

## RESEARCH ARTICLE

# A Systematic Review of Cervical Cancer Incidence and Mortality in the Pacific Region

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### Abstract

This study provides the first systematic literature review of cervical cancer incidence and mortality as well as human papillomavirus (HPV) genotype prevalence among women with cervical cancer in the Pacific Island countries and territories. The cervical cancer burden in the Pacific Region is substantial, with age standardized incidence rates ranging from 8.2 to 50.7 and age standardized mortality rate from 2.7 to 23.9 per 100,000 women per year. The HPV genotype distribution suggests that 70-80% of these cancers could be preventable by the currently available bi- or quadrivalent HPV vaccines. There are only few comprehensive studies examining the epidemiology of cervical cancer in this region and no published data have hitherto described the current cervical cancer prevention initiatives in this region.

**Keywords:** Pacific - cervical cancer - human papillomavirus

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### Introduction

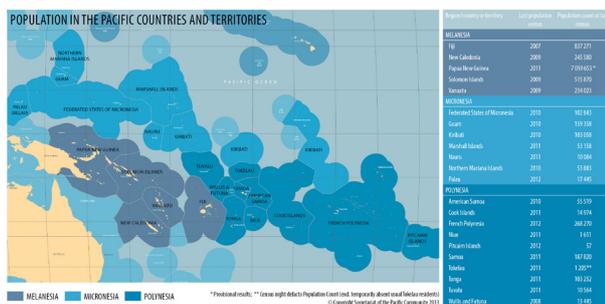
Cervical cancer is the fourth most common type of cancer in women in the world and in some low-income countries it is the most common cancer in women (Ferlay et al., 2010; IARC, 2012). Persistent infection with oncogenic genotypes of the sexually transmitted human papillomavirus (HPV) is a necessary, although not sufficient, factor in the development of this cancer. Globally, there are 528,000 new cases of cervical cancer per year, 85% of which occur in low-income countries; highlighting the significant inequities that exist in global health. Annually, 266,000 women die of cervical cancer, which is as high a death toll as that of maternal deaths. Cervical cancer incidence and mortality rates rank the highest in the Sub Saharan African, South American, South-central Asian and Pacific Regions, although substantial regional variation exists depending largely on primary and secondary cervical cancer prevention practices (Ferlay et al., 2010; Garland et al., 2012; IARC, 2012). In the recent Global Burden of Disease study, cervical cancer was ranked the 8th leading cause of death among women in the Pacific in 2010, which is by far the highest ranked cancer (Institute for Health Metrics and Evaluation, 2013).

Cervical cancer represents a disease that is largely preventable through known and well documented

prevention strategies of screening for and treating precursor lesions to cancer. In addition, more recently prophylactic vaccination against HPV has been introduced to prevent cervical cancer; however, large inequities in access to prevention exist between high- and lower income countries (Ferlay et al., 2010; Knaul et al., 2012; Sahasrabudde et al., 2012). Primary prevention by high coverage of vaccination against the HPV types 16 and 18 among young girls before sexual debut is by now a well-established strategy to prevent cervical cancer by potentially 70-80%, as HPV genotypes 16 and 18 consistently account for this proportion of cancers worldwide (WHO, 2009). The cost-effectiveness of this intervention depends largely on the cost of the vaccine; however, a recent review concludes that HPV vaccination is very likely to be cost-effective and possibly cost saving in low- and middle income countries, particularly in countries without functioning cervical cancer screening programs (Fesenfeld et al., 2013).

The present paper focuses on 22 Pacific Island countries and territories from Polynesia, Micronesia and Melanesia (Figure 1) (hereafter referred to as the Pacific Region), that since 1947 have collaborated for development, including public health strengthening, through the membership organization, the Secretariat of the Pacific Community (SPC) (SPC, 2011). As a means to estimate the magnitude of the cervical cancer burden

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**Figure 1. The Pacific Region and Population Size of Countries and Territories, 2007-2012**

and the potential preventive impact of HPV vaccination, this paper provides the first systematic literature review for the Pacific Islands and territories of current knowledge regarding cervical cancer incidence and mortality, as well as HPV genotype prevalence among women with cervical cancer.

## Materials and Methods

The PubMed database, EMBASE and the Cochrane Library were searched for published papers presenting quantitative studies on cervical cancer incidence and mortality, as well as HPV genotype prevalence among women with cervical cancer in any of the 22 island countries and territories within the Pacific Region. The search was limited to English and French languages and peer-reviewed manuscripts. Only papers published after the year 1999 were included, in order to ensure that the results were related to the present cervical cancer burden. Papers had to present original research data for inclusion. The search terms were Mesh term: “cervical cancer” OR “human papilloma virus vaccines” OR “HPV vaccines” AND “Pacific”. Additionally, a search was conducted on “cervical cancer” OR “human papilloma virus” AND the names of the 22 countries and territories in the Pacific Region. The titles and abstracts of the search result were then screened for eligibility. The full version of relevant papers was retrieved. Furthermore, the reference lists of all the papers were reviewed for identification of relevant papers. The studies included in the review were entered into a matrix of study-country and research question addressed by the study (Table 1). Age-Standardized

Rates (ASR) for cervical cancer incidence and mortality were compared with estimates from the international GLOBOCAN database (IARC, 2012).

## Results

The search resulted in a total of 186 papers. Ineligible titles and abstracts were excluded, which left 28 relevant papers. Nineteen of these were discarded as they were either not concerned with the research question, not presenting original data, or limited to studying Pacific Islanders living in New Zealand, Australia, the US or elsewhere. Reviewing the reference lists of all the eligible papers did not reveal any additional papers published after year 1999. Thus, in total, nine papers were included in the review. Three studies were multi-country studies including two or more Pacific countries and territories (Parkin et al., 2008; Moore et al., 2010; Foliaki et al., 2011). There were six country-specific studies: four from Fiji (Tabrizi et al., 2011; Kuehn et al., 2012; Law et al., 2013; Vodanaivalu and Bullen, 2013), one from Guam (Haddock et al., 2006) and one from Papua New Guinea (Tabone et al., 2012). No studies from Polynesian island countries and territories were identified.

The International Agency for Research on Cancer (IARC) published data on national and regional site specific cancer incidence and mortality based on data derived from national cancer and mortality registries. Where data was incomplete, IARC published cancer incidence and mortality by modeling estimates from neighboring country incidence and mortality rates. For several of the smaller countries and territories, IARC only provided regional estimates (IARC, 2012). Beyond the IARC published data, additional estimates of cervical cancer incidence and mortality had been published for some countries and territories (Guam, New Caledonia, Solomon Islands, Fiji, Papua New Guinea, Vanuatu and Samoa) based on country-specific studies of national registries and hospital records. A multi-country study from 2011, including Tonga, Cook Islands and Niue, provided incidence estimates based on national cancer registration as well as review of hospital and pathology registries (Foliaki et al., 2011).

Reported cervical cancer incidence rates from the Pacific Region, published by IARC or in country specific

**Table 1. Studies Identified by the Systematic Review and Research Question Addressed in Each Study**

Region	Country	First author and year of publication	Provide information on		
			Cervical cancer incidence	Cervical cancer mortality	HPV genotype in women with cancer
Micronesia	Guam	Haddock et al. 2006 <sup>††</sup>		x	
Melanesia	Fiji	Kuehn et al. 2012	x	x	
		Law et al. 2013	x	x	
		Tabrizi et al. 2011			x
		Vodanaivalu et al. 2013	x	x	
		Tabone et al. 2012			x
Polynesia <sup>†††</sup>	Multi-country studies	Foliaki et al. 2011*	x		
		Moore et al. 2010**	x		
		Parkin et al 2008***	x	x	

<sup>††</sup>The study does not provide population based estimates but only estimates for ethnic groups in Guam; <sup>†††</sup>No studies from Polynesia were identified in the systematic literature search; \*Including: Tonga, Fiji, Cook Islands and Niue; \*\*Including: Papua New Guinea, Solomon Islands, Vanuatu, Samoa, New Caledonia, Fiji, French Polynesia and Guam; \*\*\*Including: Fiji, Guam, Papua New Guinea, Samoa, Solomon Islands, New Caledonia and Vanuatu

**Table 2. Cervical Cancer Mortality and Incidence Estimates in the Pacific Region**

Country/region	Cervical cancer incidence per 100,000 women				Cervical cancer mortality per 100,000 women	
	Age Standardized Incidence rate		Crude Incidence rate		Age Standardized Mortality rate	
	GLOBOCAN Estimate year 2012 (IARC, 2012)	Study based estimate (year) (reference)	Study based estimate (year) (reference)	GLOBOCAN Estimate year 2012 (IARC, 2012)	Study based estimate (year) (reference)	
Micronesia*	8.7			2.7		
Guam	9.0	9.4 (2002) (Parkin et al., 2008)	4.5 (2005-07) (Moore et al., 2010)	2.9	5.2 (2002) (Parkin et al., 2008)	
Melanesia**	33.3			20.7		
New Caledonia	15.3	35.8 (1977-88) (Parkin et al., 2008) <sup>¶</sup>	19.7 (2007) (Moore et al., 2010)	10.3		
Solomon Islands	28.5	42.8 (2002) (Parkin et al., 2008)		17.9	23.9 (2002) (Parkin et al., 2008)	
Fiji	37.8	33.4 (2002) (Parkin et al., 2008) 50.7 (2002-05) (Foliaki et al., 2011) 27.6 (2003-09) (Kuehn et al., 2012) 29.7 (2004-07) (Law et al., 2013)		20.9	18.7 (2002) (Parkin et al., 2008) 23.9 (2003-09) (Kuehn et al., 2012) 20.8 (2004-07) (Law et al., 2013)	
Papua New Guinea	34.5	40.4 (2002) (Parkin et al., 2008)		21.7	22.6 (2002) (Parkin et al., 2008)	
Vanuatu	19.2	21.7 (2002) (Parkin et al., 2008)		9.8	12.1 (2002) (Parkin et al., 2008)	
Polynesia***	11.0			5.1		
Samoa	17.1	28.0 (2002) (Parkin et al., 2008)		6.9	15.0 (2002) (Parkin et al., 2008)	
French Polynesia	8.2	-	15.6 (2007) (Moore et al., 2010)	5.1		
Tonga	-	15.7 (2000-05) (Foliaki et al., 2011)		-		
Cook Islands	-	17.0 (2000-05) (Foliaki et al., 2011)		-		
Niue	-	25.9 (2000-05) (Foliaki et al., 2011)		-		

\*No country specific estimates are available for the following Micronesian countries and territories: Kiribati, Marshall Islands, Northern Marina Islands, Palau, Nauru and Federated States of Micronesia; \*\*No country-specific estimates are available for the Melanesian country Wallis and Futuna; \*\*\*No country-specific estimates are available for the following Polynesian countries and territories: American Samoa, Samoa, Pitcairn, Tokelau and Tuvalu; <sup>¶</sup>Ethnic Melanesian population only

studies, range from 50.7 to 8.2 and mortality rates from 2.7 to 23.9 per 100,000 women per year with the highest mortality and incidence rates found in Melanesia and the lowest rates in Micronesia (Table 2).

Several Pacific countries and territories have multiethnic populations. Studies identified by the present review indicated higher incidence and mortality rates of cervical cancer among native Pacific populations, compared to population groups of Indian and European descent. One study from Fiji found significantly different incidence and mortality among ethnic Fijian compared to ethnic Indian women living in Fiji. The age-standardized incidence and mortality per 100,000 per year was 34.7 (95% CI: 31.0-38.5) and 33.9 (95% CI: 29.4-38.3) among ethnic Fijian women respectively, and 24.0 (95% CI: 20.4-27.6) and 13.0 (95% CI: 10.0-16.1) among ethnic Indian women, respectively (Kuehn et al., 2012). Two other studies from Fiji found similar, significant differences between ethnic Fijian and ethnic Indian women living in Fiji (Law et al., 2013; Vodonaivalu and Bullen, 2013). Differences in cervical cancer incidence was also reported between ethnic Melanesian (35.8/100,000) and ethnic Europeans (20.4/100,000) in New Caledonia (Parkin et al., 2008). In Guam, ethnic Chamorro women had an ASR of mortality of 7.5/100,000 compared to no reported deaths in Micronesian women. It was suggested that this difference could be attributable to underreporting of cervical cancer among the Micronesian population, that was assumed to be a particularly underserved group (Haddock et al., 2006).

Only two studies on HPV genotype prevalence among women with cervical cancer in the Pacific Region had been published. A study conducted in Fiji analyzed HPV prevalence and type distribution in 296 biopsies from ethnic Fijian women with cervical cancer diagnosed 2003-2007 and found 99% of biopsies positive for HPV with 77% positive for HPV types 16 and/or 18. The third most common genotype was HPV 31 (Tabrizi et al., 2011). Another study from Papua New Guinea estimated HPV

genotype prevalence among 70 women identified with cervical cancer during 2006-2009, showing HPV genotype prevalence distribution comparable to global rates, with 83% of biopsies being positive for HPV type 16 and/or 18. HPV types 33 and 31 were found to be respectively the third and fourth most common types of HPV within the biopsies from Papua New Guinean women with cervical cancer (Tabone et al., 2012).

## Discussion

The cervical cancer burden in the Pacific Region is substantial. The Melanesian population in the Pacific Region has one of the highest incidence rates of cervical cancer in the world (IARC, 2012). Country specific registry based studies generally found a higher incidence rate of cervical cancer than that reported by the IARC global database. For several smaller countries and territories, specific data on cervical cancer does not exist, and has to be extrapolated from regional estimates. Only two country specific studies in the Pacific Region (Fiji and Papua New Guinea) have assessed type-specific prevalence of HPV genotypes among women with cervical cancer. In both studies the combined prevalence of HPV16 and/or 18 was high, 77% (Tabrizi et al., 2011) and 83% (Tabone et al., 2012) respectively.

The country specific studies of cervical cancer incidence and mortality identified in the current systematic review are all based on national cancer registries and in some studies the data is supplemented by review of hospital records, pathology reports and mortality data. In 7 out of 10 studies, cervical cancer incidence estimates from country specific studies were higher than the IARC estimates. However, in three studies from Fiji the country specific incidence estimates were lower than the IARC estimate (Parkin et al., 2008; Kuehn et al., 2012; Law et al., 2013). The lower incidence estimates in two of the studies from Fiji (Kuehn et al., 2012; Law et al., 2013) may have

been due to that these studies included the time frame of 2005 and 2006 with probable substantial under-reporting to the national registries, due to a military coup and general turmoil in the country. An alternative explanation for the lower incidence rate found by these two studies from Fiji could be that the studies using hospital based data had improved ability to identify double reported cases. The present review confirms high regional incidence and mortality of cervical cancer, particularly in the Melanesian region where country and regional estimates are among the world's highest, as has also been suggested by the 2010 global cancer review (Ferlay et al., 2010). For several countries and territories in the Pacific Region no estimates of cervical cancer incidence or mortality exists. Overall the higher incidence and mortality estimates from country specific studies may suggest systematic underreporting of cervical cancer from the Pacific Region to the IARC global database, but there are too few studies to evaluate the validity of the cervical cancer reporting.

Only two studies from the region examined the HPV genotype distribution among women with cervical cancer. Similar to other regions in the world (Clifford et al., 2003), the results show that high coverage of the currently available bi- or quadrivalent HPV vaccine among young girls before sexual debut is likely to prevent approximately 70-80% of cervical cancers in the Pacific Region. Cross-protection of the vaccine against other high-risk HPV genotypes may increase the effect of the vaccine further (Brown et al., 2009; Paavonen et al., 2009).

A cost-effectiveness study of 25 countries in the Asia-Pacific region, including 22 of the international public-private partnership Global Alliance for Vaccines and Immunization (GAVI) eligible countries, estimated HPV vaccination of adolescent girls at a cost per vaccinated girl of 10-25 International dollars (I\$) (corresponding to a cost per dose of vaccine of 2-5 I\$) would be very cost-effective for most countries in the region (Goldie et al., 2008). Adolescents are typically a population that is hard to reach with public health measures. It has been suggested that HPV vaccination programs may additionally benefit broader adolescent health issues, serving as a vehicle for key adolescent health interventions and information to adolescents and their parents, further strengthening the cost-effectiveness of HPV vaccine programs (Broutet et al., 2013). With the recent announcement from GAVI to support HPV-vaccination for the poorest countries at a cost of 4.5 USD per dose, as well as experience from the Latin American region where a revolving fund and bulk purchasing has enabled a reduction in price to levels of 10-15 USD per dose, the possibility of introducing HPV vaccination as part of national immunization schedules in low- and middle-income countries in the Pacific Region are now within economic reach and likely to be cost-effective (GAVI 2013; Levin et al., 2013). Available evidence has shown that countries where HPV vaccination has been rolled out and high coverage has been achieved countries experience a reduction in HPV vaccine related genotype infection, genital warts as well as high-grade cervical dysplasia (Tabrizi et al, 2014; Ali et al, 2013, Brotherton et al, 2011).

Secondary prevention through screening young and

middle-aged women for precursor lesions to cervical cancer, with appropriate treatment for women with precursor lesions, is a highly efficacious strategy to reduce the incidence of and mortality from cervical cancer in high-income countries with well-established health care systems. Recently, it has been shown that secondary prevention may also be feasible and effective in low-income settings, if prioritized and well implemented with good quality control and quality assurance, which is however most often not the case (Denny and Anorlu, 2012).

In conclusion, the cervical cancer burden in the Pacific Region is substantial, but only few comprehensive studies exist examining the epidemiology of cervical cancer in this region. Cost effective, evidence based and feasible primary and secondary prevention strategies exist. The high burden of cervical cancer within the region calls for a coordinated effort to implement screening and vaccination at scale as a means to reduce morbidity and mortality among Pacific island women. There are currently no published data describing the current cervical cancer prevention initiatives in the Pacific Region, nor examining the intent or barriers among these island countries and territories to implement cervical cancer prevention programs. Given the nature of the Pacific Region with many small island countries, a regional approach to review the current cervical cancer prevention practices and develop plans to tackle cervical cancer prevention may be useful as smaller nations could benefit from collaboration in development of effective implementation plans, a joint pool of technical assistance, bulk vaccine procurement and development of a joint operational research agenda to guide implementation.

## Conflict of Interests

SK Kjaer received lecture fees, scientific advisory board fees, and institutional research grants from Merck and Sanofi Pasteur MSD.

SM Garland has received scientific advisory board fees and grant support from CSL and GlaxoSmithKline, and lecture and consultancy fees from Merck and Co and received grant support through her institution from Merck and Co. and GlaxoSmithKline (GSK) to carry out clinical trials for HPV/cervical cancer vaccines, and she is a member of the Merck global advisory and scientific advisory boards.

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