A COMPARATIVE STUDY BETWEEN ADDITIVE AND MULTIPLICATIVE MODELS : IDENTIFYING RISK FACTORS OF REPRODUCTIVE AND BREAST CANCER IN WOMEN 40 YEARS OF AGE AND OVER

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With compliments
of
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The objectives of the study were to determine the association between the reproductive risk factors and breast cancer in women 40 years of age and over, and to compare the fit of additive and multiplicative models to the observed data of breast cancer patients and the reproductive risk factors. The design of the study was retrospective case- control study. The study used medical records of patients who were treated at the National Cancer Institute between 1 January 1993 and 31 December 1995. The cases were 489 women with histologically confirmed breast cancer and the controls were 1026 women with other cancers or without cancer.

The results revealed that the significant risk factors of breast cancer were age greater than 54 years, never married, number of children born 1 to 4 or nullparous women, parity more than 4 or nullparous women, age at first labor more than 29 years, age at the menarche less than 14 years and postmenopausal. The multiple logistic regression analysis for controlling the effect of confounding factors indicated that the women who aged more than 54 years, never married, number of children born 1 to 4 or nullparous women, parity more than 4 or nullparous women, age at first labor more than 29 years and age at the menarche less than 14 years were significantly related to breast cancer. A comparative study between additive and multiplicative models revealed that the multiplicative model was better fit in the analysis of association between the combined effect of reproductive risk factors and breast cancer than the additive model.

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ศัพท์สำคัญ : ADDITIVE และ MULTIPLICATIVE MODEL / ปัจจัยเสี่ยงด้านการเจริญพันธ์ และ โรคมะเร็งเต้านม

นัยนา วงษ์วานิช : การศึกษาเปรียบเทียบ ADDITIVE และ MULTIPLICATIVE MODEL สำหรับปัจจัยเสี่ยงด้านการเจริญพันธ์ และโรคมะเร็งเต้านมของหญิงอายุ 40 ปีขึ้นไป(A COMPARITIVE STUDY BETWEEN ADDITIVE AND MULTIPLICATIVE MODEL : IDENTIFYING RISK FACTORS OF REPRODUCTIVE AND BREAST CANCER IN WOMEN 40 YEARS OF AGES AND OVER) คณะกรรมการควบคุมวิทยานิพนธ์ : สุมาลี สิงหนิยม, วท.ม. (ชีวสถิติ), สิริศักดิ์ ภูริพัฒน์, พ.บ., TBR.(Ther.&Nuc.), ABR.(Ther.), กมลเนตร โอฬานุรักษ์, Ph.D. 47 หน้า. ISBN 974-661-315-4

การศึกษานี้มีวัตถุประสงค์ 2 ประการคือ ศึกษาปัจจัยเสี่ยงด้านการเจริญพันธ์ ในการเกิดมะเร็งเต้านมของหญิงอายุ 39 ปีขึ้นไป และเพื่อเปรียบเทียบผลการวิเคราะห์ข้อมูล ระหว่าง additive และ multiplicative model สำหรับปัจจัยเสี่ยงด้านการเจริญพันธ์ในการเกิดมะเร็งเต้านมของหญิง การศึกษานี้เป็นการศึกษาแบบ retrospective case-control ใช้ข้อมูลทุติยภูมิจาก เวชระเบียนของผู้ป่วยที่ได้เข้ามารับบริการตรวจโรคใน สถาบันมะเร็งแห่งชาติ ระหว่างวันที่ 1 มกราคม 2536 ถึง วันที่ 31 ธันวาคม 2538 กลุ่มศึกษา ได้แก่ ผู้ป่วยหญิงที่เป็นมะเร็งเต้านม จำนวน 489 คน และกลุ่มควบคุม ได้แก่ ผู้ป่วยหญิงที่เป็นมะเร็งชนิดอื่นๆ ที่ไม่ใช่มะเร็งเต้านม หรือผู้มีสุขภาพปกติ จำนวน 1026 คน

ผลการศึกษา พบว่าปัจจัยที่เพิ่มโอกาศเสี่ยงต่อการเกิดมะเร็งเต้านมอย่างมีนัยสำคัญทางสถิติมีความสัมพันธ์กับ อายุที่มากขึ้น, สถานภาพสมรส, จำนวนบุตร, จำนวนครั้งการตั้งครรภ์, อายุที่มีบุตรครั้งแรก, อายุที่มีประจำเดือนครั้งแรก และ ภาวะการหมดประจำเดือน แต่เมื่อวิเคราะห์โดยใช้ multiple logistic regression analysis เพื่อควบคุมตัวแปรแทรกซ้อน พบว่า อายุที่มากขึ้น, สถานภาพสมรส, จำนวนบุตร, จำนวนครั้งการตั้งครรภ์ และ อายุที่มีประจำเดือนครั้งแรก มีความสัมพันธ์กับการเกิดมะเร็งเต้านมอย่างมีนัยสำคัญทางสถิติ การเปรียบเทียบผลการวิเคราะห์ข้อมูลระหว่าง additive และ multiplicative model สำหรับปัจจัยเสี่ยงด้านการเจริญพันธ์ในการเกิดมะเร็งเต้านมของหญิง พบว่า multiplicative model เป็นสมการที่เหมาะสม สำหรับการวิเคราะห์ความสัมพันธ์ ระหว่างปัจจัยเสี่ยงด้านการเจริญพันธ์ในการเกิดมะเร็งเต้านมของหญิง

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CHAPTER I

INTRODUCTION

Background and the importance of the problem

Breast cancer was the most common diagnosed cancer among women in the USA., other Western and developing countries (1,2,3). In the USA and in most other high risk countries, breast cancer death in women was second to lung cancer deaths (1).

One factor that had of concern to women recently was that one out of eight women will develop breast cancer (4). It was estimated that the annual incidence of breast cancer worldwide will be more than one million cases by the year 2000 (2). Recent epidemiologic studies revealed that (1,2), breast cancer incidence and mortality rates were highest in North America and Northern Europe, followed by Southern Europe and Latin America, and lowest in Asia and Africa (1,2). However in recent years, steep increase in breast cancer incidence and mortality rates had reported in several Asian and Central European countries. Gursin et al. (1) reported that the incidence of breast cancer has increased in all countries since 1960. The large increase in incidence took place in Japan and Singapore. The incidence rate in women aged 35 to 44 years in Japan doubled between 1958 and 1960 and by 1985, it was roughly two-third of the USA. rate (1,3).

Breast cancer was ranked as the third leading cancer in the Thai female, the incidence rate per 100,000 was 2.45 in 1978 (5) and up to 11.9 in 1990 (6). The cancer study between 1988 to 1991, had shown that breast cancer ranked between the second and the third for cancer in each region of Thailand (6). In addition, the Nation Cancer Institute (NCI) reported that breast cancer ranked as the second among 10 common leading cancers (7).

For many years, certain reproductive characteristics have been associated with the risk of breast cancer. They include endogenous hormones, parity, age at fist menarche, number of children born, age at first labor, menopausal status (11).

Thailand has been in a stage of transition from being agricultural to a newly industrialization country, bringing more women into labor forces. There were many effects of industrialization on women heath such as reproductive health which impacts on changing of their life styles (12) and the reproductive factors were substantial effect on breast cancer rate (1).

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Therefore, the aims of this study were to study the association between the reproductive risk factors and breast cancer and to compare the fit of additive and multiplicative models to the observed data of breast cancer patients and the risk factors.

Objectives of the study

1. To study the association between the reproductive risk factors and breast cancer in women over 40 years of ages and over.
2. To compare the fit of additive and multiplicative models to the observed data of breast cancer patients and the risk factors.

Hypotheses

1. Women who had age older than 55 years of and over have higher risk of breast cancer than women who had age less than 55 years .

2. Women who had never married have higher risk of breast cancer than women who had ever married .

3. 3.1 The nullparous women have higher risk of breast cancer than women who had children.

   3.2 Women who had children born less than 5 have higher risk of breast cancer than women who had children born 5 and over.

4. 4.1 The nullparity women have higher risk of breast cancer than women who had parity.

   4.2 Women who had parity 4 and over have higher risk of breast cancer than women who had parity less than 4 .

5. Women who had age at first labor less than 20 years or more than 29 years have higher risk of breast cancer than women who had age at first labor 20 to 29 years .

6. Women who had age at menarche less than 14 years have higher risk of breast cancer than women who had age at menarche 14 years and over.

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7. Postmenopausal women have higher risk of breast cancer than premenopausal women .

Scope of study

The purpose of this study is to find out the reproductive risk factors related to breast cancer in women aged 40 years and older who had registered to the National Cancer Institute during 1 January 1993 to 31 December 1995 .

Definition and meaning of terminology used in this study

Reproductive factors. These factors are age, marital status, number of children born, parity, age at first labor, age at menarche, menopausal status.

Parity (birth order) means the number of previous pregnancies including abortion, premature pregnancy and full term pregnancy.

Number of children born means number of children with live born .

Hormonal contraceptive used refers to the women who received hormonal contraceptive for more than 8 weeks (contraceptive used such as progesterone, or combined estrogen and progesterone)

Premenopausal women women who are still menstruating, or who had the operations not involving removal of both ovaries and whose age at diagnosis was lower than the average age of the natural menopause in Thai female (48.7 years).

Postmenopausal women women who report a natural menopause or a bilateral oophorectomy before the diagnosis or women who report hysterectomy alone and their age at surgery were higher than 48.7 years.

Cancer registration means information based on patient database of the National Cancer Institute. The information cover histologically diagnosis, treatment and follow up.

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The limitation of this study

In this study, the cervix cancer patients were included in the control group. However, some risk factors of cervix cancer were the same as of breast cancer. Therefore, this study could only show the comparison the statistic methods, not for the analysis in the risk factors of breast cancer because the results of this study might be the effect of confounding from the selection bias .

Variables

- **Independent variables** consists of
  - Ages
  - Marital status
  - Number of children born
  - Parity
  - Age at first labor
  - Age at menarche
  - Menopausal status

- **Dependent variable :** the presence of breast cancer (Yes / No).

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CHAPTER II

A REVIEW OF LITERATURE

General overview : breast cancer

Cancers usually are named after the body organ or tissue in which the cancer originated. The specific cause or causes of breast cancer were not known, and it is unlikely that any single factor triggers the disease. Breast cancer appears to be a disease that depends on an interrelationship among a number of factors. It was found that the risks of the breast cancer were associated with the following factors.

1. Reproductive risk factors.

1.1 Age at menarche and age at menopause. Women with age at menarche before 12 years had 1.5 fold breast cancer risk compared with women who had age at menarche more than 12 years. Women whose natural menopause was delayed to age 55 or later had about twice the breast cancer risk compared with women who had age at menopause before 55 years (17).

1.2 Age at first labor. Women with age at birth of the first labor before 20 years and older than 34 years have 1.5 fold of breast cancer risk compared with women who had age at birth of the first labor 20 to 34 years (18).

1.3 Parity. Nullparity women had a higher breast cancer rate than women with children (18).

2. Other risk factors.

2.1 Environment. Urban living women have the higher incidence rate breast cancer than rural living women (17).

2.2 Breast feeding. Women who had breast feeding with long period (more than 40 months) has increase risk of developing breast cancer.

2.3 Hormonal. The postmenopausal women having estrogen for menopausal symptoms with high dose over 5 years had increase risk (18). Women who used oral contraceptives with small dose over 8 years have high risk (18,19).

2.4 Nutrition : The excessive intakes of dietary fat , beef and alcohol had increased risk in breast cancer (20).

2.5 Hair dye used. Hair dye users over 10 years had increase breast cancer risk especially patients with fibrocystic disease (17).

2.6 Radiation. Women expose to atomic bombing, and those irradiated for medical reasons (18,22) have increased risk in breast cancer.

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2.7 Family history of breast cancer. The higher risk women were those with the history of breast cancer in mothers, sisters, grand-mothers, maternal aunts and female cousins. The disease in these families develop premenopausally, often bilaterally and seem to associated with ovarian function.

The research relavant to reproductive risk factors for breast cancer.

Patamapadpong (1982) (20) showed that women who had first pregnancy after age 30 years old and nullparous women has significant association with increased risk of breast cancer.

Chariyalertsak (1989) (21) revealed that women age at first labor less than 20 or over 30 years significantly associated with increased risk of breast cancer than those age at first labor 20 to 29 years. Women with parity over 4 children have a higher risk than those whose parity were 1 to 3 children.

Shamnijarakit (1983) (22) demonstrated that the increased risk of breast cancer were single women and divorce women, women who had age group over 40 years, women who had age at birth of the first child high and age at menarche less, the nullparous women or less child (1 to 4), women who had postmenopause.

Papatestas (1994) (23) revealed that the reproductive history was a significant prognostic determinant. The parous women had a significantly higher cumulative five-year disease free survival rate compared to the nulliparous women.

Paphawasit and Vongvises (1980) (24) revealed that the women who had breast cancer average age was 51.7 years. The incidence occurred most commonly between the age of 51 to 60 years, followed by the age of 41 to 50 years.

Tantisoontorn (1981) (26) : studied the demographic characteristics of 51 women with breast cancer patients admitted to Siriraj Hospital. The seventy two percent of the patients were more than 40 years old, and 92 percent of them were Thai. Among the Thai patients, 96 percent were Buddhists. Sixty four percent finished prathom 4, and 26 percent were tradesmen. Ninety two percent married and 55.3 percent had 3 to 4 children. Age at the first labor was more than 20 years.

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MacMahon and Pugh (1970) (27) studied 4,323 breast cancer cases and 12,699 control patients in seven areas of the world . In all areas studied , a striking relation between age at first labor and breast cancer risk was observed . It is estimated that women having their first child when aged under 18 years had only about one-third of breast cancer risk of those whose first birth delayed until the age of 35 years or more . Births after the first, even if they occurred at an early age, have no or very little protective effect .

Mirra, Cole, MacMahon, et al. (1971) (28) reported that women who had a first pregnancy prior to age 20 years had only about two-third of breast cancer risk of those whose with first pregnancy occurred after age 25 years .

Bain, Willett, Rosner, et al.(1981) (29) studied the relationship between age at birth of a first child and breast cancer . A positive trend of increasing risk of breast cancer with later ages at first birth was found .

Lubin (1982) (30) revealed that the combination of low parity and late age at first birth was associated with a seven fold increase in breast cancer risk at ages 55 to 80 years but slightly decreased at ages under 45 years .

Feinleib (1968) (31) studied 6,908 women undergoing artificial menopause and 1,479 women having natural menopause. The study revealed that surgical castration prior to age 40 years reduced breast cancer risk by 75 percent . The reduced risk is seen approximately ten years later and lasts throughout life . The protective effect of early surgical castration was observed in both parous and nulliparous women . Other forms of artificial menopausal or castration after age 40 years does not afford such protection .

Helmrich, Shapiro, Rosenberg, et al.(1983) (32) showed that the risk of breast cancer increased with increasing age at first birth . Women who give birth before the age of 18 years have only one-fourth the risk of developing breast cancer of women who do not have a child until they were near age 30 years. However, the protetion associated with parity disappears for women who first give birth after age 30 years such women have a greaster risk than women who have never given birth at all.

Townsend (1980) (33) disclosed that surgical menopause before age 35 years appeared to reduce subsequent risk of breast cancer .

Trichopoulos , MacMahon and Cole (1972) (34) revealed that women going through menopause after age 55 years had twice the breast cancer risk compared to those with menopause occurred before age 55 years. It was also reported that , early surgical menopause has shown to be protective .

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Paffenbarger, Fasal, Simmons, et al (1977) (35) showed that the relative risk of developing breast cancer among ever-users of oral contraceptives was 1.1 , no statistical significant. The risk was significant for the 2 to 4 year users and significantly increased if they were still taking oral contraceptives (up to 8 years or over).

Byrd , Burch and Vaughn (1977) (36) revealed that women over age 55 years when starting estrogen had increased risk of breast cancer over a long follow up. The highest risk group were nulliparous women over 55 years .

Gunnar , Ivar and Geir (1987) (37) observed that there was protective effect of multiparity for cancers in all age groups . The nullparous women had higher risk of developing breast cancer than uniparous women . Those who reported at least one abortion had somewhat lower risk than those who did not , but no trend according to the number of abortions was observed .

Gunnar and Ivar (1987) (38) showed that relations between age at first and last full-term pregnancy and breast cancer risk were association with breast cancer and the increasing parity had higher risk than 1 to 3 parity.

The research relavant to additive and multiplicative models .

Campbell (1985) (39) It revealed that additive model can be useful in the analysis of cohort studies better than multiplicative model.

Lund (1995) (40) To test different model between additive and multiplicative models. The study design was prospective. The analysis found evidence of better fit by additive compared with the multiplicative models, consistent with the proposed mathematical model .

Marschner (1996) (41) discussed the assessment of age and time-specific disease incidence using prevalence data . A method was described for conveniently fitting a discrete-time multiplicative model , subject to positively constraints , using the EM-algorithm . Together with smoothing , it allowed essentially nonparametric assessment of incidence trends . The method illustrated using previously analyzed data on toxoplasmosis .

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Schneider, Hubert, Degrange, et al (1995) (42) compared lifetime risk estimates for radiation-induced breast cancer the Japanese, American and French populations, using demographic data, risk projection models, and assuming an individual acute exposure. The lifetime risk estimates were similar in the three populations when the additive projection models was used because of the similarity of the life tables of the three countries. However, using the multiplicative model, large differences appeared due to the discrepancies in the baseline breast cancer rates between Japanese and Occidental populations. It was for this reason that transfer of risk coefficients fitted on the Japanese population data must be considered with caution when applied to an Occidental population.

Gardner and Munford (1980) (44) found that the combined effect of two factors on disease in a case-control study, the multiplicative model was better model compared with the additive model.

Storer, Wacholder and Breslow (1983) (45) presented additive and multiplicative risk model and use of expected and observed information. An interactive computer program was available for fitting multiplicative, Additive and general risk models to stratified data. It found that the additive model was better model compared with the multiplicative model.

Breslow and Storer (1984) (46) the propose of this studies was testing relative risk functions ranging from additive to multiplicative models that was generated by varying the exponent in power transform for the log relative risk. The different relative risk models may have markedly different implications for the multifactorial nature of the disease process. Showed that the additive model was better fit model than multiplicative model.

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CHAPTER III

MATERIAL AND METHOD

The study design

The study design is a retrospective unmatched case-control.

Study groups

The samples were women who registered to the National Cancer Institute during 1 January 1993 to 31 December 1995 , aged 40 years or more. The cases were women with histologically confirmed breast cancer and the controls were women with other cancers or without cancer.

Data collection

This study used secondary data from patients's medical record at the National Cancer Institute.

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Sample size

Selection of cases The cases group consisted of 492 breast cancer patients, with 40 years of age or more .

Selection of controls The control group were women aged more than 39 years who registered to the National Cancer Institute for either annual check-up and the cancer patients other than breast cancer. They were selected by systematic sampling random. The data was used for calculating the sampling interval as follows :

Number of patients = 2,477
Sample size requirement = 1,476
Sampling interval (2,477 / 1,476) = 2

Select the random start(r) which was less than or equal 2 (the random table was used for selecting the random start, r = 2). So that the women number

$$I , I+k , I+2k , I+3k , \ldots , I(n-1)k .$$
$$2 , 4 , 6 , 8 , \ldots , 2,476$$

were selected as the control group.

Data analysis

1. Descriptive statistics

2. Univariable analysis. Study variables were examined individually to see the crude association between breast cancer and reproductive risk factors.

3. Multivariable analysis. Analysis was carried out to determine the adjusted association between the breast cancer and each dichotomous variable while simultaneously control for the effects of other variables and to assess possible interaction between variables.

4. Additive and Multiplicative models : a method for testing whether the combined presence of each dichotomous variable(age, marital status, number of children born, parity, age at first labor, age at menarche and menopausal status) and breast cancer has an additive and multiplicative model. The effect of each factor was measured by test maximum likelihood ratio test statistic under the additive and multiplicative hypothesis.

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THE COMBINED EFFECT OF TWO FACTORS ON DISEASE IN A CASE-CONTROL STUDY BY ADDITIVE AND MULTIPLICATIVE MODELS .

The distinction between the additive and multiplicative models of combined risks is important . Suppose that the background risk of a disease is 1 per 1000 , and suppose that it is increased in the presence of cause A to 5 per 1000, and in the presence of cause B to 10 per 1000 . From the equation <1> in the presence of both causes A and B the additive model would produce a risk of 14 per 1000 by summing the absolute excess risks of A and B separately , whereas the multiplicative model would produce a risk of 50 per 1000 by multiplying the relative excess risks of A and B separately . There is clearly an important difference between the two models for the risks from combined exposure to causes A and B .

METHOD

Let R , R_A and R_B be the risks (death rates) following exposure to neither A nor B , A only , and B only , respectively . Then $r_A = R_A / R$ and $r_B = R_B / R$ are the relative risks of the disease following exposure to A alone and exposure to B alone . Under the hypothesis of additive effects , the effect on risk of A is $R_A - R$ and of B is $R_B - R$ and, therefore, the effect of the joint presence of A and B is to produce a risk of

$$R_{A \text{ and } B} = R + (R_A - R) + (R_B - R) = R_A + R_B - R .$$

This leads to a relative risks of

$$r_{A \text{ and } B} = r_A + r_B - 1 . \qquad <1>$$

Under the hypothesis of multiplicative effects , the effect on risk of A is $R_A / R = r_A$, of B is $R_B / R = r_B$ and ,therefore , the effect of the presence of A and B is to produce a risk of

$$R_{A \text{ and } B} = R . r_A . r_B .$$

This leads to a relative risks of

$$r_{A \text{ and } B} = r_A . r_B . \qquad <2>$$

Relationship <1> and <2> can be re-written as

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$$r_{A \text{ and } B} = 1+e_A+ e_B \text{ and } r_{A \text{ and } B} = (1+e_A)(1+e_B) = 1+ e_A+e_B+e_B.e_A$$

where

$$e_A = (R_A - R)/R \text{ and } e_B = (R_B - R)/R .$$

If we consider a general formulation , as

$$r_{A \text{ and } B} = 1+e_A+ e_B+\beta.e_A.e_B ,$$

then $\beta=0$ and $\beta \neq 0$ correspond to the additive and multiplicative hypotheses respectively . The value of β for which the estimated likelihood function reaches a maximum can be regarded as a measure of the degree of breast cancer .

Suppose that the probabilities for cases and controls being exposed to different combinations of A and B are as shown in Table 1. Then the additive model <1> , with the approximation described in the introduction , gives

$$\frac{\pi_4\theta_1}{\pi_1\theta_4} = \frac{\pi_2\theta_1}{\pi_1\theta_2} + \frac{\pi_3\theta_1}{\pi_1\theta_3} - 1 ,$$

which can be written as

$$\frac{\pi_1}{\theta_1} - \frac{\pi_2}{\theta_2} - \frac{\pi_3}{\theta_3} + \frac{\pi_4}{\theta_4} = 0 \qquad <3>$$

Likewise from <2> , the multiplicative model imposes the following relationship among the probabilities "written for later convenience in terms of logarithms"

$$\ln (\pi_1 \theta_2 \theta_3 \pi_4) - \ln (\theta_1 \pi_2 \pi_3 \theta_4) = 0 \qquad <4>$$

If the observed frequencies corresponding to the two multinomials of Table 1. are $n_i (i =1,...,4)$ for the cases and $m_i (i =1,...,4)$ for the controls , then the joint likelihood of the observations is

TABLE 1

Probabilities of various exposures for cases and controls

Group	Exposure: None	A	B	A and B	Total
Cases	π_1	π_2	π_3	π_4	1
Controls	θ_1	θ_2	θ_3	θ_4	1

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$\Pi^4_{i=1} \pi_i^{mi} \theta_i^{mi}$. To investigate the additive hypothesis this function is maximized subject to constraint <3> , together with $\Sigma\pi_i - 1 = \Sigma\theta_i - 1 = 0$. The ratio of this value to the unconstrained maximum leads to maximum likelihood ratio test statistic . The equivalent test for the multiplicative hypothesis is obtained by the use of constraint <4>.

MAXIMUM LIKELIHOOD ESTIMATION

It is convenient to work with the logarithm of the likelihood function , which is

$$F = \sum_{i=1}^{4} n_i \ln \pi_i + \sum_{i=1}^{4} m_i \ln \theta_i \qquad <5>$$

This has to be maximized subject to $F_1 = \sum^4_{i=1} \pi_i - 1 = 0$, $F_2 = \sum^4_{i=1} \theta_i - 1 = 0$ and F_3 = l.h.s. of <3> = 0 or F_4 = l.h.s. of <4> = 0 respectively for the additive or multiplicative hypothesis . The proceed in each case by using the method of Lagrange multipliers .

ADDITIVE MODEL

For the additive model this study need a stationary value of $F_{(A)} = F + \mu_1 F_1 + \mu_2 F_2 + \mu_3 F_3$. Differentiation of $F_{(A)}$ with respect to the π's , θ's and μ's gives

$$\frac{\partial F_{(A)}}{\partial \pi_i} = \frac{n_i}{\pi_i} + \mu_1 + \frac{\delta_i \mu_3}{\theta_i} \quad , (i = 1, \ldots, 4) \ ,$$

$$\frac{\partial F_{(A)}}{\partial \theta_i} = \frac{m_i}{\theta_i} + \mu_2 + \frac{\delta_i \pi_i \mu_3}{\theta_i^2} \quad , (i = 1, \ldots, 4) \ ,$$

and

$$\frac{\partial F_{(A)}}{\partial \mu_i} = F_i \quad , (i = 1, 2, 3) \ ,$$

where $\delta_1 = -\delta_2 = -\delta_3 = \delta_4 = 1$. By use of the constraints $F_1 = F_2 = F_3 = 0$ it can be shown that

$$\Sigma\pi_i \frac{\partial F_{(A)}}{\partial \pi_i} = n + \mu_1 \text{ and } \Sigma\theta_i \frac{\partial F_{(A)}}{\partial \theta_i} = m + \mu_2 \ ,$$

where $n = \Sigma n_i$ and $m = \Sigma m_i$. At the maximum these lead to $\hat{\mu}_1 = -n$ and $\hat{\mu}_2 = -m$, and the remaining maximum likelihood equations can be written as

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$$(n_i - n\hat{\pi}_i)\hat{\theta}_i + \delta_i \hat{\pi}_i \hat{\mu}_3 = 0 ,$$

$$(m_i - m\hat{\theta}_i)\hat{\theta}_i - \delta_i \hat{\pi}_i \hat{\mu}_3 = 0 \qquad <6>$$

for $i = 1 , \ldots , 4$ and

$$\sum_{i=1}^{4} \delta_i \frac{\hat{\pi}_i}{\hat{\theta}_i} = 0 , \qquad <7>$$

Writing $x_i = \hat{\pi}_i / \hat{\theta}_i$ for $i = 1 , \ldots , 4$ and solving the appropriate pair of equations from <6> we obtain a quadratic equation for x_i with solution in terms of $\hat{\mu}_3$,

$$x_i = \frac{\delta_i m_i n - m\hat{\mu}_3 \pm \sqrt{\{(\delta_i m_i n - m\hat{\mu}_3)^2 - 4\delta_i n_i nm\hat{\mu}_3\}}}{2\hat{\mu}_3 n} \qquad <8>$$

Substitution of these solutions in <7> gives an equation for μ_3

$$mn \pm \Sigma\delta_i \sqrt{\{(\delta_i m_i n - m\hat{\mu}_3)^2 - 4\delta_i n_i nm\hat{\mu}_3\}} = 0 \qquad <9>$$

from which the appropriate solution has to be obtained . By constraining the functions under the square root signs to be non-negative , one can show that

$$- \min (a_2 , a_3) \leq \hat{\mu}_3 \leq \min (a_1 , a_4) \qquad <10>$$

where $a_i = (n/m)\{m_i + 2n_i - 2\sqrt{(n_i^2 + n_i m_i)}\}$. The roots of equation <9> in this interval can be determined numerically for each of the 16 possible sign combinations . Value for π_i and θ_i $(i = 1 , \ldots , 4)$ can now be obtained by using equation <8> and <6> .

MULTIPLICATIVE MODEL

For the multiplicative model we need a stationary value of $F_{(M)} = F + \lambda_1 F_1 + \lambda_2 F_2 + \lambda_3 F_3 + \lambda_4 F_4$ The resultant solution turns out to have similarities to that obtained for a 2×2×2 contingency table with fixed margins and zero second-order interaction , although the assumptions of the present model are markedly different . Denoting maximum likelihood estimates with stars , we get , in a comparable manner to that for the additive model , $\lambda_1^* = - n$, $\lambda_2^* = - m$. The remaining maximum likelihood equations can be written as

$$\pi_i^* = \frac{n_i + \delta_i \lambda_4^*}{n} , \qquad <11>$$

$$\theta_i^* = \frac{m_i + \delta_i \lambda_4^*}{m} ,$$

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for i = 1 , ... , 4 , and

$$\pi_1^* \theta_2^* \theta_3^* \pi_4^* - \theta_1^* \pi_2^* \pi_3^* \theta_4^* = 0 .$$

Substitution from the first eight equations into the final one results in λ_4^* being obtained as the unique solution of the cubic equations .

$(n_1 + \lambda^*_4)(m_2 + \lambda^*_4)(m_3 + \lambda^*_4)(n_4 + \lambda^*_4) - (m_1 - \lambda^*_4)(n_2 - \lambda^*_4)(n_3 - \lambda^*_4)(m_4 - \lambda^*_4) = 0.$
The estimates π_i^* and θ_i^* (i = 1 , ... , 4) are now readily found from <11> .

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CHAPTER IV

RESULTS

One thousand five hundred and fifteen samples included in this study as the subject. Four hundred and eighty-nine women with histologically proved diagnosis of breast cancer were a cases group and 1026 women who registered during the same period with non-cancer women or other site of cancer were a control group.

General characteristics of the samples :

The largest group of cases and controls was formed by age group more than 54 years. Between 40 to 54 years age represented second largest group. The average age of a case group was 62.00 years (S.D.= 1.58) and the average age of a control group was 67.50 years (S.D.= 1.64). The majority of cases and controls were ever married 83.23 percent and 90.84 percent respectively.

The largest group of cases and controls was formed by number of children born group between 1 to 4 children. The nullparous women represented second largest group of cases(23.11 percent) and the third largest group of controls (10.33 percent). The average number of children born of a case group was 7.00 children (S.D.= 0.18) and the average number of children born of a control group was 7.50 children (S.D.= 0.26).

About 42.34 percent of the samples in a case group had parity more than 4 parity and the average parity was 7.00 parity (S.D.= 0.21). While about 49.71 percent of the samples in a control group had parity between 1 to 4 parity and the average parity was 7.50 parity (S.D.= 0.32). The nullparous women of cases and controls were 22.90 percent and 10.04 percent respectively.

For both case and control group, most of the samples had age at first labor group between 20 to 29 years with 53.17 percent and 60.92 percent respectively. The average age at first labor of case and control group were 28.50 years (S.D.= 1.64) and 27.00 years (S.D.= 1.72) respectively.

The data showed that the subjects in case and control group had age at menarche group more than 13 years had 76.89 percent and 85.57 percent respectively. Age at menarche less than 14 years had 23.11 percent of the cases and 14.43 percent of the controls. The average age at menarche of case group was 15.50 years (S.D.= 1.32) and the average age at menarche of control group was 17.00 years (S.D.= 1.38) respectively. The both cases and controls were premenopausal 52.76 percent and 60.43 percent respectively and the postmenopausal were 47.24 percent of cases and 39.57 percent of controls.

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Table 1. Number and percentage of cases and controls by reproductive risk factors.

Reproductive risk factors	Case		Control	
	Case	Percent	Control	Percent
Age (Years)				
40-54	169	34.56	459	44.74
>= 55	320	65.44	567	55.26
Total	489	100.00	1026	100.00
Mean ± S.D.	62.00 ± 1.58		67.50 ± 1.64	
Marital Status				
No(never married)	82	16.77	94	9.16
Yes(ever married)	407	83.23	932	90.84
Total	489	100.00	1026	100.00
Number of children born				
0	113	23.11	106	10.33
1-4	302	61.76	554	54.00
>= 5	74	15.13	366	35.67
Total	489	100.00	1026	100.00
Mean ± S.D.	7.00 ± 0.18		7.50 ± 0.26	
Parity				
0	112	22.90	103	10.04
1-4	170	34.76	510	49.71
>= 5	207	42.34	413	40.25
Total	489	100.00	1026	100.00
Mean ± S.D.	7.00 ± 0.21		7.50 ± 0.32	
Age at first labor				
<=19	169	34.56	357	34.80
20-29	260	53.17	625	60.92
>=30	60	12.27	44	4.28
Total	489	100.00	1026	100.00
Mean ± S.D.	28.50 ± 1.64		27.00 ± 1.72	

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Reproductive risk factors	Case		Control	
	Case	Percent	Control	Percent
Age at menarche				
<=13	113	23.11	148	14.43
>=14	376	76.89	878	85.57
Total	489	100.00	1026	100.00
Mean ± S.D.	15.50 ± 1.32		17.00 ± 1.38	
Menopausal status				
premenopausal	258	52.76	620	60.43
postmenopausal	231	47.24	406	39.57
Total	489	100.00	1026	100.00

Univariable analysis

Age was significantly associated with breast cancer. It was found that the women who was more than 54 years had a higher chance of breast cancer than the women who had age between 40 to 54 years 1.530 times (OR = 1.530 ; 95% C.I. = 1.220-1.230).

This study indicated that the marital status was significantly associated with breast cancer. The women who had never married had higher chance of breast cancer than those who had ever married with 2.000 times (OR = 2.000; 95% C.I. = 1.440-2.780).

Number of children born was significantly associated with breast cancer. The result showed that the nullparous women had higher chance of breast cancer than the women who had the number of children more than 4 children with 5.270 times (OR = 5.270 ; 95% C.I. = 3.600-7.720). The women who had number of children born between 1 to 4 children had higher chance of breast cancer than the women who had the number of children more than 4 children with 2.700 times (OR = 2.700 ; 95% C.I.= 2.010-3.630).

The parity was significantly associated with breast cancer. The nullparity women had higher chance of breast cancer than the women who had 1 to 4 parity with 3.260 times (OR = 3.260 ; 95% C.I.= 2.340-4.550) and the women who had more than 4 parity had higher chance of breast cancer than the women who had 1 to 4 parity with 1.500 times (OR = 1.500 ; 95% C.I.= 1.170-1.930).

Age at first labor was significantly associated with breast cancer. The women who had the age at first labor more than 29 years had higher chance of breast cancer than the women who had the age at first labor between 20 to 29 years with 3.280 times (OR = 3.280 ; 95% C.I.= 2.120-5.070).

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Age at menarche was significantly associated with breast cancer. The women who had the age at menarche less than 14 years had higher chance of breast cancer than the women who had the age at menarche more than 13 years with 1.780 times (OR = 1.780 ; 95% C.I.= 1.340-2.360).

Menopausal status was significantly associated with breast cancer. The postmenopausal women had higher chance of breast cancer than the premenopausal women with 1.370 times (OR = 1.370 ; 95% C.I.= 1.090-1.710).

Table 2. The association between reproductive risk factors related to breast cancer indicated by relative odds (Odds Ratios) and 95% confidence interval .

Reproductive risk factors	Case	Control	Odds Ratios	95% Confidence Intervals	p-value
Age (Years)					
40-54	169	459	1.000	-	-
>= 55	320	567	1.530	1.220-1.230 *	< 0.01
Marital Status					
No (never married)	82	94	2.000	1.440-2.780*	< 0.01
Yes (ever married)	407	932	1.000	-	-
Number of children born					
0	113	106	5.270	3.600-7.720 *	< 0.01
1-4	302	554	2.700	2.010-3.630*	< 0.01
>= 5	74	366	1.000	-	-
Parity					
0	112	103	3.260	2.340-4.550*	< 0.01
1-4	170	510	1.000	-	-
>= 5	207	413	1.500	1.170-1.930 *	< 0.01
Age at first labor					
<=19	169	357	1.140	0.900-1.450	0.217
20-29	260	625	1.000	-	-
>=30	60	44	3.280	2.120-5.070 *	< 0.01
Age at menarche					
<=13	113	148	1.780	1.340-2.360 *	< 0.01
>= 14	376	878	1.000	-	-
Menopausal status					
premenopausal	258	620	1.000	-	-
postmenopausal	231	406	1.370	1.090-1.710*	0.005

(* a statistical test of significance is $\alpha = 0.01$), p-value : from Wald's test .

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Multivariable analysis

The results from multiple logistic regression in Table 3 indicated that the risk factors associated with breast cancer were age, marital status, number of children born, parity, age at first labor and age at menarche.

After controlling for confounding variables, the adjusted relative odds were estimated, it was found that the women with age more than 54 years had higher chance of breast cancer than the women who had age between 40 to 54 years 1.892 times (OR = 1.892 ; 95% C.I. = 1.486-5.321).

The result of multiple logistic regression showed that the marital status was significantly associated with breast cancer. The women who had never married had higher chance of breast cancer than the women who had ever married with 2.395 times (OR = 2.395 ; 95% C.I. = 1.318-2.544).

The adjusted relative odds of number of children born showed that number of children born was significantly associated with breast cancer. The nullparous women had higher opportunity of breast cancer than the women who had the number of children more than 4 children with 3.667 times (OR = 3.667 ; 95% C.I. = 1.742-2.102). The women who had number of children born between 1 to 4 children had higher opportunity of breast cancer than the women who had the number of children more than 4 children with 1.742 times (OR = 1.742 ; 95% C.I.= 1.254-2.145).

The nullparity women had higher chance of breast cancer than the women who had 1 to 4 parity with 2.432 times (OR = 2.432 ; 95% C.I.= 1.428-2.923) and the women who had more than 4 parity had higher chance of breast cancer than the women who had 1 to 4 parity with 1.351 times (OR = 1.351 ; 95% C.I.= 1.104-1.910).

After controlling for confounding variables, the adjusted relative odds showed that the women who had the age at first labor more than 29 years had higher chance of breast cancer than the women who had the age at first labor between 20 to 29 years with 2.081 times (OR = 2.081 ; 95% C.I.= 1.609-3.844).

The result of multiple logistic regression showed that age at menarche was significantly associated between age at menarche and the occurrence breast cancer. The women who had the age at menarche less than 14 years had higher chance of breast cancer than the women who had the age at menarche more than 13 years with 1.878 times (OR = 1.878 ; 95% C.I.= 1.766-2.211).

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Table 3. Odds Ratios and 95% confidence intervals analyzed confounding factors by multiple logistic regression*

Independent Variables	Odds Ratios	95% Confidence Intervals
Age (years)		
40-54	1.000	-
>= 55	1.892	1.486-5.321*
Marital Status		
No (never married)	2.395	1.318-2.544*
Yes (ever married)	1.000	-
Number of children born		
0	3.667	1.742-2.102*
1-4	1.742	1.254-2.145*
>= 5	1.000	-
Parity		
0	2.432	1.428-2.923*
1-4	1.000	-
>= 5	1.351	1.104-1.910*
Age at first labor		
<=19	0.926	0.982-1.574
20-29	1.000	-
>=30	2.081	1.609-3.844*
Age at menarche		
<=13	1.878	1.766-2.211*
>= 14	1.000	-
Menopausal status		
premenopausal	1.000	-
postmenopausal	0.752	0.587-1.102

* Logistic model :- dependent variable : Case
number of cases = 489 , number of controls = 1,026

(* A statistical test of significance is $\alpha = 0.01$)

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additive and multiplicative models analysis

The comparison of additive and multiplicative model indicated that the expected values of all risk factors in multiplicative model were closer the observed value than the expected values in additive model in both case and control group (Table 4).

Maximum likelihood ratio test statistic

For the additive model the maximum likelihood estimates are $\mu_1 = -560$, $\mu_2 = -1294$ and $\mu_3 = -16.0526$. The value of the maximum likelihood ratio test statistic is 0.065539 , and under the additive hypothesis $-2 \ln 0.065539 = 5.450220$ is a χ^2 variable with one degree of freedom . Since this leads to $p<0.01$, the additive model is rejected.

For the multiplicative model the maximum likelihood estimates are $\lambda_1 = -560$, $\lambda_2 = -1294$ and $\lambda_4 = -0.0295$. The value of the maximum likelihood ratio test statistic is 0.979343 , and under the multiplicative hypothesis $-2 \ln 0.979343 = 0.041746$ is a χ^2 variable with one degree of freedom . Since this leads to $p>0.80$, the multiplicative model is accepted.

The results of maximum likelihood ratio test indicated that the multiplicative model was more effective than additive model in the analysis of association between the combined effect of reproductive risk factors and breast cancer.

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Table 4. Observed frequencies and expected frequencies under the additive and multiplicative models of cases and controls were reproductive risk factors and breast cancer .

risk factors	Cases			Controls		
	Observed	Expected		Observed	Expected	
		Add*	Multi**		Add*	Multi**
Age (Years)						
40-54 @	-	-	-	-	-	-
55-70	151	138.12	150.97	385	397.88	385.97
>=71	18	16.16	17.59	74	75.84	74.41
Marital Status						
No(never married)	82	77.85	81.11	94	98.15	94.89
Yes (ever married) @	-	-	-	-	-	-
Number of children born						
0-2	270	253.22	269.97	317	333.78	317.03
3-5	171	152.31	170.89	463	481.69	463.11
>=6 @	-	-	-	-	-	-
Parity						
0-5 @	-	-	-	-	-	-
4-6	128	111.15	127.44	402	418.84	401.44
>=7	43	39.62	42.21	223	226.38	223.79
Age at first labor						
<=19	169	153.24	168.90	357	372.76	357.09
20-29 @	-	-	-	-	-	-
>=30	60	57.40	59.93	44	46.59	44.07
Age at menarche						
<=13	83	76.86	82.94	148	154.14	148.06
>= 14@	-	-	-	-	-	-
Menopausal status						
premenopausal @	-	-	-	-	-	-
postmenopausal	258	234.52	257.88	620	643.48	620.12

Add* = additive model and Multi* * = multiplicative model .
(@ = not significance)

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CHAPTER V

DISCUSSION

Discussion

The overall results of this study revealed the relationships between breast cancer and the reproductive risk factors. The factors that significantly associated with breast cancer were; age, marital status, number of children born, parity, age at first labor, age at menarche and menopausal status which could be discussed as follows :

In this study an occurrence of the women who aged more than 54 years were the risk group. This was similar to other studies (Najarian and Delancy 1981, Chariyalertsak, et al. 1992, Shamnijarakit 1983, Paphawasit and Vongvises 1980 and Kelsey 1993) which described that age was an important risk factor of breast cancer. The risk of breast cancer increased when the age increased. The women who were 45 years and over had 3 times higher chance of breast cancer than the women who were less than 45 years. Increases in cancer incidence with age was directly related to the prevalence of cancer in modern society. The increasing incidence of cancer with age reflects a fundamental feature of the biology of cancer cells. The conversion of a normal cell to a cancer cell does not occur as a single one-step event. Rather, the loss of growth control that characterizes cancer cells was the end result of accumulated damage to several different mechanisms that regulate normal cell growth. Development of cancer thus involves a series of progressive changes that gradually convert a normal cell into one that has lost control of its proliferation. Many years are required to accumulate the multiple abnormalities needed to generate most cancer cells, so the majority of cancers develop late in life.

The women who were never married had a higher chance of developing breast cancer than the women who were ever married. The results of this study were similar to other studies (Shamnijarakit 1983, Seidman 1989, Berkson 1962 and Wynder 1960) which found that the marital status was an importance risk factor of breast cancer. The Third National Survey of breast cancer in the USA (1979) indicated that the incidence of breast cancer was high in the single women and the incidence was decreased in divorce women and married women.

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The women who had 1 to 4 children and nullparous women had a higher chance of breast cancer than the women who had number of children born more than 4. The results was similar to other studies which reported that the childless women had a higher breast cancer rate than women with children (Shamnijarakit 1983, Hrafn, et al 1978, MacMahon 1970, Mirra 1971, Lowe 1970, Yuasa 1970, Najarian and Delancy 1981). It was also found that the nullparous women had a 1.9 times higher chance of breast cancer than the women who had more than 4 children born. However Chariyalertsak (1989) which concluded that the women who had more than 4 children born were a risk group of breast cancer.

The women who had the parity between 1 to 4 and nullparous women had a higher risk of breast cancer than the women who had 1 to 4 parity. The study also found that the women who had more than 4 parity had a higher risk of breast cancer than the women who had parity of 3 and less. The results were similar to other studies (Patamapadpong 1982, Papatestas, et al 1994, Chariyalertsak and Delancy 1981, Shamnijarakit 1983 and Chariyalertsak, et al 1989). But the results of this study were contrary to the studies (Helmrich, et al 1983, Kvale 1987 and Hrafn, et al 1978) who reported that the risk of the breast cancer would be decreased when the parity was increased. Parity was factor that influence breast cancer risk. Nullparous women were at greater risk for the development of breast cancer than parous women. Breast tissue may undergo differentiation as a result of the hormonal changes of a full term pregnancy and these differentiated cells are less likely to undergo malignant transformation, or the persisting changes in hormone levels after a full-term pregnancy may alter the proliferative rate of the breast epithelium. In incomplete pregnancy, the breast is exposed only to the high estrogen levels of early pregnancy and this may be responsible for the increased risk seen in these women.

The women who had age at first labor more than 29 years had a higher risk of breast cancer than the women who had age at first labor between 20 to 29 years. This results was similar to others (Patamapadpong 1982, Helmrich, et al 1983, Shamnijarakit 1983 and Chariyalertsak, et al 1992) which concluded that the women who had the first labor at the age of 30 years and older were in the risk group of breast cancer. The pregnancy has a dual effect on the breast cancer risk, independently from age at delivery.

The women who had age at menarche less than 14 years had a higher risk of breast cancer than the women who had age at menarche 14 years and older which was similar to other studies (Patamapadpong 1982, ShuYuasa, et al 1970, Helmrich, et al 1983, Farewell, et al 1977 and Drife 1981) which reported that the women who had age at menarche less than 14 years had a higher risk of breast cancer than the women who had age at menarche more than 16 years with 2 times and the importance of early menarche that the sooner of menstrual cycle begin the earlier the unopposed estrogen begins to act on the breast epithelium.

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The postmenopausal women had a higher risk of breast cancer than the premenopausal women. This result was similar to the study of Chariyalertsak *et al.* (1992). The importance of the postmenopausal status was indicated that a cycle of women with postmenopause were mainly anovular. Thus, the women experienced only more estrogen cycles, although her breast epithelium could response to progesterone if it was present, so that the postmenopausal women had a higher risk of breast cancer than the premenopausal women.

Additive and multiplicative models

The comparison of additive and multiplicative model indicated that the expected values of all risk factors in multiplicative model were closed to the observed value than the expected values in additive model in both case and control group.

The results of maximum likelihood ratio test indicated that the multiplicative model was more effective than additive model in the analysis of association between the combined effect of reproductive risk factors and breast cancer. This study had a similar results to the study of Gardner and Munford (1980) which reported that the multiplicative model was better fit on the data of case-control study than additive model especially on the studying in combined effect of risk factors.

The multiplicative formulation should be preferred because it is mathematically more tractable due to its kinship to the logistic and log-linear models which have been widely researched in the statistical literatures. However, it is hard to justify the choice of a particular model on the basis of mathematical tractability alone. The most important consideration should be that the interpretation of the results derived from the model be physically meaningful in a given context. Perhaps, the answer lies in developing appropriate analytic procedures for the desirable formulation, if only within the narrow scope of application to epidemiological studies, both prospective and retrospective.

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CHAPTER VI

CONCLUSION

Conclusion

The objectives of this study were to determine the association between the reproductive risk factors and breast cancer in women 40 years of age and over, and to compare the fit of additive and multiplicative models to the observed data of breast cancer patients and the reproductive risk factors. The design of the study was retrospective case-control study. Data were collected from the women patients' medical record at the National Cancer Institute during 1 January 1993 to 31 December 1995. The cases were 489 women with histologically confirmed breast cancer and the controls were 1026 women with other cancers or without cancer.

The results revealed that the significant risk factors of breast cancer were the women who aged more than 54 years, never married, number of children born 1 to 4 or nullparous women, parity more than 4 or nullparous women, age at first labor more than 29 years, age at the menarche less than 14 years and postmenopausal. The multiple logistic regression analysis for controlling the effect of confounding factors, indicated that the women who aged more than 54 years, never married, number of children born 1 to 4 or nullparous women, parity more than 4 or nullparous women, age at first labor more than 29 years and age at the menarche less than 14 years were significantly related to the breast cancer.

A comparative study between additive and multiplicative models indicated that the expected values of all risk factors in multiplicative models were closer to the observed values than the expected values in additive model in both case and control group. The results of maximum likelihood ratio test indicated that the multiplicative model was more effective than additive model in the analysis of association between the combined effect of reproductive risk factors and breast cancer.

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Recommendation

Based on the results of this study, the recommendation for the women can be made as follows:

1. The study clearly demonstrated that women in the risk group of breast cancer over than 54 years, never married women, had 1 to 4 children or nullparous, for example. This information can be used in health education for women in this risk group to have monthly self-examination of their breast and medical check-up every year.

2. In this study, the cervix cancer patients were included in the control group. However, some risk factors of cervix cancer were the same as of breast cancer. In the further study of association between reproductive risk factors and breast cancer, the cervix cancer patients should be excluded from the control group.

3. In this study, the multiplicative model was clearly superior to additive model in the analysis of association between the combined effect of reproductive risk factors and breast cancer than the additive model. It is recommended that further study on association between reproductive risk factors and breast cancer should use the multiplicative model.

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APPENDIX A

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ADDITIVE AND MULTIPLICATIVE MODEL

The computed multiplicative model example

$n_1 = 258$, $n_2 = 68$, $n_3 = 83$, $n_4 = 151$, $n_T = 560$
$m_1 = 524$, $m_2 = 139$, $m_3 = 246$, $m_4 = 385$, $m_T = 1294$

from <12>

$$(n_1 + \lambda^*_4)(m_2 + \lambda^*_4)(m_3 + \lambda^*_4)(n_4 + \lambda^*_4) - (m_1 - \lambda^*_4)(n_2 - \lambda^*_4)(n_3 - \lambda^*_4)(m_4 - \lambda^*_4) = 0$$

$$(258 + \lambda^*_4)(139 + \lambda^*_4)(246 + \lambda^*_4)(151 + \lambda^*_4) - (524 - \lambda^*_4)(68 - \lambda^*_4)(83 - \lambda^*_4)(385 - \lambda^*_4) = 0$$

equations :

$$191879587 + 64601180\,\lambda^*_4 - 114077\,\lambda^{*2}_4 + 865\,\lambda^{*3}_4 = 0$$

used program MATLAB solve equations :

```
» a = [865 114077 64601180 191879587];
» roots(a)
  ans =  1.0e+002 *
        -0.6514 + 2.6615i
        -0.6514  - 2.6615i
        -0.0295
```

So that $\lambda^*_4 = -0.0295$

finned the π^*_i and θ^*_i from <11>

$$\pi_i^* = \frac{n_i + \delta_i \lambda_4^*}{n} \quad , \quad \theta_i^* = \frac{m_i + \delta_i \lambda_4^*}{m} \ ,$$

for i = 1 , ... , 4 and

$$\pi^*_1 = \frac{258+1(-0.0295)}{560} = 0.460661607 \qquad \theta^*_1 = \frac{524+1(-0.0295)}{1294} = 0.404923107$$

$$\pi^*_2 = \frac{68-1(-0.0295)}{560} = 0.121375893 \qquad \theta^*_2 = \frac{139-1(-0.0295)}{1294} = 0.107441654$$

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$$\pi^*_3 = \frac{83-1(-0.0295)}{560} = 0.148266964 \qquad \theta^*_3 = \frac{246-1(-0.0295)}{1294} = 0.190130989$$

$$\pi^*_4 = \frac{151+1(-0.0295)}{560} = 0.269590179 \qquad \theta^*_4 = \frac{385-1(-0.0295)}{1294} = 0.297504250$$

finned the Multiplicative model

Cases :

$$n\pi^*_4 = 560 \times 0.269590179 = 150.97$$

Controls :

$$n\theta^*_4 = 1294 \times 0.297504250 = 385.97$$

The computed additive model example

$n_1 = 258$, $n_2 = 68$, $n_3 = 83$, $n_4 = 151$, $n_T = 560$
$m_1 = 524$, $m_2 = 139$, $m_3 = 246$, $m_4 = 385$, $m_T = 1294$

from <8>

$$x_i = \frac{\delta_i m_i n - m\hat{\mu}_3 \pm \sqrt{\{(\delta_i m_i n - m\mu_3)^2 - 4\delta_i n_i nm\hat{\mu}_3\}}}{2\hat{\mu}_3 n}$$

used program MATLAB solve equations : $\hat{\mu}_3 = -16.0526$
Test μ_3 before used

$$-\min(a_2, a_3) \le \hat{\mu}_3 \le \min(a_1, a_4)$$

where $a_i = (n/m)\{m_i + 2n_i - 2\sqrt{(n_i^2 + n_i m_i)}\}$

$a_1 = (560/1294)\{524+2(258)-2\sqrt{((258)^2+(258\times524)}\} = 61.30349202$
$a_2 = (560/1294)\{139+2(68)-2\sqrt{((68)^2+(68\times139)}\} = -16.32194903$
$a_3 = (560/1294)\{246+2(83)-2\sqrt{((83)^2+(83\times246)}\} = -35.27195227$
$a_4 = (560/1294)\{385+2(151)-2\sqrt{((151)^2+(151\times385)}\} = 51.07292551$

find the π_i and θ_i from <6>

$$(n_i - n\hat{\pi}_i)\hat{\theta}_i + \delta_i \hat{\pi}_i \hat{\mu}_3 = 0,$$

$$(m_i - m\hat{\theta}_i)\hat{\theta}_i - \delta_i \hat{\pi}_i \hat{\mu}_3 = 0$$

for i = 1 , ... , 4

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used MAPLE program solve equations :

```
>solve ({(258-560*x)*y+(x*(-16.0526)),(524-1294*y)*y-(x*(-16.052))},{x,y});
        {y = 0, x = 0}, {y = -.04146769080, x = 1.492287114},
        {y = .4177482378, x = .4311306437}

>solve ({(68-560*x)*y-(x*(-16.0526)),(139-1294*y)*y+(x*(-16.052))},{x,y});
        {y = 0, x = 0}, {y = .06139277977, x = -.2277856587},
        {y = .7469143343, x = .1970551216}

>solve ({(83-560*x)*y-(x*(-16.0526)),(246-1294*y)*y+(x*(-16.052))},{x,y});
        {y = 0, x = 0}, {y = -.04099556877, x = .4927838326},
        {y = .17777798, x = .1767069472}

>solve ({(151-560*x)*y+(x*(-16.0526)),(385-1294*y)*y-(x*(-16.052))},{x,y});
        {y = 0, x = 0}, {y = -.03861618965, x = 1.046402871},
        {y = .3074778804, x = .2466484663}
```

finned the Additive model

Case :

$n\hat{\pi}_4 = 56 \times 0.2466484663$

$= 138.12$

Control :

$n\hat{\theta}_4 = 1294 \times 0.3074778804$

$= 397.88$

Test Model

<u>additive model</u>

The maximum likelihood ratio test statistic

equation :

$$\ln \sum_{i=1}^{11} \frac{\hat{\pi}_1}{\hat{\theta}_1} - \ln \sum_{i=1}^{11} \frac{\hat{\pi}_2}{\hat{\theta}_2} - \ln \sum_{i=1}^{11} \frac{\hat{\pi}_3}{\hat{\theta}_3} + \ln \sum_{i=1}^{11} \frac{\hat{\pi}_4}{\hat{\theta}_4}$$

$$\ln \underline{(2.452613)} - \ln \underline{(2.370556)} - \ln \underline{(2.446914)} + \ln \underline{(2.464846)}$$
$$2.217481 \qquad 2.269144 \qquad 2.310054 \qquad 2.307477$$

$$\ln (1.106036) - \ln (1.044692) - \ln (1.059245) + \ln (1.068200) = 0.065539$$

The value of the maximum likelihood ratio test statistic is 0.065539 , and under the Additive hypothesis $-2 \ln 0.065539 = 5.450220$ is a χ^2 variable with one degree of freedom . Since this leads to $p<0.01$, the Additive model is rejected.

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multiplicative model

The maximum likelihood ratio test statistic equation :

$$\ln \sum_{i=1}^{n}(\pi^*_1\theta^*_2\theta^*_3\pi^*_4) - \ln \sum_{i=1}^{n}(\theta^*_1\pi^*_2\pi^*_3\theta^*_4)$$

$$\ln (8.095586) - \ln (3.040362) = 0.979343$$

The value of the maximum likelihood ratio test statistic is 0.979343 , and under the Multiplicative hypothesis -2 ln 0.979343 = 0.041746 is a χ^2 variable with one degree of freedom . Since this leads to p>0.80, the Multiplicative model is accepted.

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APPENDIX B

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สถาบันมะเร็งแห่งชาติ
แบบสอบถามการตรวจเต้านมสตรี

วันที่.....

เลขที่.....

ตอนที่ ๑- ๓ สำหรับผู้ป่วย

ตอนที่ ๑ ข้อมูลทั่วไป

๑. ชื่อ - สกุล.....อายุ.....ปี

๒. สถานภาพ ○ โสด ○ คู่ ○ หม้าย ○ หย่า

๓. ที่อยู่ปัจจุบัน บ้านเลขที่.....หมู่.....ซอย.....ถนน.....

ตำบล.....อำเภอ.....จังหวัด.....

๔. เชื้อชาติ.....สัญชาติ.....ศาสนา.....

๕. การศึกษา.....อาชีพ.....

ตอนที่ ๒ ประวัติทั่วไป

๑. ท่านมีประจำเดือนครั้งแรกอายุ.....ปี ประจำเดือนครั้งสุดท้ายวันที่.....

๒. ท่านมีบุตรจำนวน.....คน ท่านมีบุตรคนแรกอายุ.....ปี เดือน.....

๓. จำนวนบุตรที่ดูดนมแม่.....คน ระยะเวลาที่เฉลี่ยแต่ละคนดูดนมแม่.....ปี.....เดือน

๔. ประวัติการใช้ยาฮอร์โมน ○ ไม่เคยใช้ ○ เคยใช้

๕. ประวัติการใช้ยาสมุนไพร ○ ไม่ ○ เคยใช้

ตอนที่ ๓ แบบสอบถามเกี่ยวกับความรู้และอาการแสดงที่ผิดปกติของผู้ป่วย

๑. ท่านมีความรู้เกี่ยวกับการตรวจเต้านมด้วยตนเองหรือไม่ ○ ไม่มี ○ มี

๒. สาเหตุที่ท่านต้องการตรวจเต้านมเพราะ ○ ไม่มีอาการผิดปกติแต่ต้องการตรวจเต้านม

○ มีความผิดปกติจึงมาตรวจ

ถ้ามีความผิดปกติโปรดขีด ✓ หน้าข้อนั้นๆ

○ มีก้อน ○ เสียว,เจ็บ ○ อื่นๆ โปรดระบุ.....

๓. ท่านเคยรับการตรวจและรักษาเรื่องเต้านมแล้วหรือยัง ○ ไม่เคย ○ เคย

ถ้าเคย ๓.๑ เคยรักษาด้วยวิธีใด.....รักษามานานเท่าไร.....

๓.๒ เคยรักษาจาก ร.พ. ไหน.....

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ตอนที่ ๔.๕ สำหรับพยาบาลสอนวิธีการตรวจเต้านมด้วยตนเอง

๑. ท่านดู วี.ดี.โอ. เรื่องวิธีการตรวจเต้านมด้วยตนเองหรือไม่

○ ดู ○ ไม่ดู เพราะ.....

๒. ท่านได้รับเอกสารเรื่องความรู้เรื่องวิธีการตรวจเต้านมด้วยตนเองหรือไม่

○ ได้รับแล้ว ○ ไม่ได้รับ เพราะ.....

๓. ท่านได้รับฟังคำบรรยายจากพยาบาล เรื่องวิธีการตรวจเต้านมด้วยตนเองหรือไม่

○ ได้รับแล้ว ○ ยังไม่ได้รับ เพราะ.....

ตอนที่ ๕ ประเมินผลการสอน

๑. ภายหลังจากที่ท่านได้รับทราบวิธีการตรวจเต้านมด้วยตนเองแล้ว ท่านสามารถปฏิบัติการตรวจเต้านมด้วยตัวเองได้หรือไม่

○ ได้ ○ ไม่ได้ เพราะ.....

๒. ท่านสามารถให้คำแนะนำเรื่องวิธีการตรวจเต้านมด้วยตนเองที่ถูกวิธีแก่ผู้อื่นได้หรือไม่

○ ได้ ○ ไม่ได้ เพราะ.....

ผลการตรวจของพยาบาล

ก. Breast examination

ข. ความเห็นขั้นต้นจากการตรวจ หรือการวินิจฉัยขั้นต้น

.....

.....

ค. คำแนะนำจากพยาบาลผู้ตรวจ โปรดขีดเครื่องหมาย ✓ หน้าคำแนะนำนั้น

○ Breast self examination

○ ให้ไปรับตรวจและรักษาต่อกับแพทย์

○ อื่นๆ.....

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ลงชื่อพยาบาลผู้ตรวจ

สถาบันมะเร็งแห่งชาติ

ประวัติของผู้รับบริการ

แบบประประวัติของผู้รับบริการนี้จะช่วยให้แพทย์ดูแลรักษาสุขภาพของท่านได้ดี และจะเป็นประวัติอันถาวรที่เกี่ยวกับการมารับบริการของท่าน กรุณาตอบคำถามตามความเป็นจริง โดยทำเครื่องหมาย / ลงใน ( ) หรือช่องในตาราง หรือเขียนข้อความลงในช่องว่างที่กำหนดให้

ข้อมูลทั้งหมด สถาบันฯ ถือว่าเป็นความลับส่วนบุคคล จะไม่นำออกเปิดเผยไม่ว่ากรณีใดทั้งสิ้น

ถ้าเคยมาตรวจที่สถาบันฯ แล้ว ไม่ต้องกรอกประวัติของผู้รับบริการ

เลขทะเบียน_____

วันที่ _____ /_____ /_____

(ช่องว่างข้างบนนี้ สำหรับเจ้าหน้าที่บันทึก)

เลขที่บัตรประจำตัวประชาชนหรือบัตรข้าราชการฯ_____

_____

เลขที่บัตรประกันสังคม_____

1. ข้อมูลทั่วไป

1.1 ชื่อ (นาย/นาง/นางสาว)_____ นามสกุล _____

1.2 ที่อยู่ของท่านตามสำมะโนครัว

บ้านเลขที่_____หมู่ที่_____

ตรอก/ซอย _____

ถนน_____ตำบล_____

อำเภอ_____จังหวัด_____

รหัสไปรษณีย์_____โทรศัพท์_____

โทรศัพท์ที่สามารถติดต่อท่านได้รวดเร็ว (ถ้ามี)_____

ชื่อ-สกุล และที่อยู่ของญาติซึ่งติดต่อได้_____

ที่อยู่ตามความจริง

ชื่อ-นามสกุล _____

บ้านเลขที่_____หมู่ที่_____ตรอก/ซอย _____

ถนน_____ตำบล_____

อำเภอ_____จังหวัด_____

รหัสไปรษณีย์ _____โทรศัพท์_____

โทรศัพท์ (ถ้ามี)_____

น.น._____ส่วนสูง_____

1.3 เกิดวันที่_____เดือน_____พ.ศ._____ อายุ_____ปี (คิดอายุเต็มปี ถึงเมื่อวันเกิดครั้งสุดท้าย)_____

1.4 สถานที่เกิด ( ) ประเทศไทย (ระบุจังหวัด)_____

( ) ต่างประเทศ (ระบุ)_____ปัจจุบันอยู่ในประเทศไทยมาแล้ว_____เดือน/ปี

1.5 เพศ ( ) ชาย ( ) หญิง

1.6 สถานภาพสมรส ( ) โสด ( ) สมรส ( ) หย่า ( ) หม้าย ( ) แยกกันอยู่

1.7 เชื้อชาติ ( ) ไทย ( ) จีน ( ) อินเดีย ( ) ญี่ปุ่น ( ) อื่น ๆ (ระบุ)_____

1.8 ศาสนา ( ) พุทธ ( ) อิสลาม ( ) ฮินดู ( ) คริสต์ ( ) อื่น ๆ (ระบุ)_____

1.9 การศึกษาชั้นสูงสุด ( ) ไม่ได้เรียน ( ) ป.1-ป.6 ( ) ม.1-3 (ป.7-ม.ศ.3)

( ) ม.4-ม.6 (ม.ศ.4-ม.ศ.5) ( ) อนุปริญญาตรี หรือเทียบเท่า ( ) ปริญญาตรี หรือเทียบเท่า

( ) สูงกว่าปริญญาตรี

1.9 อาชีพ

1.9.1 ปัจจุบันประกอบอาชีพ_____ลักษณะงานที่ทำ_____ทำอาชีพนี้มาแล้ว_____ปี

1.9.2 ก่อนทำอาชีพปัจจุบัน ท่านประกอบอาชีพอะไรบ้าง

1. _____ลักษณะงานที่ทำ_____ทำอาชีพนี้มาแล้ว_____ปี

2. _____ลักษณะงานที่ทำ_____ทำอาชีพนี้มาแล้ว_____ปี

1.10 สาเหตุที่มารับบริการที่สถาบันมะเร็งฯ

( ) เพื่อตรวจร่างกายทั่วไป ( ) เพื่อตรวจร่างกายเฉพาะส่วน (ระบุ)

( ) แพทย์ หรือโรงพยาบาลส่งมารักษาต่อ (ระบุชื่อแพทย์ หรือโรงพยาบาล)

( ) อื่น ๆ (ระบุ)

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2. ประวัติการเจ็บป่วยด้วยโรคมะเร็งของญาติในครอบครัว

ญาติในครอบครัวท่าน (สามี/ภรรยา พ่อ/แม่ ลูกชาย/ลูกสาว พี่ชาย/พี่สาว น้องชาย/น้องสาว ปู่ ย่า ตา ยาย) เคยเป็น หรือเป็นโรคมะเร็งหรือไม่ (ถ้าตอบว่าเคยเป็นหรือเป็น ให้บอกด้วยว่า ใครเป็น และเป็นที่อวัยวะใด)

ลำดับที่	ญาติ	อวัยวะที่เป็นมะเร็ง (ถ้าบอกได้)	โรงพยาบาลที่รักษา

3. ประวัติการเจ็บป่วยในอดีต

3.1 ท่านเคยเข้าโรงพยาบาล เพื่อรับการผ่าตัด หรือรับการรักษา หรือไม่ ( ) ไม่เคย ( ) เคย

ลำดับที่	ผ่าตัดอะไร หรือโรค (ระบุชื่อโรค ถ้าเป็นมะเร็งให้บอกอวัยวะที่เป็นด้วย)	โรงพยาบาลที่ผ่าตัด หรือรักษา

3.2 ท่านเคยแพ้ สิ่งเหล่านี้ หรือไม่

3.2.1 ยา ( ) ไม่แพ้ ( ) แพ้ (ระบุ)

3.2.2 อาหาร ( ) ไม่แพ้ ( ) แพ้ (ระบุ)

3.2.3 แพ้สิ่งอื่น ๆ (ระบุ)

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4. ประวัติเฉพาะสตรี

4.1 ประวัติการมีประจำเดือน

4.1.1 ท่านมีประจำเดือนครั้งแรกเมื่ออายุ _____ ปี

4.1.2 ปกติ ท่านมีประจำเดือนครั้งละ _____ วัน

4.1.3 ระยะห่างของรอบประจำเดือน ประมาณ _____ วัน

4.1.4 ปริมาณเลือดประจำเดือน ( ) น้อย ( ) ปานกลาง ( ) มาก

4.1.5 วันแรกของการมีประจำเดือนครั้งล่าสุด (ระบุ วัน เดือน ปี) _____

4.1.6 ถ้าท่านหมดประจำเดือนแล้ว หมดประจำเดือนเมื่ออายุ _____ ปี

4.1.7 สาเหตุของการหมดประจำเดือน ( ) ตามธรรมชาติ ( ) ผ่าตัด ( ) อื่น ๆ (ระบุ) _____

4.2 ประวัติการตั้งครรภ์ การคลอดบุตร และการแท้ง (ตอบเฉพาะผู้ที่เคยเท่านั้น)

4.2.1 ท่านตั้งครรภ์มาแล้วทั้งหมด _____ ครั้ง (รวมทั้งแท้งเองและทำแท้งด้วย) ปัจจุบันนี้ ท่านมีบุตรที่ยังมีชีวิตอยู่ _____ คน

4.2.2 จากจำนวนตั้งครรภ์ทั้งหมด

คลอดครบกำหนด _____ ครั้ง เป็นการคลอดเอง _____ ครั้ง ผ่าตัด _____ ครั้ง

คลอดก่อนกำหนด _____ ครั้ง เป็นการคลอดเอง _____ ครั้ง ผ่าตัด _____ ครั้ง

คลอดบุตรครั้งแรกเมื่อท่านอายุ _____ ปี คลอดบุตรครั้งสุดท้ายเมื่อท่านอายุ _____ ปี

แท้งทั้งหมด _____ ครั้ง เป็นการแท้งเอง _____ ครั้ง ทำแท้ง _____ ครั้ง

5. ประวัติอื่น ๆ

51 การสูบบุหรี่ หรือกล้อง หรือซิการ์ (ดูคำจำกัดความข้างล่าง)

5.1.1 ท่าน ( ) ไม่เคยสูบบุหรี่เลย (ข้ามไปตอบข้อ 5.2) ( ) สูบเป็นบางครั้ง (ข้ามไปตอบข้อ 5.2)

( ) เคยสูบแต่เลิกแล้ว (สูบมาแล้ว _____ ปี เลิกสูบแล้ว _____ ปี)

( ) สูบเป็นประจำ (สูบเป็นเวลา _____ ปี)

คำจำกัดความ 1. สูบเป็นประจำ สูบบุหรี่ (หรือกล้อง หรือซิการ์) ทุกวันอย่างน้อย 1 มวน ติดต่อกันเป็นเวลาตั้งแต่ 6 เดือน ขึ้นไป

2. สูบเป็นบางครั้ง มี 2 กรณี คือ 1. สูบบุหรี่ (หรือกล้อง หรือซิการ์) ทุกวันอย่างน้อย 1 มวนติดต่อกันเป็นเวลาน้อยกว่า 6 เดือน

2. สูบบุหรี่ (หรือกล้อง หรือซิการ์) 1 มวน หรือน้อยกว่า 1 มวนต่อวัน แต่สูบไม่ทุกวัน

3. เคยสูบแต่เลิกแล้ว เคยสูบบุหรี่ (หรือกล้อง หรือซิการ์) เป็นประจำ แต่ปัจจุบันเลิกสูบมาแล้วอย่างน้อย 1 ปี)

5.1.2 ชนิดของบุรี่ สำหรับผู้ที่สูบเป็นประจำ (ยังสูบอยู่ หรือเคยสูบแต่เลิกแล้ว)

ชนิดของบุหรี่	จำนวนมวน/วัน (โดยประมาณ)	ระยะเวลาที่สูบ (เดือน/ปี)
1. บุหรี่แบบมีก้นกรอง		
2. บุหรี่แบบไม่มีก้นกรอง		
3. บุหรี่พื้นเมือง		
4. กล้องยาเส้น		
5. ซิการ์		
6. อื่น ๆ (ระบุ)_____		

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5.2 การดื่มเครื่องดื่มที่มีแอลกอฮอล์

5.2.1 ท่าน ( ) ไม่เคยดื่ม

( ) ดื่มเป็นบางครั้ง

( ) เคยดื่มแต่เลิกแล้ว (ดื่มมาแล้ว _____ ปี เลิกดื่มแล้ว _____ ปี)

( ) ดื่มเป็นประจำ (ดื่มเป็นเวลา _____ ปี)

คำจำกัดความ 1. ดื่มเป็นประจำ ดื่มเครื่องดื่มที่มีแอลกอฮอล์ มากกว่า 1 ครั้ง ต่อสัปดาห์

2. ดื่มเป็นบางครั้ง ดื่มเครื่องดื่มที่มีแอลกอฮอล์ 1 ครั้ง หรือน้อยกว่า 1 ครั้ง ต่อสัปดาห์

3. เคยดื่มแต่เลิกแล้ว เคยดื่มเครื่องดื่มที่มีแอลกอฮอล์เป็นประจำ แต่ปัจจุบันหยุดดื่มแล้วเป็นเวลาอย่างน้อย 1 ปี

5.2.2 ชนิดของเครื่องดื่มที่มีแอลกอฮอล์ สำหรับผู้ที่ดื่มเป็นประจำ (ยังดื่ม หรือเคยดื่มแต่เลิกแล้ว)

ชนิดของเครื่องดื่มที่มีแอลกอฮอล์	จำนวนครั้ง/สัปดาห์ (โดยประมาณ)	ระยะเวลาที่ดื่ม (เดือน/ปี
1. เบียร์		
2. เหล้า		
3. เหล้าพื้นเมือง (ระบุ) _____		
4. ไวน์		
5. อื่น ๆ (ระบุ) _____		

6. ประวัติการเจ็บป่วยปัจจุบัน

6.1 อาการสำคัญที่เป็นสาเหตุให้มารับบริการตรวจครั้งนี้ (โปรดระบุ ถ้ามี) _____

_____

เริ่มมีอาการเมื่อใด _____

6.2 ปัจจุบัน ท่านมีอาการผิดปกติในระบบต่าง ๆ ต่อไปนี้ หรือไม่ ถ้ามีให้ทำเครื่องหมายวงกลมหน้าหัวข้อที่ต้องการ

อาการผิดปกติในระบบต่าง ๆ	ระยะเวลาที่เป็น หรือมีอาการ (โดยประมาณ)
1. อาการทั่วไป	
1.1 เบื่ออาหาร	
1.2 น้ำหนักลดลง	
1.3 มีไข้	
1.4 ต่อมน้ำเหลืองโต	
2. อาการเกี่ยวกับผิวหนัง	
2.1 หูดหรือไฝที่เปลี่ยนขนาดหรือสี	
2.2 จุด หรือจ้ำเลือดใต้ผิวหนัง	
2.3 แผลเรื้อรังที่ผิวหนัง	
2.4 ก้อนเนื้อใต้ผิวหนัง	

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อาการผิดปกติในระบบต่าง ๆ	ระยะเวลาที่เป็นหรือมีอาการ (โดยประมาณ)
3. อาการเกี่ยวกับช่องปาก และคอ	
3.1 มีแผล หรือก้อนในช่องปาก	
3.2 ปัญหาเกี่ยวกับเรื่องฟัน	
3.3 เสียงแหบ	
3.4 เจ็บคอบ่อย ๆ	
3.5 คอหอยพอก	
4. อาการเกี่ยวกับระบบทางเดินอาหาร	
4.1 กลืนอาหารลำบาก	
4.2 ท้องอืด ท้องเฟ้อบ่อย ๆ	
4.3 ปวดท้องก่อนหรือหลังอาหารบ่อย ๆ	
4.4 อุจจาระเป็นเลือด หรือมีสีดำเหมือนถ่าน	
4.5 ท้องเดินสลับท้องผูก	
5. อาการเกี่ยวกับระบบหายใจ	
5.1 ไอเรื้อรังไม่มีเสมหะ	
มีเสมหะ	
5.2 มีเสมหะปนเลือด	
5.3 เจ็บหน้าอก	
5.4 หายใจลำบาก	
5.5 เหนื่อยหอบ	
5.6 เลือดกำเดาไหลบ่อย ๆ	
6. อาการเกี่ยวกับระบบกล้ามเนื้อและกระดูก	
6.1 ข้ออักเสบ	
6.2 ปวดหลัง	
6.3 ปวดกระดูกแขน ขา	
7. อาการเกี่ยวกับระบบประสาท	
7.1 ปวดศีรษะบ่อย ๆ	
7.2 กล้ามเนื้อกระตุก สั่น หรือบิดเบี้ยว	
7.3 แขนขาเปลี้ย รู้สึกชาหรือหนัก	
7.4 ตาพร่า มัว	
7.5 มีอาการชัก	
8. อาการเกี่ยวกับระบบขับถ่ายปัสสาวะ	
8.1 ปัสสาวะมีเลือด	
8.2 ปัสสาวะบ่อยมาก	
8.3 ปัสสาวะลำบาก	

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อาการผิดปกติในระบบต่าง ๆ	ระยะเวลาที่เป็นหรือมีอาการ (โดยประมาณ)
9. อาการเกี่ยวกับอวัยวะระบบสืบพันธุ์	
ชาย	
9.1 เป็นแผลเรื้อรัง	
9.2 มีเนื้องอก	
9.3 เป็นภามโรค (ระบุ) _____	
หญิง	
9.1 มีตกขาว	
9.2 คันแสบในช่องคลอด	
9.3 ประจำเดือนมาไม่สม่ำเสมอ	
9.4 ประจำเดือนออกมากผิดปกติ	
9.5 มีเลือดออกหลังการมีเพศสัมพันธ์	
9.6 มีเลือดออกในวัยหมดประจำเดือน	
10. อาการเกี่ยวกับเต้านม	
10.1 มีก้อนที่บริเวณเต้านม	
10.2 มีสิ่งไหลออกมาจากหัวนม	
10.3 อาการปวดบริเวณเต้านม	
10.4 มีแผล หรือการอักเสบบริเวณเต้านม	
11. อาการผิดปกติอื่น ๆ	
_____	
_____	
_____	

7. สรุปปัญหาสำคัญอื่น ๆ (โดยแพทย์ผู้ตรวจ)

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BIOGRAPHY

NAME	Miss Naiyana Vongvanich
DATE OF BIRTH	20 April 1973
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