SUPANNEE SRIAMPORN

The Epidemiology of Cervical Cancer in Khon Kaen, Northeast Thailand

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ACADEMIC DISSERTATION

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the Faculty of Medicine of the University of Tampere,
for public discussion in the auditorium of Tampere School of
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1 Introduction

Cervical cancer is an important public health problem worldwide. It is the second most common cancer among women, with an estimated 468 000 new cases and 233 000 deaths in the year 2000. Almost 80% of the cases occur in developing countries, where, in many regions, it is the most common cancer of women (Parkin et al. 2001). In countries of north America and Europe, the incidence is generally low. These low rates date from the introduction of broad-coverage, cervical screening ("Pap smear") programmes – before this, in the 1950's and 1960's, the rates were much higher, similar to those in many developing countries today (Parkin et al. 1985, Hakama et al. 1986, Coleman et al. 1993). The reduction in risk has apparently been due to detection and treatment of intraepithelial, preinvasive lesions (Hakama et al. 1982, Muñoz et al. 1992b). The extent of the decline in incidence and mortality are related to the coverage and extent of the organised programmes in the respective countries (Sigurdsson 1999), and the declines in incidence have been marked in the age groups targeted by the screening programmes (Gustafsson et al. 1997b).

In some countries, rates of invasive cancer have shown increases recently, despite the continued operation of screening programmes (Parkin et al. 2001). Such increases in women aged less than 55 have been seen in Finland, which has one of the most successful screening programmes, and when by 1991 the incidence had been as low as 2.8 per 100 000 (Anttila et al. 1999). These trends must represent an increase in the risk of disease, due to greater levels of exposure to the causative factors of the disease in younger generations of women – most likely the human papillomaviruses (HPV) which are only partly counteracted by screening.

The success of cervical cytological screening in the past has led to decreased interest in the epidemiological study of cervical cancer. In the last 20–25 years, however, there has been renewed research interest in cervical cancer, since the hypothesis that human papillomavirus could be causally involved in cervical carcinogeneis (zur Hausen 1975, 1976), which is now held to be a necessary cause of cervical cancer – that is, the disease does not occur without the virus (Walboomers et al. 1999). However, cervical infection with HPV is extremely common compared to the relatively rare development of cervical cancer. Thus, additional critical aetiologic factors must be involved, such as HPV type and intensity of infection, variability in the immunological response of the host, co-infection with other viral or bacterial agents, parity, cigarette smoking, oral contraceptive use, and diet.

There are, therefore, still challenges to be met in getting a full understanding of the aetiology and pathogenesis of cervical cancer. The key role of HPV is now accepted, and

the mechanism by which the virus disturbs the normal cycle of cell replication and death (the viral proteins E6 and E7 seem to interact with cellular proteins involved in growth control and apoptosis (Pillai et al. 1996), especially the retinoblastoma (Rb) and p53 proteins) is now better understood. It means that it may soon be possible, using a variety of molecular epidemiological approaches, to define new prevention strategies that will be more effective than cytological screening alone. For example, HPV DNA testing of older women (over age 30) may be a useful screening test to define which women are or are not at future risk of disease (Cuzick et al. 1994, 2000). In the medium term, the most exciting prospect is the primary prevention of cervical neoplasia via HPV immunization of the general population (Koutsky et al. 2002).

At present, however, screening by cytology (the Pap smear), through organised population screening programmes, remains the established method for control of cervical cancer. In Asian countries, despite the moderate-high incidence rates, there have been no truly 'organised' programmes, involving identification of women of risk, ensuring their examination at regular, defined intervals, with appropriate follow-up and treatment of those found to have as abnormal finding on cytology. Programmes have at best, offered free tests to women 'on demand', or when attending services such as family planning, pregnancy counseling, ante and post-natal clinics, sexually transmitted disease (STD) clinics and so on. Generally, however screening is even more haphazard than this, involving fee-for-service testing by doctors, with sporadic campaigns mounted by local health departments, or charitable foundations. This has been the situation in Thailand until quite recently.

In 2002, government policy has adopted the goal of screening the entire population of women in Thailand who are aged 35, 40, 45, 50, 55 and 60 (Deerasamee et al. 2002). As a first step, measures to increase the capacity for obtaining and interpreting Pap smears have been put in place with training courses for nurses and cytologists, as well as for treating the abnormalities detected by screening, with cryotherapy and loop electrosurgical excision procedure (LEEP).

It will be very important to determine the success achieved by this programme. Basically, this will involve monitoring the process of screening and its outcome. Process may be evaluated in terms of the number of tests performed and how many are positive tests, but includes, importantly, the coverage of the programme (what proportion of the female population receives a screening examination, and at what frequency). Outcome may be evaluated at the population level (incidence of invasive cervical cancer, the distribution of cases by stage at diagnosis) and also by studies of the reduction in risk of invasive disease following by a screening test after different intervals of time.

It is important, therefore, to have secure information, before the introduction of a new programme, on these factors – incidence, stage distribution, screening history of the population and the protection against invasive cancer provided by a screening test carried out locally (which implies all of the possible defects in the quality of the smear and its interpretation).

Control of cervical cancer implies more than primary prevention through modification of risk factors or immunization against HPV, and early detection through screening. An essential component of a control programme is the capacity to treat established disease, in order to maximize the sufferers' chances of survival, and to enhance their quality of life post-diagnosis. Treatment of cervical cancer involves, at least in its earliest stages, a combination of surgery and radiotherapy. Surgery, in the form of a hysterectomy (more or less extensive, to include surrounding tissues, according to spread of disease and local practices) is carried out for early stage disease. It is supplemented by radiotherapy usually a combination of brachytherapy (local irradiation of tissue with a radio active source usually caesium high in the vagina) plus external beam irradiation of tissues rather further from the cervix itself, but likely to be involved is local spread of disease. The success of treatment in prolonging life is measured as survival – the proportion (or percentage) of new cases surviving for different periods of time (1, 3, 5…. years) after diagnosis. Information on survival is an important indicator in monitoring cancer control activities (WHO 2002), and, in this context, it is the data population-based cancer registries that are most relevant, reflecting several aspects of cancer control, including screening and the organisation of treatment services. In recent years, there has been increasing attention to comparative statistics of survival between different populations and time periods, with a view to identifying where improvements is existing management are possible. Population-based survival statistics have taken on a new importance in this context, and it is now considered standard practice to have such data available, along with information on incidence, stage distribution, and mortality, as fundamental components of the planning process.

With this background a study was carried out in Khon Kaen province, Northeast of Thailand, to address the epidemiological study of cervical cancer in this area. This dissertation will present the magnitude of problem from cervical cancer (incidence), the risk factors for cervical cancer from different study designs (case-control study and cohort study), and the outcome of the clinical burden (survival) of cervical cancer patients, and discuss the implications of the results.

2 Aims of this study

To study the epidemiology of cervical cancer in Khon Kaen, Northeast Thailand. To achieve this aim the following topics will be studied:

1. The incidence of cervical cancer in Khon Kaen, Northest Thailand in the period of 1985-1999
    - 1.1 Distribution by basis of diagnosis, histological type and stage
    - 1.2 In different subgroups (age, place of residence)
    - 1.3 Incidence in different time period
    - 1.4 Comparison of the incidence rates between different registries
2. The risk factors associated with cervical cancer in Khon Kaen, Northeast Thailand from different epidemiological study designs
    - 2.1 Hospital-based case-control study
    - 2.2 Nested case-control study within a cohort and with prevalence sampling
    - 2.3 Nested case-control study within a cohort study and with incidence density sampling
3. The survival of cervical cancer patients in Khon Kaen, Northest Thailand
    - 3.1 Observed survival calculated by the actuarial method
    - 3.2 Loss-adjusted observed survival
    - 3.3 Relative survival

3 Review of the literature

3.1 The incidence of cervical cancer

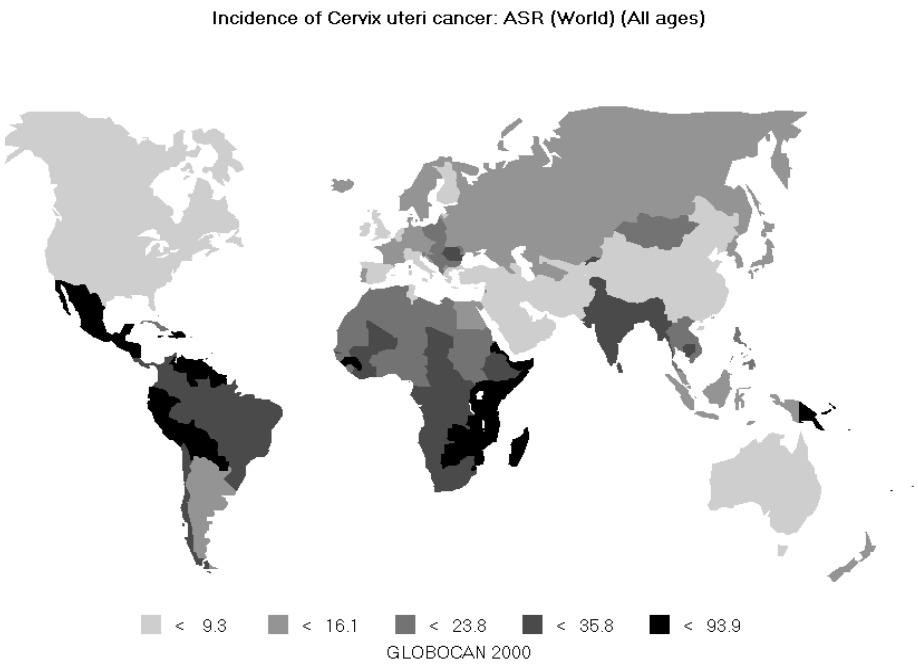
3.1.1 Cervical cancer; world patterns

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 468 000 new cases and 233 000 deaths in the year 2000. The highest incidence rates are observed in Latin America (age-standardised incidence rates; ASR 33.5 per 100 000) and the Caribbean (ASR 33.5), Sub-Saharan Africa (ASR 31.0), and South (ASR 26.5) and Southeast Asia (ASR 18.3) (Figure 1). In developed countries, the incidence rates are generally low, with age-standardised rates less than 14 per 100 000. Very low rates are also observed in China, and in Western Asia (Ferlay et al. 2001).

In populations where there has been no screening, the incidence of cervical cancer begins to rise at ages 20–29, and the risk increases rapidly to reach a peak, and then decline somewhat, although the slope is much less than for the increase in young women. Gustafsson et al. (1997a) compiled incidence data for 28 different populations, for long periods of time between 1935 and 1989 (populations unaffected by screening). Most populations fitted 1 of 2 reference curves. Most populations in the Americas, Asia, and Africa (plus Finland and Poland), had a peak at ages 50–65, followed by a decline to the 'half peak value' at 70–75 years. This profile is readily distorted by screening, and , if cross-sectional data (from a single time period) are examined, by birth-cohort specific changes in risk (Ashley 1966, Hakama and Penttinen 1981, Gustafsson et al. 1997b).

Mortality rates are substantially lower than incidence rates. Worldwide, the ratio of mortality to incidence is 49%. Five-year relative survival rates vary between regions with quite good prognosis in low-risk regions (69% in The Surveillance, Epidemiology, and End Results (SEER) and 59% in the European registries), but even in developing countries, where many cases present at relatively advanced stage, survival rates are fair: 49% on average, (Sankaranarayanan et al. 1998). The poorest survival is estimated for eastern Europe.

Time trends of cervical cancer are useful in following the possible effects of exposure to the risk factor for the disease, and partly to evaluate the impact of screening programmes. Time trend studies may use either incidence or mortality data; the latter have the great advantage of longer time series, and larger population coverage, advantages offset by the quality of the diagnostic information (especially failure to distinguish cancers of the cervix and corpus), and the confounding effect of changes in



Source: GLOBOCAN 2000 (Ferlay et al. 2001)

Figure 1. Age-standardised incidence rates (ASR) per 100 000 of cervical cancer world wide.

survival. Ponten et al. (1995) and Sparen et al. (1995) have shown that trends in stage at diagnosis and treatment may have a big impact on cervical cancer mortality. Trend studies often fail to distinguish adenocarcinomas from squamous cell carcinomas, though their epidemiology is a little different, and their susceptibility to detection by cytology screening very much so. Since most cervical cancers are squamous cell carcinomas, studies of all types combined will largely reflect trends in this histological type.

Overall, incidence and mortality have declined in the last 40 years in western Europe, U.S.A, Canada, Australia, New Zealand, and Japan. In general, this has been ascribed to a combination of a reduction in risk in more recent generations of women (improved genital hygiene, low parity, etc.), with, more recently, the beneficial effects of population screening programmes based on exfoliative cervical cytology. The best known studies of time trends in incidence are those undertaken for the Nordic countries, where it was possible to compare the trends in incidence (and mortality) across countries with their different policies in relation to screening (Hakama 1982, Hakulinen et al. 1986). The extent of the decline in incidence and mortality was related to the coverage and extent of

the organised programmes in the respective countries (Sigurdsson 1999), and the declines in incidence were most marked in the age groups targeted by the organised programmes.

The trend in the Nordic countries was increasing before screening started. Several studies have pointed out that even within the overall decline in incidence and mortality, quite often there were increases occurring in young women. This was first noted in England and Wales where generations of women born since about 1935 are at increasingly high risk (Hill and Adelstein 1967, Cook and Draper 1984, Parkin et al. 1985). A similar phenomenon has been observed in several countries, e.g. Australia (Armstrong and Holman 1981), New Zealand (Cox and Skegg 1986), Belgium (Vyslouzilova et al. 1997), Slovenia (Kirn et al. 1992), Slovakia (Vlasak et al. 1991), Spain (Llorca et al. 1999) and in several countries of eastern Europe (Beral et al. 1994). Even Finland, with its remarkably successful screening programme, which had reduced the incidence of cervical cancer in 1991 to 2.8 per 100 000, has observed quite marked increases in incidence in younger women (below 55 years of age) since 1990 (Anttila et al. 1999). Probably, these trends are due to changes in sexual lifestyles and increased transmission of papillomaviruses in younger generations of women. Because the effect has been partly obscured by the protective effect of screening, in some countries, e.g. Sweden, there has been no increase in risk in young women (Bergstrom et al. 1999), and the upward trend in England and Wales has been successfully countered by a much improved screening programme, implemented in 1988 (Quinn et al. 1999).

The large international study of Vizcaino et al. (2000), of 25 countries, found declines in incidence of squamous cell cancers for younger (25–49) and older (50–74) women in most countries. Exceptions were the increases in young women in United Kingdom, Slovenia, and Slovakia, and Israel. With respect to adenocarcinomas, several studies have shown rising risk in populations where – presumably as a result of screening – incidence rates from squamous cell carcinomas are declining. Some of the studies are based on proportions of cancers by histology. Therefore it is difficult to know whether the proportions change due to increase in incidence of adenocarcinoma or decrease in incidence of squamous cell carcinomas. In an international comparative study, Vizcaino et al. (1998) found that the increasing risk of adenocarcinoma appeared to affect relatively recent generations of women from many countries. The cytological detection of adenocarcinoma or precursor lesions is undoubtedly less efficient than for squamous cell tumours (Fu et al. 1987, Sigurdsson 1995) and a case-control study (Mitchell et al. 1995) has shown that the risk of adenocarcinoma is not reduced by screening. The increasing incidence may reflect increases in exposure to the HPV in recent generations (the effect of which on squamous cell tumours has been diminished by screening programmes).

There is less information on time trends in cervical cancer in developing countries; as might be expected, the situation is quite varied. In general terms, rates of incidence and mortality have been relatively stable, or shown rather modest declines (Sankaranarayanan et al. 2001). The absence of the declines in incidence that have been seen in Europe and North America probably reflects the lack of systematic screening programmes, or, where they have been introduced, their low population coverage and poor quality cytology (Lazcano-Ponce et al. 1998). In Cuba (Fernandez Garrote et al. 1996) and Costa Rica (Herrero et al. 1992), for example, the screening programmes seem to have had virtually no impact upon incidence of cancer. In contrast, there appear to have been dramatic declines in the incidence of cervical cancer in China, for reasons so far unexplained, though it seems unlikely that they can be ascribed to screening. In Shanghai, for example, age-adjusted incidence of cervical cancer fell from 26.7 per 100 000 in 1972–1974 to 2.5 in 1993–1994 (Jin et al. 1999). Finally, there is limited evidence that in Africa, incidence may even have increased since the 1960s (Wabinga et al. 2000).

3.1.2 Cervical cancer in Thailand

Thailand is located in Southeast Asia between latitudes 5° 37′ N and 20° 27′ N, and longitudes 97° 22′ E and 105° 37′ E. Stretching about 1600 kilometers from north to south, it is bounded in the north by Myanmar and the Lao People's Democratic Republic, in the east by Lao People's Democratic and Cambodia, and in the south by Malaysia. The southern part is a long peninsular strip between the Indian Ocean to the west and the China Sea to the east. The area is 513 120 square kilometers. The climate of the country as a whole is dominated by monsoons; there are three seasons; summer, rainy and winter. Thailand is divided into 76 provinces, with four geographical regions: the Northern, Northeastern, Southern and Central.

The 1990 census enumerated 54 548 530 persons consisting of 27 061 733 males and 27 486 797 females and the 2000 census enumerated 60 916 441 persons consisting of 30 015 233 males and 30 901 208 females (National Statistics Offices 1994b, 2002c).

The number of registered medical practitioners was 16 569. The population to doctor ration was 3670.

For many years, specialised treatment for cancer has been provided by the National Cancer Institute, and oncological units in the major teaching hospitals. In addition, there are now six regional cancer centers have been established since 1989, and under the supervision of the National Cancer Institute, Ministry of Public Health. They have a role

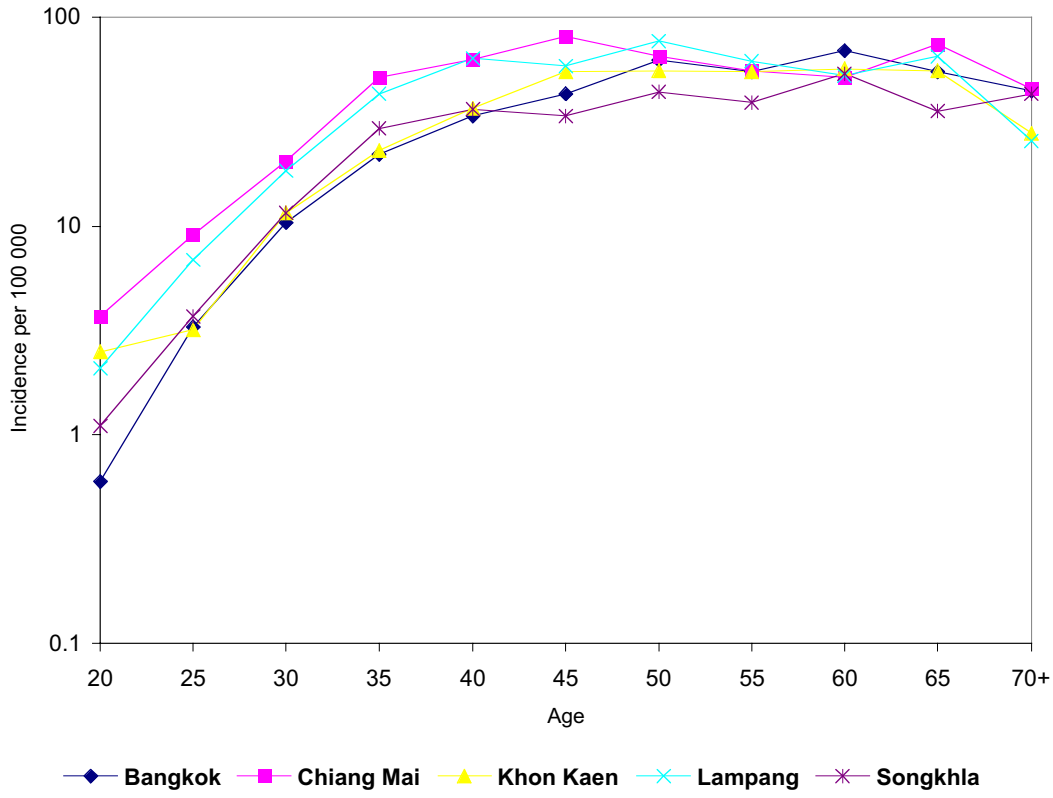
in all main activities of cancer prevention and control, including prevention, screening and tertiary care as well as having clinical cancer research activity.

Cancer registry in Thailand was started in 1971 by the National Cancer Institute (1973, 1982), with the collection of information on cancer patients treated in 53 hospitals throughout the country (7 in Bangkok and 46 provincial hospitals). Data collection was passive and relied upon notification from the hospitals. Though the collaboration has increased lately, this system was still unsatisfactory, because almost all community hospitals were not included in the registry. Incidence rate were therefore, underestimated.

The first population-based cancer registry started in 1986 in Chiang Mai, followed by Khon Kaen in 1988, Songkhla and Bangkok in 1990 and Lampang in 1993. Figure 2 shows the map of Thailand with the areas covered by these registries.

Figure 2. Thailand: regions and the areas covered by cancer registries.

The descriptive epidemiology of cervical cancer in Thailand has been reviewed in "Cancer in Thailand" volume I (Vatanasapt et al. 1993) and volume II (Deerasamee et al. 1999). In volume II cancer of the uterine cervix was the most common cancer in women with an estimated 5462 new cases in 1993. This confirms the finding in previously published case series, where cervical cancer has consistently emerged as the number one malignancy of women (Piyaratn 1959, Menakanit et al. 1971, National Cancer Institute 1982). The incidence was highest in Chiang Mai (ASR 25.7 per 100 000) followed by Lampang (ASR 23.1), Bangkok (ASR 18.5), Khon Kaen (ASR 18.0) and Songkhla (ASR 15.8). The age-specific incidence curves showed a pattern of early increase (starting before age 20), with a steep rise to about ages 45–50, followed by a plateau and a decline (Figure 3).



Source: Cancer in Thailand volume II (Deerasamee et al. 1999)

Figure 3. Age-specific incidence rates of cervical cancer in Thailand.

Eighty to eighty-six percent of the cases are squamous cell carcinoma, with adenocarcinoma accounting for 12–19% in all of the five cancer registries. Histological verification in all five registries was high and ranged from 73.6% in Khon Kaen to 98.8% in Chiang Mai (Deerasamee et al. 1999).

3.1.3 The Khon Kaen population-based cancer registry

Khon Kaen province is situated in the north-eastern region of Thailand. It covers an area of 10 886 km^2 and has a population of 1.67 million people with 50.2% males in 1995. The climate is tropical, with the mean temperature around 28°C. The average annual rainfall is approximately 119 cm. Agriculture, particularly rice cultivation, is the traditional occupation of the people; however, there has been increased industrialisation in recent years, especially in agroindustry and industrial establishments such as paper and pulp mills and breweries, which pollute the environment.

Oncologists at the Faculty of Medicine of Khon Kaen University initiated a hospital-based cancer registry in 1984 at Srinagarind Hospital. The success of this initiative and the apparent limitation hospital data for public health purposes prompted the establishment of a population-based registry with the aim of registering all incident cases in Khon Kaen province since 1988. The registry made additional efforts to collect, retrospectively information on all incident cases of cancer since 1985. Thus a cancer database with information on new cases occurring in this region became available for epidemiological and clinical research, and for public health purposes. The population-based cancer registry is under the administrative control of the Cancer Unit and a registry advisory committee consisting of representatives from each department of the university's faculty of medicine and other hospitals with major data sources.

The registry staff consists of three nurses, one computer technician-statistician and two clerks. Technical collaboration with the Unit of Descriptive Epidemiology of the International Agency for Research on Cancer (IARC), France was established at the inception of the population-based cancer registry. This helped the Khon Kaen cancer registry to develop a system of case-finding suited to local conditions.

Cancer registration is carried out using methodology described in IARC Scientific Publication No. 95, Cancer Registration: Principle and Methods (Jensen et al. 1991). Registration is mainly active: regular visits are made by the registry staff to data sources where the records are scrutinised and relevant information abstracted. The major data sources for the registry are Srinagarind Hospital (a university hospital with 800 beds), six other major public hospitals, 19 district (community) hospitals and eight private hospitals

in the province. Death certificates which mention cancer as a cause of death are obtained from the office of the Chief Medical Officer by registry staff. All certified cancer deaths are reviewed and matched with the incident case records of the registry. The cases for which no matching records found are traced back to find further relevant information. The cases which cannot be traced back to their hospital/physician records are categorised as death certificate only (DCO) registrations.

The registry covers the entire population of Khon Kaen province. The population structure is typical of a developing, country, with 29% of the population aged under 15 and only 4% aged over 65 (Figure 4).

Incidence data for the period 1988–1989 and 1990–1992 were included in volumes VI and VII, respectively, of Cancer Incidence in Five Continents (Parkin et al. 1992, 1997). Data for the period 1988–1991 were included in IARC Technical Report No. 16 "Cancer In Thailand, 1988–1991" (Vatanasapt et al. 1993) and were later peer-reviewed and published in the international literature (Vatanasapt et al. 1995). Data for the period 1992–1994 were included in Cancer in Thailand volume II (Deerasamee et al. 1999), while the results for 1993–1997 appeared in Cancer Incidence in Five Continents, volume VIII (Parkin et al. 2002).

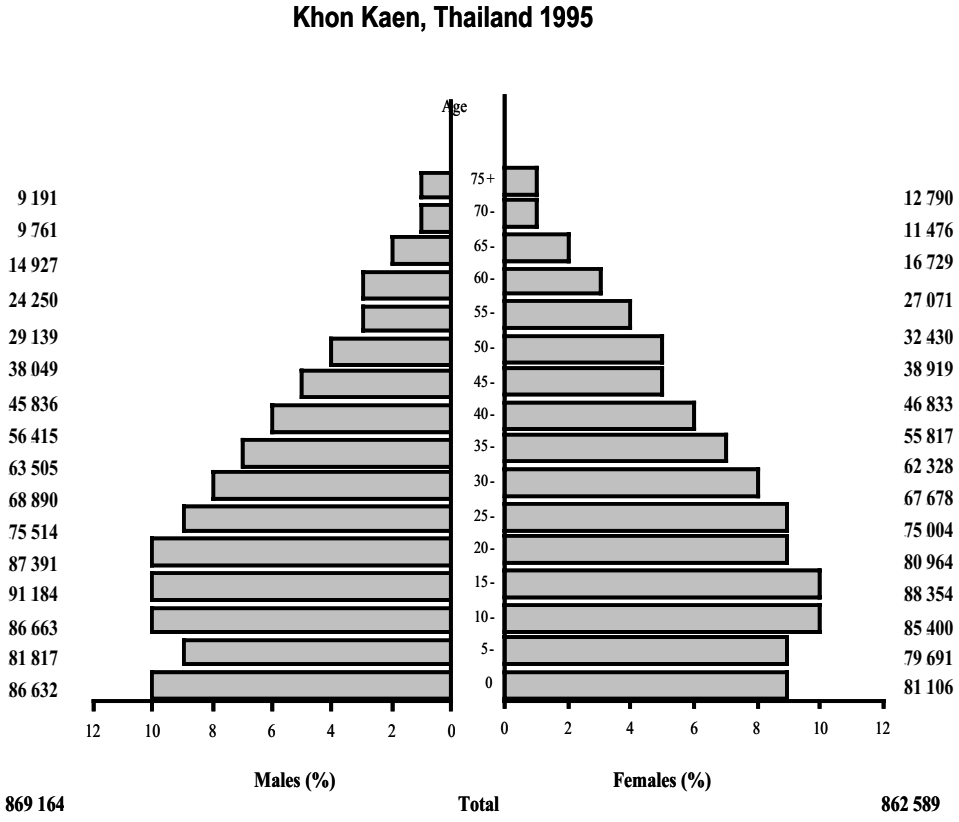


Figure 4. Population of Khon Kaen province, 1995.

3.1.4 Health care services in Khon Kaen

Health care in Khon Kaen province is provided free of charge for people of poor socioeconomic circumstances and at subsidised cost for others, in the public hospitals of the Ministry of Health. These hospitals are the major providers of primary and specialised health care in the region. The public health facilities consist of the University (Srinagarind) Hospital, the regional provincial hospital in Khon Kaen, a military hospital, two health promotion centres, in the city of Khon Kaen and 19 district hospitals. The ratio of physicians to population of the province is 1:3000.

Srinagarind Hospital provides comprehensive diagnostic and therapeutic services for cancer. Pathology, radiology, surgery, radiotherapy, chemotherapy, paediatric oncology and palliative care services are available in this institution. There are four pathology laboratories in the province, two public and two private. Diagnostic radiological facilities varying degrees of sophistication are available in seven public and eight private hospitals and the 19 community health centres.

Cancer-related surgical services are available at the University Hospital, the regional province hospital and three private hospitals. Radiation services are available only at the University Hospital since 1980. The facilities include two cobalt machines (for external radiotherapy); a low dose-rate caesium 137 after loading device and a high dose-rate cobalt 60 after loading device for brachytherapy. A linear accelerator and facilities for high dose-rate 192 are also available. Cancer chemotherapy is usually practiced only at the University Hospital and the Khon Kaen regional hospital.

3.2 Aetiology of cervical cancer

3.2.1 Studies in different countries

It was noted early that cervical cancer has quite marked differences in incidence, according to classical demographic variables (social class, marital status, ethnicity, religion). Later, epidemiological studies (mainly case-control studies) showed a consistent association between risk and early age at initiation of sexual activity, increasing number of sexual partners of females or of their sexual partners, and other indicators of sexual behaviour (Muñoz et al. 1992a, b). The part played by sexual behaviour of male partners in increasing risk was also the focus of interest in those areas

where cervical cancer was frequent, and where the median number of sexual partners in men is quite high much greater than many women, who are largely monogamous, such as in Latin America (Brinton et al. 1987, 1989a, 1989b). These findings were strongly suggestive of a causative role for a sexually transmitted agent.

3.2.1.1 Human papillomavirus (HPV)

Since the development of technologies for detecting the deoxyribonucleic acid (DNA) of human papillomavirus (HPV) in tissues was developed, the important role that they play in the aetiology of cervical cancer has been recognised. In the review by International Agency for Research on Cancer (IARC) in 1995 (IARC 1995), it was concluded that types 16 and 18 are definitely carcinogenic to humans. Types 31 and 33 were classified as probably carcinogenic and some other types as possibly carcinogenic. Epidemiological studies published later show that other types – notably 31, 33, 35, 45, 51, 52, 58 and 59 – can be considered carcinogenic to humans. IARC reviewed the case-control studies of HPV and cervical cancer available in the early 1990s, which showed a great majority of cervical cancers to contain HPV DNA, compared with some 5–15% of controls. It is now clear that, using sufficiently sensitive probes, HPV may be detected by PCR in virtually all cases of cervical cancer. It is therefore proposed that presence of HPV is necessary for development of the cancer (Wallboomers et al. 1999, Bosch et al. 2002).

HPV is clearly a sexually-transmitted infection. Cross-sectional studies, comparing women with and without infection, show that the risk is associated with sexual activity: number of sexual partners, age at which sexual intercourse began, and the probability that the sexual partner is a carrier of HPV (Hildesheim et al. 1993, Kjaer et al. 1997, Rousseau et al. 2000). The prevalence of infection with HPV is highest in young women, soon after sexual debut, and declines later in life to a plateau after the age of 30–35 (Jacobs et al. 2000, Molano et al. 2002). The prevalence in women after age 30 seems to be somewhat variable, but seems to be related to the risk of cervical cancer in the population: in many developing countries, it is around 10–12%, but lower than this in more affluent, or low risk populations (Herrero et al. 2000).

The role of infection with HPV in the development of cervical intraepithelial neoplasia (CIN), the precursor of invasive cervical cancer, has been demonstrated in two types of studies:

(i) Follow-up studies with repeated specimens from the same women

Repeated sampling of women has shown that the median duration of HPV infections is longer (around eight months) for high risk HPV types, compared with the low risk HPV types (Franco et al. 1999). The continuous presence of high risk HPV (HR-HPV) is necessary for the development, maintenance, and progression of progressive CIN disease (Koutsky et al. 1992, Remmink et al. 1995, Ho et al. 1995, 1998). A substantial fraction (15–30%) of women with HR-HPV DNA who are cytologically normal will develop CIN II or CIN III within four years (Rozendaal 1996, 2000, Moscicki et al. 1998). Conversely, among women found to be HR-HPV DNA negative and cytologically identified as either atypical squamous cells of undetermined significance (ASCUS) or borderline or mild dysplasia, CIN II/III is unlikely to develop during a follow-up of two years, and their cytology is likely to return to normal (Nobbenhuis et al. 2001a, Zielinski et al. 2001a).

Women found positive for low risk HPVs rarely become persistent carriers and their probability of progression to CIN II/III is extremely low (Manos et al. 1999, Zielinski et al. 2001b). In a cohort study in Sao Paulo, Brazil (Schlecht et al. 2001), the incidence of cervical lesions in women who were positive for HPV 16 or HPV 18 on repeat smears was 12 times higher than in those who were HPV negative twice. The clearance of HR-HPV in women with abnormal cytology is associated with the regression of CIN lesions, while persistence of HPV DNA after treatment for CIN II/III is an accurate predictor of relapse, and is at least as sensitive as repeated vaginal cytology (Nobbenhuis et al. 2001a, b).

(ii) Nested case-control studies are carried out within retrospective cohorts

These studies are based upon cohorts of healthy women recruited in the past, and for whom there are stored large banks of biological specimens. Linkage studies can then identify cases of cervical cancer (or any other condition) that have occurred in the interval and the original specimens can then be analysed for the presence of HPV biomarkers. HPV DNA prevalence can then be compared with the corresponding prevalence in specimens of control subjects (individuals from the same cohort who did not develop the condition under otherwise equivalent exposures). These studies have documented the existence of HPV exposure years before the development of the disease, thus reproducing the conditions of a longitudinal study. With this approach, a RR estimate of 16.4 (95% CI, 4.4–75.1) was seen for invasive cervical cancer in Sweden using DNA extracted from stored Papanicolaou (Pap) smears (Wallin et al. 1999) and a RR of 32 (95% CI, 6.8–153) was seen in the Netherlands (Zielinski et al. 2001a). In a similar study design, an OR of

2.4 (95% CI, 1.6–3.7) was obtained using serological markers of HPV exposure (Dillner et al. 1997).

Progression to CIN or invasive cancer has been shown to be related to the amount of HPV present (viral load) (Josefsson et al. 2000, Ylitalo et al. 2000). The reduction of viral load or clearance of viral DNA in repeated visits was shown in another study to predict regression of CIN lesions to normalcy (van Duin et al. 2002). These studies suggest that measuring viral load, at least of HPV 16, may distinguish between clinically relevant infections and those that are unlikely to progress.

The geographic distribution of HPV infection has been studied mainly in correlation with cervical cancer incidence rates, to determine whether variation in prevalences of HPV measured by DNA would be reflected in cancer rates. Recent geographic studies using sensitive PCR DNA testing methods to detect a wide spectrum of HPV types have generally observed HPV prevalences to correlate with the population risks of cervical cancer, although it has not always been possible to take into account the relative efficacy of regional screening programs (Muñoz et al. 1992b, Pham et al. 2003).

The recognition of the key aetiologic role of HPV infection has greatly changed the epidemiological study of cervical cancer. Yet although the essential role of HPV is now recognised, it remains important to determine which of the longer established "risk factors" for cervical cancer (demographic and behavioural variables) are just correlates of HPV infection, which are cofactors operating in the presence of HPV infection, and which are independent risk factors. It is therefore a reasonable approach to summarise what is known of the role of the longer established risk factors, without considering HPV infection, analogous to a "crude" statistical analysis that precedes consideration of confounding. Then, we should consider these established risk factors in light of the central role for HPV.

3.2.1.2 Social status

Many studies have demonstrated that women of lower socio-economic status (which may be defined by income level, educational level, housing type etc.) are at relatively higher risk of cervical cancer. These studies have been summarised by de Sanjose et al. (1997). HPV infection appears to be more prevalent in women of lower educational and income levels (Hildesheim et al. 1993, Varghese 2000). To some extent, this may be related to sexual behaviour of women in different social strata, but equally important, especially in some developing countries, is the sexual behaviour of males, and, in particular, use of the services of prostitutes. In addition, other correlates of social status such as nutrition, genital hygiene, parity, smoking, other genital infections, and use of preventive services

(especially screening) may be responsible for the observed differences. In a study in India, Varghese (2000) found that there was a significant association between social status and HPV infection, and social status remained a determinant of risk, even after adjustment for presence of HPV.

3.2.1.3 Religion

Certain religious groups in the USA, e.g. the Amish (Cross et al. 1968) and Mormons (Lyon et al. 1980) have been reported to have relatively low risks of cervical cancer, compared to the general population. Quite marked differences in incidence have been reported among the different religious communities in Bombay (Mumbai), India (Jussawalla and Yeole 1984). The extent to which these different cancer risks reflect prevalence of HPV infection has not been studied.

3.2.1.4 Marital status

Risk is higher in women who are divorced or separated, compared with married women. The risk of cervical cancer is especially high among women marrying at young ages (Boyd and Doll 1964). These associations are related to other aspects of sexual behaviour: number of sexual partners and age at initiation of intercourse (Terris et al. 1967).

3.2.1.5 Number of sexual partners

Women with cervical cancer more frequently report multiple sexual partners than controls. The risk appears to increase directly with the number of sexual partners reported (Brinton et al. 1987, Bosch et al. 1992, Eluf-Neto et al. 1994). Some studies showed a stronger risk associated with multiple sexual partners for cervical precursor conditions than for cancer, but this may be because the subjects were younger, and younger women generally report more sexual partners than older subjects. When HPV infection is taken into account, the effect of lifetime number of partners is weakened or disappears (Bosch et al. 1992, Schiffman et al. 1993, Hildesheim et al. 2001).

3.2.1.6 Age at first sexual intercourse

A number of studies have found that women having sexual relationships at early ages are at higher risk than either virgins or women whose sexual experiences begin later in life. However, age at first intercourse and number of sexual partners are usually highly correlated. Some studies, primarily of non-invasive lesions, have not found age at first intercourse to persist as an independent factor after adjustment for number of sexual partners (Harris et al. 1980, Slattery et al. 1989), while others found independent effects of both (La Vecchia et al. 1986, Brinton et al. 1987). Age at first intercourse might be viewed logically as a proxy for time of HPV infection; that is, the start of "latency". However, it might also suggest a "vulnerable period" of the cervix when the transforming effect of HPV is greatest. In this context, the number of sexual partners at different age intervals has been of interest. Brinton et al. (1987) and Herrero et al. (1990) failed to find that number of partners before age 20 was any more of a risk discriminator than lifetime number of partners but Peters et al. (1986a, b) found that the effect of lifetime number of partners was totally attributable to effects associated with number of sexual relationships before the age of 20. Most investigations have failed to detect any independent effect of frequency of intercourse on risk (Boyd and Doll 1964, Terris et al. 1967, Brinton et al. 1987, Herrero et al. 1990).

3.2.1.7 Menstrual and reproductive factors

There is little evidence that risk of cervical cancer is linked to age at menarche or age at menopause (Boyd and Doll 1964, Brinton et al. 1987).

In many studies, multiparity has been found to significantly increase cervical cancer risk (Brinton et al. 1987, 1989b). The prevalence of HPV infection is not increased in multiparous women (Hildesheim et al. 1993), so that it is not surprising to find that the increased risk of cancer is independent of HPV infection (Bosch et al. 1992, Eluf-Neto et al. 1994, Hildesheim et al. 2001, Bayo et al. 2002, Muñoz et al. 2002). It has been suggested that pregnancy could influence cell growth either directly or indirectly through immunological or hormone-dependent influences on HPV (Pater et al. 1990). Alternatively, the effect of pregnancy could reflect cervical trauma during parturition.

Some studies have found that there is an inverse association between age at first birth, and the risk of CIN III (Cuzick et al. 1990) or invasive cancer (Bosch et al. 1992). However, there is a strong correlation between the number of pregnancies (and age at first

intercourse) and the age at first birth. Adjustment for these factors weakens, or abolishes an independent effect of early age at pregnancy, or birth, on risk (Brinton et al. 1987, Muñoz et al. 1993, 2002). There is therefore little evidence that pregnancy at an early age increases cervical cancer risk per se, on account of some specific susceptibility of the cervix in adolescent women.

3.2.1.8 Genital hygiene

Some studies failed to find an association between hygiene factors and risk of cancer (Brinton et al. 1987, Herrero et al. 1990). However, in essentially rural populations from developing countries in Africa (Chaouki et al. 1998, Bayo et al. 2002) and in China (Zhang et al. 1989) significant elevations in risk have been found with poor hygiene (absence of genital washing and use and re-use of home made sanitary napkins). In the two studies in Africa, the associations are the same when adjusted for HPV infection.

3.2.1.9 Characteristics of the male sexual partner

The role of the male in the aetiology of cervical cancer has been suspected for some time, given that the disease is common in many societies where women have very few sexual partners in their lifetime (Skegg et al. 1982). This hypothesis has been studied comparing sexual and other behavioural characteristics of husbands of cervical cancer patients with husbands of women free of cervical disease (Brinton et al. 1989b, Kjaer et al. 1991). Husbands of cases reported significantly more sexual partners than husbands of controls, and, in several studies, husbands of cervical cancer cases were also more likely to report histories of various genital conditions, including genital warts, gonorrhoea and genital herpes. Consistent with these associations were low risks of cervical cancer when husbands reported frequent usage of condoms (Kjaer et al. 1991).

Of specific interest in these studies has been the relationship of cervical cancer risk to the type of sexual activity engaged in by the husbands. Although several studies have found excess risks associated with visits to prostitutes (Kjaer et al. 1991, Bosch et al. 1992), not all have done so (Brinton et al. 1989b). Nevertheless, this is clearly a very important consideration with respect to the elevated incidence in Thailand, as described below (Section 3.2.2) (Niruthisard and Trisukosol 1991, Thomas et al. 1996, 2001c). It is difficult to measure HPV presence in males, so that the relationship of infection to male sexual behaviour, and prostitute use, has not been investigated in detail. However, studies

of prostitutes confirm their high prevalence of infection (Ishi et al. 2000, Thomas et al. 2001c), and they are probably an important reservoir of infection in many societies.

3.2.1.10 Male circumcision status

Poor hygiene of the male partner has long been thought to play a role in the aetiology of cervical cancer, with special attention given to the effects of circumcision. Despite early reports of a protective effect associated with circumcision of the partner, many studies did not find much difference between case and control husbands (Boyd and Doll 1964, Brinton et al. 1989a). Prevalence of infection with HPV is lower in circumcised than in uncircumcised men (Moses et al. 1998, Castellsague et al. 2002).

3.2.1.11 Cigarette smoking

Cigarette smoking emerged as a possible aetiological factor for cervical cancer in many case-control studies (Winkelstein 1990). The effect was independent of various sexual and lifestyle variables such as sexual behaviour, but as the relative risk was not great (around two-fold), the suspicion remained that the effect was due to residual confounding for variables related to sexual activity (Phillips and Smith 1994). Recent studies, adjusting for presence of HPV, suggest that tobacco smoking does have an independent effect, with a relative risk of about 2.0 (Hakama et al. 2000, IARC 2003). Smoking effects appear to be restricted to squamous cell tumours, with no relationship observed for the rarer occurrences of adenocarcinoma or adenosquamous cancer (Brinton et al. 1986b). High levels of smoke-derived nicotine and cotinine found in the cervical mucus of smokers (Schiffman et al. 1987) suggest a possible biological mechanism for the smoking association, although the immunosuppressive effects of smoking should also be considered (Barton et al. 1988), particularly with respect to enhancing the effects of infectious agents, including HPV.

3.2.1.12 Contraceptive methods

Evaluating the effect of oral contraceptives on cervical cancer risk is complicated by the potential effects of confounding factors, especially sexual behaviour (Brinton 1991). However, most studies show some evidence of an increased risk, rising to approximately

a two-fold excess for users of five or more years, with, in several studies, higher risks observed for adenocarcinomas (WHO 1985, Brinton et al. 1986a, Beral et al. 1988, Moreno et al. 2002).

The effect of oral contraceptives on cervical cancer and precursor conditions might operate through enhanced viral persistence, or carcinogenicity, but studies of this question will need to carefully disentangle interactive effects from detection bias, since studies have shown increased HPV expression in oral contraceptive users (Lorincz et al. 1990). There has been particular concern about the possible increased risk in women using injectable contraceptives, but Thomas and Ray (1995) reported no trend in risk with duration of depot-medroxyprogesterone acetate (DMPA) use, the time since first or last use, or age at first use. The result provides reassurance that use of DMPA for over four years does not enhance risk of adenomatous cervical carcinomas, and risk is not increased after a potential latent period of over 12 years since initial exposure.

In a number of studies, users of barrier methods of contraception (diaphragm or condom) have been shown to be at low risk of cervical cancer (Boyd and Doll 1964, Wright et al. 1978), although the effect is not always very strong, and the role of confounding factors has not always been taken into account. The protective effect has been ascribed to the reduced opportunity for exposure to infectious agents, but this may not be HPV, since transmission of this virus has been shown to be little affected by condom use (Moscicki et al. 2001).

3.2.1.13 Dietary factors

The role of nutritional status to risk of cervical neoplasia has been of recurrent interest, mainly with respect to the possible protective effect of vegetables and fruits rich in carotenoids, and high dietary intake of vitamins A, C and E, as well as beta-carotene. Neither of the National Academy of Sciences reports, Diet, Nutrition and Cancer (NAS 1982) and Diet and Health (NAS 1989), nor the WHO report “Diet, Nutrition and the Prevention of Chronic Diseases” (WHO 1990) came to any firm conclusion. The review “Diet, nutrition and the prevention of cancer: a global perspective” (WCRF/AICR 1997) concluded that diets high in vegetables and fruits, and in carotenoids, vitamin C and E, found in foods of plant origin, are possibly protective.

3.2.1.14 Genetic factors

That there is some genetic predisposition to cervical cancer seems relatively clear, and this may be related to mutations in genes affecting immune response to infection or viral DNA replication (Allen et al. 1996, Odunsi et al. 1996). Several investigators have observed associations with human leucocyte antigen (HLA) alleles or haplotypes with cervical cancer, with most interest focused on genotypes of the HLA-D loci (Beskow and Gyllensten 2002).

3.2.1.15 Infectious agents other than HPV

Most attention has focused on herpes simplex virus type 2 (HSV 2) and *Chlamydia trachomatis*.

Laboratory studies have demonstrated that HSV can transform cells in culture, and because HSV 2 proteins and integrated DNA can be found in some cervical cancers (McDougall et al. 1986). Epidemiological support for the association of cervical cancer risk with HSV 2 infection derives from serological studies demonstrating higher prevalence of antibody to HSV 2 among cases of cervical neoplasia than controls. The virus may play a role, independent of HPV, since antibodies to HSV 2 are found to be related to modest increases in risk of cervical cancer in HPV positive women (de Sanjose et al. 1994). In one of the first studies on this topic (Hildesheim et al. 1991), a significant interactive effect of HPV 16/18 (as measured by the filter *in situ* hybridization technique) and HSV 2 was noted for invasive cervical cancer. In a meta-analysis of prospective studies no increased risk for cervical cancer overall was found (Lehtinen et al. 2002).

Chlamydia has been suspected to cause cervical cancer, based on cohort and case-control comparisons of serology (Schachter et al. 1982, Koskela et al. 2000). The IARC multicentre study found a two-fold increase in risk for the presence of antibodies, in women positive for HPV (Smith et al. 2002). There was proposed an antagonistic interaction of chlamydia and HPV on cervical cancer incidence (Hakama et al. 2000).

3.2.1.16 Immunosuppression/AIDS

The Center for Disease Control (CDC) has designated HGSIL (moderate & severe dysplasia) as a category B defining condition (symptomatic conditions in an HIV-infected

adolescent or adult), and invasive cervical cancer a category C defining condition (clinical conditions listed in the Aids surveillance case definition) of AIDS (CDC 1992). Studies in the USA, Italy, and France linking cohorts of subjects with HIV/AIDS to cancer registries have found an increased risk of invasive cancer of the cervix (Goedert et al. 1998, Franceschi et al. 1998, Serraino et al. 1999, Frisch et al. 2000), although a similar study in Australia was negative (Grulich et al. 1999). Estimates of the risk in these studies are between 5 and 15. It is not clear how much of the excess risk is due to the confounding effect of HPV infection, which is known to be associated with HIV infection, because of their common mode of transmission. The prevalence of cervical intraepithelial neoplasia (CIN) is clearly higher in HIV-infected women, although most of the early studies failed to adjust for infection by HPV. Careful adjustment for such confounding suggests that there is an independent effect of HIV on risk of CIN, although it is not very large, and that there is an interaction between the effects of HIV and HPV, as might be expected if the role of HIV was indirect, through creation of immune dysfunction (Mandelblatt et al. 1999).

In a linkage study between a register of recipients of renal transplants (who would be receiving immunosuppressive therapy) and the cancer registries of the Nordic countries, Birkeland et al. (1995) found a risk of cervical cancer 8.6 times (95% CI 5.7–13.0) that in the general population.

3.2.2 Studies in Thailand

The first study on aetiology of cervix cancer reported from Thailand (Punyaratabandhu et al. 1982) compared 212 cases of histologically-confirmed cervical cancer from 4 hospitals in Bangkok, with age matched (1:1) controls from 3 of them. Controls were women from gynaecology wards, without cancer. Although this probably over-matches for some exposure variables related to cervical cancer and other conditions, there were significant differences in the number of marriages, number of sexual partners, age at first intercourse, parity, and history of STD in the husband. Those who had multiple marriages, multiple sexual partners, lower age at first intercourse, higher parity and had a history of STD in the husband had higher risk for cervical cancer. The independent effect of these factors was not studied.

The study by Wangsuphachart et al. (1987), compared 189 women with histologically proved invasive cervical cancer admitted to Siriraj Hospital, Bangkok, in 1979–1983 with 1023 controls randomly selected from non-gynaecology wards of the same hospital. The risks associated with level of education, number of sexual partners,

age at first intercourse, parity, oral contraceptive use, intrauterine device (IUD) use were all non-significant. There was an increase in risk with increasing number of episodes of vaginal discharge. The study demonstrated the effectiveness of Pap smears in preventing invasive disease.

HPV DNA was found in 82–91% of cervical carcinomas in Thai females (63–65% were HPV 16 and HPV 18) (Sukvirach et al. 1994, Bhattarakosol et al. 1996) and in 9–20% of normal cervical smears (Sukvirach et al. 1994, Ekalaksananan et al. 1996, 2001). The role of HPV in cervical cancer in Thailand was first studied by Chichareon et al. (1998) in a case-control study in Hat Yai hospital in southern Thailand. A total of 338 cases of squamous cell carcinoma and 39 cases of adenocarcinoma were compared with 261 controls from the same hospital (without ano-genital cancers or tobacco-related diseases). HPV was detected in 95% of squamous cell carcinomas and 90% of the cases of adenocarcinoma, corresponding to odds ratios associated with HPV infection of 119 (95% CI 64–222) for squamous cell tumours and 53 (95% CI 17–163) for adenocarcinomas. In a model adjusted for HPV and other mutually confounding variables, there was an increased risk with lifetime number of sexual partners and the number of episodes of STDs. There was no independent effect of parity, after adjustment for HPV.

It has been pointed out (Skegg et al. 1982), that, in countries such as Thailand, where for the most part of women do not commence intercourse until after marriage, and generally have only one lifetime partner, the high risk of cervical cancer in the population cannot be due to female sexual behaviour. All studies in Thailand find that few women have multiple sexual partners, even in urban settings. For example, only 11% of control women in the study of Wangsuphachart et al. (1987) and 19% in women from Hat Yai, southern Thailand (Chichareon et al. 1998) reported having more than a single sexual partner. Thai men, in contrast, generally have many sexual partners, and visits to prostitutes are a common behaviour. Niruthisard and Trisukosol (1991) interviewed the husbands of cervical cancer cases and controls. They found that a history of venereal diseases (VD) in the husband was associated with an increased risk of cervical cancer (OR 2.1, 95% CI 1.1–4.0), and that visits to prostitutes were common (83% of control husbands). Even without a history of VD, prostitute visits were associated with a clear risk factor for cervical cancer in the wives (OR 6.5, 95% CI 1.3–61.5). Furthermore, the failure to use condoms during prostitute visits was associated with a risk 4.9 times (95% CI 1.2–23.9) greater than for husbands who did use condoms on these occasions. These results were confirmed in a larger study by Thomas et al. (1996), who found a trend in risk with the number of prostitute visits of the husband, and the age at which prostitute visits had begun.

Thomas et al. (2001b) present the results of a case-control study in Siriraj Hospital, Bangkok, conducted in 1991–1993. Cases were women with histologically proved invasive or in situ cervical cancer, born in 1930 or later. Two controls were selected per case, from otorhinolaryngology and surgical wards, matched by age (same 5 year group) and region of residence. An additional control (admitted for hysterectomy for non-malignant condition) had been recruited for the first 50 cases. As well as interviews with the women, an attempt was made to interview the husbands of married cases and controls. A total of 338 cases (75 of whom had carcinoma in situ) and 490 controls were interviewed. Cervical scrapes were obtained from all but one case, and from 60.4% (306) controls. There were 79% of the 190 cases of invasive squamous cell carcinomas positive for oncogenic HPV (Types 16,18,31,33,39,45) and 76% of the adenocarcinomas, compared with 3% of controls. HPV 16 was commonest in squamous cell carcinomas and HPV 18 in adenocarcinomas.

The case-control comparison reported is between women with invasive cancers positive for HPV 16 and /or 18, and HPV negative controls. The reason for this strange choice is not given, but the result is that one is examining differences between individuals with cancer and HPV, and those without either. Cases were more likely to have had more than one sexual partner (OR 1.5, non-significant), and the risk was increased with early age at first intercourse (OR 3.9, 95% C.I. 2.1–7.2 for age at first intercourse < 19 compared to >23). The association with use of oral contraceptives or DMPA was non-significant. The risk of HPV-positive cervical cancer was reduced in women using IUDs, but there was no association with smoking. There was no significant association with antibody to other STDs (syphilis, HSV 1, HSV 2, hepatitis B).

Results for the 75 in situ cases (Thomas et al. 2001a) showed a lower HPV prevalence (57%), but there were no significant differences in the distribution of the risk factors described above between in situ and invasive cancers. This suggested that they could be considered as the same disease, from an aetiological point of view.

Comparing the husbands (50) of women with invasive cancer reporting only one lifetime sexual partner, with 98 husbands of reportedly monogamous controls, Thomas et al. (2001c) found that risk of cancer in the women increased with the number of prostitute visits by their husbands, especially at a young age, and with infrequent use of condoms in this situation. However, HPV was rarely found in penile scrapings, and was no different in husbands of cases (7.0%) and controls (5.5%). Examination of groups of women working in a Bangkok brothel and massage parlour confirmed the higher prevalence of oncogenic HPV than in women attending family planning clinics.

3.3 Screening for cervical cancer

3.3.1 Screening in different countries

Screening for cervical cancer, using the PAP test, aims to identify the presence precursor lesions by cytology, allowing for their treatment. Screening programmes were introduced in many countries in the 1950's and 1960's. Evaluation of the effectiveness has been based upon observational studies of established programmes.

One method has been to follow incidence rates of invasive cervical cancer from cancer registries, especially if the changes can be linked to the intensity or coverage of screening programmes. Lynge (1983) examined data on incidence in women aged 30–59 in different counties of Denmark in relation to intensity of screening, and observed the greatest falls in incidence in those with most screening (particularly in organised programmes). In 24 counties of Sweden, Mahlck et al. (1994) found that the declines in death rates from cervical cancer since the early 1960s were related to the intensity of screening. The best known studies are those comparing incidence trends in the five Nordic countries (Hakama et al. 1982, Läärä et al. 1987). The extent of the decline in cumulative mortality rates was related to the coverage and extent of the organised screening programmes in the respective countries.

Considering the risk in individuals, rather than in populations, in relation to screening history, the cohort study (incidence rates of invasive cervical cancer in screened and unscreened women in a prospective approach) has been rarely used. Such studies require population registers linked to screening records, so that appropriate denominators can be calculated. Fidler et al. (1968) estimated the ever-screened and never-screened populations in British Columbia and calculated an age-adjusted relative risk for clinical carcinoma of 6.8 in the unscreened compared to the screened group.

In Sweden, Sparen et al. (1996) linked the population register and screening register for two counties, in order to calculate incidence rates between 1968 and 1992 in relation to screening history. Overall, the relative risk in ever- versus (vs) never-screened was 0.55, but with much lower risks (0.27–0.38) at ages 40–59. In Finland, Hakama and Räsänen-Virtanen (1976) followed up women invited to the national screening programme in 1963–1971. In age group 30–59, the risk of developing an invasive cancer by the end of 1972 was 0.2 in screened women, compared with average incidence of all women in the period before screening. In those invited who did not attend, it was 1.6. The estimated was protective effect of the screening programme 58%.

A complication with respect to evaluation of cervical cancer screening is that, although it aims mainly at detection and treatment of preinvasive precursor lesions (cervical intra epithelial neoplasia (CIN), etc.), and hence to prevent invasive cancer,

some of the benefit derives from detection and treatment of early, asymptomatic, invasive disease. Studying this latter component would require the cases to be confined to symptomatic cancers, advanced cancers, or even deaths from cervical cancer. However, the case group in most studies comprises all cases of cervical cancer, including cases found by screening. In these circumstances, screening tests at which the cancer was diagnosed should not be counted as exposure, which should include all previous tests during an interval corresponding to the pre-clinical detectable phase of cervical cancer. The natural history of cervical cancer includes a period of variable, but rather long (10 years or more) duration, during which CIN lesions are present. It is conventional to exclude tests after the first one found to be positive, since a positive test is often followed by one or more confirmatory tests, prior to definitive diagnostic procedures, and these cannot be considered as screening tests. It is important to exclude Papanicolaou (Pap) smears performed for diagnostic purposes – because of symptoms – since if they are included the cases will have an apparent excess of screening tests. However, because it is very often difficult to decide the motivation for a Pap test (on the part of the subject and/or the examiner), exclusion of symptomatic or diagnostic tests is difficult, and many investigators choose instead to exclude all tests within 6 months or 1 year of diagnosis in the cases, and for an equivalent period in matched controls. This will result in exclusion of some screening tests that proved to be positive, mainly in the cases, and lead to an underestimate of screening in cases and hence an overestimate of its protective efficacy.

Case-control studies of the efficacy of the Pap smear test have been reviewed by Parkin (1997) and by Zappa and Ciatto (2001). All studies show a lower risk of cervical cancer in screened compared to unscreened women. A major concern, as in all observational studies of screening, is the selection bias involved, that is, women who choose to be screened are at lower (or higher) risk of disease, irrespective of receiving the test. One approach to this problem has been to adjust for obvious confounders – factors related to the risk of cervical cancer which are also related to probability of being screened – usually (in addition to age) such items as socioeconomic status/education, parity, sexual history. In general, adjustment makes little difference, and in no study was the conclusion concerning the protective effect of screening changed. Weiss et al. (1992) have proposed confining analysis to a comparison of tests in a defined interval before diagnosis in the cases (and associated controls), and use earlier tests (which could not possibly have found an asymptomatic cancer) to control for selection bias. Intention to screen principle removes this bias (Hakama and Räsänen-Virtanen 1976) but is applicable only in organised programmes with individual invitation.

It is unlikely that cytological screening has any effect in reducing the risk of adenocarcinoma of the cervix. Adenocarcinomas occur within the cervical canal (from the

glandular epithelium) and do not share the same risk factors or natural history as squamous cell tumours. Many studies show rising incidence rates of adenocarcinoma, in populations where screening has reduced the incidence of cervical cancer (Vizcaino et al.1998) and a case-control study (Mitchell et al. 1995) has shown that the risk of invasive adenocarcinoma is not reduced by screening.

3.3.2 Screening for cervical cancer in Thailand

In Thailand, as in most Asian countries, there has been no truly 'organised' programmes of screening for cervix cancer, involving identification of women of risk, ensuring their examination at regular, defined intervals, with appropriate follow-up and treatment of those found to have as abnormal finding on cytology. For the most part, screening has been provided to women 'on demand', or when attending services such family planning, pregnancy counselling, ante and post-natal clinics, sexual transmitted diseases (STD) clinics and so on. Generally, however screening is even more haphazard than this, involving fee-for-service testing by doctors, with sporadic campaigns mounted by local health departments, or charitable foundations. In 2002, government policy has adopted the goal of screening the entire population of women in Thailand who are aged 35, 40, 45, 50, 55 and 60 (Deerasamee et al. 2002). As a first step, measures to increase the capacity for obtaining and interpreting Pap smears have been put in place with training courses for nurses and cytologists, as well as for treating the abnormalities detected by screening, with cryotherapy and loop electrosurgical excision procedure (LEEP).

Although a national cancer control committee has recently been established, there is as yet no official cancer control programme in Khon Kaen province. However, the Cancer Unit at the University Hospital has assumed a leading role in providing cancer preventive and therapeutic services in the province. Opportunistic Pap smear screening is offered in the district hospitals through the gynaecology services. So far, it has been the more health-conscious people who have been screened, whereas some high-risk groups, such as promiscuous women, have not been the targets of screening.

There have been few studies of the effectiveness of screening with Pap smears in Thailand. In the hospital-based case-control study by Wangsuphachart et al. (1987), women who had had a previous Pap test decreases with increasing frequency of having a Pap smear. Those women who had Pap smear once a year had a lower risk for cervical cancer than who never had Pap smear (OR 0.25, 95% CI 0.1–0.6). Thomas et al. (2001b) in a similar study in the same hospital, found that a history of previous Pap smear was protective, with a very low risk (OR 0.15 95% CI 0.01–0.70) in women who had had a

smear 1–12 months previously. Chichareon et al. (1998) in a larger hospital-based case-control study in southern Thailand, found that the risk of cervical cancer increased with the interval since the the previous Pap test.

Other methods of screening are being tested in Thailand. In Roi Et province, near to Khon Kaen, an experimental project is evaluating the safety and efficacy a programme based on screening by visual inspection following acetic acid (VIA), followed by immediate treatment of observed lesions by cryotherapy ("see and treat") (Gaffikin et al. 2003). This approach has been suggested to be a more cost effective method of reducing death and disability in developing country populations than the conventional Pap smear programme (Goldie et al. 2001, Mandelblatt et al. 2002).

3.4 Survival of cancer patients

3.4.1 Interpretation of survival statistics

Information on survival has long been recognised as an important indicator in monitoring cancer control activities (WHO 2002). Survival statistics are derived from three types of sources: the randomised controlled clinical trial, which represents the 'gold standard' for the evaluation of different methods of treatment; the hospital-based study, which gives information about the outcome of treatment in particular settings; and population-based survival from cancer registries, which reflects on an average, the result of the whole range of cancer control activities, including screening and the organisation of treatment services (Black et al. 1998).

Survival information from trials and published hospital series is relevant to selected groups of patients. The idea of the clinical trial is to eliminate the confounding effects of factors such as age and co-morbidity in order to isolate the effects of treatment. This is achieved in two ways: by adopting selection criteria which exclude some subjects (such as those with co-morbidity conditions) and randomisation of the remainder into groups in which the only systematic differences are the treatments to be received. This approach is essential in order to get an accurate idea of the efficacy of particular treatments for choice of treatment.

However, the effectiveness of cancer services in general depends not only on the treatment given to patients but also the context in which they are applied. Evaluating effectiveness requires estimation of survival in unselected groups of cancer patients, which is a key aim of population-based cancer registries. Population-based survival is measured on the totality of cancer patients – including those who receive no treatment whatsoever. Estimates of survival in such groups may be influenced by a range of

prognostic and other factors. To study the influence of these the approaches familiar to epidemiologists in the context of observational studies of cancer cause must be used. This means using statistical adjustment for the variables known to affect survival, which are not the primary focus of the analysis. Some prognostic factors, such as age and sex, are always available, and usually so too are tumour-related variables such as sub-site and histological type.

Stage of disease at diagnosis is generally the most important factor determining the survival of cancer patients, so that variations in the stage distributions of tumours in populations being compared are of particular concern. Many cancer registries attempt to collect data on extent of disease. However, there are known variations in the diagnostic techniques used to determine stage, and in the adequacy of recording and abstracting the relevant data, which lead to considerable measurement error. Comparisons of stage-specific survival data between population-based registries should therefore always be done with this potential problem in mind.

It should be noted that survival is not an adequate indicator of the effectiveness of cancer control by itself, and observed difference must be taken in context, together with incidence and mortality. Since earlier diagnosis of cancer will bring forward the date of diagnosis of a condition, duration of survival will improve, whether or not there is any improvement in the effectiveness of treatment in reducing risk of death from the disease (Welch et al. 2000). This is called lead-time bias. In addition, screening programmes may result in the detection of disease that never otherwise have been diagnosed during the life of the patient – so-called 'overdiagnosis bias'. Including cancer cases that are not at risk of death in the series of subjects will necessarily result in a marked improvement in survival, and one that is independent of any 'downstaging' effect of screening. Stage shift resulting from screening can, theoretically at least, be monitored in cancer registry data.

3.4.2 Estimation of survival

3.4.2.1 Statistical methods

If we were able to obtain complete follow-up information for each individual in a group under study, then the probability survival during a period t_i could be estimated simply from the proportion of survivors at the end of the period (t_i) among all subjects alive at the beginning of the period. With cancer registry data, we are usually concerned with periods of elapsed time between the date of an incident case and some fixed point of follow-up time such as five years after the date of incidence. In practice, the follow-up of persons registered with cancer is not complete, either because the follow-up of a patient is

less than t_i or subjects become lost to follow-up during $(0, t_i)$, for example by moving out of the area of surveillance or failure to reach the patient. The former cases are called withdrawals, the later ones losses. This is illustrated in the upper part of Figure 5, which shows follow-up of three subjects A (death during follow-up = d), B (loss to follow-up = l) and C (withdrawal at the end of follow-up = w). The date of incidence is shown as i.

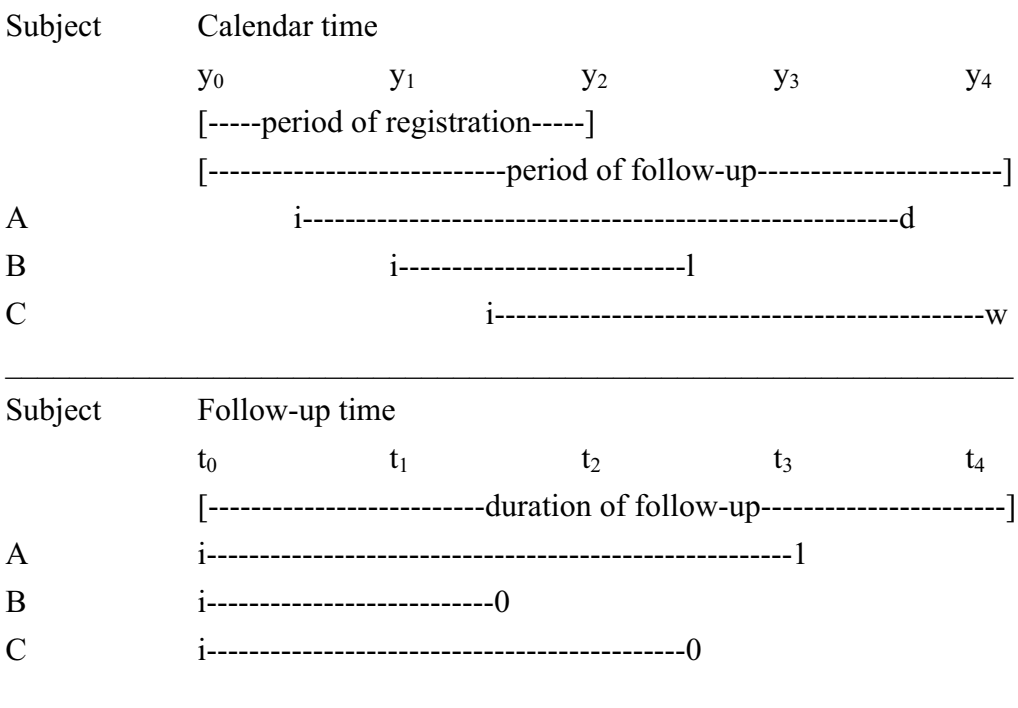


Figure 5. Illustration of follow-up of subjects in a survival study.

The second part of Figure 5 illustrates the same information in terms of the duration of follow-up. This is the usual way in which survival data have been analysed from cancer registry data sets. Subject A is diagnosed with cancer during the first year of the period of registration y_0 to y_2, and dies between y_3 and y_4, denoted d, which is within the period of possible follow-up by the registry. In the second part of the figure, this is shown in terms of the duration of follow-up as three years between incidence and death. Subject B is diagnosed at the beginning of y_1 but is lost to follow-up (l) between y_2 and y_3, for a duration of follow-up 1.5 years. Finally, subject C is diagnosed between y_1 and y_2 and is still alive at the end of the follow-up period of the study, y_4. Subject C is withdrawn alive after 2.5 years of follow-up time t. It will be seen that the characters d, l and w have been replaced with the values 1, 0 and 0, respectively, in the second part of the figure. This reminds us that, when we come to enumerate the number of deaths during follow-up, only Subject A's death is known to us. Subject B has incomplete follow-up and C has

completed follow-up without dying and both will be censored (Black and Swaminathan 1998). Although there is no information about the deaths of subjects B and C, we can use the information that they did not die during the period in which they were being followed-up in estimating the probability of survival for the study group as a whole.

To prepare data for survival analysis, the time elapsed between the date of incidence and the date of death, or date of censorship, for each individual must be defined. The precision of these survival times calculated from cancer registry data depends on the method of follow-up used by the registry. Some registries employ passive follow-up, which relies on notifications of deaths of cancer patients to the registry by national statistical organisations. Other registries use active follow-up, in which information on the survival status of patients is sought by the registry some time after the date of incidence, (ideally) at the anniversaries of this date. Active follow-up by cancer registries can be achieved by using clinical follow-up systems, by contacting patients' family doctors, or by contacting the patients or their families directly, by postal enquiries or even home visits. The quality of follow-up information depends on quality of national statistical organisations, on coverage of active follow-up and on quality of linkage methods.

3.4.2.2 Actuarial (life-table) methods

There are two related approaches to the estimation of survival: the Kaplan-Meier and actuarial, or life-table, methods. The former is particularly useful when exact survival times are available, since smooth estimates of survival as a function of time since diagnosis can be obtained. The actuarial method requires a life-table with survival times grouped usually into intervals which permits the calculation of the cumulative probability of survival at time t_i from the conditional probabilities of survival during consecutive intervals of follow-up time up to and including t_i. The layout of calculation of the elements of a life-table is shown in Table 1.

Table 1. Calculation of the cumulative probability of survival using the actuarial method (525 patients with cervical cancer in Khon Kaen, Thailand in 1986–1990, follow-up to the end of 1990).

Interval	Years	Alive at t_i	With-drawal	Lost	Last seen alive during interval (wi+li)	Number of deaths during interval	Effective number at risk	Proportion dying during interval	Proportion surviving to t_{i+1}	Cumulati-ve prob. of survival t_{i+1}
I	t_i, t_{i+1}	n_i	wi	li	ci	d_i	N_i	q_i	s_i	S_{i+1}
1	0-1	525	84	73	157	54	446.5	0.1209	0.8791	0.8791
2	1-2	314	75	6	81	34	273.5	0.1243	0.8757	0.7697
3	2-3	199	75	2	77	17	160.5	0.1059	0.8941	0.6882
4	3-4	105	48	0	48	6	81	0.0741	0.9259	0.6373
5	4-5	51	49	0	49	2	26.5	0.0755	0.9245	0.5892

For each time period t_i to t_{i+1}, the n_i is the number of subjects at risk of death at the beginning of the interval. The numbers of cases which are censored during the interval, whether because of loss to follow-up or because they were withdrawn alive at the end of the follow-up period, are denoted = c_i (l_i + w_i). The d_i is the number of subjects who died during interval. Values for the n_i, c_i and d_i can be obtained directly from the survival times and outcomes (1=death, 0=censored) from the data set out as in Figure 5. The effective number of subjects at risk on each interval is calculated as

$$N_i = n_i - (c_i/2).$$

Hence, subjects who were censored at some point during the interval t_i to t_{i+1} are assumed to have been followed-up for, on average, half of the interval. Having estimated the effective number of subjects at risk, the probability of death during the interval from is

$$q_i = d_i/N_i \ .$$

The probability of survival during the interval t_i, t_{i+1} is then

$$s_i = 1 - q_i$$

from which the cumulative probability of survival up to time t is derived from the product of the s_i,

$$S_i = \prod_{j=1}^{i} s_j .$$

The final quantity estimated, S_i, is often multiplied by 100 to give the 'percentage survival' at time t_{i+1}.

In the actuarial method, information from all cases is used in the estimation of survival, including cases which are lost to follow-up. However, the estimation of the effective number of subjects at risk involves the assumption that censored cases are actually followed-up for, on average, half the length of a given interval and that such cases are subject to the same probability of death as the cases with complete follow-up

during the same interval. In the analysis of registry data, this assumption may be invalid. For example, at the beginning of follow-up, when cases are under short-term clinical surveillance but are then lost to follow-up by the registry, the average survival times of the censored cases may be less than half of the length of the first interval. Furthermore, the true probability of death of the censored cases may be greater than assumed if cases of poor prognosis are more likely to be lost to follow-up (Black and Swaminathan 1998). These problems are addressed by methods of "loss adjustment" as described in 3.4.3.

Also includes deaths from intercurrent disease (not cancer) column d_i, along with deaths from the cancer of interest. "Observed survival" is therefore influenced not only by mortality from the cancer of interest, but by deaths from other causes. If we wish to compare survival in groups which are heterogeneous in terms of their risk of death from causes other than a particular cancer of interest, then observed differences between the groups concerned may be due in part to variations in risks of death from these other causes rather than from the cancer under study. Estève et al. (1990) describe the 'net survival', which is the survival which would pertain if deaths from other causes did not occur. In other words, net survival is the inverse of cause-specific mortality. One way of estimating the net survival is to censor cases at the point of death from causes other than the cancer of interest. This is called the 'corrected survival'.

3.4.2.3 Kaplan Meier (K-M) or Product-Limit (P-L) method

This P-L method in the analysis of censored data was suggested by Kaplan and Meier in 1958, especially for studies/trials in which the exact survival is being analysed while a number of patients are still surviving. One important assumption is the independence of survival times and censored variables. This is an alternative method to the actuarial method for computing survival rates. In the P-L method, precise survival time is used and therefore the information is used with greater efficiency than in the actuarial method. If death from the disease under study is regarded as an end point then deaths due to intercurrent diseases are taken as censored variables. The only difference between the actuarial and P-L methods is that the intervals in the latter are smaller (in principle without any limit), and estimates are obtained at the point of occurrence of an event. This method yields a step function. For samples N, the P-L estimate is obtained by listing the N observed life times (either death or loss to follow-up) in increasing orders of magnitude such that $0<t_1< t_2< t_3<..< t_N$.

The P-L estimates are derived using products of conditional probabilities of surviving in interval, so that

$$P(t_i) = \prod_{k \le i} P_k$$

Where P_k = $1 - 1/R_k$, if death occurs at t_k

= 1, otherwise

and R_k = the number of individuals alive at t_k

3.4.2.4 Relative survival

As described above, the method of calculation of observed actuarial survival relates to deaths from all causes among the group of cancer patients under follow-up. Although "corrected survival" can in principle avoid this problem, good enough information about the cause of death of cancer patients is often not available. This may be because of incomplete follow-up of all subjects or because the death certification is not sufficiently accurate to discriminate between deaths due to the cancer under study and deaths due to other causes. Relative survival method does not need cause of death to be specified. The relative survival at the end of an interval beginning at t_i is defined as

$$R_i = S_i / S_i^*$$

where S_i is the observed survival for subjects with a particular cancer and S_i^* is the expected survival of a group of individuals with the same demographic characteristics (age, sex, year of diagnosis etc.) who are at risk of death only from causes of death other than the cancer under study (Ederer et al. 1961). As long as the cancer of concern does not make a large contribution to overall mortality, we can estimate the expected number of survivors from life tables based on all causes mortality in the general population to which the cancer patients belong.

3.4.2.5 Age standardisation

For comparisons between different populations, some age standardisation of survival is necessary. This is because for many types of cancer, the risk of dying as a result of the cancer itself is clearly associated with a subject age at diagnosis as discussed above. The method of relative survival takes account of variations in the age structure of the groups only to the extent that age is correlated with risk of death from all causes. Direct standardisation of age-specific relative survival estimates provide the age-standardised relative survival (ASRS),

$$ASRS_i = \left(\sum_x r_{ix} w_x\right) / \sum_x w_x$$

where the r_{ix} is the age-specific relative survival estimate of age group X at the end of follow-up period t_i and w_x is the weight for each age group. For survival studies, weights may be taken from a 'standard case series' – for example the age-specific proportions from the world standard cancer patient population for the appropriate site of cancer (Black and Bashir 1998).

3.4.3 Loss to follow-up

We already described how the actuarial and P-L methods use information from all subjects, also from those who are lost to follow-up before death or withdrawn alive at the closing date of the study. But, in doing so, it is assumed that the censoring is necessarily random. This assumption may not be true in practice. It is very important therefore that the proportion of patients followed-up to death, or to the closing date of the study, should be as high as possible.

3.4.3.1 Determinants of loss to follow-up

In most circumstances, especially in developing countries, censorships are due to loss to follow-up and not only due to withdrawal, i.e. to technical reasons e.g. termination of study. Several factors contribute to the general dropout from medical care and hence will tend to increase the proportion of cases with incomplete follow-up information.

Typically, in developing countries, cancer patients no longer being follow-up in hospital have to be traced by active methods, involving postal enquires or home visits, as described later. For economic reasons, patients may migrate from their usual place of residence to that of their relatives and the hospital/medical centre may not be informed of the change in address. This makes tracing of patients at home difficult, since the new contact address must be obtained from other sources, neighbours or friends, for example.

Loss to follow-up may be associated with several characteristics of the subjects, and some of these characteristics are associated with the prognosis. Loss to follow-up is more frequent among elderly patients. Rural patients living far from hospital facilities may seek initial treatment and then fail to report for further medical care for various possible reasons e.g. lack of transport. Due to a lack of health awareness, some patients seek medical care at advanced stages of disease, and patients with advanced disease may be more likely to be lost to follow-up than those with localised disease. The treatment itself may contribute to dropout from medical care since the patient may be weak from malnourishment (due to financial status of the individual), especially when undergoing

therapies with serious side effects. Such patients are more likely to be lost to follow-up. In these circumstances, it is easy to see that the loss to follow-up is not random, but is likely to be correlated with death, so that estimates of survival assuming that "lost" patients are a random sample of the whole, are likely to be biased. Application of standard methods suggested in the literature for estimating the survival rates are not appropriate in situations where the losses are related to outcome. Because of this, methods have been developed to adjust for loss to follow-up so as to provide less biased estimates of true survival.

In summary, it is important to realise the qualitative difference between an informative and non informative censoring. If the loss to follow-up is associated with the outcome event studied, say death, the conventional methods of estimating the survival probability introduce a bias. Hence it will be appropriate to test the randomness of the loss to follow-up.

3.4.3.2 Adjustment for loss to follow-up

Regression method is one of the techniques to adjust for loss to follow-up that developed by Ganesh (1995), using logistic regression (Breslow and Day 1980) to predict the probability of death of a patient lost to follow-up based on his/her background factors e.g. age, stage. Logistic regression is applied to calculate the expected deaths among those lost to follow-up by assigning the same probability of death as for patients with complete follow-up.

The model used for prediction is $q = \exp(u)/[1+\exp(u)]$ or $\exp(u) = (q/1-q)$

Where the ratio$(q/1-q)$ is the odds of an event.

Taking the natuaral logarithm, we have $\ln(q/1-q) = u$ where u is a linear function of the prognostic variables, i.e. it is expressed as $u = (b0+b1X1+ \ldots. +bnXn)$

Where b1, b2, …, bn are unknown regression coefficients of variables X1, X2, …. ,Xn and b0 is the baseline hazard with covariate zero.

3.4.4 Factors influencing cancer patient survival

Survival is influenced by several important demographic and prognostic variables.

3.4.4.1 Age at diagnosis

As described above, relative survival method takes into account the effect of age, in that it allows for mortality at different ages from causes other than the cancer we are studying. But survival from cancer also depends upon age of the patients. In the Eurocare study (Berrino et al. 1999) for example, relative survival of cervical cancer cases aged 15–44 years at diagnosis (75% at five years) was more than twice that of women who were aged 75 or more (36%), with a clear decreasing trend in survival with increasing age. In particular, increasing age may be accompanied by the presence of co-morbidity-disease such as hypertension, cardiovascular disease etc. that made the patient less likely to receive optimum treatment, or to have a good result from it. Clarification of this question might provide some insight into the biological aspects of the tumour and tumour-host relationships.

3.4.4.2 Socioeconomic factors

The influence of social environment in relation to survival has been a major topic of research in recent survival studies and efforts have been made to evaluate the relationship between social class and survival of cancer patients. Social class has been defined in many different ways. Income, education, occupation and rent paid have been used as indicators of social class. Auvinen et al. (1995) studied social class and cancer patient survival in Finland, and found a statistically significant linear effect of social class on age-adjusted relative risk of cancer death, with the risk being higher for those in the lowest social class. The relative risk of death due to cervical cancer was 0.58 (95% CI 0.39–0.89) for patients with social class I (the highest social class) compared to patients with social class IV (the lowest social class). These findings indicate that social class is an important determinant of cancer patient survival.

Kogevinas and Porta (1997) have summarised the results of 30 studies (23 population-based and 17 hospital-based) examining social class differences in cancer survival. Ten studies had examined survival from cancer of the cervix. In eight of these studies, patients of lower social class had poorer survival than those in high classes, although the differences were not very big. The differences may relate to timing of diagnosis (lower social class patients present later), in treatments applied, in the biological characteristics of the neoplasm, or in host factors. Staging procedures may be less intensive in lower social class patients, so that there may be misclassification of more advanced cancer to earlier stage disease. The life-tables (all-cause mortality) used to

calculate relative survival do only seldom allow for differences in competing causes of death between social classes. In general it is thought that this is not an important source of error, however.

3.4.4.3 Stage of disease

It is known that stage of the disease is an important determinant in prognosis of cancer patient survival. The International Union Against Cancer (UICC 1987) published a classification and coding manual for staging of cancer tumour/node/metastasis (TNM) for uniform reporting and comparison with International Federation of Gynaecology and obstetrics (FIGO). Shambaugh and Weiss (1977) grouped stage I (A,B) as localised, stage II (A,B) and III (A,B) and stage IV(A) as regional involvement and stage IV (B) as Distant metastasis. This summary stage has been used in the results for comparison between the registries in the result chapter.

Dickman et al. (1999) studied the survival of cancer patients in Finland from 1955 up to 1994, patients were followed-up to the end of 1995. Results showed that patient survival improved over time for almost all anatomical sites. The increasing survival rates reflect improvements that have taken place in various areas of cancer control, from health education and early diagnosis to treatment and after care. The main exception is in cancer of the cervix uteri, where patient survival has decreased slightly from 1965–1974 to 1985–1994 due to the selective prevention of less aggressive tumours through cytological screening.

3.4.5 Previous studies of survival from cervical cancer in Thailand

Survival statistics from cancer registries in developed countries such as the US, Canada, European countries, Japan and Australia have been published over the years (Hakulinen et al. 1981, Berrino et al. 1995, Inoue et al. 1998, Berrino et al. 1999, SEER 2002). Publications on cancer survival from developing countries were sparse until 1995 (Nandakumar et al. 1995, Sriamporn et al. 1995). Sankaranarayanan et al. (1998) dealt with the comparison of survival experience from several registries in developing countries. There has been a spurt in the survival studies from developing countries in recent times following international collaboration which paved the way for the improvement of the infrastructure for follow-up (Graupera et al. 1999, Gajalakshmi et al. 2000, Yeole et al. 2001).

Few studies of survival from cancer of the cervix have been published from Thailand. Martin et al. (1998) reported a five-year relative survival of 68.2% during

1988–1992 in Chiang Mai. The five-year observed survival was 89% for localised disease, 64.5% in cases with regional extension and 34.5% in patients with distant metastasis, while in Khon Kaen, the five-year observed survival with localised stage was 75%, 50% in regional extension and 25% in distant metastasis patients. The overall 5-year relative survival in Khon Kaen in 1985–1992 was 57.5%. (Sriamporn et al. 1995, Vatanasapt et al. 1998).

Srisupandit et al. (1990) reported on survival in a hospital-based series of cervical cancer cases in Bangkok, in 1979–1983, five-year observed survival was 93.8% in patients stage I, 63.1% in patients stage II and 42.2% in patients stage III. The overall five-year observed survival was 61.6%.

3.5 Mortality data on cervical cancer

Statistics on death in Thailand in both urban and rural areas are complete, since all deaths must be certified and reported to the district office within 24 hours. Tabulations of mortality statistics are published annually by the Ministry of Public Health. The person responsible for certifying death varies from medical doctors, other medically qualified personnel to the head man of the village. The information recorded on the death certificate particularly the medical information on cause of death in remote villages is correspondingly poor. There is a strong tendency to record "heart failure" as the first cause of death on the certificate, even in the case of hospital deaths. The proportion of certificates issued by non-medical personnel in Bangkok and other provinces varies between 7.0% and 19.4%. The quality of the information recorded on death certificates can be evaluated from the percentage of deaths which are coded as "Symptoms, signs, and ill-defined conditions (including senility)". This was almost 60% in 1970, but had fallen to 48% by 1987 (Vatanasapt et al. 1993).

The proportion of cancer deaths which are recorded with inadequate specification of primary site is very high – in 1987 this was 53% in men and 57% in women.

With respect to death due to cervical cancer, the recorded mortality appears to have been increasing over the years. However, the mortality rate reported is very low, in comparison with incidence rates from the cancer registries (the age-standardised incidence rate was estimated as 20.9 per 100 000 in 1993, for example, compared with a reported age-standardised mortality rate of just 0.91 per 100 000 in 1994). As well as uncertainly about completeness and accuracy of recording cause of death, it is clear from Table 2 that a varying number of uterus cancer deaths may be coded as “uterus, unspecified” or corpus uteri from one year to another, so that any interpretation of trends in mortality is impossible, or that any estimate of corrected survival is biased.

Table 2. Mortality rates (per 100 000) from cancer of cervix uteri, corpus uteri, and uterus NOS, in Thailand.

Year	Cervix	Corpus	Uterus NOS
1975	0.68	0.00	3.33
1976	0.49		
1977	0.62	2.42	0.09
1978	0.98	2.63	0.04
1979	0.57	0.52	2.58
1980	1.26		
1981	1.23	2.18	0.02
1982	1.07	2.71	0.00
1983	1.29	2.29	0.00
1984	0.61	2.01	0.00
1985	1.21		
1986	0.55	0.84	0.94
1987	0.67	1.46	0.77
…….*			
1994	0.91	0.13	2.05

*1988–1993 data not available Source: WHO Mortality database (WHO 2003)

4 The present study series – subjects and methods

4.1 The incidence of cervical cancer

4.1.1 Study materials

4.1.1.1 Cervical cancer data

Data on cases of cervical cancer recorded in the 15-year period 1985–1999 by the population-based cancer registry of Khon Kaen province have been used. For each case, the following variables were extracted from the registry database: age at diagnosis, sex, area (district) of residence, date of birth, date of diagnosis, basis of diagnosis, topography, morphology, stage of disease.

4.1.1.2 Population denominators

The population denominators used for the calculation of incidence rates at provincial level were taken from the population projections for each individual year between 1986 and 1991, produced by working group on population projections (1986) and the population projections by individual year between 1990 to 2020, produced by working group on population projections (1995). The person-years for calculating the incidence were estimated by summing individual years of the periods studied.

Population by age and sex for districts within the province were available from the 1990 and 2000 Population and Housing Census (National Statistics Office 1994a, 2002b). Incidence rates at district level were calculated for the period 1985–1999 (15 years), using person-years based on the mid period (1992) population estimate, multiplied, within each age-sex group, by 15.

4.1.2 Analytical methods

4.1.2.1 Data analysis

The calculation of incidence rates was based on the number of new cancer cases registered in each year. The period considered was 1 January 1985 to 31 December 1999. The results were presented as numbers of cases registered, as percentage frequencies, and as incidence rates. The following rates were calculated as described in "Cancer Incidence in Five Continents, volume VII" (Parkin et al. 1997):

(1) crude incidence rates per 100 000 woman-years
(2) average annual age-specific incidence rates per 100 000 by age groups
(3) age-standardised rates per 100 000, by the direct method using the world standard population
(4) truncated age-adjusted incidence rates for ages 35–64

For province, three five-year periods were considered: 1985–1989, 1990–1994, 1995–1999. For district level, a single fifteen-year period (1985–1999) was considered.

4.2 The studies of risk factors for cervical cancer

4.2.1 Introduction: study materials

Three epidemiological studies were designed to study risk factors for cervical cancer in women resident in Northeast Thailand: a hospital-based case-control study of invasive cervical cancer, with non-hospital controls (study 1) and two nested case-control studies within the ongoing cohort study in Khon Kaen (study 2 and 3).

The Khon Kaen cohort study began in 1990. Initially, it was conceived as a community-based early detection and health education project, designed to improve the outcome of cancer and some other non-communicable diseases, in the rural population of Khon Kaen province in Northeast Thailand. Thus, the initial intervention comprised a questionnaire, concentrating on demographic and health-related variables, followed by a physical examination (including height, weight, and blood pressure), ultrasound examination of the abdomen, and a Pap smear for female participants. Blood was taken for estimation of haemoglobin concentration, and blood sugar, and a faecal specimen for detection of eggs of liver flukes. In 1992 a collaborative project was established with IARC. This sought to formalise the recruitment, so that the epidemiology of the major cancers (liver, cervix uteri, and breast) might be studied. The target population was

restricted to men and women aged 35+ resident in villages of Khon Kaen province, Thailand. The questionnaire was improved and extended, in particular by the addition of a dietary section (based on extensive pilot work using 24-hour dietary recalls), and arrangements made to store biological; specimens on all participants – blood (serum and buffy coat) and cells from the cervix.

Recruitment was performed by selecting a village in the province at random (from about 100 municipalities) and enrolling the eligible population during 2–3 weeks of field-work, depending on the size of the resident population. First the Head of the Village was contacted and the aim of the intervention is explained. Lists of the resident population were obtained, and files of eligible people prepared. The village was visited by the study team, with a mobile unit equipped with an ultrasound machine. The unit was then installed in the village, and the population invited to participate. Village residents willing to participate were informed of the examinations and procedures they would undergo, as well as details of tests and exams performed and rationale of keeping part of their biological samples for future research investigations. Those who accepted to participate signed a consent form .

Exposure assessment included an interview, with a structured questionnaire, including the following sections:

- demographic and socio-economic characteristics
- usual diet including alcohol consumption, by means of a food-frequency questionnaire structured by meals
- the subject's current occupation, recorded according to pre-defined standard categories
- tobacco smoking and betel nut chewing
- past history of active infection with *opisthorchis viverrini* (OV) and of treatment with the drug praziquantel
- reproductive & sexual history and practices of contraception and spouse’s occupation (additional for women subjects).

The subjects enrolled underwent visual inspection of the oral cavity and ultrasound examination of the liver. Women received a gynaecological examination during which a cervical Pap smear was taken and their breasts were examined by palpation. Blood pressure, height and weight were measured and recorded.

Biological specimens included cervical cells, which were collected from women using a spatula. A Pap smear was prepared, and examined for abnormal cytology in the laboratory. All Pap smears were archived for future reference. A sample of cells suspended in phosphate buffered saline (PBS) is stored at –20°C. Participants who were found to have an abnormal Pap test were informed, and advised to seek treatment.

Subjects enrolled donated 10–20 ml of venous blood. Specimen of plasma, buffy coat and clot are stored at –20°C.

By April 2001, a total of 24 723 subjects had been enrolled, including 16 652 women. Blood specimens were obtained 18 138 of the cohort and Pap smears from 10 954 women; cervical cells from 10 073 women have been stored. Follow-up of this cohort is being carried out by linkage of the study database with that of the cancer registry. As described earlier, the provincial population is covered by the Khon Kaen cancer registry. A software procedure has been developed to perform automatic record linkage between the files of the cohort and those of the cancer registry and of death certificates. The programme makes use of name and surname, date of birth, sex and residence. The programme allows for differences in the spelling and in the date of birth. It computes a score of the likelihood that two records refer to the same subject. This is based on weights assigned to the variables involved expressing their discriminating value (e.g. low in the case of sex), and the likelihood that it is correctly recorded (e.g. low for date of birth).

4.2.2 Study subjects

Study 1: Hospital-based case-control study among farmers

Cases: Case subjects were rural women (occupation as farmer) diagnosed as having invasive carcinoma of the cervix in Srinagarind Hospital, Khon Kaen during 1993. A total number of 179 subjects were interviewed using a standardised questionnaires developed for the population-based cohort study described above. All cases were histologically confirmed.

Controls: Controls were women enrolled into the cohort study during 1993–1994. For each case subject, one control was selected at random, matched by age ($\pm$1 year). All control women had an intact uterus, and a negative Pap smear, and gave their occupation as farmers. The variables of interest are similar to the cohort study as described above.

Study 2 A nested case-control study within the cohort study: prevalent cases

In order to carry out a nested case-control study, cases of cervical cancer diagnosed within the cohort study were identified. This was in the basis of a record linkage of the cohort, and the cancer registry file, based upon personal identities (name, surname, date of birth, residence). Linkage considered cancer cases registered up until end of 2001.

Cases: Prevalent cases of histologically confirmed cervical cancer (invasive or in situ) were defined as those diagnosed at the time of enrolment into the cohort study, or within three months of recruitment.

Controls: Density matched control selection was performed. Four controls per each case were randomly drawn from the cohort; same sex, age (± 3 years), date of recruitment ± 4 months.

Study 3 A nested case-control study within the cohort study: incident cases

The methods were same as study 2, the only difference being the definition of cases. Incident cases are women diagnosed with invasive or in situ cervical cancer more than three months after recruitment into the cohort up to the end of 2001.

4.2.3 Analytical methods

4.2.3.1 Data management and statistical analysis

Data from questionnaires of cases and controls were entered into the computer using the Access programmes. The variables obtained from the questionnaires included marital status (status of marriage at the time of interview), reproductive factors (age at menarche, age at first child birth, total number of pregnancies, contraceptive methods), socio-economic factors (occupation, income), sexual lifestyle (number of sexual partners, age at first sexual intercourse, STD, prostitutes), Pap smear screening history, smoking, alcohol consumption, betel nut chewing and history of cancer in the family.

The relationships between cervical cancer and possible risk factors were measured using odds ratios (OR) and their 95% confidence intervals (CI). Factors found to have a strong association with cervical cancer in univariate analysis, and factors with no association on univariate analysis but found to be important as risk factors for cervical cancer in other studies, were included in a further analysis, using multivariate modelling by conditional logistic regression using Stata version 7.0 (STATA 2001).

4.3 Survival study

4.3.1 Study material

Data on all cases of cervical cancer resident in Khon Kaen province, and recorded in the Khon Kaen population-based cancer registry between 1985 and 1990 were included in

this study. The variables were age at diagnosis, sex, area (district) of residence, date of diagnosis, topography, morphology, stage of disease, date and status (alive or dead) at last contact.

A total of 630 invasive cervical cancer cases were registered during the period 1985–1990. Of these, 29 cases (4.6%) were death certificate only (DCO) registrations. There were 78.4% of cases with histologically verified. Those registered as DCO cases were excluded from the survival analysis. This left 601 cases for further analysis.

Follow-up methods: Patients were followed up until death or date of loss to follow-up or 31 December 1995 (closing date). The registry used both passive and active measures to establish the vital status (alive/dead) of cancer patients.

4.3.1.1 Passive follow-up

All death certificates mentioning cancer (ICD-9 140–208) as underlyning or contributing cause of death were made available to the cancer registry by the Provincial Health Department. The death certificates were linked to the cancer registry file at annual intervals. This allowed identification of a few new cancer cases, not previously found by the registry (death certificate notification (DCN) cases), as well as for updating the existing cases with the date of death.

4.3.1.2 Active follow-up

For the remaining cases, follow-up information was collected by routine scrutiny of hospital case records, enquiries with treating physicians and general practitioners.
Annual follow-up on the anniversary of the date of incidence was attempted for presumed survivors by sending a reply-paid postcard inquiring about the current status of the patient. If no reply was received a second postcard was sent to the headman of the village requesting the same information. House visits were also performed in a few cases.

4.3.2 Analytical methods

For analysis purposes, cases were grouped by age (<40, 40–49, 50–59, 60+), stage of disease (I, II, III & IV, unknown), treatment (yes/no) and place of residence (Muang and surrounding districts/other).

The test for randomness of loss to follow-up was done using odds ratio by logistic regression. The duration of survival for each case was calculated as the time elapsed from the date of diagnosis of cancer to date of death or the last date of follow-up or closing date whichever was earlier.

Cumulative observed and relative survival rates were calculated using Hakulinen's method (Hakulinen 1982, Hakulinen et al. 1994), by the SURV3 relative survival analysis programme (Dickman et al. 2002). The abridged life-table for the whole of Thailand for the period under study was used for calculating expected survival (National Statistics Office 1992, National Statistics Office 1994b).

For comparison of the relative survival with the results reported from elsewhere, an age standardisation procedure was used. The calculated age-specific relative survival rates were used in a direct standardisation, using as weights the age distribution of cervical cancer cases from the estimated global incidence major cancers in 1985 (Black and Bashir 1998).

To investigate the potential bias introduced by failure to trace all registered patients, loss-adjusted survival, using prognostic variables for age, stage of disease, treatment and place of residence was estimated by logistic regression methods (Ganesh 1995) as described in 3.4.3. The patients who had complete follow-up were grouped into one category and the probabilities of death were computed for this group. All the loss to follow-up patients were grouped into another category. The same model was applied to predict probabilities of death for the loss of follow-up group. This procedure was computed for each interval (<1, 1–3, 3–5), and for each of the prognostic variables: age, stage of disease, treatment and place of residence. Stata version 7.0 software (STATA 2001) was used for logistic regression.

5 Results

5.1 Incidence of cervical cancer

5.1.1 Number of cervical cancer

A total of 1848 cases of invasive cervical cancer were registered in the 15 year period, 1985–1999. Cancer of the uterine cervix was the second leading site of cancer in females, after liver cancer, accounting for 14% of all cancer (Figure 6).

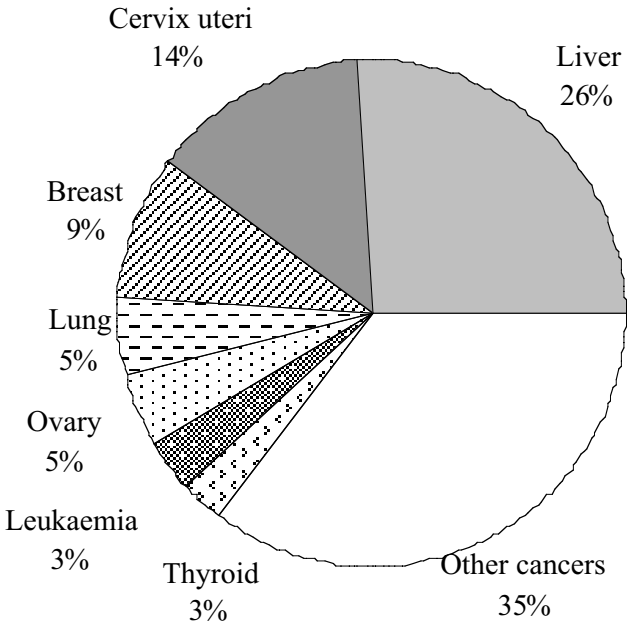


Figure 6. Percentage distribution of female cancers registered in Khon Kaen, Northeast Thailand 1985–1999.

5.1.2 Basis of diagnosis and histological type

Seventy-five percent of the cervical cancer were histologically confirmed. Eighteen percent were registered based upon a clinical diagnosis. There were 3.5% of cases registered from death certificate only. Sixty-one percent of registered cases were squamous cell carcinoma, 8.6% were adenocarcinoma (Table 3–4).

Table 3. Cervical cancer in Khon Kaen, Northeast Thailand 1985–1999, by basis of diagnosis.

Basis of diagnosis	Number	%
Death certificate only	64	3.5
Physical examination	336	18.2
Radiology	23	1.2
Surgery without biopsy	11	0.6
Cytology	34	1.8
Histology	1380	74.7
Total	1848	100

Table 4. Cervical cancer in Khon Kaen, Northeast Thailand, 1985–1999, by histological type.

Histology	Number	% of Total	% of Microscopically verified cases
Squamous cell carcinoma	1130	61.2	79.9
Adenocarcinoma	159	8.6	11.3
Other	125	6.8	8.8
No microscopic verification	434	23.5	
Total	1848	100	100

5.1.3 Distribution by stage

About 30% of cases were of unknown stage. Of the remainder, stage of disease at diagnosis was often advanced. Twelve to sixteen percent of cervical cancer patients presented themselves to the hospital at early stage (localised) during each five year period (1985–1989, 1990–1994, 1995–1999). About 50% were at regional stage, 5–6% were with distant metastasis (Figure 7).

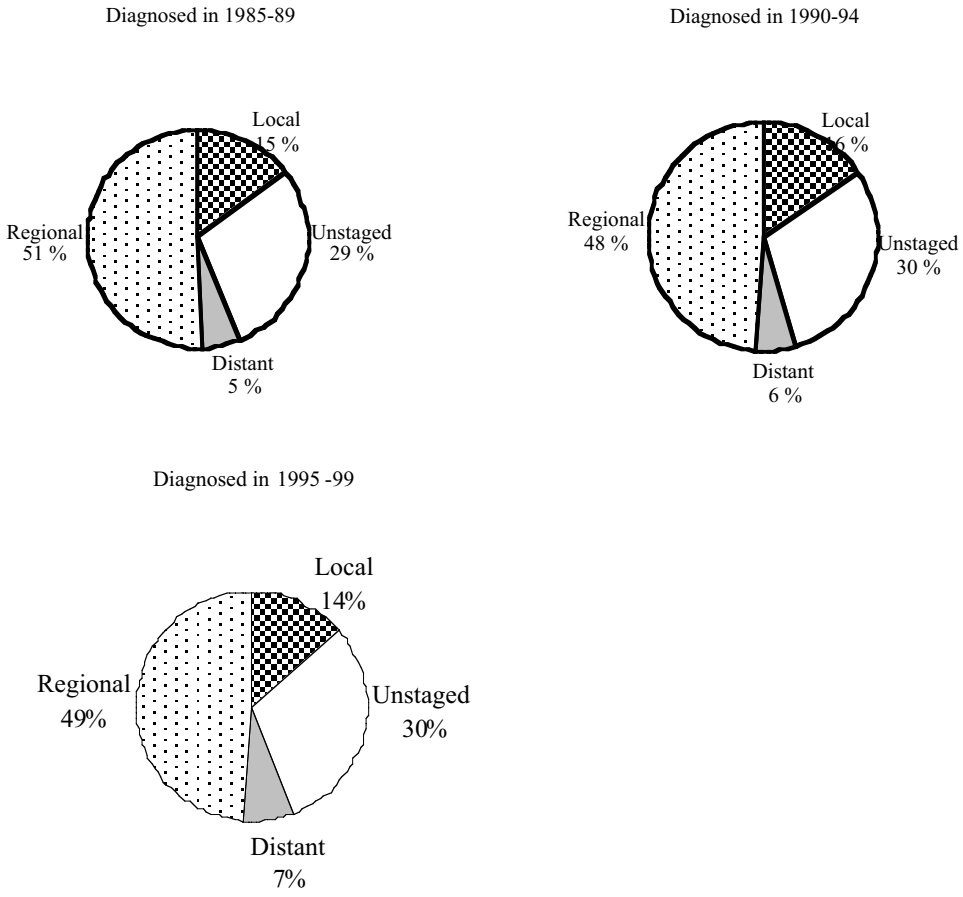


Figure 7. Stage distribution of cervical cancer in Khon Kaen, Northeast Thailand, in three time periods.

5.1.4 Incidence by place of residence

For the period 1985–1999, the overall crude incidence rate for the province was 14.9 per 100 000, and the ASR 16.8 per 100 000. ASRs by district are shown in Figure 8 and Table 5. The highest incidence was observed in Muang district (ASR = 23.8). Table 5 also shows those districts with rates significantly ($p<0.05$) above (*) or below (**) the provincial average.

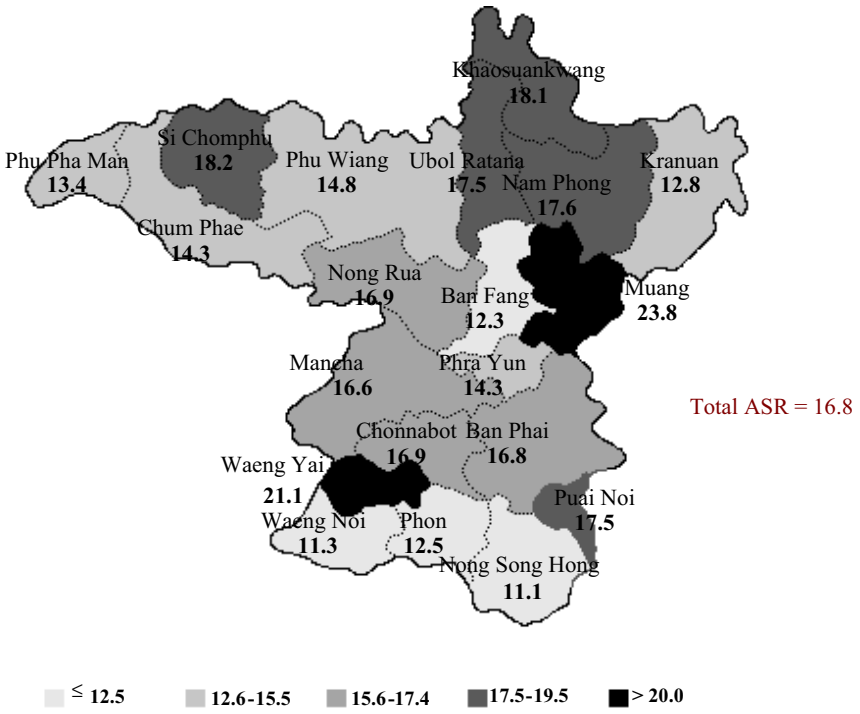


Figure 8. Age-standardised incidence rates per 100 000 women-years of cervical cancer in Khon Kaen, Northeast Thailand 1985–1999, by district.

Table 5. Annual incidence rates per 100 000 of cervical cancer in Khon Kaen, Northeast Thailand 1985–1999, by district.

District	Number of cases	Crude rate	ASR	95% CI of ASR
Muang	485	20.0	23.8*	21.6–26.0
Waeng Yai	42	20.1	21.1*	14.7–27.6
Si Chomphu	78	14.6	18.2*	14.0–22.4
Khaosuankwang	34	13.8	18.1*	11.9–24.3
Nam Phong	123	16.1	17.6*	14.5–20.8
Ubol Ratana	41	13.8	17.5*	12.0–22.9
Puai Noi	20	13.5	17.5*	9.6–25.4
Nong Rua	99	15.5	16.9	13.5–20.3
Chonnabot	66	17.6	16.9	12.8–21.1
Ban Phai	168	14.6	16.8	14.2–19.4
Mancha Khiri	118	16.1	16.6	13.6–19.6
Phu Wiang	104	12.9	14.8**	11.9–17.8
Phra Yun	35	14.7	14.3**	9.5–19.1
Chum Phae	134	12.5	14.3**	11.8–16.8
Phu Pha Man	17	10.8	13.4**	6.6–20.1
Kranuan	75	11.0	12.8**	9.8–15.8
Phon	78	12.0	12.5**	9.7–15.4
Ban Fang	42	11.3	12.3**	8.5–16.1
Waeng Noi	34	11.3	11.3**	7.5–15.2
Nong Song Hong	55	10.1	11.1**	8.1–14.1
Total	1848	14.9	16.8	16.1–17.6

* above the provincial average ** below the provincial average

5.1.5 Trends of incidence

Table 6 compares incidence rates in three time periods, 1985–1989, 1990–1994 and 1995–1999. The rates were relatively stable over time.

The age-specific incidence curves show a pattern of early increase (starting before age 20), with a steep rise to about ages 45–50, followed by a plateau and a decline (Figure 9). There is little change in the shape of the curve with time.

Table 6. Annual incidence rates per 100 000 of cervical cancer in Khon Kaen, Northeast Thailand 1985–1999, in three time periods.

Year of diagnosis	Number	Crude rate	ASR	95% CI of ASR	Truncated rate (35-64)
1985–1989	511	13.0	16.2	14.8–17.7	40.8
1990–1994	652	15.8	17.7	16.3–19.1	43.6
1995–1999	685	16.1	16.2	15.0–17.5	40.1

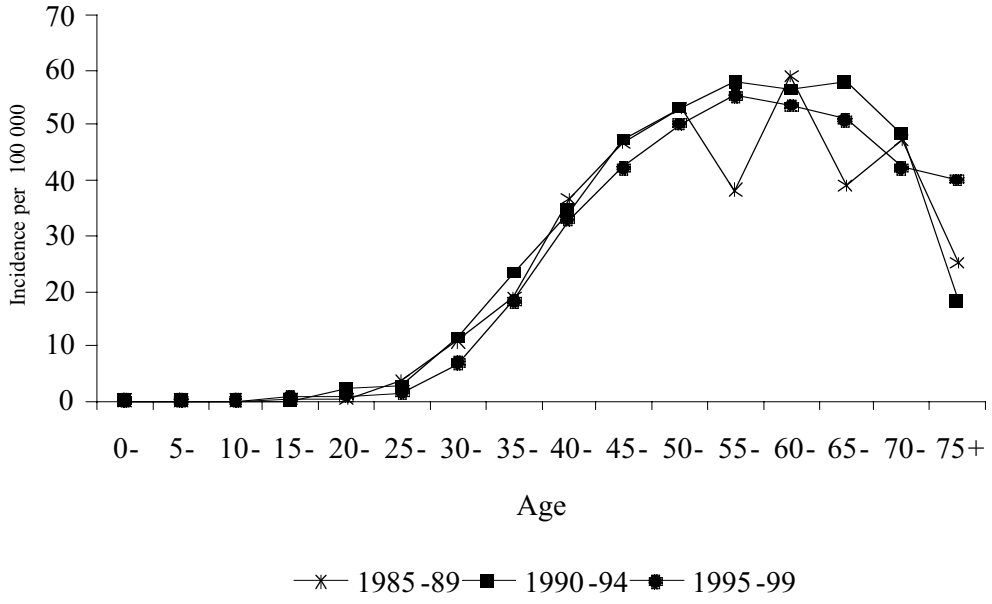
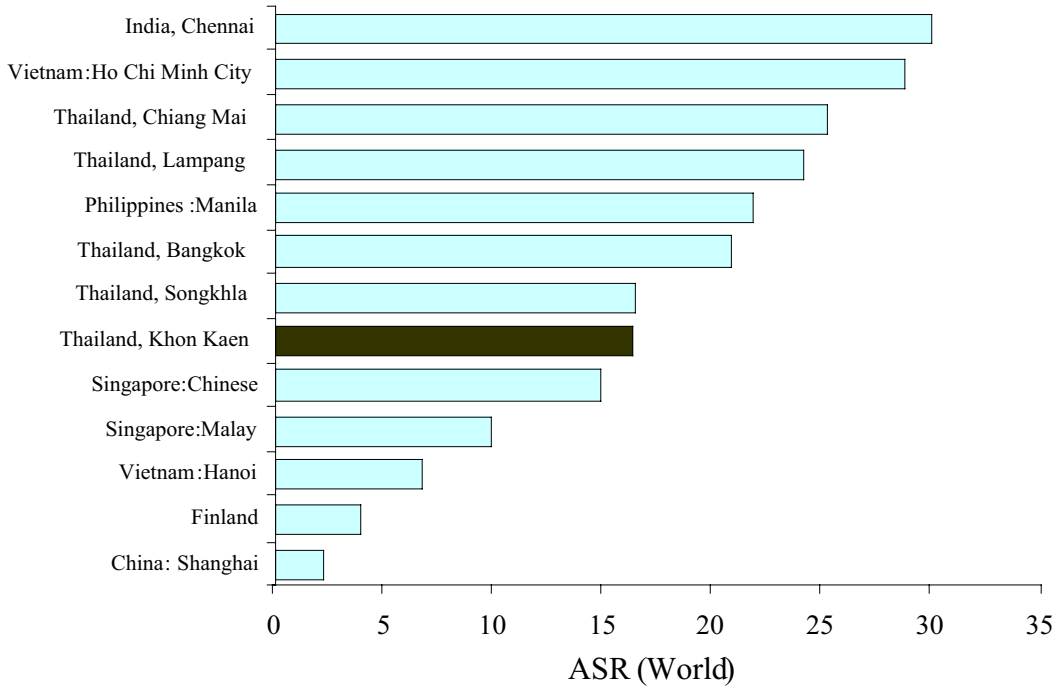


Figure 9. Age-specific incidence rates per 100 000 of cervical cancer in Khon Kaen, Northeast Thailand 1985–1999, in three time periods.

5.1.6 Comparison with other registries

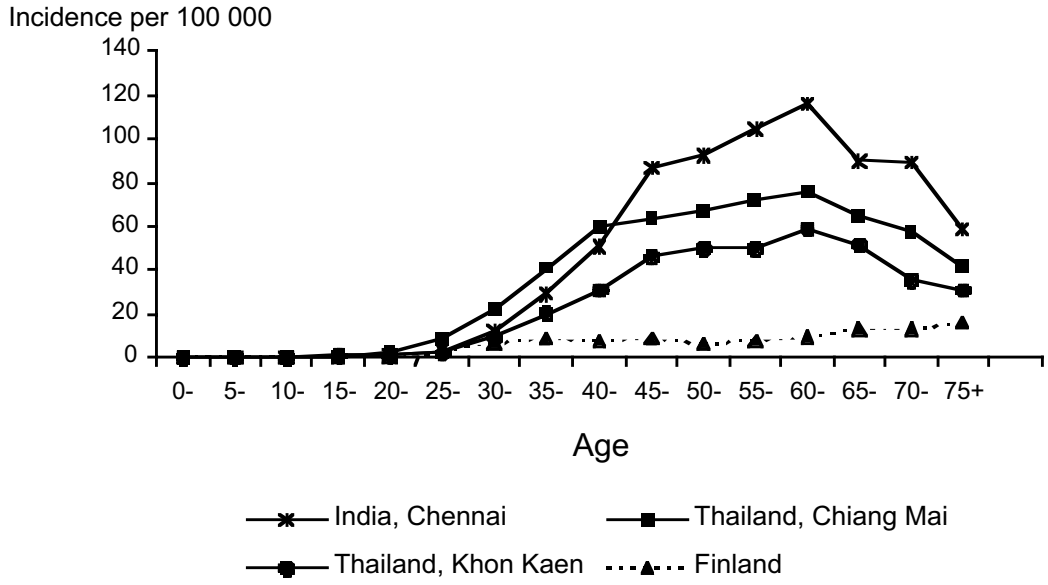
Figure 10 compares incidence rates in Khon Kaen province in 1993 to 1997, with the results from other registries for the same period. The rates in Khon Kaen were in the middle range. The incidence in Chennai, India was double that in Khon Kaen. Within the registries in Thailand, the incidence of cervical cancer in Khon Kaen was the lowest. Nevertheless, the incidence of cervical cancer in Khon Kaen was three times higher than in Finland, and much higher than observed in Shanghai, China.

Age-specific incidence curves showed similar pattern to the other registries such as Chiang Mai, Thailand and Chennai, India. All showed early increase (starting before age 20), with a steep rise to about ages 45–50, followed by a plateau and a decline (Figure 11). The pattern was different from the incidence in Finland, where there is only a relatively small increase in rates (less than two-fold) after the age of 35–39.



Source: CI5 volume VIII, Parkin et al. 2002

Figure 10. Incidence rates (age-standardised per 100 000) of cervical cancer in selected registries 1993–1997.

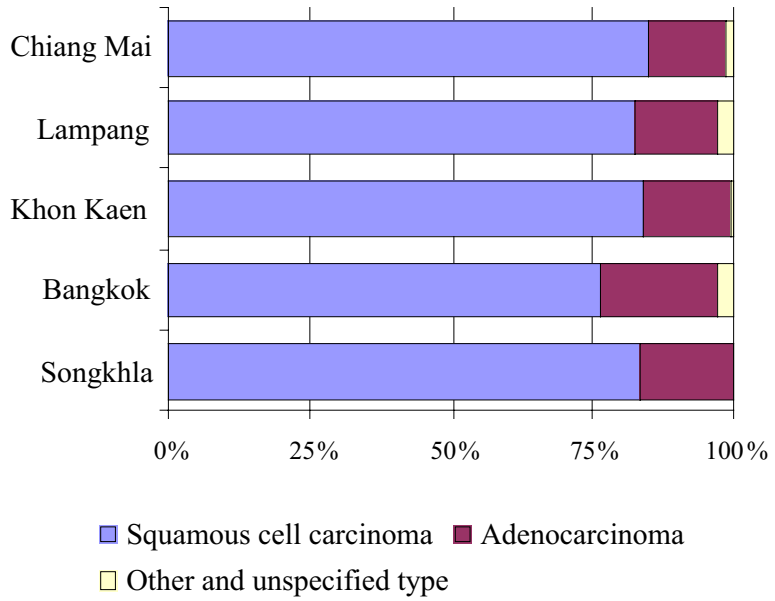


Source: CI5 volume VIII, Parkin et al. 2002

Figure 11. Comparison of age-specific incidence rates per 100 000 by age group of cervical cancer in selected registries 1993–1997.

Distribution of histological types of cervical cancer in Khon Kaen was similar to that observed in the other registries in Thailand, with some 15–20% of cases with histologically verification being adenocarcinomas, and the majority of cases were squamous cell carcinoma (75–85%) (Table 7 and Figure 12).

The proportion of cervical cancer with local stage was low in Khon Kaen when compared to other registries in Thailand, and much lower if compared with developed country such as the US, data of 1992–1994 (Figure 13) (Deerasamee et al. 1999).



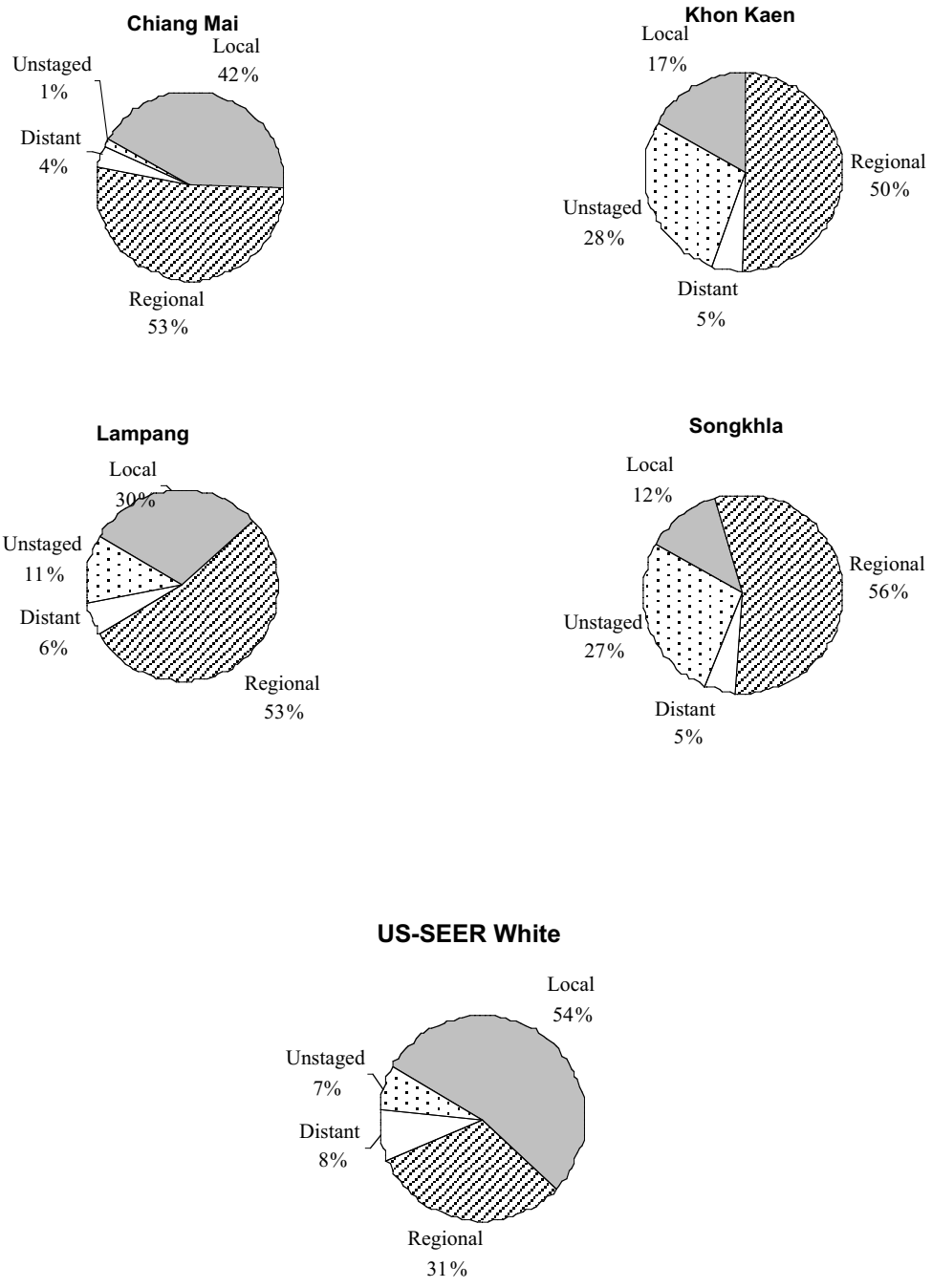
Source: Cancer in Thailand volume II, Deerasmee et al. 1999

Figure 12. Distribution of histological type of cervical cancer in Khon Kaen, Northeast Thailand and other registries in Thailand 1992–1994.

Table 7. Histological type of cervical cancer in Khon Kaen province and other registries worldwide 1993–1997.

Registries	Total cases	Histologically verified cases		
		Number	SCC (%)	Adeno CA (%)
India, Chennai (Madras)	2358	2022	96.1	2.8
Philippines, Manila	1903	1534	68.4	18.6
Singapore: Chinese	996	983	79.2	16.9
Singapore: Malay	88	87	70.1	25.3
Thailand, Bangkok	1882	1630	76.2	21.5
Thailand, Chiang Mai	974	942	85.0	13.7
Thailand, Khon Kaen	653	488	84.2	15.4
Thailand, Lampang	531	468	82.7	14.5
Thailand, Songkhla	365	347	83.6	16.4
Viet Nam, Ho Chi Minh City	2289	1925	81.4	12.2
Viet Nam, Hanoi	344	251	66.1	23.9
USA, SEER (white)	4372	4294	68.8	25.1
Finland	811	790	67.6	27.8

Source: CI5 volume VIII (Parkin et al. 2002)



Source: Cancer in Thailand volume II, Deerasmee et al. 1999

Figure 13. Comparison of stage at diagnosis of cervical cancer in Khon Kaen, Northeast Thailand with other registries 1992–1994.

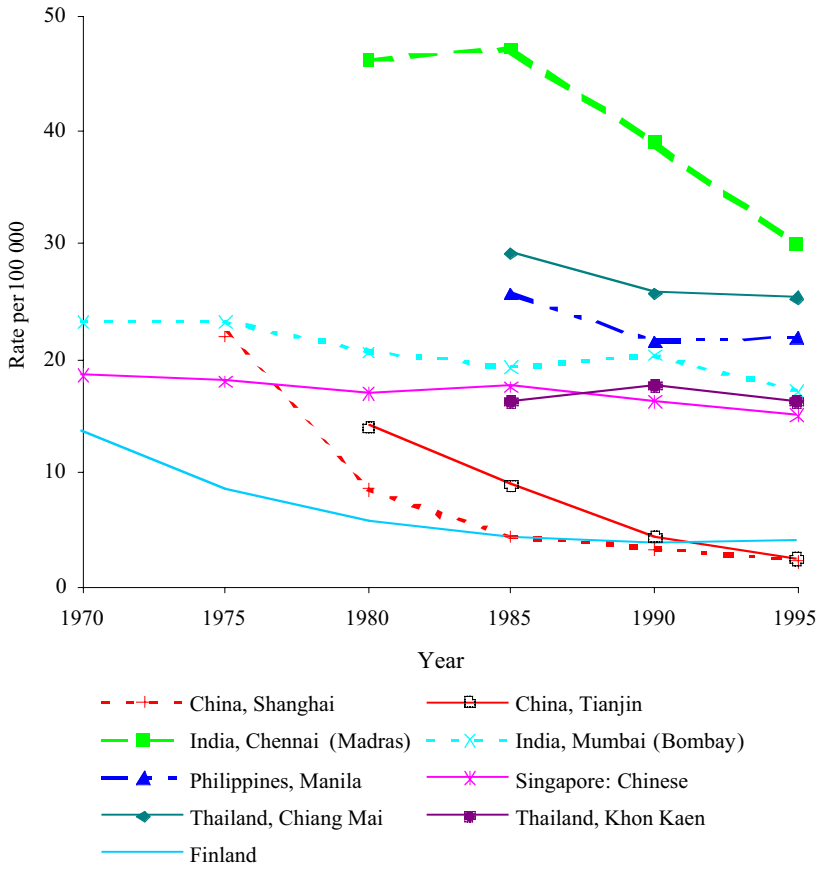


Figure 14. Trends of cervical cancer incidence in different cancer registries.

Figure 14 shows time trends in age-adjusted (world standard) incidence rates of cervical cancer in cancer registries in Asia, and in Finland, taken from the last five volumes of Cancer Incidence in Five Continents (Waterhouse et al. 1982, Muir et al. 1987, Parkin et al. 1992, Parkin et al. 1997, Parkin et al. 2002) and the incidence of cervical cancer in Khon Kaen, Thailand of the three different period (1985–1989, 1990–1994 and 1995–1999) from this present study. For most registries in Asia (including Chiang Mai, in northern Thailand), there have been rather small declines in incidence. In India, the large decline observed in Chennai (Madras) since 1985 contrasts with the relative stability in Mumbai (Bombay). In China, both cancer registries (Shanghai and Tianjin) showed quite large falls in incidence, so that the rate since 1990 was much the same as in Finland.

5.2 Risk factors for cervical cancer

5.2.1 Characteristics of study subjects

Study 1: A hospital-based case-control study in Khon Kaen, Northeast Thailand

There were 179 cases and 179 controls. All cases were invasive cervical cancer and histologically confirmed. The mean age was 46.4 (minimum 30, maximum 65 years). All cases and controls were farmers, and all had only primary education, or less. All of the cases were married (149) or formerly-married (30), whilst 2 control subjects were single.

Study 2: A nested case-control study within cohort study in Khon Kaen, Northeast Thailand : prevalent cases

There were 32 cases of histologically confirmed invasive cancer, or carcinoma in situ, diagnosed among women at the time of recruitment into the cohort study, or within the following three months. They comprised 17 invasive cervical cancers and 15 carcinoma in situ. These 32 cases, and 4 matched controls per case (a total of 128 controls) were included in the analysis.

The mean age of cases was 54.2 (minimum 38, maximum 76 years). Seventy-eight percent of cases and controls' occupation were farmers. The education level of both cases and controls were primary education, or less, only one case was higher than primary school. Only one case and one control reported being single, the rest were married or formerly-married

There were 12.5% of cases reported an average monthly income of less than 1000 Baht per family, 53% reported between 1000 to 2999 Baht and 34.4% reported 3000 Baht or more. For controls, 18% had a family income of less than 1000 Baht per month, 40.6% had an income of 1000–2999 Baht and 41.5% had 3000 Baht or more per month. The occupation of the spouse of the subject was farmer for 77 % of the cases and 80% of the controls.

Study 3: A nested case-control study within cohort study in Khon Kaen, Northeast Thailand : incident cases

There were 27 cases of cervical cancer with histologically confirmed invasive or in situ cancer found in the cohort study three or more months after the date of recruitment. There were 21 invasive cervical cancers and 6 carcinomas in situ. These 27 cases, with 4 incidence density-matched controls per each case (a total of 108 controls) were included in the analysis.

The mean age of the cases was 53.8 (minimum 33, maximum 70 years). Eighty-two percent of cases' occupation were farmers and 78.7% in controls. The education level of both cases and controls was primary education, or less, one case and one control had higher education. Most of cases and controls were married or formerly-married, only three control subjects reported being single.

Fifteen percent of cases reported an average monthly income of less than 1000 Baht per family, 53.8% reported between 1000 to 2999 Baht and 30.8% reported 3000 Baht or more. For controls, 21.7% had a family income less than 1000 Baht per month, 54.7% had an income between 1000 and 2999 Baht, and 23.6% had an income of 3000 Baht or more per month. The occupation of the spouse of the subject was farmer for 87% of the cases and 88% of the controls.

5.2.2 Results from the univariate analysis

Table 8, 9 and 10 present number of cases and controls, crude OR and 95% CI for each variable of each study design.

Study 1: A hospital-based case-control study in Khon Kaen, Northeast Thailand (Table 8).

The crude (univariate) odds ratio associated with a non-farming occupation in the husband (OR 1.9, 95% CI 1.1–3.5); there were too few subjects to investigate if this related to any specific occupation.

Young age at first sexual intercourse was associated with an increased risk of cervical cancer. Those who had first sexual intercourse at age 18 or less had a higher risk than those with later first intercourse (OR 2.6, 95% CI 1.6–4.1). Most women had only one lifetime sexual partner, but the number with more than one was higher among the cases than the controls. The crude OR for those who had more than one sexual partner was 3.2 (95% CI 1.5–6.6). High parity was also associated with increased risk with a crude OR of 2.5 (95% CI 1.6–3.8) for more than 3 children and 2.3 (95% CI 1.5–3.5) for first birth age 20 or below.

There was no association between cervical cancer and contraceptive use, smoking and alcohol consumption.

According to the history given by the women, there was an increased risk of cervical cancer in women whose husbands had ever been infected by VD (OR 2.6, 95% CI 1.3–5.5).

We did not investigate Pap smear history, since all the control women had had a Pap test (at enrolment into the cohort study), and it was also clear that the cases were confused between diagnostic investigations, and screening tests.

Study 2 A nested case-control study within cohort study in Khon Kaen, Northeast Thailand : prevalent cases (Table 9).

There were no statistically significant associations between cervical cancer and marital status, occupation (woman or husband), income level, contraceptive use, smoking, alcohol consumption, age at first sexual intercourse, number of sexual partners, family history of cancer, or past history of genital infections of subject's spouse.

From the univariate analysis, the crude (univariate) odds ratio was 2.6 (95% CI 1.2–6.1) for women with an age at menarche 15 years or less compared with those who were older at menarche. High parity was associated with slightly increased risk, but non significant with a crude OR of 1.2 (95% CI 0.5–2.7) for women who had more than 3 children vs those with fewer.

A number of 60 from 125 (48%) of control subjects reported having received a previous Pap smear test (prior to that at the time of recruitment), compared with 12/31 (38.7%) of the cases (the corresponding OR is 0.7, 95% CI 0.3–1.5). When the analysis was confined to the invasive cases and their controls only, the results obtained are not much different (OR is 0.8 and 95% CI 0.3–2.6). Those who had had two or more Pap smear in the past had a lower risk than those who had never been screened by Pap smear (OR 0.5, 95% CI 0.1–2.7).

Study 3 A nested case-control study within cohort study in Khon Kaen, Northeast Thailand : incident cases (Table 10).

There were no statistically significant associations between cervical cancer and marital status, occupation (subject or husband), income level, contraceptive use, smoking, alcohol consumption, age at first sexual intercourse, number of sexual partners, family history of cancer, past history of genital infections of subject's spouse, or previous Pap smears.

From the univariate analysis, the risk associated with young age (20 or less) of first child birth was increased with a crude (univariate) OR of 2.7 (95% CI 1.1–6.7). An OR greater than 1, but not statistically significant, was observed with the following variables; age at first sexual intercourse (OR of 1.6, 95% CI 0.6–3.9 for those who had first sexual intercourse at 18 years or less), and number of full term pregnancies more than 3 with OR of 2.2 (95% CI 0.8–5.7). The ORs associated with more than 3 pregnancies were 2.1 for 4–6, and 2.3 for 7 or more, neither value statistically different ($P<0.5$) from 1. Women

who used an IUD for contraception were at lower risk (OR 0.4, 95% CI 0.1–1.7) than those who did not.

Only 25 of 105 controls (23.8%) reported having had a Pap smear, prior to recruitment into the cohort study, compared with 10/27 (37%) of those developing cervical cancer. The calculated OR is 1.9 (95% CI 0.8–4.7) for a previous test, compared to women never tested by Pap smear. When the analysis was confined to the invasive cases and their controls only, the OR was a little lower (OR 1.5, 95% CI 0.5–4.3). Subjects who had received a single Pap smear and those who had had two Pap smear or more had higher ORs than those who had never been screened by Pap smear (OR 1.7, 95% CI 0.3–10.1 and OR 1.3, 95% CI 0.3–5.4).

Cases reported consuming alcohol more frequently than controls, the OR was 2.7 (95% CI 0.9–8.3) in alcohol consumers vs abstainers.

Table 8. Crude odds ratios and 95% confidence intervals of risk factors for cervical cancer in a hospital-based case-control study in Khon Kaen, Northeast Thailand (Study 1).

Variables	No. of cases	No. of controls	Crude OR	95%CI	P- value
Marital status					
Married	149	158	1.0		
Divorced, widow	30	19	1.7	0.9–3.2	0.09
Age at menarche					
>15 yrs	91	112	1.0		
<=15 yrs	75	66	1.4	0.9–2.2	0.13
Age at 1st sexual intercourse					
>18 yrs	90	128	1.0		
<=18 yrs	86	47	2.6	1.6–4.1	<0.01
Number of sexual partners					
1 partner	147	161	1.0		
>1 partners	32	11	3.2	1.5–6.6	<0.01
Number of full term pregnancies					
<=3	60	99	1.0		
>3	113	76	2.5	1.6–3.8	<0.01
Number of full term pregnancies					
1–3	60	99	1.0		
4–6	75	59	2.1	1.3–3.4	
7+	38	17	3.7	1.9–7.3	P for trend < 0.01
Age at first child birth					
>20 yrs	65	99	1.0		
<=20 yrs	106	71	2.3	1.5–3.5	<0.01

Table 8. Crude odds ratios and 95% confidence intervals of risk factors for cervical cancer in a hospital-based case-control study in Khon Kaen, Northeast Thailand (Study 1) (continued).

Variables	No. of cases	No. of controls	Crude OR	95%CI	P- value
Ever used oral contraceptive					
Yes	58	64	1.0		
No	121	115	1.2	0.8–1.8	0.50
Ever used DMPA					
Yes	18	31	1.0		
No	161	148	1.9	1.0–3.5	0.046
Ever used an IUD					
Yes	20	28	1.0		
No	159	151	1.5	0.8–2.7	0.22
Smoking					
No	172	176	1.0		
Yes	1	1	1.0	0.1–16.6	0.99
Alcohol consumption					
No	164	163	1.0		
Yes	9	16	0.6	0.2–1.3	0.17
Spouse’s occupation					
Farmer	111	148	1.0		
Not farmer	32	22	1.9	1.1–3.5	0.03
Spouse ever had VD					
No	120	151	1.0		
Yes	25	12	2.6	1.3–5.5	<0.01
Spouse ever had herpes simplex					
No	150	147	1.0		
Yes	12	7	1.7	0.6–4.4	0.29
Spouse's prostitute visit					
No	136	136	1.0		
Yes	26	16	1.6	0.8–3.2	0.15

IUD = Intrauterine device, DMPA = Depot-medroxyprogesterone acetate, VD = Venereal disease

Table 9. Crude odds ratios and 95% confidence intervals of risk factors for cervical cancer in a nested case-control study in Khon Kaen, Northeast Thailand : prevalent cases (Study 2).

Variables	No. of cases	No. of controls	Crude OR	95%CI	P-value
Marital status					
Married	26	92	1.0		
Divorce, widow	5	35	0.5	0.2–1.4	0.19
Education					
<= Primary school	31	128			
Higher than primary School	1	0	n.a.		
Occupation					
Farmer	25	101	1.0		
Not farmer	7	27	1.0	0.4–2.7	0.92
Family income per month (Baht)					
< 1000	4	22	1.0		
1000–2999	17	50	1.9	0.6–6.3	
3000+	11	51	1.2	0.3–4.2	P for trend = 0.91
Age at menarche					
>15 yrs	12	81	1.0		
<=15 yrs	18	46	2.6	1.2–6.1	0.02
Age at 1st sexual intercourse					
>18	21	88	1.0		
<=18 yrs	10	38	1.1	0.5–2.6	0.82
Number of sexual partners					
1	29	113	1.0		
>1	2	14	0.6	0.1–2.6	0.45
Number of full term pregnancies					
<=3	12	57	1.0		
>3	19	71	1.2	0.5–2.7	0.65
Number of full term pregnancies					
1–3	12	54	1.0		
4–6	15	46	1.5	0.6–3.5	
7+	4	25	0.7	0.2–2.5	P for trend =0.86
Age at first child birth					
>20 yrs	17	61	1.0		
<=20 yrs	14	64	0.8	0.4–1.7	0.55
Ever used oral contraceptive					
Yes	9	33	1.0		
No	22	94	0.9	0.4–2.1	0.73
Ever used DMPA					
Yes	5	19	1.0		
No	26	108	0.9	0.3–2.7	0.87

Table 9. Crude odds ratios and 95% confidence intervals of risk factors for cervical cancer in a nested case-control study in Khon Kaen, Northeast Thailand: prevalent cases (Study 2) (continued).

Variables	No. of cases	No. of controls	Crude OR	95%CI	P-value
Ever used an IUD					
Yes	8	35	1.0		
No	23	92	1.1	0.4–2.7	0.84
Betel nut chewing					
No	22	90	1.0		
Yes	10	34	1.2	0.5–2.8	0.67
Alcohol consumption					
No	25	98	1.0		
Yes	6	26	0.9	0.3–2.4	0.84
Smoking					
No	30	123	1.0		
Yes	1	1	4.1	0.2–68.8	0.29
History of family cancer					
No	26	104	1.0		
Yes	6	24	1.0	0.4–2.7	1.00
Ever had Pap smear					
No	19	65	1.0		
Yes	12	60	0.7	0.3–1.5	0.35
Confined to invasive cases only					
Ever had Pap smear					
No	10	39	1.0		
Yes	6	28	0.8	0.3–2.6	0.76
Number of Pap smear					
No	10	39	1.0		
1 time	4	13	1.2	0.3–4.5	
2+ times	2	15	0.5	0.1–2.7	0.53
Spouse's occupation					
Farmer	20	75	1.0		
Not farmer	6	19	1.2	0.4–3.4	0.75
Spouse ever had VD					
No	28	111			
Yes	0	6	n.a.		
Spouse ever had herpes simplex					
No	28	112			
Yes	0	2	n.a.		
Spouse's prostitute visit					
No	27	109	1.0		
Yes	2	8	1.0	0.2–5.1	0.99

IUD = Intrauterine device, DMPA = Depot-medroxyprogesterone acetate, VD = Venereal diseas n.a. = not applicable

Table 10. Crude odds ratios and 95% confidence intervals of risk factors for cervical cancer in a nested case-control study within cohort study in Khon Kaen, Northeast Thailand: incident cases (Study 3).

Variables	No. of cases	No. of controls	Crude OR	95% CI	P-value
Marital status					
Married	23	83	1.0		
Divorced, widow	4	22	0.7	0.2–2.1	0.48
Education					
Primary school or less	26	107	1.0		
Higher than primary school	1	1	4.1	0.3–69.5	0.29
Occupation					
Farmer	22	85	1.0		
Not farmer	5	23	0.8	0.3–2.5	0.75
Family income per month (Baht)					
< 1000	4	23	1.0		
1000–2999	14	58	1.4	0.4–4.7	
3000+	8	25	1.8	0.5–7.1	P for trend =0.36
Age at menarche					
>15 yrs	17	69	1.0		
<=15 yrs	10	38	1.1	0.4–2.6	0.88
Age at 1st sexual intercourse					
>18	17	76	1.0		
<=18 yrs	10	28	1.6	0.6–3.9	0.30
Number of sexual partners					
1	24	88	1.0		
>1	3	11	1.0	0.3–3.9	1.0
Number of full term pregnancies					
<=3	7	46	1.0		
>3	19	57	2.2	0.8–5.7	0.10
Number of full term pregnancies					
1–3	7	46	1.0		
4–6	10	31	2.1	0.7–6.3	
7+	9	26	2.3	0.7–7.0	P for trend =0.13
Age at first child birth					
>20	9	59	1.0		
<=20	18	44	2.7	1.1–6.7	0.03
Ever used oral contraceptive					
Yes	12	33	1.0		
No	14	70	0.6	0.2–1.3	0.18
Ever used DMPA					
Yes	2	10	1.0		
No	24	93	1.3	0.3–6.3	0.75

Table 10. Crude odds ratios and 95% confidence intervals of risk factors for cervical cancer in a nested case-control study within cohort study in Khon Kaen, Northeast Thailand: incident cases (Study 3) (continued).

Variables	No. of cases	No. of controls	Crude OR	95%CI	P-value
Ever used an IUD					
Yes	3	24	1.0		
No	23	79	2.4	0.6–8.6	0.19
Betel nut chewing					
No	19	81	1.0		
Yes	8	23	1.5	0.6–3.8	0.41
Alcohol consumption					
No	19	93	1.0		
Yes	6	11	2.7	0.9–8.3	0.08
Smoking					
No	25	103			
Yes	0	1	n.a.		
History of family cancer					
No	21	86	1.0		
Yes	6	22	1.1	0.4–3.1	0.83
Ever had Pap smear					
No	17	80	1.0		
Yes	10	25	1.9	0.8–4.7	0.17
Confined to invasive cases only					
Ever had Pap smear					
No	14	61	1.0		
Yes	7	20	1.5	0.5–4.3	0.43
Number of Pap smear					
No	14	61	1.0		
1 time	2	5	1.7	0.3–10.1	
2+ times	3	10	1.3	0.3–5.4	0.61
Spouse's occupation					
Farmer	20	74	1.0		
Not farmer	3	10	1.1	0.3–4.4	0.88
Spouse ever had VD					
No	18	68	n.a.		
Yes	0	4			
Spouse ever had herpes simplex					
No	16	61	n.a.		
Yes	0	2			
Spouse's prostitute visit					
No	14	55	n.a.		
Yes	0	6			

IUD = Intrauterine device, DMPA = Depot-medroxyprogesterone acetate, VD = Venereal disease n.a. = not applicable

5.2.3 Results from the multivariate analysis

Table 11 shows the adjusted OR and 95% CI from the multivariate models, fitted in the three different study designs.

Study 1:A hospital-based case-control study in Khon Kaen, Northeast Thailand.

In the multivariate analysis, the variables that still appeared to confer an elevated risk for cervical carcinoma were the number of sexual partners of the woman with an OR of 3.5 (95% CI 1.1–11.2) for 2 or more vs 1, the number of full term pregnancies with an OR of 3.2 (95% CI 1.1–9.0) for more than 3 pregnancies vs 3 or less, and those whose spouse are not farmer with an OR 2.4 (95% CI 1.0–5.8), age at first child birth lower than 20 vs more with an OR of 3.7 (95% CI 1.5–9.4) and spouse ever had VD with an OR of 3.0 (95% CI 1.0–9.3).

Study 2 A nested case-control study within cohort study in Khon Kaen, Northeast Thailand: prevalent cases.

In the multivariate analysis, the only variable that still appeared to confer an elevated risk for cervical carcinoma was age at menarche; the OR was 4.2 (95% CI 1.6–11.3) for women whose age at menarche was 15 years or less, compared with those with menarche over 15 years of age. The risk associated with 3 or more full term pregnancies was elevated when adjusted with the other variables (OR of 1.4), but was not statistically significant.

Study 3 A nested case-control study within cohort study in Khon Kaen, Northeast Thailand: incident cases.

In the multivariate analysis, the variables that still appeared to confer an elevated risk for cervical carcinoma were the number of full term pregnancies (OR of 7.2, 95% CI 1.3–39.1) for women who had more than 3 pregnancies compared to those who had less than 3 pregnancies and age at first child birth (OR of 5.5, 95% CI 1.4–21.3, for women who had first child birth at age 20 years or less compared to those with first birth at age 20 or more). Age at first sexual experience had no association with cervical cancer in this analysis, and the risk was reduced when adjusted by other variables.

Table 11. Adjusted odds ratios and 95% confidence intervals of risk factors for cervical cancer from the three different study designs in Khon Kaen, Northeast Thailand.

Variables	Adjusted[1] OR Study 1	95% CI	Adjusted[2] OR Study 2	95% CI	Adjusted[3] OR Study 3	95% CI
Marital status						
Married	n.i.		1.0		1.0	
Divorced, widow			0.4	0.1–1.4	0.9	0.2–4.3
Age at menarche						
>15 yrs	1.0		1.0		n.i.	
<=15 yrs	1.2	0.6–2.6	4.2	1.6–11.3		
Age at 1st sexual intercourse						
>18 yrs	n.i.		1.0		1.0	
<=18 yrs			1.1	0.3–3.5	0.4	0.1–1.6
Number of sexual partners						
1 partner	1.0		n.i.		n.i.	
>1 partners	3.5	1.1–11.2				
Number of full term pregnancies						
<=3	1.0		1.0		1.0	
>3	3.2	1.1–9.0	1.4	0.5–3.9	7.2	1.3–39.1
Age at first child birth						
>20 yrs	1.0		1.0		1.0	
<=20 yrs	3.7	1.5–9.4	0.5	0.1–1.5	5.5	1.4–21.3
Spouse's occupation						
Farmer	1.0		n.i.		n.i.	
Not farmer	2.4	1.0–5.8				
Spouse ever had VD						
No	1.0		n.i.		n.i.	
Yes	3.0	1.0–9.3				

Adjusted[1, 2, 3] adjusted for all variables in the same column in the table, excepted n.i. (not included)
VD = Venereal disease

5.3 Survival study

5.3.1 Description of study population

A total of 601 out of 630 cases of cervical cancer diagnosed among residents of Khon Kaen province, Northeast Thailand during 1985 to 1990 were included in the survival study. Fifty-three percent were aged under 50 years, 21% were over 60 (Table 12). Fifteen percent were stage I, 22.3% stage II, 31.5% stage III, 5.5% stage IV and 25.3% were of unknown stage at diagnosis. Eighty-three percent were diagnosed microscopically.

Places of residence were classified into two groups, the first group consists of Muang and surrounding districts and the second one includes all other districts. Muang district is in the center of Khon Kaen province where Khon Kaen city is located. Forty-six percent of cases were residents of Muang and surrounding districts.

Seventy-one percent of patients received treatment either surgery or radiation or chemotherapy.

Table 12. Number and percentage of cervical cancer cases in Khon Kaen, Northeast Thailand 1985–1990, by age-group.

Age-group (years)	Number	%
<40	122	20.3
40–49	194	32.3
50–59	158	26.3
60+	127	21.1
Total	601	100

5.3.2 Risk of loss to follow-up and death

The proportion and risk (odds ratio) of death and loss to follow-up at five years from the index date, by prognostic factors are presented in Table 13. The risk of loss to follow-up by age at diagnosis (P=0.70), stage of disease (P=0.20) and place of residence (P=0.32), each of which were adjusted for the others in the table, were not statistically significant. The risk of loss to follow-up among cases not treated was two-fold higher than those treated (P=0.001).

The risk of death increased significantly with increasing age at diagnosis (P=0.002), and with stage of disease (P<0.001), with the highest risk observed in Stage III and IV (OR 5.0, 95% CI 2.7–9.5). Those with stage unknown also had a higher risk of death (OR 1.5 but not significant). Patients with no treatment had a two-fold higher risk

of death (P=0.01) and patients who lived far away from the center of the province had a 50% higher risk (P=0.04) than those who lived nearby.

Table 13. Five years cumulative proportion and risk (odds ratio, OR) to death and loss to follow-up and 95% confidence interval by factors studied.

Factors studied	Proportion		Odds ratio and confidence interval			
	Lost	Dead	Lost		Dead*	
	%	%	OR	95%CI	OR[1]	95%CI
1) Age group				P=0.70		P=0.002
<40	27.9	24.6	1.0	–	1.0	–
40–49	24.2	35.1	0.9	0.5–1.5	1.5	0.8–2.7
50–59	29.1	36.7	1.2	0.7–2.0	2.0	1.1–3.7
60+	29.9	49.6	1.2	0.7–2.1	3.5	1.8–6.9
2) Stage of diseases				P=0.20		P<0.001
Stage I	23.7	20.4	1.0	–	1.0	–
Stage II	28.4	29.1	1.2	0.7–2.2	1.8	0.9–3.6
Stage III and IV	21.6	53.6	0.8	0.4–1.5	5.0	2.7–9.5
Stage unknown	37.5	27.6	1.4	0.7–2.6	1.5	0.7–3.1
3) Treatment				P=0.001		P=0.01
Received treatment	22.4	36.2	1.0	–	1.0	
No treatment	39.9	37.0	2.0	1.3–3.1	2.0	1.2–3.4
4) Residency				P=0.32		P=0.04
Muang and surrounding districts	28.1	32.9	1.0	–	1.0	
Other districts	26.9	39.4	0.8	0.6–1.2	1.5	1.0–2.3

[1] ORs of each factor adjusted for all other factors in the table

* Estimated among those with complete follow-up only

5.3.3 Survival in cervical cancer

Survival for all patients, and for subgroups defined by age group, stage of disease, place of residence and treatment was performed. Loss-adjusted survival rate (LAR) was estimated by taking into account loss to follow-up at various levels of these factors (age group, stage of disease, place of residence and treatment), and adjusting by logistic regression methods. Actuarial, loss-adjusted and relative loss-adjusted survival are presented for each prognostic factors.

5.3.3.1 All cases

The proportion of patients lost to follow-up during the five-year period was 27.6% (Table 14). During the first year of follow-up, 13.3% of patients were lost. The proportion of cases lost reduced in the next period (5.1% in the second and third years) and increased again to 19.3% in the fourth and fifth years. The proportion of cases dying during the five-year period was 36.4%.

For five-year survival, the value of the LAR by regression method was 54.7%, 2.1 percent units less than the actuarial survival (56.8%) when adjusted for age, stage of disease, place of residence and treatment. The results obtained by the adjustment procedure suggest that patients who were lost to follow-up had poorer survival than those still under observation but the degree of bias introduced into the actuarial estimate by differential loss to follow-up is small.

The overall five-year relative LAR corrected survival for all subjects diagnosed with cervical cancer was 57.4%.

Table 14. Number of cases, proportion (%) lost to follow-up, deaths and survival rates estimated by different methods and by year of follow-up among cervical cancer in Khon Kaen, Northeast Thailand 1985–1990.

	Year of follow-up						Total at end of 5-year follow-up period	
	<1		1–3		3–5			
	N	%	N	%	N	%	N	%
Number of cases	601		447		321			
Deaths	74	12.3	103	23.0	42	13.1	219	36.4
Lost to follow-up	80	13.3	23	5.1	62	19.3	165	27.6
Survival rate								
Actuarial		86.8		66.3		56.8		
LAR		85.2		64.8		54.7		
Relative LAR		86.0		66.7		57.4		

5.3.3.2 Age

The proportion of subjects lost to follow-up during the five-year period varies only slightly by age: 29.9% in patients aged over 60 years to 24.2% in patients aged 40–49 years (Table 15). The proportion of subjects dying during the five-year follow-up was highest in patients aged over 60 years (49.6%) and least in patients aged under 40 years (24.6%), indicating a decreasing trend with decreasing age.

Patients aged less than 40 years had the best survival by all estimation methods. The poorest survival was found in patients aged more than 60 years at diagnosis. Adjustment for differential loss to follow-up by stage of disease, place of residence and treatment resulted in a reduction in survival compared with the actuarial method in all age-groups. The relative reduction of survival rates with loss adjustment was greatest in patients aged 50–59 years (4.1%, from 55.7% to 53.4%), and least in patients aged more than 60 years (3.1%).

Patients aged <40, 40–49, 50–59 and over 60 years at diagnosis had five-year relative LAR corrected survival rates of 68.9, 59.2, 55.9 and 43.0% respectively.

Table 15. Number of cases, proportions (%) lost to follow-up, deaths and survival estimated by different methods, year of follow-up and age among cervical cancer in Khon Kaen, Northeast Thailand 1985–1990.

Age group	Year of follow-up						Total at end of 5-year follow-up period	
	<1		1-3		3-5			
	N	%	N	%	N	%	N	%
1) <40 years								
Number of cases	122		97		78			
Deaths	9	7.4	15	15.5	6	7.7	30	24.6
Lost to follow-up	16	13.1	4	4.1	14	17.9	34	27.9
Survival rate								
Actuarial		92.1		77.5		71.0		
LAR		90.2		75.6		68.1		
Relative LAR		90.4		76.1		68.9		
2) 40–49 years								
Number of cases	194		145		110			
Deaths	27	13.9	28	19.3	13	11.8	68	35.1
Lost to follow-up	22	11.3	7	4.8	18	16.4	47	24.2
Survival rate								
Actuarial		85.3		68.4		59.7		
LAR		84.0		67.0		57.8		
Relative LAR		84.2		67.8		59.2		
3) 50–59 years								
Number of cases	158		121		81			
Deaths	15	9.5	32	26.4	11	13.6	58	36.7
Lost to follow-up	22	13.9	8	6.6	16	19.8	46	29.1
Survival rate								
Actuarial		89.8		65.4		55.7		
LAR		87.9		63.7		53.4		
Relative LAR		88.7		65.5		55.9		
4) 60 years and over								
Number of cases	127		84		52			
Deaths	23	18.1	28	33.3	12	23.1	63	49.6
Lost to follow-up	20	15.8	4	4.8	14	26.9	38	29.9
Survival rate								
Actuarial		80.3		53.0		38.8		
LAR		79.0		51.9		37.6		
Relative LAR		81.0		55.9		43.0		

5.3.3.3 Stage of disease

The proportion of loss to follow-up in each stage of the five-year period was highest in patients with unknown stage group (37.5%) and lowest in patients with stage III and IV (21.6%). The proportion cases dying by the five-year follow-up was the highest in patients with stage III and IV (53.6%) and smallest in patients with stage I (20.4%) (Table 16).

Table 16. Number of cases, proportions (%) lost to follow-up, deaths and survival estimated by different methods, year of follow-up and stage of disease among cervical cancer in Khon Kaen, Northeast Thailand 1985–1990.

Stage of disease	Year of follow-up						Total at end of 5-year follow-up period	
	<1		1–3		3–5			
	N	%	N	%	N	%	N	%
1) Stage I								
Number of cases	93		85		72			
Deaths	1	1.1	12	14.1	6	8.3	19	20.4
Lost to follow-up	7	7.5	1	1.2	14	19.4	22	23.7
Survival rate								
Actuarial		98.9		84.8		77.1		
LAR		97.5		83.5		74.6		
Relative LAR		98.1		85.1		77.1		
2) Stage II								
Number of cases	134		111		82			
Deaths	10	7.5	19	17.1	10	12.2	39	29.1
Lost to follow-up	13	9.7	10	9.0	15	18.3	38	28.4
Survival rate								
Actuarial		92.2		75.6		65.5		
LAR		90.7		73.7		63.0		
Relative LAR		91.3		75.4		65.5		
3) Stage III and IV								
Number of cases	222		156		94			
Deaths	46	20.7	53	34.0	20	21.3	119	53.6
Lost to follow-up	20	9.0	9	5.8	19	20.2	48	21.6
Survival rate								
Actuarial		78.3		51.0		39.0		
LAR		77.6		50.4		38.2		
Relative LAR		78.4		52.1		40.6		
4) Stage unknown								
Number of cases	152		95		73			
Deaths	17	11.2	19	20.0	6	8.2	42	27.6
Lost to follow-up	40	26.3	3	3.2	14	19.2	57	37.5
Survival rate								
Actuarial		87.1		69.5		63.3		
LAR		83.9		66.7		59.8		
Relative LAR		84.8		68.6		62.9		

Patients with stage I had the best survival with all methods used to estimate survival. The poorest survival was found in patients with stage III and IV disease at diagnosis. Adjusting for differential loss to follow-up by age, place of residence and treatment resulted in a slight reduction in survival compared with actuarial method for all stages of disease. The relative reduction of survival when compared with the results from the actuarial method highest in patients at unknown stage (5.5%), and smallest in patients stage III and IV (2.1%). These differences from the actuarial estimate indicated the presence of a small bias in the actuarial estimate resulting from the slightly poorer survival of patients lost to follow-up compared with those still under observation.

Five-year relative LAR corrected survival in cervical cancer patients was highest in patients with stage I (77.1%) and lowest in patients with stage III and IV (40.6%).

5.3.3.4 Treatment

The proportion of cases lost to follow-up in the treatment group during the five-year period was lower (22.4%) than in those patients who received no curative treatment (39.9%). The proportion of subjects dying during the five-year follow-up was similar in both groups (Table 17).

Table 17. Number of cases, proportions (%) lost to follow-up, deaths and survival estimated by different methods, year of follow-up and treatment among cervical cancer in Khon Kaen, Northeast Thailand 1985–1990.

Treatment	Year of follow-up						Total at end of 5-year follow-up period	
	<1		1-3		3-5			
	N	%	N	%	N	%	N	%
1) Received treatment either surgery, radiotherapy, chemotherapy								
Number of cases	428		360		256			
Deaths	39	9.1	81	22.5	35	13.7	155	36.2
Lost to follow-up	29	6.8	23	6.4	44	17.2	96	22.4
Survival rate								
Actuarial		90.6		69.5		59.2		
LAR		89.6		68.4		57.5		
Relative LAR		90.3		70.1		60.0		
2) No treatment								
Number of cases	173		87		65			
Deaths	35	20.2	22	25.3	7	10.8	64	37.0
Lost to follow-up	51	29.5	0	0	18	27.7	69	39.9
Survival rate								
Actuarial		76.3		57.0		49.9		
LAR		74.3		55.5		47.5		
Relative LAR		75.2		57.6		50.8		

Patients who received treatment had better survival than the no treatment group in all methods used to estimate survival. Introduction of age, place of residence and stage of disease into the adjustment procedure for loss to follow-up by regression method gave a relative reduction of 2.9% in estimated survival in patients who received treatment, and 4.8% in those who received no treatment, indicating that patients who were lost to follow-up had poorer survival than those still under observation.

Those who received treatment had a five-year relative LAR corrected survival of 60.0%, while five-year relative survival among patients not receiving curative therapy was 50.8%.

5.3.3.5 Place of residence

The proportion of loss to follow-up in patients who lived in Muang and surrounding districts was 28.1% slightly higher than in those resident (26.9%) in other districts. The proportion of subjects dying during the five-year follow-up was 32.9% in patients living in Muang and surrounding district and 39.4% in those who living in other districts (Table 18).

Table 18. Number of cases, proportions (%) lost to follow-up, deaths and survival estimated by different methods, year of follow-up and residency among cervical cancer in Khon Kaen, Northeast Thailand 1985–1990.

Residency	Year of follow-up						Total at end of 5-year follow-up period	
	<1		1-3		3-5			
	N	%	N	%	N	%	N	%
1) Muang and surrounding districts								
Number of cases	274		212		153			
Deaths	26	9.5	48	22.6	16	10.5	90	32.9
Lost to follow-up	36	13.1	11	5.2	30	19.6	77	28.1
Survival rate								
Actuarial		89.8		69.0		61.1		
LAR		88.1		67.3		58.6		
Relative LAR		88.9		69.1		61.4		
2) Other districts								
Number of cases	327		235		168			
Deaths	48	14.7	55	23.4	26	15.5	129	39.4
Lost to follow-up	44	13.5	12	5.1	32	19.0	88	26.9
Survival rate								
Actuarial		84.3		64.1		53.2		
LAR		82.8		62.6		51.4		
Relative LAR		83.5		64.4		54.1		

Patients who lived in Muang and surrounding districts had better survival according to all methods used to estimate survival than patients who lived in other districts. Adjustment for differential loss to follow-up by age, stage of disease and treatment resulted in a reduction in estimated survival compared with the estimated by the actuarial method, for both residence groups. The relative reduction of survival was 4.1% in patients living in Muang and surrounding districts, and 3.4% for those living in other districts.

For patients who lived in Muang and surrounding districts, the five-year relative LAR corrected survival rate was 61.4%, compared with 54.1% in patients resident in more distant districts.

5.3.4 Comparison of survival with results from elsewhere

For comparison of the relative survivals in Khon Kaen with the results obtained elsewhere, age standardisation of the relative survival rates was carried out. The age-standardised five-year relative survival of cervical cancer in Khon Kaen province, Thailand during 1985–1990 (56.2%) is in the middle range between the US White population in the SEER program (70.1%) and Philippines (28%). The survival of cervical cancer in Khon Kaen is similar to the survival of patients in Cuba (54.3%) and India (Table 19) (Sankaranarayanan et al. 1998).

Table 19. Comparison of five-year relative survival (age-standardised) among cervical cancer patients in Khon Kaen, Northeast Thailand, and comparison registries.

Registry	% of loss to follow-up at the end of 5 years	5-year relative survival (age-adjusted)
US White 1986–1991		70.1
Thailand (Chiang Mai 1983–1992)	28.6	64.9
Europe 1978–1985		61.5
India (Chennai) 1984 –1989	15.5	56.7
Thailand (Khon Kaen) 1985–1990	27.6	56.2
Cuba 1988–1989	5.4*	54.3
India (Bombay) 1982–1986	26.7	49.5
China (Qidong) 1982 –1991		42.0
Philippines 1987	16.6*	28.0

Note: * % of loss to follow-up of all cancers
Source: Cancer survival in developing countries (Sankaranarayanan et al. 1998)

6 Discussion

6.1 Incidence of cervical cancer

Cancer of the uterine cervix is a common cancer of women in Khon Kaen province, Northeast of Thailand. It is the second most common cancer in females. In general, rates of this cancer are higher in economically developing societies. When compared with incidence rates from other registries in Asia, the risk of cervical cancer is moderate, less than, for example, Chennai (India), Manila (Philippines), and Ho Chi Minh (south of Vietnam), but higher than in China (Shanghai) and the north of Vietnam (Hanoi). Compared with the results from the other registries in Thailand, the rates in Khon Kaen are lower than seen in the northern region (Chiang Mai and Lampang), or in the capital, Bangkok (central Thailand), but similar to those obtained by the registry in Songkhla in the south.

Within Khon Kaen province itself, there is some variability by district, with the highest rates in the central district (Muang) where the city of Khon Kaen, with the major treatment facilities, is located. The lowest rates are seen in districts in the extreme south of the province (Nong Song Hong and Waeng Noi). It may be that some patients from these districts are missed by the registry, perhaps going for treatment in the adjacent province (Nakornratchasima) which has cancer treatment facility.

Data quality can be evaluated from indicators such as the percentage of cases registered from DCO, and the percentage of cases with histological confirmation of diagnosis (Parkin et al. 1997). In Khon Kaen, during the 15 year period, 77% of cases of cervical cancer were registered with histological confirmation of the diagnosis and 3.5% from the information contained on a death certificate only. Histological confirmation in other registries in Thailand was 88% in Bangkok and 98% in Chiang Mai (Deerasamee et al. 1999).

The proportion of adenocarcinoma among histologically verified cases is about 15%, similar to other registries in Thailand. In high risk countries, SCC comprises the majority of cases – e.g. in Chennai, more than 95%. But, where rates are low due to screening, the proportion of adenocarcinoma is higher than 15%. This is because cytological screening differentially prevents SCC, but is less effective in detecting and preventing adenocarcinomas (Fu et al. 1987, Sigurdsson 1995).

The distribution of cases by stage at diagnoses is similar to what is observed in other developing countries, for example in Chennai, India or Bangalore, India (Shanta et al. 1998, Nandakumar et al. 1998). It is clear that the stage is very advanced when compared

with developed countries, such as reported in US white (Sankaranarayanan et al. 1998). A study from Sweden shows a good example of trends in stage of disease at diagnosis which has improved over the years (Ponten et al. 1995). The authors suggest that this is a result of the general improvement of living standards and education, which has greatly contributed to the possibility of spreading and acquiring knowledge about cancer and its early symptoms. This is also expected to be going on in Thailand along with the improvement in the health education programme as well as the national education system in the future.

The incidence rates in three time periods, 1985–1989, 1990–1994 and 1995–1999, are relatively stable: 16.2, 17.7 and 16.2 per 100 0000. In other regions of Asia, in which cancer registries have been established for some time, the declines in incidence have also been rather modest, although the dramatic decrease in incidence in Shanghai, China, is an exception age-adjusted incidence fell from 26.7 per 100 000 to 2.5 between 1972–1974 and 1993–1994 (Jin et al. 1999). On the other hand, incidence rates have declined over time in those parts of the developed world with widespread screening programmes. The success of cervical cancer control has been shown in western Europe, U.S.A, Canada, Australia, New Zealand, and Japan (Hakama et al. 1986). In general, this has been ascribed to a combination of a reduction in risk in older generations of women, with, the success of population screening programmes.

The best known studies of time trends in incidence are those undertaken for the Nordic countries, where it was possible to compare the trends in incidence and mortality across countries with their different policies in relation to screening (Hakama 1982, Hakulinen et al. 1986). Läärä et al. (1987) investigated the trends in mortality from cervical cancer in Nordic countries in relation to the extent and intensity of organised screening programmes. The results support the conclusion that organised screening programmes have had a major impact on the reduction in mortality from cervical in Nordic countries. Sigurdsson (1999) also studied the Icelandic and Nordic cervical screening programmes: trends in incidence and mortality rates found that organised programme is more effective than spontaneous screening in reducing the risk of cervical cancer.

In Thailand, though a national cancer control committee has recently been established, there is as yet no official provincial cancer control programme. Recently a study of the coverage of cervical cancer screening by Pap smear was done in Nam Phong district, Khon Kaen province, found that there is still high proportion of women who have never been screened for cervical cancer during their life time (33%) (Kritpetcharat et al. 2003). Only 85 of the 230 age-matched controls – 37% – from the two nested cases control studies within the community-based cohort study (mean age 53.9, range 30–69)

reported having had a previous Pap smear. However, self report of Pap smear may not be accurate. In the USA (Gordon et al. 1993) found that women in a medical care programme had a tendency to over report Pap tests, compared with the records of actual tests.

6.2 Risk factors for cervical cancer

Three studies investigated the effect of demographic and lifestyle (reproductive history, sexual history, contraception, infections, smoking, alcohol consumption) variables, obtained by questionnaire, on the risk of cervical cancer in the Khon Kaen population. In addition, the potential protective effect of the Pap smear was studied in two of them.

The studies took place within the population of Khon Kaen province, Northeast Thailand. This is a rather homogeneous population, with respect to several variables which have been shown to be related to cervical cancer in studies elsewhere such as socio-economic status, occupation, education and income. The same is true for variables related to sexual history for example, number women with more than one sexual partner is small. The low prevalence of several exposures of potential interest (e.g. tobacco smoking, or sexual history of the woman and (as reported by her) the husband) – means that the studies have low power to detect any true effects.

The results from the three studies are consistent in some studied factors but some of them are different. How could this be explained? Although the results in each study design were different for some risk factors, this does not mean that the causes of cervical cancer are different.

6.2.1 Why the three different studies give different results?

The hospital-based case-control study has been one of the most widely used designs in analytic epidemiology. The advantage is the ready accessibility to cases of cancer, while they are hospital inpatients. In the study in Khon Kaen, 179 cases of invasive cancer could be identified during a single year, and included in the study, providing much more power to detect modest relative risks, than in the smaller case-control studies nested within the cohort study.

A major problem of hospital-based studies is to ensure that the controls are truly a representative sample of the population from which the cases were derived. A commonly used choice of controls is the use of patients with other diseases from the same hospital.

The idea is that the cases and controls will be similar (matched) for whatever factors lead to the use of a particular hospital (for example place of residence, income, social status), although there is no real guarantee that the "catchment population" of a hospital is the same for all diseases. The controls also have diseases that may be related in some way to the factors we want to study. A difference between cervical cancer cases and "controls" may mean that it is the "controls" that are unlike the general population (as to the risk factors of cervical cancer), not the cases.

In the present hospital-based study in Khon Kaen, the controls were all healthy women. They were women who had been enrolled into the cohort study, all, like the cases, gave their occupation as farmers. They were age matched (± 1 year), and drawn at random from cohort study members who were interviewed at the same time (same year) as the case. Only women who had an intact uterus, and were found to have a negative Pap smear were eligible as controls. These women were healthy, and they may, therefore, not be truly representative of the population from which the cases came. They probably were more healthy than average woman since they were selected by indicator of women's health (Pap smear) and they were not matched with respect to hospital attendance. There is, in other words, the potential for the results to be affected by selection bias. In fact, the cases and controls seem rather similar with respect to demographic and socio-economic variables, reflecting the rather homogeneous nature of the population in rural Khon Kaen province, but this cannot guarantee that the controls will be representative of the source population for all of the variables of interest.

A second major defect of case-control studies is bias introduced by differences in accuracy of the information obtained from cases and controls. There may be inaccuracies in the measurement of any variable. For questionnaires, the response may be wrong because the question was not clear, the subject forgot, or replied wrongly, or the reply was wrongly recorded. This leads to misclassification (wrongly recorded data), but provided that it is wrong to the same extent in cases and controls, the result is non-differential misclassification. It can result in a weakening of the apparent association between the variable and disease, but not an incorrect association. The latter can arise if misclassification is differential, that is, different in cases and controls.

Observer bias is introduced when the interviewers are aware of the case-control status, and obtain information from the two groups in different ways. This is inevitable, if it is obvious to interviewers which are cases of disease, and which are controls. This was obviously the situation in the present study, in which there were number of interviewers, although they had been trained to perform the interviews in the same way. What is more, the interviews of cases and controls took place in different settings (in hospital, in community clinics), and at rather different times and with different interviewers.

In all case-control studies, responder bias is also a possibility. That is, the subjects answer questions differently, according to whether they have the disease studied, or not. Using community-based controls means that the subjects were not sick, and may not have thought so carefully about possible causes of their condition (for example, past history of other diseases, contraceptives, sexual history).

The nested case-control studies involved fewer subjects than the hospital-based study, and so have much lower power to detect moderate sized relative risks. The size is constrained not only by the size of the cohort but also by the time interval that has elapsed since the cohort was established. As far as new, incident cases of cervical cancer are concerned, it takes some years for sufficient numbers to accumulate, to form the basis of a case-control study. The subjects followed up are healthy (at the time of enrolment), since all had a Pap smear, and women with any abnormality were investigated – those proving to have cervical cancer (invasive or in situ) are studied as "Prevalent cases". The rate of accrual of new, incident cases will depend upon the size of the population at risk (the cohort), its age distribution, and the age-specific incidence of cervical cancer in this population.

The expected numbers of invasive cases of cervical cancer in the Khon Kaen cohort, at the end of 2000 is 42 and 2005 is 62.

At the time that the analysis described in this thesis was carried out, only 27 new cases had been found among cohort members (21 invasive cancers, and 6 cases of carcinoma in situ). The latter had been found by some examination – perhaps a routine or more likely opportunistic screening test, the framework of the cohort study. Seventeen cases of invasive cancer, and 15 cases of carcinoma in situ had been found at the time of enrollment into the cohort. Detection and treatment of the CIS cases found at this time will mean that the numbers of future invasive cancers will be fewer than predicted by the calculation based upon incidence rates of invasive cancer in a mainly unscreened population.

There are several advantages of the nested case-control studies. First, they do not suffer from selection bias. Cases and controls are from the same population, and have been recruited into the cohort without any knowledge of disease status. This was presumably so, even for "prevalent" cancers, whom, so far as we were aware, were unaware of their disease when they were recruited, and its (unknown) presence did not directly influence their decision to participate in the cohort study. A second advantage of these studies is that there is no observer bias. Interview and recording of results were done in the same way for cases as for controls, with no knowledge of their disease status. There should be no respondent bias either, if the prevalent cases were indeed healthy and

symptom-free at the time of recruitment. Therefore, any misclassification of exposure variables should be non-differential.

With respect to the two nested case-control studies, the difference between them should lie mainly with respect to the measurement of variables that will have been affected by the presence of the disease, since the "prevalent" cases already had cervical cancer, although undiagnosed and maybe asymptomatic, at the time of interview and specimen taking. In fact, it is not likely that the responses to questions about past events would differ between the two groups. For some biological parameters, there may well be differences. For example, the presence of infection of the genital tract , by HPV, or herpes simplex, for example, is probably influenced by the presence of a cancer (malignant cells). Thus, it is nearly always the case that HPV infection is more readily observed in cervical cancers, that in precursor lesions, and the intensity of infection is greater (Muñoz et al. 1992a).

Another difference between the prevalent and incident nested case-control studies is the timing of exposure, relative to diagnosis of the cases. For prevalent cases, the information was obtained at the time of diagnosis, for incident cases, it was months or years beforehand. For most variables, this probably makes little or no difference, but, the interval since the most recent Pap test is important to determining the risk (IARC 1986). A "previous negative test" before the enrolment to the cohort will have been longer ago for the incident cases, and their controls, than for the prevalent cases and controls.

In summary it seems that the nested case-control study with incidence density sampling would give least bias but substantial random error compared to the two other designs. Hence, in case of inconsistent results most weight was given on the study with incident cases.

6.2.2 Results from the present studies

Social status

In our studies, all subjects are considered to be in a lower socio-economic status. The income of most subjects is lower than the average that reported by National Statistics Office, which reported the monthly family income of people in the Northeast of Thailand as 4800 Baht (National Statistics Office 2002a). There is a trend to increase in risk with increase in income in both studies of nested case-control studies.

Studies in western countries generally suggest that risk of cervical cancer increases with lower social status. This may not be relevant in Thailand. Higher income levels may

give more chance to men for using services from prostitutes that is believed to be one of sources of HPV transmission, and has been shown to be associated with increases in risk in Thai studies (Niruthisard and Trisukosol 1991, Thomas et al. 1996). The observation in the hospital-based case-control study, that women whose husbands were not farmers were at higher risk may have the same explanation. Since data on HPV infection is not available, study of independent effect of income is not possible.

There is insufficient variation in the distribution of subjects according to education, religion, and marital status to allow these variables to be studied. But the effect of education, if any, points to the same direction of high socio-economic status having high risk.

Sexual behaviour

Many studies have found that the risk of cervical cancer is higher in women who are divorced or separated, compared with married women. The risk of cervical cancer is especially high among women marrying at young ages (Boyd and Doll 1964). These associations are related to other aspects of sexual behaviour: number of sexual partners and age at initiation of intercourse (Terris et al. 1967).

In the present study, the inconsistent results were observed for the association of marital status at the time of interview and cervical cancer. The hospital-based study gave a positive association of the divorce or widow women and risk of cervical cancer, OR more than 1 but the ORs from nested case-control study were less than 1. This may in part be due to small numbers in the studies although the 95% confidence intervals suggest that the association is not strong even if present. In fact, it is quite possible that married status would not confirm much protection against HPV infection in Thailand, so that any association with risk of cervical cancer will be small.

There have been several previous hospital-based case-control studies of cervical cancer in Thailand, concentrating on behavioural risk factors in women (Punyaratabandhu et al. 1982, Wangsuphachart et al. 1987) or in their husbands (Niruthisard and Trisukosol 1991, Thomas et al. 1996), or on the presence of HPV DNA in cases and controls (Chichareon et al. 1998). These have demonstrated that the number of sexual partners of women was a clear determinant of risk. Age at first intercourse was not an independent risk factor. However, the lifetime number of sexual partners, even in women from urban setting, is low: 8% of control women in Bangkok (Wangsuphachart et al. 1987) and 19% in women from Hat Yai, southern Thailand (Chichareon et al. 1998) with more than one

sexual partner. Thus, the high risk of cervical cancer in the population cannot be due to female sexual behaviour.

In the present hospital-based case-control study in Khon Kaen, only 18% of cases and 6% of controls had more than one lifetime sexual partner, so that, with an associated relative risk of 3.5 the fraction of cases attributable to non-monogamy was 31%.

In the nested case-control studies, the great majority of women have had only one sexual partner (89% in the two control groups combined). In these two studies, the positive association found in the hospital-based study was not observed. The OR associated with having more than one sexual partner was 0.6 in the prevalent cases (negative association but not statistically significant), no association was found in an incident cases of the univariate analysis. However, because of the small number of subjects, and low prevalence of exposure (more than one sexual partner) the confidence limits are wide. It seems fair to conclude that there was no substantial evidence on the effect of sexual partners on the risk of cervical cancer.

Likewise, age at first sexual intercourse is late, with 70 to 73% of control women in the three studies reporting the age over 18. In the present studies, age <18 at first sexual intercourse was positively associated in univariate analysis of a hospital-based study with OR of 2.6 (95%CI 1.6–4.1). In a nested case-control study of prevalent cases, there was no association but the study of an incident cases, there was positive association in the univariate analysis. When adjusted for other risk factors the association became negative but not statistically significant. In keeping with the results from the earlier studies from Thailand, female sexual behaviour is probably of little importance as a risk for cervical cancer. The role of the male partner is probably more relevant.

In summary, as far as the risks associated with sexual behaviours is concerned, results from the hospital-based study seem to be more in keeping with the findings elsewhere. However some other explanations should be considered. In the hospital-based case-control study, responder bias may arise more than in the studies based on the cohort: the case subjects may be aware of the possible importance of sexual variables (they have a gynaecological condition) and thought more carefully to get correct answers than control subjects who are healthy women in community settings. Since cases are more correctly classified with respect to sexual behaviour than are the controls, the bias will be in favour of a positive association. In contrast, the results from the nested case-control studies, both case subjects and control subject were interviewed when they were in healthy condition. Any misclassification of sexual variables will be the same with respect to outcome (cervical cancer or not). The bias introduced will be towards a null result, or no association.

Age at menarche

There is a positive association between age at menarche and risk of cervical cancer in the nested case-control study of prevalent cases, which remains significant and with larger point estimate (OR 4.2) in the multivariate model.

Peters et al. (1986a, b) found some evidence that subjects with short intervals between menarche and initiation of sexual intercourse were at elevated risk (with relationships stronger than that observed with age at first intercourse alone), but this effect was not subsequently confirmed (Brinton et al. 1987). Since there is small number of subjects we could not study this effect in our study.

Parity

The most important risk factor found in the hospital-based case-control study was parity. The effect of number of full term pregnancies and age at first birth was a strong risk of cervical cancer, which was even stronger in the adjusted model. The two nested case-control studies also found positive association of cervical cancer risk and number of pregnancies. This association was statistically significant only in the study of incident cases. Based on the results of the study of incident cases (Study 3) with a multivariate OR of 7.2, the fraction of disease attributable to high fertility (>3 children) is very high (74%), but the level of uncertainty about this estimate is very high (95% CI 14%–95%).

The three present studies give relevant results of the association between parity and cervical cancer as finding elsewhere. Many studies, both in Thailand (Wangsuphachart et al. 1987, Niruthisard and Trisukosol 1991), and elsewhere (Brinton et al. 1989a, Eluf-Neto et al. 1994) suggest that high parity contributes to the risk of cervical cancer. In the latter studies, the parity-associated risk is not related to HPV infection, suggesting that it contributes independently to carcinogenic risk. In a pooled analysis of eight case-control studies, Muñoz et al. (2002) examined the effect of reproductive factors in women who were HPV positive. They found an association between the risk of squamous cell carcinoma and number of full term pregnancies – the OR associated with one or more full term pregnancies (vs none) was 2.3 (95% CI 1.6–3.2), and was 3.8 (95% CI 2.7–5.5) for seven full term pregnancies or more. There was no association with adenocarcinoma. One of the studies contributing to the pooled analysis was carried out in southern Thailand. In that study (Chichareon et al. 1998), there was no independent effect of parity, after adjustment for HPV. Clearly, further work on this important aspect is required. The

strongest association (OR 7.2 for >3 births) was found with the incidence density design, which gives credibility for the importance of parity.

Possible explanations for the association include cervical trauma during parturition and hormonal or nutritional influences of pregnancy. Ectopic columnar epithelium on the exocervix is increased with increasing parity (Autier et al. 1996) and the presence of the transformation zone in this area for more years may increase the risk of exposure to HPV. In addition, investigations showing high detection rates of HPV among pregnant women (Schneider et al. 1983) raise the possibility of an effect of pregnancy on viral activity.

Age at first birth

In two of the three studies (hospital-based study and the nested case-control study of incident case), age at having first child had a statistically significant positive association with cervical cancer. The risk remained significant in the multivariate models.

A variable such as this should not be differently recorded in case-control or cohort study designs, and there is no reason why responder bias should influence the result. Present-day consensus is that age at first birth is not an independent risk factor for in situ or invasive cancer, when age at first intercourse and parity are included in multivariate models (see section 3.2.1.7). The reason for the finding is obscure. It has not been investigated in previous studies in Thailand.

Contraceptive practice

In the present studies, none of the analyses shows any significant association between the use of contraceptive and risk of cervical cancer.

In Thailand, long-term use of oral contraceptives, or injectable contraceptives, is unusual. Most women in rural area are convinced by health personnel to have permanent contraception (tubal ligation) after having desired number of children in the family.

IARC (1999) reviewed the evidence for the effect of oral contraceptive use in cervical cancer. Five cohort studies and sixteen case-control studies were included, and it was noted that there was a consistent small increase in relative risk associated with long duration of use. A recent large-scale cohort study including 46 000 women in the UK (Beral et al. 1999) for example, found a relative risk of 2.5 (95% CI 1.1–6.1) in current or recent used versus never used, and there was a significant trend in risk with increasing duration of risk. Several early studies adjusted the odds ratios for possible confounding

factors e.g. social status, parity, sexual variables. More recent studies were able to restrict the analyses to cases and controls who were HPV positive in cervical screening (Bosch et al. 1992, Chaouki et al. 1998, Ngelangel et al. 1998), all showed positive association. Moreno et al. (2002) pooled the data from these and four other case-control studies (including that by Chichareon et al. (1998) in southern Thailand) to examine further effects of oral contraceptive in HPV positive women. There was no increase in risk for users of less than five years duration (OR 0.73, 95% CI 0.5–1.03), but the odds ratio for 5–9 years use was 2.8 (95% CI 1.5–5.4) and 4.0 (95% CI 2.1–8.0) for 10 years or more.

The effect of oral contraceptive on cervical cancer might operate through enhanced viral persistence but this still unclear some studies have shown increased HPV expression in oral contraceptive users (Lorincz et al. 1990).

In contrast, studies that have examined the association between progesterone-only contraception, such as depot-medroxyprogesterone (DMPA) and cervical cancer have not found an increased risk (IARC 1999). In the WHO collaborative study (WHO 1991) which included one center in Chiang Mai, Thailand, the overall multivariate relatives risk was 1.2 (95% CI 0.9–1.5) and there was no trend for the risk to increase with longer duration of use.

Characteristics of male sexual behaviour

As noted above, the women participating in the three studies were mainly monogamous, only a minority reporting more than one sexual partner. This is consistent with earlier studies from Thailand; these studies also demonstrated that Thai males have, in contrast, generally had many sexual partners, and that visits to prostitutes is a common behaviour. Niruthisard and Trisukosol (1991) interviewed the husbands of cervical cancer cases and controls and found that a history of VD in the husband was associated with an increased risk of cervical cancer (OR 2.1, 95% CI 1.1–4.0), and that even without a history of VD, prostitute visits were a clear risk factor for cervical cancer in the wives (OR 6.5, 95% CI 1.3–61.5). Furthermore, the failure to use condoms during prostitute visits was associated with a risk 4.9 (95% CI 1.2–23.9) times greater than for husbands who did use condoms on these occasions. These results were confirmed in a larger study by Thomas et al. (1996) who found a trend in risk with the number of prostitute visits of the husband, and the age at which prostitute visits had begun.

In our studies, the information on husband's behaviour comes from interviews with the women themselves, and, although Thai women may know more about the sexual activities of spouses than in Europe or North America, there is still surely a considerable

inaccuracy in such reports. This may make the observed associations between cervical cancer and spouse's behaviour of prostitute visits and history of VD rather weak or underestimated. Nevertheless, compared with the information from interviews of women in urban Bangkok (Thomas et al. 1996), the husbands of women in this rural community seem to have a low frequency of prostitute visits (9% control husbands) or a history of VD (6% control husbands). We can compare this with the results from two studies in Thailand – both in Bangkok – where the husbands of the women were directly interviewed. Niruthisard and Trisukosol (1991) found that visits to prostitutes were common (83% of control husbands); in the study by Thomas et al (2001c) 67% of control husbands reported this behaviour. It is likely that the situation is different in the rural setting of our study- in any case, the low prevalence of these behaviours means that the studies have no power to investigate their role.

With respect to a history of VD in the husband, only the hospital-based study was useful (no cases in the nested case-control study reported VD in the husbands). In the hospital-based study a history of VD or herpes simplex in the spouse increase risk of cervical cancer in wives, adjusting for the confounding did not remove the effect (OR 3.0 95% CI 1.0–9.3).

HPV

In the study 1 there is no information on infection by HPV. In the study series in the present studies 2 and 3, the nested case-control studies, the testing of the specimens of cervical cells for the presence of HPV is at the planning stage. The results are not yet available.

However, the prevalence of HPV in the same rural population in which our case-control study was performed, was studied in 289 women aged 30–59 by Ekalaksananan et al. (1996). Fifty-seven (19.7%) women were positive for 4 types of HPV (6,16,18,33), with the highest observed prevalence (18%) for HPV 16. This is very similar to the prevalence of 15.7% in the control subjects (mean age 49.7) in southern Thailand (Chichareon et al. 1998).

Other factors

In Thailand, the habit of smoking and alcohol consumption in women is not common. In the northeast of the country, especially, smoking and drinking among women is popularly associated with having loose morals.

There was an association found in the univariate analysis between alcohol consumption and cervical cancer in the nested case-control study of incident cases but not in the other two studies. This positive association was based on only 6 observed cases, and was not statistically significant (P=0.08). Almost no women in this population are smokers. Chewing of betel nut is more prevalent. It does not seem to pose a significantly increase risk in any study.

In some studies, cigarette smoking emerged as a possible aetiological factor for cervical cancer in many case-control studies (Winkelstein 1990). The effect was independent of various sexual and lifestyle variables such as sexual behaviour, but as the relative risk was not great (around two-fold), the suspicion remained that the effect was due to residual confounding for variables related to sexual activity (Phillips and Smith 1994). High levels of smoke-derived nicotine and cotinine found in the cervical mucus of smokers (Schiffman et al. 1987) suggest a possible biological mechanism for the smoking association, although the immunosuppressive effects of smoking should also be considered (Barton et al. 1988), particularly with respect to enhancing the effects of infectious agents, including HPV.

The information of history of cancer in a family was also obtained in the nested case-control studies. In both of them there were only 6 cases with cancer in the family, and there was no association with cervical cancer.

Pap smear

In case-control studies investigating the effect of screening tests on risk of disease, cases are the disease that the screening test tries to prevent (Morrison, 1982). In situ cases should not be included in the case series, therefore – they are detected by the screening examination, not prevented by it. The analysis was restricted to invasive cancer cases.

We only investigate tests previous to diagnosis. For prevalent cases, we might expect that persons who had a previous test would be at lower risk of disease. In fact, resulting odds ratio is only slightly below 1 (OR 0.8, 95% CI 0.4–2.6). Nor was there any trend in the risk with number of previous tests.

For incident cases, all would have had at least one prior screening test at the time of enrolment into the cohort. Therefore, the variable 'previous test' means tests carried out prior to this one (women reporting no previous test had therefore had only the one at enrolment). Furthermore all subjects may have had tests after enrolment. They were not re-interviewed when diagnosed, so screening history will be misclassified. For this reason, we may expect that there would be no clear effect of "previous test" on risk. – and indeed the variable 'previous test' gives an OR of 1.5 (95% CI 0.5–4.3).

It is quite likely that the women were not very clear about the nature of previous examination, and there may therefore be a lot of misclassification in the response to this question. Even in developed countries, with much better awareness of health issues, reports an Pap smear history may not well reflect actual history, as shown by laboratory results (Gordon et al. 1993).

6.3 Survival of cervical cancer

One of the important steps in carrying out an end result study is to ensure good and complete follow-up of patients. The actuarial (life table) method gives true estimates of survival rates only if censorship is independent of risk of death. In developing counties, it is difficult to obtain complete follow-up information for all patients for various reasons. This situation is different from that in developed countries, where the health information system is adequate, and the question of losses to follow-up may not arise. The censorship in such situations is technical withdrawal and is due to termination of the study or closing date and thus is usually independent of the outcome and thus the actuarial estimates obtained are approximately true with complete follow-up.

In the Thailand situation censorships are not entirely technical and may be related to chance of survival. This feature is seen in many developing countries where death registration is incomplete. Cutler and Ederer (1958) remarked that the survival experience of individuals who had incomplete follow-up may be better or worse than that of individuals continuing under observation.

In the present study, the actuarial survival method has been used to compute survival rates under normal assumptions. Because the patients were diagnosed in 1985–1990 and followed up to 31 December 1995 there were no withdrawals up to the estimated five-year survival. The proportion of cases lost to follow-up at five years from diagnosis is quite large (27.6%). The losses to follow-up were greatest during the first year, then reduced in the succeeding two years and increased again in the fourth and fifth years. The main basis for application of the standard actuarial method is the assumption

of independence of risk of loss and risk of death, that is, the losses are random. Because of the large number of cases lost to follow-up, it is important to test this assumption, to ensure that the survival calculated by the actuarial method does not give a biased estimate.

The test for randomness of loss to follow-up was done using odds ratio by logistic regression. In our study, treatment was statistically significant determinants of a loss (P=0.001), indicating an evidence of non randomness of loss to follow-up while age at diagnosis, staging of disease and residence were not related to the loss. The OR of death was increasing with increasing age at diagnosis (P=0.002), stage of disease (P<0.001), and treatment (yes/no) (P=0.01). Under these circumstances, survival probabilities were adjusted for the determinants of loss to follow-up, and loss-adjusted survival rates (LAR) were estimated by logistic regression methods.

A method for computing loss-adjusted survival rates (LAR) (Ganesh 1995) by taking into consideration differences in patient withdrawal with respect to prognostic factors was developed. The main assumption of the proposed method is that cervical cancer patients lost to follow-up with respect to a specific age, stage, residence and treatment group have the same probability of death as those still remaining under observation and belonging to the same group. It is reasonable to expect more similar survival experience in patients lost to follow-up and those with complete follow-up within a prognostic group than within the group of all patients. The actuarial survival rates were compared to the LAR's to find out the magnitude of the effect of loss to follow-up on the survival of cervical cancer patients treated at health center in Khon Kaen province, Northeast Thailand.

The five-year survival rate obtained by the actuarial survival method when considering the loss to follow-up to be independent of the risk of death, was 56.8%, and the loss-adjusted survival (LAR) 54.7%. The small reduction obtained by LAR indicated that age, place of residence, stage of disease and treatment were only marginal determinants of loss.

Examination of the survival estimates according to age revealed that cervical cancer patients aged over 60 years had the poorest survival and patients aged less than 40 had the best prognosis. The proportions of losses in each age group were not much different.

The proportion of loss to follow-up among patients who were residents of Muang and surrounding districts (28.1%) was a little higher than those who living in other districts (26.9%). One might have expected follow-up to be easier for patients living close to the hospital, but this may be offset by the fact that village dwellers are more stable in their residence, and so easier to trace. The survival was better in the first group (61.1% at five year) than in the latter group (53.2%). By adjusting for losses to follow-up by stage

of disease, age and treatment, there was only a small reduction in survival rate in both groups (2.5 and 1.8 percent unit, respectively).

The five-year actuarial survival rates decrease with more advanced clinical stage of the diseases. The proportions of deaths are higher among patients with the severity of disease. By adjusting for age, place of residence and treatment, a reduction in LAR in all stage groups was seen. For patients with unknown stage, the risk of loss to follow-up was high, and the survival rate was higher than those with stage III and IV but the reduction from LAR is wider. This unknown stage may include patients with early stage under good follow-up and advance stage with many losses to follow-up.

The five-year relative loss-adjusted survival in the treatment group (either surgery, chemotherapy or radiation) and among those who did not receive such treatments (classified as 'no treatment group') were 60.0% and 50.8% respectively, the differences was rather small. There are more subjects lost to follow-up in the no treatment group. The difference between LAR and actuarial survival rates was more apparent in the no treatment group (2.4 percent units), which was slightly higher than in the treatment group (1.7 percent units) but the difference was small enough to have no effect on the conclusions.

One might have expected to observe a more favourable survival in the patients who received treatment, compared to those who did not. However, an observational study such as this cannot be used to infer the effectiveness, or otherwise, of therapy; that is the role of the randomised controlled trial. A recent study in Uganda (Wabinga et al. 2003) also found no difference in survival in patients who had received radiotherapy, compared with those who had not. Furthermore, there is probably misclassification of treatment status. Some cases who did receive treatment may not have been so recorded by the registry. Subjects classified as having received 'no treatment ' means that no treatment had been recorded in any hospital in Khon Kaen province (registrations are updated with treatment details in subsequent admissions). For cervical cancer cases from Khon Kaen who were treated in Bangkok, Chiang Mai and in hospitals in other registration areas, information on treatment received was available. But for other cases going outside the province, no information would be available if they received treatment. So some cases in the 'no treatment' group may be misclassified. If treatment outside the province implies good survival (because of patient selection or treatment itself), there indeed may be incomparability between the groups that adjusting for losses does not disclose.

The small difference between the actuarial survival rates and LAR that was observed in this study is much less than in other studies. For example Ganesh (1995) studied the effect of loss to follow-up on the estimated survival rate of breast cancer patients in India, and found that LAR was less than actuarial rates to the extent of 6.7%

that, furthermore, varied substantially by prognostic groups. A similar finding was reported by Swaminathan et al. (2002), in an international comparison of actuarial and loss-adjusted survival rates of cervical cancer from different population-based cancer registries in developing countries, which revealed that the maximum difference between LAR and actuarial estimate was 4.1 percent unit with a loss to follow-up of 44%. In the Khon Kaen study the loss to follow-up was 27.6% and the difference in survival rate was 2.1 percent unit.

Comparisons of survival in different populations used the relative survival rates (Table 19). In these studies, the proportion of cases lost to follow-up is quite variable, from 5.4% in Cuba to 28.6% in the Thailand (Chiang Mai) and it is unknown to what extent the differences in survival are due to bias due to nonrandom losses.

The large variation in proportion lost to follow-up is a further indication of potential bias and incomparability. Ideally, there is a need to adjust for loss to follow-up for the prognostic factors (age, stage of disease etc.) before comparison, but the practical meaning of this adjustment in Khon Kaen data is rather small.

7 Summary

The results from the three components of the epidemiological study of cervical cancer in Khon Kaen, Northeast of Thailand can be summarised as follows:

The incidence of cervical cancer in Khon Kaen province is moderately high, with not much change over the last 15 years. Stage at presentation is considerably later than in the United States and Europe. There is about a two-fold variation in incidence between districts within the province. Eighty percent of cases are squamous cell carcinomas. Until a vaccine is available, which may prevent infection with HPV, control through early detection and treatment remains the best approach. This can be through encouragement of women to present at an earlier stage of disease, which has a much better prognosis (survival) that for cases in Stage III or IV (as shown in our results, section 5.3). Stage at presentation can be improved along with better knowledge and awareness. This can be achieved in a short period of time, by health education programmes, as was shown by Jayant et al. (1995) among rural populations in India, where a significant stage shift was observed in a population in regular contact with health workers enquiring about cancer cases.

Otherwise, early detection through screening is the best-established method of reducing incidence and death. Current screening programmes in Thailand are not very effective. The quality of the smear taking, preparation, and reading in many programmes, particularly in developing countries, is not good (Lazcano-Ponce et al. 1998, Sankaranarayanan et al. 2001). In addition, it has been shown in Northeast Thailand that the follow-up of women found to have a positive smear at screening is quite defective (Thinkhamrop et al.1998). The national cancer control programme aims to increase the coverage of screening, by limiting examinations to women at ages of 35, 40, 45, 50, 55 and 60 (Deerasamee et al. 2002). The population-based cancer registry in Khon Kaen will provide an effective and economical method of evaluating the impact of early diagnosis and screening at community level (Sankila et al, 2000).

Results from the three studies for risk factors of cervical cancer in Khon Kaen, Thailand are similar to those of studies elsewhere. Consistently, number of pregnancies and age at having first child were associated with the risk of cervical cancer. However, the usual risk factors of age at first sexual intercourse, number of sexual partners and a history of sexually transmitted disease among the subjects were not observed to be associated with risk of cervical cancer in Khon Kaen. The negative findings may be due to the small size of the studies, or to differences in the epidemiology - particularly with respect to infection with human papillomavirus (HPV) – in the Khon Kaen population.

The hospital-based case-control study has the advantage of large numbers of cases and controls, and is simple and cheap to conduct. But, the design is open to various biases that may have influenced the results. The cohort study is a classical design in epidemiology, the results are much less influenced by potential bias in measurement of exposure or outcome, and multiple outcomes can be studied. However, this design needs a lot of financial support and is time consuming in countries where these studies cannot rely on existing linkable registries. In fact, the first aim of the Khon Kaen cohort is the study of liver cancer. The main problem was the relatively small size of the cohort itself, which means that there are few cases for study, and that we will have to wait many years before there is enough power to investigate small risks, or interactions between the different factors.

The overall five-year survival of cervical cancer in Khon Kaen, Thailand is rather low compared to the study in developed countries. Extent of disease at diagnosis is the most important determinant of survival, implying that early detection is more important in improving outcome than improvement in the modality of treatment. The importance of different methods for estimating survival is addressed. Adjusting the estimate for cases lost to follow-up provided results that were similar to those obtained with the actuarial method, suggesting that the conventional use of the actuarial estimate in the calculation of the relative survival is satisfactory for this population.

Abbreviations

AICR = American Institute for Cancer Research Fund
AIDS = Acquired immunodeficiency syndrome
ASCUS= Atypical squamous of undetermined significance
ASR = Age-standardised rate
CDC = Center for Disease Control
CI = Confidence interval
CI5 = Cancer incidence in five continents
CIN = Cervical intra epithelial neoplasia
CIS = Carcinoma in situ
DCN = Death certificate notification
DCO = Death certificate only
DMPA = Depot-medroxyprogesterone acetate
DNA = Deoxyribonucleic acid
FIGO = International Federation of Gynaecology and Obstetrics
HGSIL = High grade squamous intraepithelial lesion
HIV = Human immunodeficiency virus
HPV = Human papillomavirus
HR-HPV =High risk type human papillomavirus
HSV = Herpes simplex virus
IARC = International Agency for Research on Cancer
ICD = International classification of diseases
IUD = Intrauterine device
LAR = Loss-adjusted survival rate
LEEP = Loop electrosurgical excision procedure
LSIL = Low grade squamous intraepithelial lesion
NAS = National Academy of Sciences reports
NOS = Not otherwise specified
OR = Odds ratio
OV = *Opisthorchis viverrini*
PAP = Papanicolaou smear
PCR = Polymerase chain reaction
RR = Relative risk
SCC = Squamous cell carcinoma
SEER = Surveillance, Epidemiology, and End Results
STD = Sexually transmitted disease
VD = Venereal disease
VS = Versus
WHO = World Health Organization
WCRF = World Cancer Research Fund

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