardasil®.

Before histopathological diagnosis, cervical exfoliated cells were collected in Thinprep® media using a Cervex-brush® combi for subsequent HPV genotyping. The study protocol was approved by the Ethics Committee at each hospital and the National Institute of Infectious Diseases, and written informed consent for study participation was obtained from each patient.

HPV Genotyping

DNA extraction and HPV genotyping were centralized in a laboratory at the National Institute of Infectious Diseases. Total DNA was extracted from a 200-μl aliquot of cervical exfoliated cells using the QIAamp DNA Blood Mini Kit (Qiagen) and a MagNA Pure LC 2.0 (Roche Diagnostic). An aliquot of the purified DNA was then used for PCR amplification with AmpliTaq Gold® polymerase (GE Healthcare Bio-Sciences), biotinylated PGMY09/11 primers to amplify the L1 DNA of mucosal HPVs, and biotinylated HLA primers to amplify cellular HLA DNA. Positive control (0.1 pg/mL of HPV16 DNA as a plasmid) and negative control (dH_2O) were included to verify the sensitivity of PCR and monitor contamination of HPV DNA in reagents. The PCR products were run on 1.5% agarose gels to assign the positivity of HPV DNA amplification and to confirm the integrity of the extracted DNA by amplification of HLA DNA. Reverse blotting hybridization was performed as described (12, 13). Briefly, 15 μl denatured PCR products were allowed to hybridize with oligonucleotide probes specific for 31 HPV types (HPV6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66, 68, 69, 70, 73, 82, 83, and 84) immobilized on a Biodyne C membrane (Pall corporation) using a Miniblotter MN45 (Immunetics, Cambridge, MA, USA). The hybridized DNA was detected using streptavidin–HRP (GE Healthcare Bio- Sciences, Piscataway, NJ, USA) and the ECL detection reagent (GE Healthcare Bio-Sciences). For adenocarcinoma samples with negative results from the L1 PCR, E6 PCR was performed using PCR Human Papillomavirus Typing Set (Takara, Ohtsu, Japan) that detects HPV16, 18, 31, 33, 35, 52 and 58.

Statistical Analysis

A generalized linear model with binomial distribution and log link was used to calculate the prevalence ratio (PR) of high-risk HPVs between different histological grades with 95% confidence intervals (CI). The PR was adjusted with the

Table 1. Human papillomavirus (HPV) genotype distribution in CIN2/3 in Japanese women

Type	CIN2 ($n = 164$)	%	CIN3 ($n = 334$)	%	PR (CIN3 vs. CIN2) (95% CI)	P (Wald test)
High risk						
16	48	29.3	150	44.9	**1.62 (1.26–2.13)**	**0.0003****
18	11	6.7	24	7.2	1.03 (0.53–2.15)	0.93
26	1	0.6	0	0.0	ND	
31	16	9.8	42	12.6	1.30 (0.77–2.32)	0.35
33	6	3.7	15	4.5	1.33 (0.54–3.69)	0.55
35	5	3.0	6	1.8	0.63 (0.19–2.19)	0.45
39	6	3.7	8	2.4	0.67 (0.23–2.03)	0.46
45	4	2.4	3	0.9	0.35 (0.07–1.61)	0.18
51	16	9.8	20	6.0	0.65 (0.34–1.25)	0.18
52	45	27.4	87	26.0	0.93 (0.68–1.28)	0.63
53	10	6.1	4	1.2	**0.23 (0.06–0.69)**	**0.013***
56	9	5.5	8	2.4	0.43 (0.16–1.12)	0.08
58	36	22.0	58	17.4	0.81 (0.56–1.20)	0.28
59	1	0.6	1	0.3	0.41 (0.02–10.5)	0.53
66	3	1.8	3	0.9	0.39 (0.08–1.78)	0.22
68	5	3.0	5	1.5	0.66 (0.18–2.35)	0.51
73	0	0.0	0	0.0	ND	
82	8	4.9	10	3.0	0.66 (0.26–1.72)	0.38
Low risk						
6	3	1.8	6	1.8		
11	2	1.2	0	0.0		
40	1	0.6	0	0.0		
42	1	0.6	0	0.0		
43	0	0.0	0	0.0		
44	1	0.6	0	0.0		
54	2	1.2	2	0.6		
55	4	2.4	2	0.6		
57	0	0.0	0	0.0		
69	3	1.8	1	0.3		
70	2	1.2	1	0.3		
83	0	0.0	1	0.3		
84	0	0.0	2	0.6		
Negative	6	3.7	4	1.2		
Multiple	63	38.4	99	29.6		

Single and multiple infections combined.
$^{**}P < 0.001$; $^{*}P < 0.05$; ND, not determined. Statistically significant values are indicated in boldface.
One case having HPV vaccination history (HPV16, 18, 53 and 58 positive) is included in CIN2.
CIN2, cervical intraepithelial neoplasia Grade 2; CIN3, cervical intraepithelial neoplasia Grade 3; PR, prevalence ratio; CI, confidence interval.

women's age at the time of diagnosis. Pearson's χ^2 test with Yates' continuity correction was used to examine differences in the proportion of HPV infections. Two-sided P values were calculated and considered to be significant at <0.05. All statistical analyses were performed using R version 2.11.1.

RESULTS

HPV Prevalence and Type Distribution

Overall, HPV DNA was detected in 158 of the 164 CIN2 cases (96.3%), 330 of the 334 CIN3 cases (98.8%) and 131 of