RELATION BETWEEN ORAL CONTRACEPTIVE USE AND BREAST CANCER IN WOMEN

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RELATION BETWEEN ORAL CONTRACEPTIVE USE AND BREAST CANCER IN WOMEN.

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ABSTRACT

The main objective of the study was to determine the relationship between oral contraceptive use and breast cancer in women. The study was conducted between 1 July and 31 December 2000, and data were obtained from female patients who registered to Siriraj Hospital, Ramathibodi Hospital, and Rajvithi Hospital. This study of 250 patients with historically confirmed carcinoma of the breast and 355 patients of control obtained from the same hospital. The questionnaires were used to collect data by interviewing patients. Data collection was also conducted by reviewing medical records. Using a statistical and epidemiological test, the two groups were compared results showed no association between ethnicity, place of birth, place of residence, subject's income, education level, occupation, current marital status, and oral contraceptive use and breast cancer, history of irregular menstruation menopause, hormone treatment after menopause, duration of use of oral contraceptive, age first pregnancy, and total number of children.

There are the same indications of association with lack of knowledge on breast cancer, (OR = 4.67, 29, 95%CI =1.31-16.73), early menarche (OR= 4.41,95%CI =1.27-15.32), age when first married at more than 25 years (OR = 9.45, 95%CI =1.38-37.55), family history of breast cancer (OR =10.84, 29, 95%CI =1.53-76.56), and history of benign breast disease (OR =68.09, 95%CI =14.10-328.70).

Women with associated factors had higher risk associated factors, and the most effective is the history benign breast disease.

KEY WORDS: BREAST CANCER / ORAL CONTRACEPTIVE USE / ORAL CONTRACEPTION / CONTRACEPTIVE PILL

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บทคัดย่อ

วัตถุประสงค์เพื่อศึกษาความสัมพันธ์ระหว่างยาเม็ดคุมกำเนิดและมะเร็งเต้านมในสตรี การศึกษาทำในหญิง เป็นมะเร็งเต้านมซึ่งได้รับ การวินิจฉัยทางพยาธิวิทยาแล้วจำนวน 250 รายจาก โรงพยาบาลศิริราช โรงพยาบาลรามาธิบดี และ โรงพยาบาลราชวิถี และกลุ่มหญิงเปรียบเทียบจาก โรงพยาบาลดังกล่าว โดยการสัมภาษณ์ และเก็บข้อมูลจากแบบบันทึกประวัติผู้ป่วยในเวชระเบียน ผลการศึกษาโดยวิธีการทางสถิติ และการคำนวณทางระบาดวิทยาโดยที่กลุ่มทั้งสองนี้คล้ายคลึงกัน ในด้านเชื้อชาติ สถานที่เกิด บริเวณที่อยู่อาศัย ระดับรายได้ ระดับการศึกษา อาชีพ และสถานภาพสมรส พบว่า ไม่มีความสัมพันธ์ระหว่างการเกิดโรคมะเร็งเต้านมกับการ ประวัติการมีประจำเดือนไม่สม่ำเสมอ การหมดประจำเดือน ใช้ยาเม็ดคุมกำเนิด การใช้ฮอร์โมนรักษาหลังหมดประจำเดือน ระยะเวลาของการใช้ยาเม็ดคุมกำเนิด อายุเมื่อมีบุตรครั้งแรก และจำนวนบุตร จากการศึกษาครั้งนี้ ปัจจัยที่มีความสัมพันธ์กับการเกิดมะเร็งเต้านมคือ การไม่มีความรู้ในการตรวจเต้านมด้วยตนเอง และการไม่เคยตรวจเต้านมด้วยตนเอง (OR = 4.67, 29, 95% CI =1.31-16.73) การมีประจำเดือนครั้งแรกเมื่ออายุน้อยกว่า 12 ปี (OR= 4.41, 95% CI =1.27-15.32) อายุเมื่อแต่งงานครั้งแรก (OR = 9.45, 95% CI =1.38-37.55) ประวัติครอบครัวป็นมะเร็งเต้านม(OR =10.84, 95%CI =1.53-76.56) และประวัติการเป็นเนื้องอกธรรมดาของเต้านม (OR= 68.09, 95% CI = 14.10-328.71) หญิงที่มีปัจจัยที่มีความสัมพันธ์กับการเกิดมะเร็งเต้านม ตามผลการศึกษา ข้างต้น มีโอกาสในการเกิดมะเร็งเต้านมได้มากกว่าหญิงที่ไม่มีปัจจัยดังกล่าว และในจำนวนปัจจัยต่างๆที่เกี่ยวข้องกับมะเร็งเต้านม พบว่าปัจจัยที่มีความสัมพันธ์มากที่สุด ได้แก่ ประวัติการเป็นเนื้องอกของเต้านม

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ABBREVIATIONS

AJCC	=	The American Joint Committee on Cancer
CI	=	Confidence interval
CON	=	Condom
FFTP	=	First Full Term Pregnancy
F.STER	=	Female Sterile
IUD	=	Intra Uterine Device
NOR	=	Norplant
OCs	=	Oral Contraceptives
OR	=	Odds Ratio
OTH	=	Others
RR	=	Relative Risk
U.S	=	United State
VAS	=	Vasectomy
WHO	=	World Health Organization

CHAPTER I
INTRODUCTION

1.1 Blckground And Rationale

Since man must suffer the ravages of illness, it is inevitable that he should search for causes and make attempt to reduce it. Although in some diseases it is relatively easy to identify the cause, more puzzling are the diseases which appear to have no obvious cause and resulted in the death of many thousands. Concerning the diseases man could just observe, record details, search out methods of treatment and prevention. Though it is possible to give adequate treatment to many diseases without identifying the causative agent, but such recognition was frequently resulted in improved therapy, early diagnosis and prevention.

Breast cancer is a major public health problem and is of great interest i to all clinicians. It is a major affliction of women in women in affluent countries. On the basic of incidence rates for 1988-1992 and mortality rates for 1988 in the United State of America 12% of all women would be given a diagnosis of breast cancer and 35% died due to disease (1).

Despite the easiness in identification of causes in many diseases; for example: in plaque, cholera, certain inflammatory diseases; the etiology of malignant diseases present more problems. Cancer is a term which covers a group of diseases o different etiology, of different clinical picture and having a wide variety of prognosis after treatment. Cancer is one of the great health problems in the world which resulted in social and economic loss for the family, society and country as a whole. Breast cancer is one of the most common malignant neoplasms and the leading cause of death in developed countries especially in female population (1).

Reversible contraception is defined as temporary prevention of fertility. Sterilization should be considered permanent prevention of fertility.A perfect method of contraception for all individuals is not now available and probably will never be developed. Oral contraceptive is a method use for prevention of fertility. It may protect against ovarian and endometrial cancer but may also be associated with an

increased risk of breast and cervical cancer. According to a recent WHO multicentre study, the relationship between oral contraceptive use and breast cancer remains unclear (2).

Cancer is a significant cause of chronic illness. . Burger (3) mentions that about one in three women in the United States developed breast cancer at one time in their life between 35 to 55 years of age. Out of 107,000 diagnosed new case of breast cancer 35,000 died in one-year period in 1989. The most common cause of death among British women aged 35 to 59 in 1991 was malignant neoplasm of the breast.

Breast cancer is the most common disease of women in England and Wales, which causes 12,000 deaths every year. It is estimated 1 in 14 of all female children born will develop the disease during their life time (4).

Women between the age of 45-55 are the most frequent victims of breast cancer. It occurs more commonly in nulliparous than in nulliparous women and less commonly in women, who have their first child at an early age, have late menarche and have early menopause. Breast cancer develops in approximately 1 in 9 women at some point in their life them (5).

The impact of breast cancer was magnified because women were at risk from their middle to later years of age. The incidence rate increases rapidly during the fourth decade and is substantially such age. After menopause, the incidence rate continues to increase with age but less strileingly than before. Breast cancer is the leading cause of death among American women who were 40 to 55 years of age. In less affluent part of the world and in the Far East, the same age pattern was seen but the absolute rates were much lower at each age. In Japan, the overall incidence of breast cancer had been only about one fifth of that in the United States. Between 1989 and 1993, the incidence in the United State rose more sharply, at 4% per years and most of the increase between 1980 and 1991 was accounted for by tomors with estrogen receptors suggesting a hormonal influence and the possibility that the increase may be due to more benign of breast cancer (1).

The Ministry of Public Health of Thailand established The National Family Planning Programme to implement family planning activities and to improve the economic and social development of the nation. Family planing of Thailand about 50% used acceptor contraceptive methods such as pills (6).

Table 1 New acceptors reported to the Thai National Family Planning Programe

Year	OC	INJ	TUD	F.STER	VAS	NOR	CON-OTH	TOTAL
1995	511,891	663,616	68,450	128,095	5,020	24,480	97,032	1,498,584
	(34.2)	(44.3)	(4.6)	(8.5)	(0.3)	(1.6)	(6.5)	(100.0)
1996	486,755	628,458	52,462	117,521	6,235	68,295	85,385	1,445,111
	(33.7)	(43.5)	(3.6)	(8.1)	(0.4)	(4.7)	(5.9)	(100.0)
1997	510,197	650,618	45,784	120,852	4,786	30,763	104,559	1,467,559
	(34.8)	(44.3)	(3.1)	(8.2)	(0.3)	(2.1)	(7.1)	(100.0)
1998	574,109	541,326	40,994	130,227	5,547	74,392	106,128	1,472,723
	(39.0)	(36.8)	(2.8)	(8.8)	(0.4)	(5.1)	(7.2)	(100.0)
1999	500,736	455,299	52,183	124,980	5,744	24,219	130,907	1,294,068
	(38.7)	(35.2)	(4.0)	(9.7)	(0.4)	(1.9)	(10.1)	(100.0)
2000	454,566	462,768	38,645	121,862	6,338	18,783	96,890	1,199,852
	(37.9)	(38.6)	(3.2)	(10.2)	(0.5)	(1.6)	(8.1)	(100.0)

Source: Bureau of Health Promotion, Department of Health, Ministry of Public Health, Fiscal Year 1995-2000

The seven leading cause of death, reported by The Ministry of Public Health of Thailand, the Malignant neoplasm was the first rank of the leading cause of death in Thai population (7).

Table 2 Number of death and death rates per 100,000 population by leading cause of death, 1996-1999

Cause of death	1996		1997		1998		1999	
	Number	Rates	Number	Rates	Number	Rates	Number	Rates
Malignant neoplasm	30,172	50.5	26,237	43.4	29,812	48.7	36,091	58.6
Heart	46,286	77.4	42,968	71.1	38,815	63.5	30,697	49.9
Hypertension	9,350	15.6	8,016	13.3	6,312	10.3	9,618	15.6
Suicide, homicide	7,518	12.6	6,190	10.2	6,099	10.0	9,444	15.3
Pneumonia	4,869	8.1	5,085	8.4	5,981	9.8	6,745	11.0
Tuberculosis	4,622	7.7	3,697	6.1	4,252	7.0	5,265	8.6
Dengue	293	0.5	277	0.5	339	0.6	132	0.2
Total	103,110	172.4	92,470	153.0	91,610	149.9	97,992	159.2

Source: Registration Administry Bureau, Department of Local Administration, and Ministry of Interior

In Thailand cancer has become a major public health problem, surpassing infection disease (except HIV/AIDS) which was important in the past. Cancer Statistics according to the statistical report of the Ministry of Public Health showed that death rate due to breast cancer among women was 2.9 per 100,000 population in 1999 (8).

Table 3 Number death and death rates of leading cancer in Thai women per 100,000 population

	1,996		1,997		1,998		1,999	
Location	Number	Rates	Number	Rates	Number	Rates	Number	Rates
Liver and Intra hepatic	1,580	5.2	1,622	5.3	2,145	7.0	2,254	7.3
Lung, Bronchus	798	2.7	845	2.8	1,014	3.3	1,289	4.2
Breast	527	1.8	490	1.6	519	1.7	890	2.9
Colon, Rectum	456	1.5	502	1.7	720	2.0	713	2.3
Cervix Uteri	380	1.3	318	1.0	408	1.3	672	2.2
On specified parts of uteri	344	1.1	275	0.9	553	1.8	538	2.2
Ovary	103	0.3	76	0.3	89	0.3	136	0.4
Brain	259	0.9	201	0.7	292	1.0	395	1.3
Lip and Oral cannily	228	0.8	142	0.5	211	0.7	259	0.8
Stomach	154	0.5	98	0.3	145	0.5	191	0.6
Other	222	0.7	65	0.2	88	0.3	157	0.5
Total	5,051	16.8	4,634	15.3	6,184	19.9	7,494	24.7

Source: Health Information Division, Bureau Health Policy and Planning, 1999

Realizing the problem caused by breast cancer, many countries in the world try to solve this problem. A lot the cause of this disease and how to prevent it. The patient and family must face many traumatic experiences not only physical and mental health but also the problem of inability to continue on their job which in turn yield, a loss of their income. The loss of one's job means the loss of national production. Besides, the government is also affected by a burden of long-term care which loaded with the need of medical specialty and medical supplies. Those effects plus the increasing trend of the National Cancer Institute service provide a very good reason to find means and ways to prevent breast cancer. Knowledge about relationship between oral contraceptive and breast cancer seems to be important.

1.2 Objectives

The objectives of this study are as follows:

1. To study the association between oral contraceptive use and the occurrence of breast cancer among women

2. To determine the use of oral contraceptive as a risk factors that related to breast cancer in Thai females

1.3 Research Hypothesis

Oral contraceptive use are associated with breast cancer

1.4 Scope And Limitation

The study was conducted to determine factors related to breast cancer in Thai women, who sought treatment at Siriraj Hospital, Ramathibodi Hospital and Rajvithi Hospital from July to December 2000.

Conceptual framework

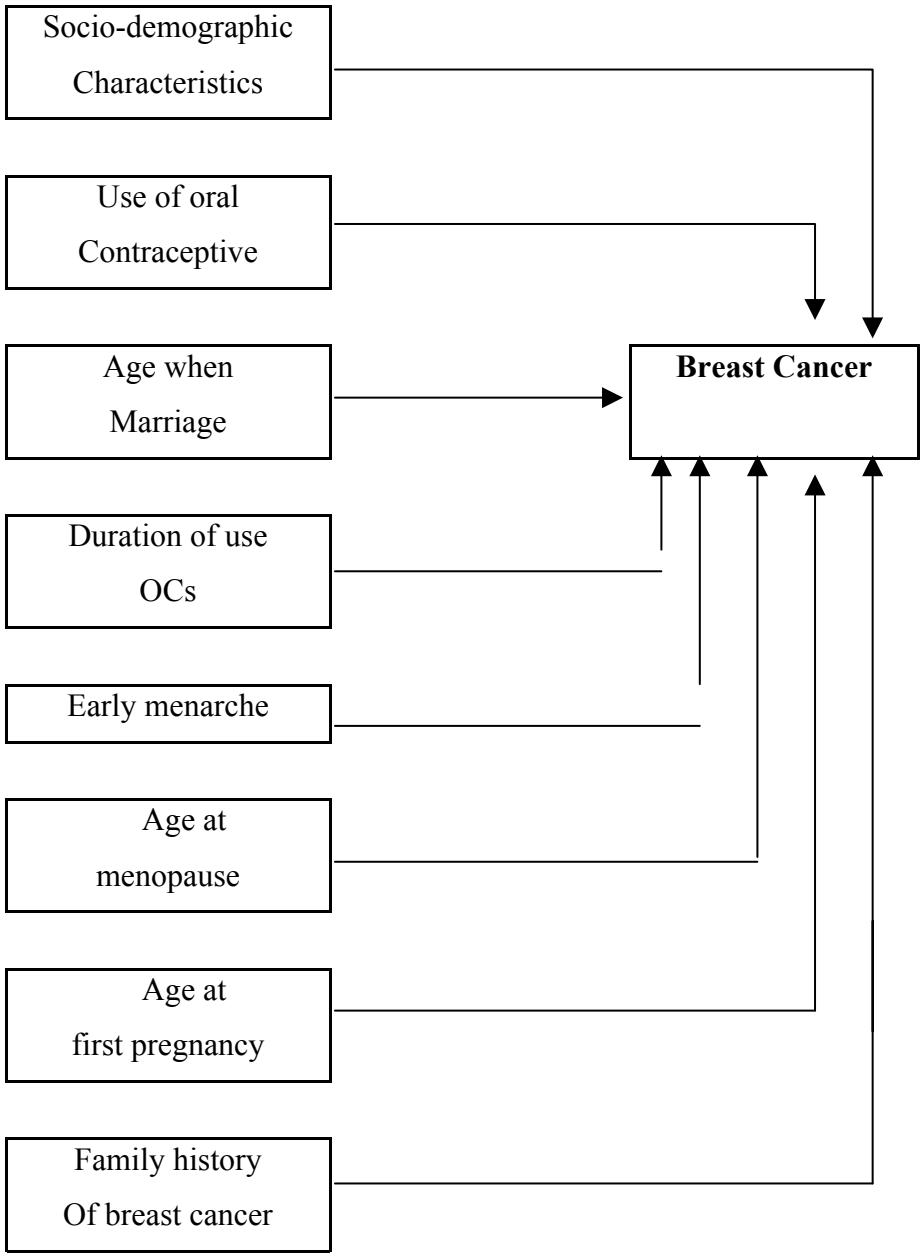

Figure 1 Conceptual framework of the study

1.5 Expected Outcomes

This study was expected provide:

1. The findings of the present study could be used as a guideline in developing a health education program for female population who have a high risk of breast cancer.
2. The study findings could be applied by nursing staff and other health care providers to better provide advice and care to women who use oral contraceptive.

CHAPTER II
LITERATURE REVIEW

2.1 Knowledge On Oral Contraceptive

Oral steroid contraceptives (OCs) were first marketed in the United States in 1960. Because of their extremely high rate of effectiveness and ease of administration, they soon became the most widely used method of reversible contraception among both married and unmarried women. The initially marketed formulations of OCs contained 150 μg of the estrogen component mestranol and 9.85 mg of the progestin component morethynodrel. However the minor side effects produced by each of these steroids, such as nausea, breast tenderness, and weight gain, were common and occasionally severe enough to cause discontinuation of use. During the past 30 years, many other formulations have been developed and marketed with steadily decreasing dosages of both the estrogen and progestin components. All the formulations marketed after 1975 contain less than 50 μg of ethinyl estradiol and 1 mg or less of several progestins. The use of these agents is associated with very low pregnancy rates, similar to those formulations with higher doses of steroid (9) and with a significantly lower incidence of adverse metabolic effect (10).

2.1.1 Pharmacology

There are three major types of OC formulations: fixed-dose combination, combination phasic, and daily progestin. The combination formulations are the most widely used and most effective. They consist of tablets containing both an estrogen and progestin given continuously for three weeks. The original sequential type, which is no longer marketed, provided a regimen of estrogen alone given for about two weeks, for this carcinogenic effect. Contraceptives containing these progestins are no longer being made.

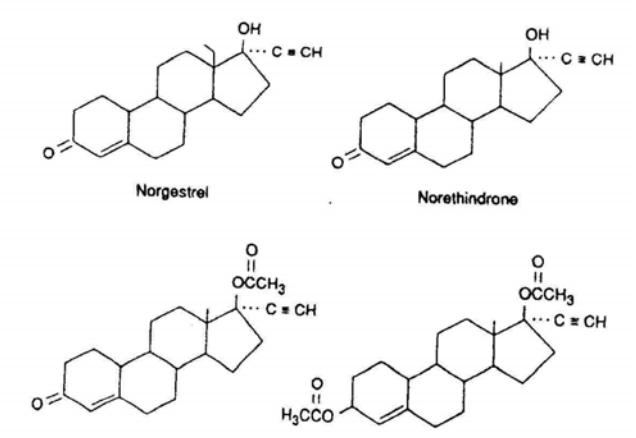

Figure 2 Structural formulas of four progestin OCs manufactured

All OC formulations now available in the United States consist of varying dosages of one of the following four 19-nortestosterone progestins: norethindrone, norethindrone acetate, ethynodiol diacetate, or norgestrel (Figure 2). The patent compound of the later steroid, dl-norgestrel consists of two isomers, only one of which is biologically active. Currently, formulations containing only the active isomer of dl-norgestrel, levonorgestrel are being produced primarily. In Europe, formulations containing three additional progestins-desogestrel, gestodene, and norgestimate, which have greter progestational activities but are less androgenic than the currently used progestins, have been marketed for several years (Figure 3). Clinical testing with these formulations in the United States is under way or has been completed, and approval for their use is expected shortly.

With the exception of two daily progestin-only formulations, the progesins are combined with varying dosages of two estrogens, ethanyl estradiol and ethanol estradiol 3-methyl ether, also known as mestranol (Figure 4). All older higher-dosage formulations contained mestranol, and this steroid is still present in some 50 -μg formulations. All formulations with less than 50 μg of estrogen contain the parent compound ethanol estradiol. All the synthetic estrogens and progestins in OCs have an ethinyl group at position 17. The presence of this ethanol group enhances the oral activity of these agents, because their essential functional groups are not as rapidly hydroxylated and then conjugated as they initially pass through the liver via the portal system, in contrast with what occurs when natural sex steroids are ingested orally.

The synthetic steroids thus have greater oral potency per unit of weight than the natural steroids.

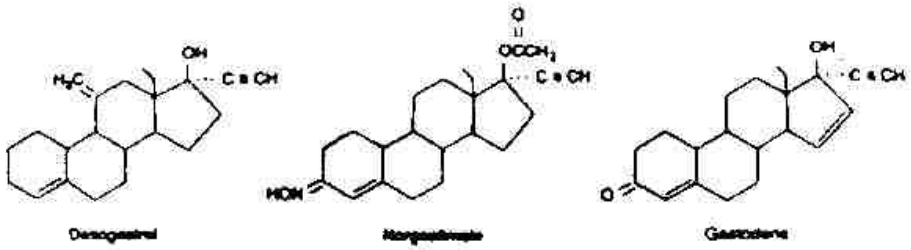

Figure 3 Structural formulas of three new progestins used in OC formulation

The various modifications in chemical structure of the different synthetic progestins and estrogens also affect their biologic activity. Thus, the pharmacologic activity of the progestin or estrogen in a particular contraceptive steroid formulation can not be judged only by the amount of steroid present. The biologic activity of each steroid also has to be considered. When testing for progestational activity in animals, it has been found that a given weight of norgestrel is several times more potent than the same weight of norethindrone. Studies in humans, using delay of menses (11) or endometrial histologic alterations such as subnuclear vacuolization (12,13) as end points, also conclude that norgestrel is several times more potent than the same weight of norethindrone. Norethindrone acetate and ethynodiol diacetate are metabolized in the body to norethindrone. Studies in humans, measuring progestational activity as described above, as well as other studies comparing the effects on serum lipids in humans, indicate that each of these three progestins has approximately equal potency per unit of weight, whereas levonorgestrel is ten to 20 times as potent (14). Thus, when considering which contraceptive to prescribe, the physician needs to consider both the dose and the potency of each steroid. The currently marketed triphasic contraceptive formulations with levonorgestrel contain about 10% as much progestin as triphasic formulations containing norethindrone and have similar effects on lipid and carbohydrate metabolism. Several fixed-dose monophasic formulations currently marketed in the United States have a lower total dose of norethindrone per treatment cycle than the triphasic formulations containing norethindrone.

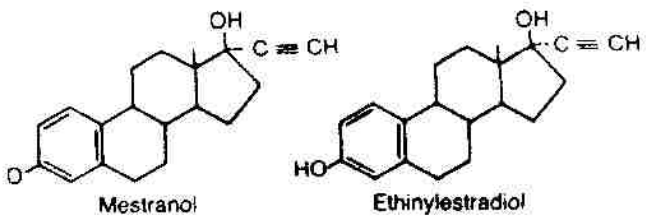

Figure 4 Structures of the two estrogen used in combination OCs

The two estrogenic compounds used in OCs, ethanol estradiol and its 3-methyl ether, mestranol, also cause different biologic activitives in women. To become biologically effective, mestranol must be demethylated to ethanol estradiol, because mestranol does not bind with the estrogen cytosol receptors. The degree of conversion of mestranol to ethanol estradiol varies among individuals; some are able to convert it completely, whereas others convert only a portion of it. Thus, in some women, a given weight of mestranol is as potent as the same weight of eghinyl estradiol, and in other women it is only about half as potent. Overall, it has been estimated that ethanol estradiol is about 1.7 times as potent as the same weight of mestranol. This factor was determined using human endometrial response and effect on liver corticosteroid-binding globulin production as end points. Thus, it is important to evaluate the biologic activity as well as the quantity of both steroid components when comparing potency of the various formulations.

Radioimmunoassay methods have been developed to measure blood levels of these synthetic estrogens and progestins. Peak plasma levels of ethanol estradiol occur about one hour after ingestion, and then rapidly decline. However, measurable amounts of ethanol estradiol are still found in plasma 24 hours after ingestion. Peak levels of ethanol estradiol are lower after ingestion of mestranol than after ingestion of ethanol estradiol, and the peaks occur from two to four hours after ingestion. This delay is due to the time necessary for mestranol to be demethylated to ethanol estradiol in the liver.

When different doses of norgestrel are administered to women, it has been found that the serum levels of levonorgestrel are related to the dosage. Peak serum levels are found 0.5 to three hours after oral administration, followed by a rapid, sharp

decline (15). However, 24 hours after ingestion, 20 to 25% of the peak level of levonorgestrel is still present in the serum. After five days of norgestrel administration, measurable amounts of levonorgestrel are present for at least the following five days.

In addition, in one study, serum levels of levonorgestrel, follicle-stimulation hormone (FSH), luteinizing hormone (LH), estradiol, and progesterone were measured three hours after ingestion of a combination OC containing 0.5 mg of dl-norgestrel and 50 μg of ethanol estradiol in three women during two consecutive cycles, as well as during the intervening pill-free interval. Daily levels of levonorgestrel rose during the first few days of medication, plateaued thereafter, and declined after ingestion of the last pill (16). Nevertheless, substantial amounts of levonorgestrel remained in the serum for at least the first three to four days after the last pill was ingested. These steroid levels were sufficient to suppress gonadotropin release; hence follicle maturation, as evidenced by rising estradiol level, which did not occur during the pill-free interval.

In studies conducted with rats and in a few studies in humans, this inhibitory action of the contraceptive steroids could be overcome by the administration of GnRH. However, in a majority of other human studies, most women who had been ingesting combination OCs had suppression of the release of LH and FSH after infusion of GnRH, indicating that the steroids had a direct inhibitory effect on the pituitary as well as on the hypothalamus (17).

It is possible that when hypothalamic inhibition is prolonged, the mechanism for synthesis and release of gonadotropins may become refractory to the normal amount of GnRH stimulation. However, in a few OC users studied, after serial daily administration of GnRH, there was still a refractory response to a GnRH infusion. Thus, the combination contraceptive steroids probably do have a direct inhibitory effect on the gonadotropin-producing cells of the pituitary, in addition to affecting the hypothalamus. This effect occurs in about 80% of women ingesting combination OCs. It is unrelated to the age of the patient or the duration of steroid use, but it is related to the potency of the preparations. The effect is more pronounced with formulations containing a more potent progestin (18) and with those containing 50 μg or more of estrogen than with 30-to 35-μg formulations (19). It has not been

demonstrated that the amount of pituitary suppression is related to the occurrence of postpill amenorrhea, but if there is a relationship, the lower-dose formulations should be associated with a lower frequency of this entity. There are data showing that the delay in the resumption of ovulation after discontinuation of OC use is shorter in women ingesting preparations with less than 50 μg of estrogen than in those ingesting formulations with 50 μg of estrogen or more (20).

The daily progestin-only preparations do not consistently inhibit ovulation. They exert their contraceptive action via the other mechanisms listed above, but because of the inconsistent ovulation inhibition, their effectiveness is significantly less than that of the combination types of OCs (21). Because a lower dose of progestin is used, it is important that these preparations be consistently taken at the same time of day to ensure that blood levels do not fall below the effective contraceptive level.

2.1.2 Reproductive Effects of Contraceptive Use

In one study attemping to determine whether the reproductive endocrine system recovers normally after cessation of OC therapy, measured serum levels of FSH, LH, estradiol, progesterone and prolactin were in six women every day for two months after they discontinued use of high-dose OCs (22). Except for a variable prolongation of the follicular phase of the first post contraceptive cycle, the patterns and levels of all of these hormones were indistinguishable from those found in normal ovulating subjects. In the six subjects of the study the initial LH peak occurred from 21 to 28 days after ingestion of the last tablet. These results indicated that after a variable, but usually short, interval after the cessation of oral steroids, their suppressive effect on the hypothalamic-pituitary-ovarian axis disappears. The delay in the return of fertility is greater for women discontinuing use of OCs with 50 μg of estrogen or more than with those containing lower doses of estrogen (20). However, use of the low-dose formulations still results in a reduction in conception rates for at least the first six cycles after discontinuation. For women stopping use of OCs in order to conceive, the probability of conception is lowest in the first month after stopping their use and increases steadily after that. There is little, if any, effect of duration of OC use on the length of delay of subsequent conception, but the

magnitude of the delay to return of conception after OC use is greater among older pre-menopausal women.

2.1.3 Neoplastic Effects

OCs have been extensively used for about 30 years, and numerous epidemiologic studies of both cohort and case-control designs have been performed to determine the relationship between use of these agents and the development of all types of neoplasms. Because as yet no elderly women have used OCs during the early reproductive years, the studies that have been published usually restrict the analysis to women under 60 years of age. In 1987, Prentice and Thomas published a comprehensive review of all epidemiologic studies of OC use and various disorders, including all neo-plasms that had been reported in the literature prior to that year.

One comprehensive study is the Cancer and Steroid Hormone (CASH) study performed by the United State Centers for Disease Control. Because hormones are considered to be promoters, not initiaters, of cancers, any adverse oncologic effects of these steroids should show a dose response, as demonstrated by an increased risk occurring with increased duration of use. In 1989, Schlesselman addressed this issue by reviewing all the epidemiologic studies reported since 1980 that analyzed the effect of OCs according to their duration of use on cancer of the breasts and the organs of the female reproductive tract (23).

2.1.4 Breast Cancer

No study has reported a significant increase or decrease in the risk of breast cancer among the entire population of OC users. The combined risk estimate of the 16 case-control studies and four cohort studies summarized (24). In Schlesselman's review of 17 different studies in which the risk of breast cancer developing in women under 60 years of age was compared with the duration of OC use, no overall dose response was found to exist, and long-term use did not increase the risk of breast cancer.

The issues of latency time since first use of OCs, and risk of breast cancer have also been studied. In groups of women using OCs for more than 19 years, no changes in risk of breast cancer with increasing duration of time since first use was found. Thus, there is no evidence supporting a long-term latent effect. In addition,

although several studies have presented data regarding the risk of breast cancer developing in the women aged under age 45 years by duration of OC use prior to the age of 25, the combined data fail to show a dose response, indicating that early age at first OC use is not by itself a risk factor for development of breast cancer (23). Studies estimating risk of breast cancer in women under 60 years of age by duration of OC use prior to first term pregnancy have also failed to show an increased risk or a dose response. However, an analysis of the studies estimating the relative risk of breast cancer developing in women under 45 years of age has suggested that there is a trend of increasing risk with increasing duration of overall use as well as increasing duration of use prior to first term pregnancy, with the increased risk in both groups becoming most evident after eight years of use (23).

The suggest that prolonged use of OCs might increase the risk of breast cancer developing, but only when initially diagnosed at an early age. Analysis of data from the cohort study of Kay CR, et al. (25) has revealed that increased risk of breast cancer among OCs use occurs only among women whose breast cancer developed between the ages of 30 and 34, not in other age categories. Secondly, a large British case-control study found that prolonged use of OCs, for more than five years increased the risk of breast cancer under age 36, with the risk increasing with more than eight years of use. In this study, there was a lower risk associated with low-estrogen (less than 50 μg) formulations (26). Finally, a detailed analysis of the large amount of data obtained in the CASH study indicates that the only subset of women with an increased risk of development of breast cancer are nulliparous women whose menarche was prior to age 13 and who used OCs for more than eight year (27). In order to provide a rational basis to explain the observations of these studies, Stadel et al. (28) performed additional analysis of the data in the CASH studies. They found no overall change in the risk of pre-menopausal breast cancer developing under age 55 with increasing duration of OC use as well as no change in risk among parous women using OCs developing breast cancer under the age of 45 or between ages 45 and 54.

Because low-dose estrogen formulations have been used by the majority of women ingesting OCs only since 1983, the effect of these agents, if any, on early development of breast cancer can only be determined several years from now. However, the latest review of these by the governmental drug regulatory body of the

United States as well as the World Health Organization resulted in statements that no change in OC use or prescribing practice is warranted (29). Finally, there have been several studies of OC use and breast cancer risk in women at increased risk for the disease those with a family history of breast cancer and those with existing benign breast disease. The results of these studies indicate that OC use by each of these high-risk groups is not associated with any increased risk of development of breast cancer (29, 30).

2.1.5 Cervical Cancer

The epidemiologic data indicate that long-term use of OCS is associated with an increased risk of preinvasive cervical neoplasia as well as both epidermis carcinoma and adenocarcinoma of the cervix, when compared with matched control groups. Confounding factors such as the women's age at first sexual intercourse, the number of sexual partners, exposure to human papillomavirus (possibly greater among OC users), cytologic screening (more frequent among OC users), and the use of barrier contraceptives or spermicides (primarily by women in the control group) as well as cigarette smoking (an independent risk factor for this disease) could have influenced these results. (31).

2.1.6 Endometrial Cancer

According to the 1987 CASH study and the review by Schlesselman, 1989 at least eleven studies have been published on the relation between OCS and endometrial cancer and nine of these studies have indicated that the use of these agents has a protective effect against endometrial cancer, the third most common cancer among U.S. women (23, 32, 33). Women who use OCs for at least one year have an age-adjusted relative risk of 0.5 for development of endometrial cancer between the ages of 40 and 55 as compared with nonusers. This protective effect is related to duration of use, increasing from a 20% reduction in risk with one year of use to a 40% reduction with two years of use to a 60% reduction with four years of use. This protective effect appears within ten years of initial use and persists for at least 15 years after stopping use of OCs. The greatest protective effect is in nulliparous women (relative risk 0.2) or women of low parity, who are at greatest risk of acquiring this disease.

2.1.7 Ovarian Cancer

As summarized by Schlesselman,1989(23) studies investigating the use of OCs with subsequent development of ovarian cancer show a reduction in risk, specifically of the most common type--epithelial ovarian cancers (33,34). OCs reduce the risk of the four main histologic types of epithelial ovarian cancer--serous, mutinous, endometrioid, and clear-cell. The relative risk of ovarian cancer is 0.6 for women who use OCs for three or more years, and as little as six months of use provides protection. The magnitude of the decrease in risk is directly related to the duration of use, increasing from a 50% reduction with four years of use to a 60 to 80% reduction with seven or more years of use. The protective effect begins within ten years of first use and continues for at least 15 years after the use of OCs ends. As with endometrium cancer, the protective effect occurs only with women of low parity ≤4, who are at a greatest risk for this type of cancer.

2.1.8 Liver Adenoma and Cancer

The development of a benign hepatocellular adenoma is a rare occurrence in long-term users of Ocs, and the increased risk of this tumor is associated with prolonged use of high-dose formulations, particularly those containing mestranol. Although two British studies reported an increased risk of liver cancer among users of OCs, the number of patients was small and the results could have been influenced by confounding factors (35,36). The rate of death from this disease has remained unchanged in the United States over the past 25 years, a period when millions of women have used these agents. Data from a large multi-center epidemiological study coordinated by the World Health Organization, 1989 also found no increased risk of liver cancer associated with OC users in countries with a high prevalence rate of this neoplasm (37). No change in risk with increasing duration of use or time since first or last use was found either**.**

Pituitary Adenoma

Ocs masks the predominant symptoms produced by prolactinoma-amenorrhea and galactorrhea. When OC use is discontinued, these symptoms occur, suggesting a causal relation. However, data from previous studies (38) indicate that

the incidence of pituitary adenoma among users of OCs is not higher than that among matched controls.

2.1.9 Malignant Melanoma

Several epidemiologic studies have been undertaken to assess the relation of OC use and the development of malignant melanoma. The results are ambiguous, since an increased risk, a decreased risk, and no effect have all been reported. In the review by Prentice and Thomas, 1987 the summary of relative risk for eight case-control studies was 1.0(24).

2.1.10 Anatomy of the Breast

Ablative cure of mammary carcinoma by surgical or radiation therapy is based on the assumption that viable cancer is limited to the mamma or to the mamma and the regional lymph nodes. Confinement of cancer to the lymph nodes further requires that the cancer cells have arrived in the nodes via afferent lymphatics, that the nodal sinuses have retained the cancer cell, and that some of these cells have survived and are engaged in metastatic growth and replication.

If the metastatic foci in the lymph nodes are not removed or destroyed, sustained cancerous growth will result in increasing morbidity from uninhibited local progression and generalized dissemination. Resection of the lymph nodes, therefore, is pertinent to the surgical management of mammary cancer and local control of cancer on the chest wall. Knowledge of the presence or absence of metastases in the lymph nodes is essential in prognostication.

The design of surgical and radiation therapy has been based largely on an empirical knowledge of the location of the mamma and regional lymph node anatomy. Of equal importance is a consideration of functional lymphatic anatomy as studied by injection and by statistics of the distribution of lymph node metastases and the dissemination of cancer beyond its locoregional confines.

This chapter reviews the pertinent parts of the developmental topographic, fascial, muscular, neural, lymphatic, and vascular anatomy of the breast and mammary region. Emphasis is placed on the functional anatomy of lymphatic.

2.1.11 Diagnosis

There is only one method of making a definitive diagnosis of breast cancer—histologic examination of tissue. By contrast, there are many techniques for detecting its signs and symptoms. These include medical history, physical examination, mammography, thermography, ultrasonography, and cytologic examination of aspirates and nipple discharge. An accurate diagnosis is fundamental to appropriate staging and treatment.

Most complaints referred to the breasts are not cancer related; benign diseases are far more frequent, cancer ranks low in the overall frequency of diagnosis, but as it can almost all benign conditions and poses the most important threat to continued well-being, it must always be suspected. The physician must agree with Haagensen, 1986 (39), that expertise in this field comes with the knowledge that any sign of disease in the breast can be produced by cancer. Its invidiousness and its capacity to spread widely permit the axiom to be carried a step further with the observation that any histologically compatible metastasis in a woman without an obvious source can be generated by occult carcinoma of the breast.

Mammary cancer is primarily a disease of women. Less than 1% of cases occur in men, and it is unusual under the age of 30 years in either sex. In children, it is a medical curiosity. Particularly prone are those with a strong family history of the disease, women who are nulliparous or who have a late initial full-term pregnancy, and those who have had a previous biopsy showing atypical hyperplasia. Nevertheless, most cases are not at high risk by the usual standards, and all symptomatic women should be suspected.

The upper outer quadrant of the breast is the most common location for mammary carcinoma. Among 2045 consecutive cases at Ellis Fischel State Cancer Hospital (EFSCH) in which the site of the primary lesion was identified, cancer was located in the upper outer quadrant in 37%.The lower inner quadrant was the least frequently involved (5 % of cases)(41), and the upper inner, lower outer, and central areas were intermediate. Twenty per cent of the cancers involved more than one quadrant or were diffuse at the time of diagnosis, and a few could not be allocated to one quadrant or another. The concentration of breast tissue in the upper outer quadrant likely accounts for this particular pattern, as does the slight predominance in

the left breast, which averages somewhat larger, rarely carcinoma in ectopic mammary tissue along the axillary or abdominal portions of the primitive milk lines (40). These cancers serve as a reminder that breast tissue is heir to the same diseases regardless of location (41).

Table 4 Diagnostic capabilities of current imaging modalities in breast cancer

Method	Diagnosis and staging capability	Recommendation
Primary tumor and regional node		
Mammography	Visualizes approximately 90% of breast cancers	Film/screen and Similar diagnostic Accuracy.
Ultrasound (dedicated)	Limited to identification of cystic lesions and evaluation of dense breast	Dedicated units are Expensive and not suitable for stand-alone screening.
CT	Limited to evaluation of chest wall and internal mammary node Involvement	Use of dedicated CT breast imaging systems has been abandoned
MRI	Good for discrete lesions; calcifications are difficult to distinguish	Dedicated units are Expensive. Used for follow up.
Metastatic breast cancer		
Chest x-ray film	Adequate for diagnosis; CT usually not needed	Essential for all tumor types
Radionuclide bone scans	Essential for baseline verification and evaluation of symptomatic	Abnormal bone scan requires film
Liver and adrenal imaging	Indicated with abnormal chemistry or symptoms	Initial imaging study: radionuclide

Source: Oncology Imaging Elmsford, New York, Pergamon Press, 1985.

Modern radiology of the breast uses molybdenum radiation source and intensifying screens to produce a negative image viewed as standard x-ray film (Table 4). Effective screening mammography is performed on a dedicated machine and consists of a medial lateral oblique and a craniocaudal view (two views) of each breast. These four films are reviewed at a later time by a radiologist and a report is issued . This system is suited to a high volume of tests and minimizes the cost of each screening study. If abnormalities are found, additional diagnostic mammography is

performed in addition to physical examination. The goal of diagnostic mammography is to provide a differential diagnosis and suggestions for further evaluation (42).

2.1.12 Signs and Symptoms

The initial signs and symptoms of mammary carcinoma are varied.

Mass

By far the most common physical sign of mammary cancer is a mass in the breast (76% of cases). The mass may be tender, but it is more often painless, and in about 73% of cases it is discovered by the patient during bathing or on self-examination. Occasionally a spontaneous sensation of "drawing" or discomfort, or an accidental blow to the breast, leads to its discovery. Husbands sometimes discover such masses. The fact that almost 15% of cancers are painful emphasizes the point that pain or tenderness is no guarantee of innocence.

Nipple Discharge

Nipple discharge is not a frequent complaint or a frequent sign of mammary carcinoma. Only 3 to 5 % of consultation (43), and only 7.4 % of breast operations are for discharge. No more than 2 % of cancers were associated with discharge in Devitt's (44) series; most of those (80 %) also appeared as a mass. Only 12 to 20% of cancer-associated discharges are without a mass, and only 10.4 % were without a mammographic abnormality.

Skin Retraction

Dimpling or retraction of the skin by cancer is produced by shortening of Cooper's ligaments associated with infiltration of cancer. Although this was once considered virtually diagnostic of mammary cancer, it is now appreciated that some benign lesions can produce this chance, notably fat necrosis and plasma cell mastitis. Mondor's disease, originally described by Fiessinger et al. (45), can also cause retraction of the skin and mimic cancer. This condition occurs spontaneously in pendulous breasts or after minor breast operations. It appears as a painful groove in the skin or as a subcutaneous cord on the breast, in the axilla or on the anterior chest wall, mimicking lymphatic permeation from an occult mammary carcinoma. Histopathologic examination usually demonstrates a sclerosing endophlebitis, but arteries and lymphatics may also be involved. The process is self-limiting and

requires only symptomatic treatment. Although the clinical picture is usually diagnostic, a biopsy will resolve the issue when doubt exists.

Skin Changes

Attachment to the overlying dermis with alteration of the normal contour of the breast is sometimes the only visible change produced by carcinoma. Deviation of the affected breast or straightening of its normally curved contour (edge sign) disrupts the two breasts' normal symmetry. Direct infiltration of the skin may appear as a firm cutaneous plaque. Prominent veins may mark the involved breast. In advanced cases, marked retraction of the entire breast results in appearance satellite nodules.

Axillary Adenopathy

As early as 1907, Halsted pointed out that enlarged axillary lymph nodes could be the only sign of occult mammary carcinoma. One percent or less of all cases first become manifest in this fashion. The Yorkshire Breast Cancer Group (46) documented 15 such cases among 1205. Also, Pierce and associates (47) reviewed 222 biopsies of isolated clinically enlarged axillary lymph nodes and found that 6.9%, or one in 14 cases, contained adenocarcinoma.

The list of possible origins for metastatic adenocarcinoma is long ,and includes liver, lungs, ovary, kidneys, stomach, pancreas, colon and breasts. When a primary cancer of the gastrointestinal tract or lung can be excluded with appropriate examinations, the ipsilateral breast becomes the most likely source. Estrogen receptors and electron microscopic examination can be helpful (48), In the course of evaluation, a mammogram of the breast will reveal an occult primary tumor in 12 to 50% of cases.

Inflammatory Carcinoma

Redness, heat, tenderness, and edema of the skin are the hallmarks of "inflammatory" carcinoma. This dramatic variant so closely mimics an acute infection that the unwary physician may be led into prolonged diagnosis.

Inflammatory carcinoma runs a rapid course. The duration of symtoms averages four to six months. A tumor mass may be noticed first, followed rapidly by enlargement of the breast, swelling, and redness (49).

Nipple Changes

Breasts removed for cancer often show extension of tumor to the nipple histologically (50). Nipple involvement is found in 30% of mastectomy specimens. Such involvement is particularly likely if primary tumors are within 2.5 cm of the nipple or are larger than 2.0 cm in diameter. As clinical signs are absent in 50% of cases with nipple involvement, the former practice of removing the apparently normal nipple before mastectomy and "banking" it for reconstructive purposes has been abandoned. From the clinical standpoint, two nipple changes are notable-retraction and Paget's disease. Inversion of the nipple is often a normal condition, but when cancer is responsible, the nipple is fixed and cannot be everted as is otherwise usually possible. On closer examination, an underlying mass may be felt.

2.1.13 Staging of Breast Carcinoma

Staging refers to the grouping of patients according to the extent of their disease. It is useful in determining the choice of treatment for individual patients stimulating their prognosis, and comparing the result of different treatment programs. Staging can be based on either clinical or pathologic findings (51).

Table 5 Columbia Clinical Classification

Stage	Description
A	No skin edema, ulceration, or solid fixation of the tumor to the chest wall. Axillary nodes are not involved clinically.
B	No skin edema, ulceration, or solid fixation of the tumor to the chest wall. Axillary nodes are involved clinically.
C	Any one of the five grave signs of advanced breast carcinoma: - Edema of the skin of limited extent (involving less than one- third of the skin over the breast) - Skin ulceration - Solid fixation of the rumor to the chest wall - Massive involvement of axillary lymph nodes (measuring 2.5 cm or more in transverse diameter) - Fixation of the axillary nodes to overlying skin or deeper structures of the axilla
D	All other patients with more advanced breast carcinoma, including: - A combination of any two or more of the five grave signs listed for stage C - Extensive edema of the skin (involving more than one -third of the skin over the breast) - Satellite skin nodules - The inflammatory type of carcinoma - Clinically involved supraclavicular lymph nodes - Internal mammary metastases as evidenced by a parasternal tumor - Edema of the arm - Distant metastases

Source: The Columbia Clinical Classification System, Columbia-Presbyterian Hospital U.S.A., 1942.

Currently, staging of cancer is determined by the American Joint Committee on Cancer (AJCC), which is jointly sponsored by the American Cancer Society, the National Cancer Institute, the College of American Pathologists, and the American Colleges of Physicians, Radiology, and Surgeons(51). The AJCC system is a clinical and pathologic staging system and is based on the TNM system, in which *T* refers to tumor, *N* to nodes, and *M* to metastasis. The current edition, the fourth, published in 1992, differs substantially from previous versions and its implications are discussed below.

Clinical staging (designated cTNM or TNM,) according to the 1992 AJCC system, is based on all information available prior to the first definitive treatment and includes the findings on physical examination, imaging studies, operative findings, and pathologic examination of the breast or other tissues. The extent of tissues examined pathologically for clinical staging is less than that required for pathologic staging. Operative findings that are appropriate for clinical staging include the size of the primary tumor, the presence of chest wall invasion, and the presence of regional or distant metastases. The clinical stage is useful in selecting and evaluating therapy.

Pathologic staging (designated pTNM) includes all data used for clinical staging and surgical resection as well as pathologic examination of the primary carcinoma and axillary lymph nodes. A tumor is inevaluable for pathologic staging (pTX) if the excision of the primary carcinoma reveals tumor in any margin of resection by *gross* pathologic examination. Regional nodes are inevaluable for pathologic staging (pNX) if less than the low axillary lymph nodes (level I) have been resected. Metastatic nodules in the fat adjacent to the mammary carcinoma, without evidence of residual lymph node tissue, are considered regional lymph node metastases. The pathologic stage provides the most precise data to estimate prognosis and to calculate end results.

There are several important rules and definitions for the use of the current staging system:

cT size: The clinical measurement used for classifying the primary tumor should be the one judged most accurate (e.g. physical examination or mammography).

PT size: The pathologic tumor size is a measurement of the invasive component. Specifically, if there is a large in situ component and a small invasive

component, the tumor is classified by the size of the invasive component.

Multiple, simultaneous, ipsilateral (infiltrating, grossly measurable) cancers: One should sue the largest lesion to classify T stage and should specify that this is a case of multiple lesions. Such cases should be analyzed separately.

Simultaneous bilateral breast cancers: These should each be staged separately.

Paget disease of the nipple: Without an associated tumor mass (clinical) or invasive carcinoma (pathologic), this is classified as Tis. Paget disease with a demonstrable mass (clinical) or invasive component (pathologic) is classified according to the size of the mass or invasive component.

Dimpling of the skin or nipple retraction: This or any other skin change except those described under T4b and T4d can occur in T1, T2, or T3 without changing the classification.

Chest wall: This includes the ribs, intercostal muscles, and serratus anterior muscle, but not the pectoral muscles.

Inflammatory carcinoma: This is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. This clinical presentation is due to tumor embolization of dermal lymphatics.

If there is doubt concerning the correct T, N, or M category to which a particular case should be allotted, then the lower (less advanced) category should be chosen.

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner should use the major headings (T1, T2, or T3). If other measurements, such as mammographic or phthologic, are used, the examiner can use the subsets of T1. The primary tumor **(T)** is classified as follows.

Primary site The mammary gland consists of tissue within a dense fibroareolar stoma situated on the anterior chest wall. Deep to the breast is the fascia overlying the pectoralis major, which in turn corners the ribs and intercostal muscles of the first six intercostal spaces.

Tx Primary tumor cannot be assessed

T0No Evidence of primary tumor

Tis Carcinoma in situ: intraductal carcinoma, lobular carcinoma in situ, or paget disease of the nipple with no tumor

T1 Tumor 2 cm or less in greatest dimension

T1a 0.5 cm or smaller

T1b More than 0.5 cm but not more than 1 cm in greatest dimension

T1c More than 1 cm but not more than 2 cm in greatest dimension

T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension

T3 Tumor more than 5 cm in greatest dimension

T4 Tumor of any size with direct extension to chest wall or skin

T4a Edema (including peau d'orange), ulceration of the skin of the breast, or satellite skin nodules confined to the same breast

T4c Both (T4a and T4b)

T4d Inflammatory carcinoma (see previous definition)

Nodal stations

The breast lymphatic drains by way to three major routes-axillary, transpectoral and internal mammary trunks into numerous surrounding first station nodes such as axillary (low, middle), axillary, apex, and infraclavicular.

The regional lymph nodes (N) are classified clinically as follows:

Nx - Regional lymph nodes cannot be assessed (e.g. previously removed)

N0- No regional lymph node metastasis

N1- Metastasis to one or more movable ipsilateral axillary node

N2- Metastasis to one or more ipsilateral axillary lymph node fixed to one another or to other structures

N3- Metastases to ipsilateral internal mammary lymph node(s)

The regional lymph nodes are classified pathologically as follows:

pNx Regional lymph node metastasis cannot be assessed

pN0 No regional lymph node metastasis

pN1 Metastasis to one or more movable ipsilateral axillary node

pN1b Metastasis to one or more lymph node, any of which is larger than 0.2 cm

pN1bi Metastases in one to three lymph nodes, any of which is larger than 0.2 cm in greatest dimension

pN1bii Metastases to four or more lymph nodes, any of which is larger than 0.2 cm and all of which are less than 2 cm in greatest dimension

pN1biii Extension of tumor beyond the capsule of a lymph node metastasis less than 2 cm in greatest dimension

pN1biv Metastasis to a lymph node 2 cm or more in greatest dimension

pN2 Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures

pN3 Metastasis to one or more ipsilateral internal mammary lymph node.

Metastatic site all distant visceral sites are potential site of metastasis disease. The four major sites are bone, lung, brain, and liver, but this widely metastasizing disease has been found in vitually all remote sites.

Distant metastasis (M) is classified as follows:

Mx Presence of distant metastases cannot be assessed

M0No Distant metastasis

M1 Distant metastasis (including metastases to one or more ipsilateral supraclavicular node)

Table 6 TNM Classification and Stage Grouping

Stage	TNM Grouping
0	Tis N0 M0
I	T1* N0 M0
IIA	T0 N1 M0
	T1 N1 M0
	T2 N0 M0
IIB	T2 N1 M0
	T3 N0 M0
IIIA	T0 N2 M0
	T1 N2 M0
	T2 N2 M0
	T3 N1 M0
	T3 N2 M0
IIIB	T4 Any N M0
	Any T N3 M0
IV	Any T Any N M1

Source: From AJCC, the American Cancer Society, U.S.A., 1997

Stage grouping is as shown in Table 6

The current AJCC system differs significantly from previous versions (52) in allowing all information available prior to when the first definitive treatment is used, including the operative findings and pathologic examination of the resected breast specimen with the primary tumor. In earlier systems, clinical staging was restricted to findings available before surgery, namely, physical examination and imaging studies. The many changes in the AJCC system over time and its complexity have greatly limited its use and usefulness. In addition, the current system does not address present-day issues in clinical decision making, such as a patient's suitability for breast-conserving treatment or the risk of distant relapse with and without systemic therapy. In practice, most clinicians simply use the tumor size and histologic findings of axillary dissection, often grouped for convenience into negative nodes, one to three positive nodes, four to nine positive nodes, and ten or more positive nodes. Attempts are underway to develop more useful staging systems.

Evaluation of breast masses

Determining whether a breast mass is related to benign or malignant disease usually begins with recording the patient's medical history and physically examining the breasts. Often a tentative diagnosis can be made on the basis of clinical findings if the physician knows the characteristic features of the various diseases to be considered and the ages at which they commonly occur. For definitive diagnosis, further diagnostic procedures are usually necessary. Adjunctive measures for diagnosis are as follows:

Transillumination

Transillumination of the breast with a cold bright light in a darkened room is of use in distinguishing solid from cystic masses. Cysts and lipomas generally are translucent; solid lesions are not. As one cannot distinguish by this method whether solid masses are malignant or benign, the examination has limited usefulness.

Xeroradiography and Mammography

These tests are performed on patients with large breasts, in women over the age of 50, or when carcinoma is strongly suspected (53).

Xeroradiography is a radiographic procedure based on the use of selenium-coated plates. Xerograms require less exposure to radiations, and the breast structures are recorded with clarity on one image. However, false positive rate of xerography is rather high. This is attributed to the remarkable detail demonstrated by this technique. Whereas false negatives also may occur, occult carcinoma may be found.

Mammography Mammography, soft tissue roentgenography of the breast, is an important adjunct in the diagnosis of breast diseases. Mammography can detect lesions less than 1 cm in diameter, or smaller than the smallest clinically palpable breast mass. The overall diagnostic accuracy of mammographic technique is about 85%. Mammography can contribute to the survival benefit obtained by early breast cancer detection. When nonpalpable tumors are discovered by mammography and treated appropriately, the incidence of spread to the regional lymph node is very low and five-year year survival rates of over 90% have been achieved.

Biopsy

Biopsy is the removal and microscopic examination of tissue from the living patient in order to establish a diagnosis. The primary purpose of breast biopsy is to confirm or exclude the presence of cancer and to remove positive premalignant lesions. It is the most definitive means of diagnosing breast disease having an accuracy that approaches 100 %.

The established indications for biopsy are as follows:

1. Clinical evident cancer
2. A palpable mass in the breast
3. A dominant nodule in the breast
4. Blood or cytologically suspicious cells in the aspirated from a suspected cyst
5. A suspicious lesion demonstrated by mammography
6. Persistent nipple discharge from the non-lactating breast
7. An ulcer or dermatitis of the nipple of undetermined nature
8. Inflammation of the breast which does not respond properly to specific therapy
9. Unexplained axillary adenopathy

Other laboratory discriminants

Testing patients with early carcinomas of the breast found that half of them excreted subnormal amounts of urinary metabolites of androgen and cortisol. This finding suggested that patients who are about to develop cancer, or with early subclinical carcinoma of the breast, may be discovered by this excretory deficiency. Extensive studies of urinary estrogen profiles in relation to the risk of cancer of the breast have been recommended. Carcinoembryonic antigen (CEA) has been found elevated in patients with hepatic metastasis (54).

2.1.14 Breast self - examination (BSE)

Women should begin monthly self-examinations of the breast at the age of 21 years, according to the American Cancer Society. Beginning this early may be particularly wise for those with a strong family history of breast cancer. The potential advantages that can accrue from establishing a routine justify the small amount of

time that is required. One week after menstruation begins, or when there is least each month, serves as an easily remembered routine for postmenopausal women. A convenient time for the examination is during bathing, as wet soapy skin and fingers optimize the ability to feel masses. The examination includes two parts, in whatever order is convenient (55):

Inspection in mirror

1. With arms at sides, look for
   - change in size and shape of breast
   - skin change (dimpling? redness? swelling? depression?)
   - changes in nipples and areola (discharge? pulled inward? point askew/scaling?)
2. With arms overhead
   - repeat inspection as in step 1
   - check underneath parts and sides of breasts
   - note whether one breast moves up higher than the other
3. With hands pressing on hips and chest muscles tensed
   - repeat general inspection as in step 1
   - look especially for lumps or skin retraction

Palpation

Lying down and with a pillow or folded towel under the shoulder on the side to be examined, feel the entire breast by gently pressing breast against chest wall:

1. With arm down at side, examine outer quadrants of breast
2. With arm overhead to help flatten breast, palpate inner quadrants and gently squeeze nipple for any signs of discharge or bleeding.

Women most likely to practice BSE are those who have been shown how to perform it, who are confident with it, and whose mother has had breast cancer.

Differential Diagnosis

Once a dominant breast mass has been found, the next step is to determine what it is. In order of decreasing frequency, the most common pathologic lesions of the female breast are fibrocystic disease, carcinoma, fibroadenoma, intraductal papilloma, and duct ectasia. Benign lesions are by far the most common comprising 70% of all breast lesions excised. In evaluating a dominant breast mass, the physical

characteristics of the mass and the patient's age are the most important indicators of the type of lesion present.

In younger women, the common lesions are fibroadenoma and fibrocystic disease. Intraductal papillomas, duct ectasia, and cancer are found predominantly in older or postmenopausal women. Occasionally, in older women a solid hard breast mass can appear rapidly after local trauma. Usually the mass is located in the area adjacent to the areola and is due to fat necrosis. It is a totally benign condition with no malignant potential what so ever.

Treatment

There are many methods used for the treatment of breast cancer such as segmental mastectomy, radical mastectomy, castration, radiotherapy, and chemotherapy. The use of one or a combination of any methods mentioned above for treatment depends on the histological types and stages of cancer.

Prognosis

Prognoses of women with breast cancer are described as the survival rate at five or ten years. The important factors that influence the survival depend upon age, reproductive period, histological grade of carcinoma, and pathological characteristic of tumor.

Age

The age of the patient in itself does not have any prognostic value. The prognosis in women under 40 years of age with cancer of the breast is similar to that in older women with tumors of comparable extent.

Histological grade of carcinoma

The histologic grading of the tumor also is related to prognosis. Minimal cancer, defined as infiltrating carcinoma 5 mm. or less or lobular carcinoma in situ or noninfiltrating intraductal carcinoma, has an excellent prognosis the five-year and ten year survival rates are 98% and 95%, respectively. Moreover, patients with Grade I carcinoma have a more favorable prognosis than those with a Grade II or a Grade III tumor, regardless of stage.

Pathologic characteristic of tumor

The prognosis in-patients with carcinoma of the breast is definitely related to the varied pathologic character of the tumors. In any group of these tumors, the

collective prognosis depends above all on the proportion of low-metastasizing tumors contained in the group. These are medullary, intraductal papillary, and well-differentiated carcinomas plus the lobular carcinomas in situ and carcinomas with excess mucin production.

2.2 Literature Review

The oral contraceptive use and risk of breast cancer.

Sattin et al. (56) states that since 1960, more than 30 different formulations of oral contraceptives have been marketed in the United States of America. Through the Surveillance, Epidemidogy, and End Results (SEER) Centers of the National Cancer Institute in eight areas (the metropolitan areas of Atlanta, Detroit, San Francisco, and Seattle, the states of Connecticut, Iowa and New Mexico, and four urban counties of Utah), a case- control study was conducted. Cases were women 20 to 54 years old with histologically confirmed primary breast cancer newly diagnosed between December 1, 1980 and December 31, 1984, who resided in one of the eight SEER reporting areas. Altogether, 4,711 cases were selected. Controls were women selected according to method of random digit dialing in the geographic area of cases and the number was 4,676. Each study participant was interviewed in person according to a pretested standardized questionnaire. The finding regarding relative risk of breast cancer among women who used oral contraceptives sometimes in their lives as compared with women who never used OC for 15 years or more revealed that there was no statistically significant trend in the relative risk of breast cancer according to duration of oral contraceptive use. Women, who used only sequential oral contraceptives or only progestin or more than one, or an unknown type of oral contraceptives, had RR of 0.8, 1.3, 0.9, and 1.1, respectively. Women who used the formulations containing 2.5 mg. of norethynodrel and 100 mg. of mestranol had a significantly decreased RR. This effect, however, was not related to duration of use. Women who used that particular formulations for more than five years had a risk of 1.0. Overall, as for women who had used oral contraceptives containing only mestranol or only ethinyl estrogen component, the relative risk did not increase with increasing milligram months of use. The RR of breast cancer did not significantly increase with the use of any specific progestin contained in a combination of oral

contraceptives, and women who exclusively used oral contraceptives containing the progestin ethynodiol diacetates, norethindrone, nor ethindrone acetate, or norgestrel had a relative risk of 1.1, 1.1, 1.1, and 1.0, respectively.

Sattin et al. (56) point out that confounding was also unlikely to account for those findings. In no instance did the estimates of relative risk, adjusted individually for potentially confounding factors including parity, age at menarche, and age at first fulllterm pregnancy of use of medical services differed from the crude relative risk estimate by 10 %.

Meirik et al. (57) studied oral contraceptive use and breast cancer in young women in Sweden and Norway. A joint national population based case - control study was conducted to investigate the possible association between oral contraceptive use and the risk of breast cancer developing before the age of 45. The information was gathered by personal interview from 422 (89.2%) eligible patients with a newly diagnosed breast cancer from May 1985 to May 1986 and from 722 (82.6%) of all contracted age matched controls. A multivariate analysis, which accounted for several possible confounding factors, revealed a significant ($p = 0.03$) association between total duration of OC use and breast cancer risk. The RR of breast cancer after using OCs for twelve years or more was 2.2 (CI 1.2-4.0). OC use for more than seven years before first full term pregnancy entailed an increased breast cancer risk RR - 2.0 (CI 1.0-4.2) which was of borderline significance. The results suggested that long-term use of OC may increase the risk of breast cancer in young women.

Thomas et al. (58) conducted a study in 1992 concerning breast cancer in relation to the use of combined OCs. A case-control study was conducted at 13 participating centers in ten countries with 2116 cases and 12,077 controls. The RR of breast cancer in women who ever used oral contraceptives was estimated to be 1.15 (1.02, 1.29). Estimated values of the relative risk based on data from three developed countries and seven developing countries were 1.07 (95% CI = 0.91, 1.26) and 1.24 (95% CI = 1.05, 1.47), respectively, and these estimates were not significantly different (p-value = 0.22). Furthermore, estimates for women under and over 35 were 1.26 (95% CI = 0.95, 1.66) and 1.12 (95% CI = 0.98, 1.27), respectively, and these estimates were not significantly different (p-value = 0.38). Risk did not increase with duration of use after stratifying on time since last use. Also, risk did not increase

significantly with increasing duration of use before age 25, RR = 1.49, before a first live birth, RR = 1.24 (95% CI = 0.78, 1.79). No single source of bias or confounding was identified that could explain the small increase in risk that was observed. This result could be due to a combination of chance and potential sources of bias, or they could represent a weak causal relationship.

Thomas et al. (59) conducted a study among 2,754 cases and 18,565 controls from a multinational hospital based case control. The data were analyzed to determine whether there was an association between combined oral contraceptives with varying types and doses of estrogens and progestin. After stratifying on duration of use, risk was found to be increased in current and recent users and to decline with time since last use. Relative risk in women who used mestranol and ethanol estradiol containing formulations before age 25 were estimated, respectively, to be 1.05 (0.82, 1.34) and 1.10 (0.88, 1.36) for ever users, and 1.78 (1.0, 319) and 1.81 (1.15, 2.84) for women who used these products three years before age 25. However, estimates were based on small numbers of users and had wide confidence limits. Oral contraceptives were grouped in to those that contain progestin that were 17-alpha hydroxyl progesterone derivative (medroxy progesterone acetate and chlormadinone) and those that were 19-nor-testosterone derivatives (all others except megesterol). Relative risks in women who ever used these two classes of formulations were estimated to be RR = 1.16 (95% CI = 1.05, 1.29)) and RR = 1.17 (95% CI = 1.05, 1.30), respectively. Oral contraceptives with more than 0.08 mg. mestranol or more than 0.04 mg. ethanol estradiol were grouped together as high dose products, and those with lower levels were considered low dose products. Relative risks of breast cancer in women who ever used only low dose products were estimated to be RR = 1.10 (95% CI = 0.94, 1.29), 1.17 (95% CI = 1.03, 1.34), and 1.21 (95% CI = 0.99, 1.43), respectively. The relative risk in relation to duration of use and months since last use were not consistently higher in women who used only the high dose preparations than in woman who used only low products.

Wingo et al. (60) studied age-specific differences in the relationship between oral contraceptive use and breast cancer, a population based case-control study in eight geographic areas in the United States during 1988-1990. The subjects were women aged 20-54 years. Among women aged 20-34 years at diagnosis or

interview, those who had ever used OCs had a slightly increased a risk of breast cancer (OR = 1.4, 95% CI = 1.0-2.1) when compared with women of the same ages who had never used OC. Among women aged 35-44 years, there was no association between OC use and breast cancer (RR = 1.1, 95% CI = 0.9-1.3). Among women 45-54 years, those who used OC had a slightly decreased risk of breast cancer (RR = 0.9, 95% CI = 0.8-1.0). Among those women, the risk estimated decreased significantly with increasing time since first and last use. The hypothetical annual agespecific breast cancer incidence rates in American women aged 20-50 years, showed that for those aged 20-34 with history of no OC use was equal to annual incidence of 11.9, RR = 1.4 (95% CI = 1.0-2.1) and the rate difference per 100,000 women between history of with out and with OC use was 3.4. In the same way, for those aged 35-44 with no OC use, the incidence was 74.8 and for those who use the incidence = 82.2, RR = 1.1 (95% CI = 0.9-1.3).

Romieu et al. (61) conducted a study among 118,273 female nurses 30-35 years of age with no history of cancer who were asked to complete a questionnaire regarding possible risk factors in 1980. By 1986 after a follow-up, they had documented 1,799 newly diagnosed cases of breast cancer. Compared with the risk of breast cancer for non-users of oral contraceptives, the multivariate relative risks were 1.07 (95% CI = 0.97, 1.19) for all users, 1.06 (95% CI = 0.96, 1.18) for past users and 1.53 (95% CI = 1.06, 2.19) for current users. They concluded that overall past use of oral contraceptives is not associated with a substantial increase in the risk of breast cancer.

Miller et al. (62) studied a relationship between the risk of breast cancer before 45 years of age and oral contraceptives use in a case-control study in four centers from 1985 to 1988 of 407 patients with breast cancer and 484 control. With allowance for confounding, for ever use, the multivariate relative risk estimate was 2.0 (95% CI = 1.14, 2.9), for < 10 years of use, the estimate approximated 2.0 in all categories duration, including < 3 months, for ≥10 years of use it was 4.1 (95% CI = 1.8, 9.3). The results suggested that oral contraceptive users, particularly those with very long duration of use, may be at increased risk of breast cancer.

Studies of younger women have been conducted to evaluate the risk of breast cancer associated with long-term use of OCs. To assess this relation

adequately, women participating in case-control or cohort studies must have had access to OCs during the early years of their reproductive lives. Because oral contraceptive first became available during the 1960s, only studies completed during the 1980s or later, which evaluated risk for young women (under age 45 years) would have been adequate to assess risk associated with long-term use. The results of hospital-based case-control studies are not considered here because the magnitude of potential bias in such studies is large in relation to the size of the fairly modest OCs breast cancer association. Eight populations based studies conducted in 1980s that evaluated total OC use and breast cancer among women younger than age 45 years at diagnosis are summarized. All eight studies show an increased breast cancer among OC users. Although the results of the study by Kay (63) do not permit the calculation of percentage of change per year of OCs, a comparison of OCs with that show a statistically significant 3.1% increase in breast cancer. Based on this analysis, young women who had taken OCs for ten years had a higher risk 9.36% (RR = 1.36). The case-control studies which considered breast and it's associated with OC use before first birth found a positive association (59, 61); three were statistically significant. The duration effects of these studies are statistically consistent. Combined analysis of these studies shows that on average, breast cancer increased 3.8% per year among OC use before first birth. This translates into an RR of 1.45 for women who take OC use for ten years when compared with women with no such OC use.

UK(64) national case-control group study about breast cancer about the risk factor for breast cancer in England during 1982-1985 of 755 patients under age 36 years old from South Thames regions, and 755 control found that (1:1) women who had no use of oral contraceptives pill had a RR =1.0.

2.3 The Other Risk Factors Of Breast Cancer

Harris et al. (65) reviewed articles about breast cancer regarding suggested risk factors of breast cancer. The relations of a risk factor to the disease, however, can be complex for a number of reasons. Many risk factors are measured as continuous variables. The established risk factors for breast cancer include a family history of breast cancer, early menarche, late age at first child birth, late age at

menopause, history of benign breast disease, and exposure to ionizing radiation which are generally associated with only weak or moderate elevation in risk. A family history of breast cancer, particularly when the diagnosis was made in the mother or a sister at a young age, could be an important risk factor for breast cancer. As compared with the risk among women having no first relative with breast cancer, overall the relative risk (RR) was on the order of 1.4 to 2 for women who had one first degree relatives with breast cancer, and might be as high as six for those with two affected first degree relatives.

WHO (66) carried out a collaborative study of Neoplasia and Steroid contraceptives about breast cancer and combined oral contraceptives. In addition, the results from a multinational study explained the relative risks of breast cancer in relation to various previously recognized risk factors. As expected, the risk of breast cancer was increased in women with history of a biopsy for benign breast disease (RR = 1.84, 95% CI = 1.51-2.24). Risk also increased with the age at which a women first gave birth to a live child (RR = 2.71, 95% CI = 2.21, 3.32). Women who had never been pregnant (RR = 2.23, 95%CI = 1.85, 2.69), and women who had previously been pregnant but had not delivered a living child (RR = 2.31, 95% CI = 1.64-3.25) were also at increased risk relative to women with a first birth at a young age (RR = 1.55, 95% CI = 1.35-1.79). The relative risk of breast cancer decreased with increasing number of live births (RR = 0.29, 95% CI = 10.20-0.41). Single women were at greater risk than women who had ever been married RR was 1.00.Women whose mother of grandmother (maternal or paternal) had breast cancer were also at increased risk (RR = 3.11, 95% CI = 2.38 – 4.06). Risk was reduced in women with an early menopause (RR = 0.58, 95% CI = 0.48-0.70).

Pike et al. (67) found that oral contraceptives use and early abortion are risk factors for breast cancer in young women in Los Angeles Country, California, with 165 very young breasts cancer cases all aged 32 or less at diagnosis. The study investigated the rate, if any, of oral contraceptives in the development of disease. OC use before first full term pregnancy (FFTP) was associated with increased risk which increased with duration of OC use (RR = 2.2 at six years of age, p-value = 0.01). This increased risk could not be explained by other risk factors. OC use after FFTP was not associated with any change in risk. A first trimester abortion before FFTP,

whether spontaneous or induced, was associated with a 2.4 total increase in breast cancer risk (p-value < 0.005).

Tao (68) conducted a case control study about the risk factors for breast cancer of Chinese women in Beijing with a self administered questionnaire filled by 497 subjects with histologically proved breast cancer with an equal number of age and neighborhood matched control. It was discovered that nulliparity and late age at first birth were associated with an elevated risk of breast cancer. In comparison to parous women who had their first child before age 20, those who delayed this event until after age 29 had RR of 1.65 (95% CI = 0.88, 3.08). The comparable RR for nulliparous women was 3.72 (95% CI = 1.67, 8.31).

Helmrich et al. (69) studied about risk factors for breast cancer. Since 1990, data had been collected to evaluate the risk factors for breast cancer in a hospital based case control study of 1,185 women with breast cancer and 3,227 controls. The risk of breast cancer increased with increasing age at first birth (30^{+} years; RR = 2.8, 95% CI = 1.8, 4.2). An early age at first birth appeared to reduce the risk relative to no pregnancy (< 20 years, RR = 0.6, 95% CI = 0.5, 0.8). High parity was also associated with a reduction in the risk that was independent of that of age at first birth: for parity ≥5, compared with parity 1-2, the relative risk estimate was 0.7 (95% CI = 0.5, 1.0).

Williams (70) carried out an epidemiological study of risk factor of breast cancer, including age at menarche and menopause. Women who had started menstruating early in life (< 12 years of age, RR = 1.8) had an increased risk of developing breast cancer. Women whose menopause occurred before the age of 45 years (RR = 1.00) had a breast cancer risk one half that of those menstruating until 55 years of age (RR = 1.47). There is an inverse relationship between parity and breast cancer risk. The protective effect of increased parity is entirely consequent upon early age at first birth (< 20 years, RR = 0.50; 20-24 years, RR = 0.60; 25-29 years RR = 0.78) 30-34 years (RR = 0.94), and age > 34 years (RR = 1.22). Family risks of breast cancer, as indicated in the cancer

Townsend (71) point out that when taking into account the menstrual history, the physician should note the age of menarche and menopause, since both early menarche and late menopause have been associated with increased risk of

cancer. However surgical menopause before age 35 appears to reduce subsequent risk of breast cancer.

Najarian et al. (72) point out that parity was once thought to related to a decreased risk being related to the number of child born. More sophisticate analyses have shown that this projective effect is related solely to age at first pregnancy. Group of child less women have a higher breast cancer rate than women with children. For pregnancy to be protective, however the first pregnancy must occur before age thirty. First pregnancy after age thirty actually increases the risk over in nulliparous.

Henderson et al. (73) conducted a study of overall mortality among users and nonusers of postmenopausal hormone replacement showed a statically significant increase in mortality from all causes ($RR = 0.8$, $p < 0.05$)

Kokurishio et al. (74) conducted case – control study of about 1,700 women in Japan, of 355 patients with BSE-detected breast cancer, and 1,327 patients with breast cancer detected by BSE incidentally; the BSE-detected cancer were significant with breast cancer.

Hutchinson et al. (75) studied about risk factors for breast cancer and since 1986, data had been collected to evaluate the risk factors for breast cancer of benign breast disease has been shown to confer a two- to threefold increase in risk for the subsequent occurrence of breast cancer conducted at Rosewell Park Memorial as having benign breast disease during the 1978 to 1986.Follow up of this group and of a matched control population through mailed questionnaires, tumor registry reports, and death certificates, showed the age adjusted incidence of breast cancer was three times higher in the benign breast disease group than in the control group.

Furnival (1998) conducted a study to examine the relationship between age and breast cancer, according to age increase two times over each ten years period until menopause. After menopause stabilizes or slight increase older than 60 years it’s risk of breast cancer (76).

CHAPTER III
MATERIALS AND METHODS

3.1 Research Design

The study was a hospital based matched case-control, comparison of 250 cases and 375 controls.

3.2 Study Population

The study took place at Siriraj Hospital, Ramathibodi Hospital, and Rajvithi Hospital, data were collected between 1 July and 31 December 2000 by means of interview questionnaires.

3.3 Sample Method

The populations were divided onto two groups:

3.3.1 Case group.

The population was Thai females who were diagnosis with breast cancer. The study group consisted of 250 of female breast cancer patients who were registered at Siriraj Hospital, Ramathibodi Hospital, and Rajvithi Hospital. These patients' breast cancer patient was histologically confirmed from the following units:

1. Tumor Clinics
2. Surgery Wards
3. The Radiation Therapy Clinic
4. The Breast Clinic that conducted followed- up after the completion of chemotherapy or admission.

3.3.2 Control group

The controls consisted of 375 cases selected from those who were admitted to surgery wards, medicine wards, and out- patient department in Siriraj Hospital, Ramathibodi Hospital, and Rajvithi Hospital during the same period when the cases

were selected. The patients in the control group had neither positive history of cancer nor any evidence of breast cancer in the study period.

3.4 SMPLE SIZE ESTIMATE

AS for the sample size in an unmatched case-control study, the exposure of interest were oral contraceptive use and expected proportion of oral contraceptive in women, when was 59%. The sample was calculated by the following formula (77).

$$n = \frac{[Z_\alpha \sqrt{2\bar{p}\bar{q}} + Z_\beta \sqrt{p_1 q_1 + p_0 q_0}]^2}{(p_1 - p_0)^2}$$

$p_1 = p_0 \,.\, R/\ [1 + p_0 (R-1)] = 0.59$

p_0 = Estimated use of OC among control = 0.42

$\bar{p} = \frac{1}{2}(p_1 + p_0) = 0.51$

$\bar{q} = 1 - \bar{p} = 0.49$

$q_1 = 1 - p_1 = 0.41$

$q_0 = 1 - p_0 = 0.58$

R = Hypothesis and fixed of risk relation of breast cancer among the OC used = 2.00

Z_α = 1.96(2 – tailed)

Z_β = 1.28

$$n = \left[\frac{1.96\sqrt{2(0.51)(0.49)} + 1.28\sqrt{(0.59)(0.41) + (0.42)(0.58)}}{(0.59 - 0.42)^2}\right]^2$$

The required study sample size = 179.48 = 180

The ratio of case to control was 1.5

Thus, the required number of cases was 250, and study period was 375 controls were included.

3.5 Collection Of Data

The research instrument was a set of interview questionnaires, which were constructed from the advisor of advisor. Before data collection took place, the subjects were approached participation in the study.The researcher explain the maim

objectives of study which was to determine some associations of environmental factor that may be the ethnology of the disease in human being and assured that the matter information obtained from them used be kept confidential. . (The questionnaire is shown in Appendix)

The qquestionnaire consisted of the following six parts:

Part 1 Information on the sociodemographics characteristics including age, ethnicity, religion, place of birth, place of residence, current marital status, occupation, educational level, subjects' income.

Part 2 Information on health behavior concerning smoking, alcohol drinking, and breast self-examination menstruation.

Part 3 Information on menstrual history such as age at first menstruation and menopause.

Past 4 Information on use of oral contraceptive including age when used first oral contraceptive .

Part 5 Information on marrital status and fertility history age at first pregnancy, total umber of pregnancy.

Part 6 Information on family history such as history of breast cancer in the family, and benign breast disease.

3.6 DEFINITION OF TERMS

1. Breast cancer patients mean Thai female with histologically confirmed breast cancer.
2. Control subjects mean Thai females who came for examination but were not diagnosed with breast cancer other types of cancer.
3. Oral contraceptives mean the combined estrogen and progesterone hormones synthesis taken to prevent conception.
4. Breast cancer arises from the breast tissue and has the characteristics of malignant tumors .It is histologically proved as carcinoma, duct carcinoma, medullar carcinoma, paget's disease of the nipple, and lipomatous carcinoma.
5. Soico-demographic characteristic refer to social characteristics and general characteristics of individuals such as gender, age, occupation, income, educational level, and marital status.

6. Place of residence means residential area in which the study cases and control groups lived for over 5 years by the time the study was conducted.
7. Mass history of breast means physicians diagnosis of having mass of breast which was breast cancer.
8. Age at menarche means the age when menstruation first start.
9. Early menarche means menstruation cycle staring before the age of 12 years.

3.7 Data Analysis

3.7.1 Statistics used in data analysis

3.7.1.1 Descriptive statistics

Descriptive statistics were presented by means of frequency, percentage, mean, and standard deviation following demographic characteristics, of cases and controls

3.7.1.2 Analytic statistics

3.7.1.2.1 Sample characteristics

The comparison of the characteristics of cases and controls was conducted with the Chi -Square test, the Fisher Exact test, and t-test.

3.7.1.2.2 The comparison of mean dosage of antipsychotic drugs

The differences of the mean of between case and control groups were tested by unpaired t-test. The analysis with unpaired t-test was applied because the sample was considered to be continued data and independent samples.

3.7.1.2.3 The association between oral contraceptive use and breast cancer

The analysis of association between oral contraceptive use and breast cancer was conducted by means of multiple logistic regression analysis. Logistic regression analysis was performed to simultaneously control the confounders, the strength of these association are evaluated, and to assess possible interaction by using the following equation:

$$\text{Logic (breast cancer)} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots\ldots\ldots + \beta_k x_k$$

Where β_0 = baseline logistic regression coefficient

β_1 ,β_2 + …+ β_k = logistic regression coefficient of each corresponding regression variable

x_1 , x_2 + ……+ x_k = set of values for regression variables

k = number of logistic regression variables

To assess interaction, a cross-product term, such as xx = x1*x2, was added into the equation.

The dose-response analysis was applied by the equation of logistic regression when other variables were controlled :

odds ratio = $e^{\beta k Xi}$, 95 % confidence interval = OR[$e^{\pm 1.96(S.E)}$]

e = exponential transformation

β_k = logistic regression coefficient of each corresponding regression variable

xi = dosage of logistic regression variables

S.E = standard error of each corresponding logistic regression variable

CHAPTER IV
RESULTS

4.1 Sample Charateristics

4.1.1 Demographic characteristics

Data collection was conducted between July and December 2000. The sample of this study included 250 cases of women with histologically proved diagnosis of carcinoma of breast cancer and 375 cases female patients admitted during the same period with other diseases except malignant disease as the control.

This investigation included 250 cases admitted in three leading hospitals in Bangkok and 375 controls who were also registered at Siriraj, Ramathibodi, and Rachavithi Hospitals. There were 100 patients (40.0%) from Siriraj Hospital, 80 patients (32.0%) from Ramathibodi Hospital, and 70 patients (28.0%) from Rachavithi Hospital.

The control group consisted of female patients with no breast cancer from the same hospitals during the same period as the cases. There were 150 subjects (40.0%) from Siriraj Hospital, 120 subjects (32.0%) from Ramathibodi Hospital, and 105 subjects (28.0%) from Rachavithi Hospital.

The proportion and the dependent variable and independent variable of study cases and controls collected from each hospital is shown in Table 7 to 12.

Table 7 Association between breast cancer and information used oral contraceptive

Characteristics	Case group (%)	Control group (%)	p -value	OR (95% CI)
Used of oral contraceptives				
Yes	109 (43.6)	122 (32.5)	6.46×10^{-3}	1.60 (1.14-2.26)
No	141 (56.4)	253 (67.5)		1.00
χ^2test = 7.4167	df = 1			
Duration of used oral contraceptives (years)				
> 3	39 (35.8)	26 (21.3)	2.18×10^{-2}	2.06(1.10-3.85)
≤ 3	70 (64.2)	96 (78.7)		1.00
Mean	3.40	4.39		
Standard deviation	1.47	1.96		
χ^2 test = 5.2655	df = 1			
t test = 4.2624	df = 229		2.96×10^{-5}	

Used of oral contraceptives

The result of this study showed that 43.6% of the subject in the case group and 32.5% in the control group used oral oral contraceptive, while 56.4% in the case group and 67.5% in the control group.

When every group of those who used oral contraceptives pills were compared to the group of non-users of oral contraceptives as the base-line, the result of analysis showed that there was a relationship between use of oral contraceptives and breast cancer (OR = 1.60, 95% CI = 1.14-2.26, p- value = 6.46×10^{-3}).

Duration of use of oral contraceptives

The study revealed that 35.8% of the subject on the case group and 21.3% in the control group used oral contraceptives for more than 3 years, while 64.2% the case group and 78.7% in the control group used oral contraceptives for less than 3 years. The mean duration of oral contraceptive use in the case group was 3.40 years in the control group was 4.39 years.

The comparison of the mean duration of use of oral contraceptives between the subjects in the two groups revealed that there was a statistically significant difference in mean duration of use of oral contraceptives of the subjects the two groups (p- value $= 2.96 \times 10^{-5}$). The risk of breast cancer in those who used oral contraceptive more than three years was 0.65 times greater than that of the group with less than three years of use. It was discovered that there was no statistically significant association between the duration of use of oral contraceptives and breast cancer in both groups (OR = 2.16, 95% CI = 1.15- 4.07, p- value $= 1.45 \times 10^{-2}$).

Table 8 Association between breast cancer and socio-demographic characteristics

Characteristics	Case group (%)		Control group (%)		p -value	OR (95% CI)
Age group (years)						
≤ 30	6	(2.4)	71	(18.9)	1.00*	
30-40	41	(16.4)	105	(28.0)	7.81×10^{-4}	4.62 (1.76-12.82)
41-50	112	(44.8)	137	(36.5)	< 0.001	9.67 (3.87-25.71)
51-60	91	(36.4)	62	(16.5)	< 0.001	17.37 (6.73-47.46)
Total	250	(100.0)	375	(100.0)		
Mean	47.20		40.09			
Standard deviation	7.75		9.64			
χ^2 test = 68.6789	df = 3					
t test = 8.6438	df = 623				< 0.001	
* Base line for computation of odd ratio						
Place of birth						
Bangkok	103	(41.2)	101	(26.9)	2.14×10^{-3}	2.91 (1.43-6.01)
Central (except Bangkok)	94	(37.6)	140	(37.3)	0.0730	1.92(0.95-3.93)
North	11	(4.4)	32	(8.5)	0.8452	0.98(0.36-2.70)
Northeast	27	(10.8)	62	(16.5)	0.7078	1.24 (0.55-2.85)
South	14	(5.6)	40	(10.7)		1.00*
χ^2 test = 20.2561	df = 4					
Place of residence						
Bangkok	108	(43.2)	189	(50.4)	0.9946	1.06(0.51-2.24)
Central (except Bangkok)	96	(38.4)	127	(33.9)	0.4376	1.40(0.66-3.00)
North	9	(3.6)	12	(3.2)	0.7462	1.39(0.41-4.71)
Northeast	23	(9.2)	21	(5.6)	0.1699	2.03(0.77-5.40)
South	14	(5.6)	26	(6.9)		1.00*
χ^2 test = 5.7498	df = 4					

Table 8 Association between breast cancer and socio-demographic characteristics (cont.)

Characteristics	Case group (%)		Control group (%)		p- value	OR (95% CI)
Ethnicity						
Thai	247	(98.8)	369	(98.4)	0.4822**	1.34(0.30-6.81)
Others	3	(1.2)	6	(1.6)		1.00
χ^2 test = 0.0047	df = 1					
Religion						
Buddhism	246	(98.4)	354	(94.4)	$2.19x10^{-2}$	3.65(1.17-12.71)
Others	4	(1.6)	21	(5.6)		1.00
χ^2 test = 5.2517	df = 1					
Current marital status						
Separate/Divorced	155	(62.0)	175	(46.7)	$2.33x10^{-4}$	1.86(1.33-2.62)
Married	95	(38.0)	200	(53.3)		1.00
χ^2 test = 13.5425	df = 1					
Educational level						
No formal education	6	(2.4)	18	(4.8)		1.00*
Primary school	156	(62.4)	290	(77.3)	0.4355	1.61(0.59-4.65)
> Primary school	88	(35.2)	67	(17.9)	$7.34x10^{-3}$	3.94(1.38-11.81)
χ^2 test = 25.1096	df = 2					
Occupation						
None	53	(21.2)	89	(23.7)		1.00*
Government official	99	(39.6)	75	(20.0)	$8.06x10^{-4}$	2.22(1.37-3.58)
Agriculturist	60	(24.0)	105	(28.0)	0.9559	0.96(0.59-1.57)
Wife house	38	(15.2)	106	(28.3)	0.0631	0.60(0.35-1.03)
χ^2 test = 33.1468	df = 3					
Subjects' income (baths / month)						
None	89	(35.6)	90	(24.0)	0.1471	1.43(0.89-2.30)
≤ 5,000	105	(42.0)	204	(54.4)	0.1964	0.74(0.48-1.15)
> 5,000	56	(22.4)	81	(21.6)		1.00*
Mean	4,392.43	4,103.88				
Standard deviation	5077.17	5022.01				
χ^2 test = 11.7563	df = 2					
t test = 0.7006	df = 623				0.4838	

** Fisher's Exact test 2 tailed

Age group

The subjects with breast cancer ranged in age from 17-60 years olds. The largest group of them 44.8%, were in the age group of 41-50 years old. Only six (2.4%) were younger ≤ 30 years old for the control group, 36.5% were 41-50 years old and 16.5% the mean age of the subject in the case group was 47.20 years, and that of the subjects in the control group was 40.90 years.

A comparison with the ≤ 30 years group as baseline with those who were in the 30-40 years old group showed a 4.62 times chance in developing breast cancer (p-value = 7.81×10^{-4}). There was a relationship between age and breast cancer in this group (95% CI = 1.76-12.82). When compared with baseline, those who were between 41and 50 years had 9.67 times higher chance of developing breast cancer than the ≤ 30 years of age group (95% CI = 3.87-25.71). There was a relationship between age and breast cancer in the 41-50 years and group (p- value < 0.001). When compared with baseline, those who were between 51 and 60 years old had 17.37 times greater chance of developing breast cancer than the ≤ 30 years of age group (95% CI = 6.73 - 47.46). There was a relationship between age and breast cancer in the 51-60 year group (p-value < 0.001). A comparison of the mean age among the subjects in the four groups revealed that there was a statistically significant difference in the mean ages of the subjects of the four groups (p- value < 0.001).

Place of birth

It was found that 41.2% of the case group lived in Bangkok (103cases), while the largest group of the controls (37.3%) lived in the central area (140 cases).

The comparison with the south group as baseline with those who were living in Bangkok showed 2.72 times greater chance of developing breast cancer (95% CI = 1.43-6.01). There was a relationship between place of birth and breast cancer in this group (p- value = 2.14×10^{-3}). When compared different groups of residence (Central, North and Northeast) with baseline, it was discovered that there was no relationship between the three variable (OR = 1.92, 0.98, 1.24), 95% CI = 0.95-3.93, 0.36-2.70, 0.55-2.85 and p- value = 0.0730, 0.8453. 0.7078).

Place of residence

It was found that the largest group of the cases (108 cases or 43.2%) lived in Bangkok, while haft (50.4%) of the controls lived in Bangkok.

When the relationship between place of residence and breast cancer, it was discovered that there was no relationship between the five variables in five groups (OR = 1.06, 95% CI = 0.51-2.12, 1.40, 95% CI = 0.66 - 3.00, 1.39, 95% CI = 0.41-4.71, 2.03, 95% CI = 0.87-5.40) and (p -value = 0.9946, 0.4376, 0.7462, 0.1699).

Ethnicity

Almost all of the cases (247cases or 98.8%) were Thai.Only 3 cases (1.2%) were not Thai. The majority of the controls (98.4%) were also Thai; while six subjects ((1.6%) were not.

Ethnicity subjects .It found that there was no statistically significant association between ethnicity of the subjects breast cancer in both groups (OR = 1.34, 95% CI = 0.30-6.81, p- value = 0.4822).

Religion

Was found that 249 cases (98.4%) from the case group and 354 cases (94.4%) from the control group were Buddhists.

Most of the subjects in both groups were Buddhists. The result of this study showed that there was a relationship between religion and breast cancer in both groups. The chance of developing breast cancer was 3.65 times greater in Thai than in others (OR = 3.65, 95% CI = 1.17-12.71, p -value = 2.19×10^{-2}).

Current marital status

The result showed that 95 cases (38.0%) from the case group were married, while 200 cases (53.3%) of the control group were separated or single.

There was a statistically significant association between marital status of the subjects and breast cancer in both groups (OR = 1.86, 95% CI = 1.33- 2.62, p- value = 2.33×10^{-3}).

Educational level

The majority (62.4%) of the case group and 77.3% of the control group graduated from a primary school.

The result showed that the subjects who were illiterate had higher chance of getting breast cancer 0.25 times getting breast cancer when compared to those who had higher than primary education. of respondents who has more than primary school (OR = 3.94, 95% CI = 1.3811.81, p- value = 7.34×10^{-3}). The subjects who had more than primary education had 1.61 times higher risk than those who graduated from a primary school, (OR = 1.61, 95% CI = 0.59-4.65, p -value = 0.4355).

Occupation

More than one-third (39.6%) of the subjects in the government officials, where as more than one-fourth (28.3%) of the wife's. house.

Every group of occupation was compared with those who had no occupation as the baseline. The result indicated that there was a statistically significant association between being government official and breast cancer in three groups (OR = 2.22, 95% CI = 1.37-3.58, p - value = 8.04×10^{-4}).

Subjects' income

About 42 % of the subjects in the case group earned less than 5,000 baht per month, while more than half of the control group (54.4%) earned was less than 5,000 baht per month.

The comparison of every group of subjects' income with the group of subjects who had income more than 5000 baht per month as the baseline, showed no relationship between income and breast cancer (OR = 1.43, 95% CI = 0.89-2.30, p- value = 0.1471, OR = 0.74, 95% CI = 0.48-1.15, p value = 0.1964). The comparison of the mean of subjects income showed that there was no statistically significant difference in the mean between the case and control groups (p- value = 0.4838).

Table 9 Association between breast cancer and health behavior

Characteristics	Case group (%)	Control group (%)	p- value	OR (95% CI)
Smoking				
Yes	12 (4.8)	36 (9.6)	3.99×10^{-2}	0.47 (0.23-0.97)
No	238 (95.2)	339 (90.4)		1.00
χ^2 test = 4.8744	df = 1			
Alcohol drinking				
Yes	121 (48.4)	153 (40.8)	7.29×10^{-2}	1.36 (0.97-1.90)
No	129 (51.63)	222 (59.2)		1.00
χ^2 test = 3.2171	df = 1			
Lack of knowledge on breast self - examination and check breast				
Yes	167 (66.8)	197 (52.5)	5.40×10^{-4}	1.82 (1.29-2.57)
No	83 (33.2)	178 (47.5)		1.00
χ^2 test = 11.9735	df = 1			

Smoking

In the case groups 4.8% smoked, while 9.6% of the control group did. More than half of the subjects did not smoke. From the identification of the relationship between smoking and breast cancer, it was discovered that there was no relationship between the two variables, in both groups (OR = 0.82, 95% CI = 0.44-1.50, p - value = 0.5870).

Alcohol drinking

Table 8 shows that close to haft (48.4%) of the case group drank alcohol while 40.8% of the control group did.

The result of this study revealed that there was a statistically significant association between alcohol drinking and the related of breast cancer in both groups (OR = 1.36, 95% CI = 0.97-1.90, p - value = 7.29×10^{-2}).

Lack of knowledge on breast self – examination

About 37.2% of the subjects in the case group of knowledge on breast self and 47.5% in the control group had knowledge on breast self – examination.

More than half of the subjects did not have knowledge on breast self-examination. When identifying an association between the two variables, it was found that there was a statistically association between knowledge on breast self - examination breast cancer in both groups (OR = 1.82, 95% CI = 1.29-2.51, p- value = 5.40×10^{-4}).

Table 10 Association between breast cancer and information on menstruation

Characteristics	Case group (%)	Control group (%)	p- value	OR (95% CI)
Early menarche (years)				
≤ 12	124 (49.6)	79 (21.1)	< 0.001	3.69 (2.56-5.32)
> 12	126 (50.4)	296 (38.9)		1.00
Mean	13.64	14.59		
Standard deviation	2.25	1.60		
χ^2 test = 54.3928	df = 1			
t test = 6.1764	df = 623		(1.18×10^{-9})	
History of irregular menstruation				
Yes	22 (8.8)	37 (9.9)	0.7587	0.88 (0.49-1.58)
No	228 (91.2)	338 (90.1)		1.00
χ^2 test = 0.0944	df = 1			
Menopause				
Yes	98 (39.2)	89 (23.7)	5.17×10^{-5}	2.07 (1.44-2.98)
No	152 (60.8)	286 (76.3)		1.00
χ^2 test = 16.3834	df = 1			
Hormone treatment after menopause				
Yes	7 (2.8)	19 (5.1)	0.2357	0.54 (0.20-1.38)
No	243 (97.2)	356 (94.9)		1.00
χ^2 test = 1.4063	df = 1			

Early menarche

About half, or 49.6% ; of the subjects in the case group had the first menstruation when they were younger was than 13 years old, and 21.1% in the

control group did. The mean age at first menstruation of the subjects in the case group was 13.64 years and in the control group was 14.59 years.

The comparison of the age at fist menstruation indicated that there was a statistically significant difference in the mean of the age at first-menstruation between the two groups (p value $= 1.18 \times 10^{-9}$). From the association between the interval of age at first menstruation and the relation to breast cancer, it was discovered that there was a statistically significant association between the two variables (OR = 3.69, 95% CI = 2.56-5.32, p -value < 0.001).

History of irregular menstruation

There was 8.6% of the subjects in the case group and 9.9% in the control group, who had history of irregular menstruation cycle.

When compared the groups of women who had history of regular menstruation cycle as the baseline with those who had history of irregular menstruation cycle, the result suggested that there was no relationship between history of irregular menstruation and breast cancer (OR = 0.88, 95% CI = 0.49-1.58, p - value = 0.7587).

Menopause

Of the total, 39.2% in the case group and 23.7% in the control group were menopause.

More than half of the subjects did not have menopause. When compared those who had menopause and those who had menstruation, the result showed a statistically significant association between the two variable (OR = 2.07, 95% CI = 1.44-2.98, p- value $= 5.17 \times 10^{-5}$).

Hormone treatment after menopause

Only a few subjects used hormone after menopause 2.8% in the case group and 5.1% in the control group.

When identifying the association between the two variables, it was found that there was no statistically significant association between used hormone after

menopause and breast cancer in both groups (OR = 0.54, 95% CI = 0.20-1.38, p - value = 0.2357).

Table 11 Association between breast cancer and information fertility history

Characteristics	Case group (%)	Control group (%)	p- value	OR (95% CI)
Age when first married (years)				
> 25	184 (73.6)	194 (51.7)	1.00×10^{-7}	2.60 (1.81-3.74)
≤ 25	66 (26.4)	181 (48.3)		1.00
Mean	25.02	22.17		
Standard deviation	5.33	4.03		
χ^2 test = 29.0995	df = 1			
t test = 7.6878	df = 623		< 0.001	
Age at first pregnancy				
> 25	194 (77.6)	261 (69.6)	3.49×10^{-2}	1.51 (1.03-2.23)
≤ 25	56 (22.4)	114 (30.4)		1.00
Mean	24.15	22.58		
Standard deviation	9.23	6.33		
χ^2 test = 0.9835	df = 1			
t test = 2.5236	df = 123		1.19×10^{-2}	
Total number of children				
None	38 (15.2)	25 (6.7)	4.77×10^{-4}	2.76(1.52-5.01)
≤ 2	110 (44.0)	165 (44.0)	0.3157	1.21 (0.85-1.73)
> 2	102 (40.8)	185 (49.3)		1.00*
Mean	2.33	2.35		
Standard deviation	1.42	1.46		
χ^2 test = 13.2146	df = 1			
t test = 0.1699	df = 623		0.0014	

* Base line for computation of odd ratio

Age when first married

The majority of the case group, 73.6% and, half a 51.7% of the control group got married when they were older than 25years old in the case group and, the majority of age when first married in the case group 26.4% of the 48.3 % in the control group got married when younger than 25 years of age. The mean age at first married of the case group was 25.05 years and of the control group was 22.17 years.

A comparison of the mean of age when first married between the case and control groups showed that there was statistically significant difference in the average age when first married and breast cancer between the two groups (p - value < 0.001). It was discovered that there was a relationship between age more than twenty-five years and breast cancer and age less than twenty-fire years and breast cancer and groups (OR = 2.60, 95% CI = 1.81-3.74, p - value $= 1.00 \times 10^{-7}$).

Age at first pregnancy

The majority of in the case group 77.6%, and the control group,69.6% became pregnant for the first time when they were older than 25 years . The majority of age at first pregnancy in case while 22.4% of the case group 30.4% of the control group became pregnant when they were younger than 25 year. The mean age at first pregnancy in the case group was 24.15 years and in the control group was22.58 years.

The comparison of the mean age at first pregnancy between the case and control groups showed that there was a statistically significant difference in the average age at first pregnancy and breast cancer between the two groups (p- value 1.19×10^{-2}). When compared between the groups of women who when younger than 25 years when first become pregnant as the baseline with the women who were older than 25 years, the result showed that there was a relationship between age of first pregnancy and breast cancer (OR = 1.51, 95% CI = 1.03-2.23, p- value $= 3.49 \times 10^{-2}$).

Total number of children

AS for the total number of children, both the in case and control groups 44% had fewer than 2 two children. On the other had 40.8 of the case group and 49.3% in the control group had more than two children. Finally 15.2% and 6.7% in

case and control groups had no children. The mean of total number of children was 2.33 in the case group and 2.35 in the control group.

A comparison of the mean total number of children in the two groups revealed that there was no statistically significant difference in the total number of children of the subjects in the two groups (p- value = 0.0014). When compared between the groups of women who had more than two children as the baseline with the women who had no children, the result indicated that there was a relationship between the total number of children and breast cancer (OR = 2.76, 95% CI = 1.52-5.01, p - value = 4.77×10^{-4}). When compared between the groups of women who had children fewer than two, the result showed that there was a relationship between the total number of children and breast cancer (OR = 1.21, 95% CI = 0.85-1.73, p- value = 0.3157).

Table 12 Association between breast cancer and family history of breast cancer and mass history on breast

Characteristics	Case group (%)	Control group (%)	p- value	OR (95% CI)
Family history of breast cancer				
Yes	70 (28.0)	28 (7.5)	< 0.001	4.82 (2.93-7.96)
No	180 (72.0)	347 (92.5)		1.00
χ^2 test = 46.2932	df = 1			
History benign breast disease				
Yes	226 (90.4)	166 (44.3)	< 0.001	11.86 (7.27-19.08)
No	24 (9.6)	209 (58.7)		1.00
χ^2test = 134.5675	df = 1			

Family history of breast cancer

The positive family history of breast cancer was 28.0% in the case group and 7.5% in the control group, while the negative family history was 72.0% in the case group and 92.5% in the control group.

When comparing between the groups of subjects who had no family history of breast cancer as the baseline and the group of subjects who had family history of breast cancer, the result showed that there was a relationship between family history and breast cancer (OR = 4.82, 95% CI = 2.963-7.96, p -value < 0.001).

History benign breast disease

The positive mass history on breast was 90.4% in the case group and 44.3% in the control group, while the negative mass history was 9.6% in the case group and 55.7% in the control group.

The comparison between the group of subjects who had no mass history on breast as the baseline and the group of subjects who had mass history on breast, it was found that there was a relationship between mass history on breast and breast cancer (OR = 11.86, 95% CI = 7.27-19.48, p- value < 0.001).

4.2 The Multiple Logistic Regression Analysis

The significant variable after crude analysis were screened further for possible inclusion in the model that would best describe the odds of having breast cancer .The significant variable are the age, subjects' income, knowledge of breast cancer, early menarche, age at first married, family history of breast cancer and benign breast disease.

Although the oral contraceptive use was not statistically significant (OR=0.29, 95%CI = 0.035-2.206, P-value = 0.232) but this factor is the variable of interest so, it is the most important part for the discussion point of view.

Table 13 Association between use oral contraceptive and breast cancer by using multiple logistic regression analysis

Variable	Level	Exp(B)	95%CI	p-value
Use of OCs	No	1.00		
	Yes	0.2912	0.0384-2.2060	0.2324
Place of birth	South	1.00		
	Bangkok	9213.6749	0.0010-8.640	0.2651
	Central	2844.5564	0.0003-2.539	0.3301
	North	0.0709	0.0000-3.580	0.9243
	North East	488.3435	0.0001-3.934	0.4454
Place of residence	South	1.00		
	Bangkok	0.0001	0.0000-1.001	0.2563
	Central	0.0007	0.0000-6.441	0.3683
	North	9.9753	0.0000-5.813	0.9343
	North East	0.0099	0.0000-2.335	0.5701
Ethnicity	Others	1.00		
	Thai	0.6348	0.2153-18.7382	0.7931
Current marital status	Married	1.00		
	Separate/Divorced	0.6175	0.0102-37.3263	0.8178
Educational level	Illiterate	1.00		
	Primary school	6.0096	0.0001-3.0007	0.7458
	>Primary school	16.2054	0.0003-9.1666	0.6180
Occupation	None	1.00		
	Government office	1.0477	0.1608-6.8258	0.9612
	Agriculture	0.2464	0.4591-1.3224	0.1023
	Wife house	1.9238	0.2825-13.1022	0.5038
Subjects' income	None	38.8044	5.6022-268.7845	0.0002
	≤ 5,000 baths	2.2712	0.6537-7.8907	0.1967
	> 5,000 baths	1.00		
Smoking	No	1.00		
	Yes	0.2328	0.0165-3.2895	0.2957

Table 13 Association between use oral contraceptive and breast cancer by using multiple logistic regression analysis (cont.)

Variable	Level	Exp(B)	95%CI	p-value
Alcohol drinking	No Yes	1.00 3.3106	 0.9493-11.5460	 0.0606
Lack of knowledge on breast self-examination and check breast	Yes No	1.00 4.6744	 1.3057-16.7335	 0.0178
Early menarche	≤ 12 years > 12 years	4.4126 1.00	1.2712-15.3166	0.0194
History of irregular Menstruation	No Yes	1.00 0.4304	 0.0570-3.2493	 0.4137
Menopause	No Yes	1.00 1.1467	 0.0948-13.8720	 0.9143
Hormone treatment After menopause	No Yes	1.00 0.0695	 0.0044-1.0874	 0.0574
Duration of used oral contraceptive	≤ 3 years > 3 years	1.00 1.0095	 0.2499-4.07733	 0.9894
Age group(years)	≤ 30 30-40 41-50 51-60	1.00 6.6844 62.4801 27.7570	 0.7563-59.0802 6.1813-361.4982 2.3354-329.9057	 0.875 0.0045 0.0085
Age when first married	≤ 25 years > 25 years	1.00 9.4509	 1.3785-37.5529	 0.0014
Age first pregnancy	≤ 25 years > 25 years	1.00 0.5941	 0.0628-5.6246	 0.6498
Total number of children	> 2 ≤ 2 None	1.00 1.1602 0.7391	 0.0609-22.0924 0.2136-2.5576	 0.9213 0.6331
Family history of Breast cancer	No Yes	1.00 10.8393	 1.5346-76.5601	 0.0169
History benign breast disease	No Yes	1.00 68.0851	 14.1028-328.7000	 0.0000

Tale 13 shows the association between breast cancer and factors, by the method using multiple logistic regression analysis: it is shown that the group of highest relative for breast cancer is benign breast disease. Odd ratio for benign breast disease is 68.09

CHAPTER V
DISCUSSION

5.1 Methodological Critique Of The Study

5.1.1 Research design

This study was a hospital-based, matched case-control study. The remains one of the most concise descriptions of the basis procedures of this study design to date: " a case control study is an inquiry in which groups of individuals are selected in terms of whether they do (the cases) or do not (the controls) have the disease of which the etiology is to be studied, and the groups are then compared with respect to existing or past characteristics judged to be of possible relevance to the etiology of the disease." Recently, a case-control study is not only used to find outcomes of diseases but also to find another outcome of interests. The case-control design is advantageous for the study of rare condition, and it is a relatively rapid and inexpensive method of inquiry. Therefore, it is popularly employed. However, case-control studies are much more susceptible to various forms of bias, and there are many limitations because it is a retrospective study. For example, they cannot be used to compute rate of disease occurrence in the population at risk, but only the relative rate between the exposed and unexposed. The association between the exposed and outcome occurrence measured in the study may be different from the true magnitude. Case-control studies are usually restricted to a single outcome of interest, and are not efficient for studying rare exposure(78). The reason case-control study is selected to use in the present study. The outcome of interest(breast cancer). Nevertheless, attempts had been made to control factors that may have been systematic errors in this study.

A hospital-based study is often used in case-control studies when the source population is obtained from hospitals. Hospital-based case-control studies have several advantages. Typically, they are easier and quicker to conduct than population-based studies since cases and controls are efficiently identified. As a

consequence, they may be less expensive and more convenient. However, hospital-based studies are susceptible to distorted results. Cases and controls may not arise from a single, well-defined population in contrast to the population-based studies. This could happen, for example, if referral patterns to particular hospitals varied across different diagnoses. Moreover, controls in hospital-based case-control studies are in hospitals because they are ill, and that condition may be associated with events caused by the exposure of interest. If so, then the exposure histories of controls may differ from the source population and a case-control comparison may result(79).

5.1.2 Selection of the studied population

The study setting was not randomly selected. Rather, it was purposefully selected. Therefore, the results be breast cancer patients. Siriraj Hospital, Ramathibodi Hospital, and Rajvithi Hospital was selected because it was the biggest hospital in Thailand, and it has enough number of sample**.**

5.1.3 Statistical Approach

The main part of statistical analyses was to determine factors associated with breast cancer and oral contraceptive use The multi- logistic regression was used in this study. Three basic features of the logistic regression model are: the appropriateness of binary outcome variables, estimation of adjusted odds ratios, and the effective analysis of both continuos and discrete risk factors(80). The multi- logistic regression analyses yielded more reliable results as the effects confounding factors were controlled. In this study, the variables were quantitative data that were oral contraceptive use for test of hypothesis to search for the association between oral contraceptive use and breast cancer. The results of association have been shown in equation of logistic regression. In addition, epidemiology analysis , as well as methods for control of continuous confounders, should be expanded beyond simple categorical and linear(single-coefficient) approaches to include flexible curves that make use of intracategory information.

However, we must critically evaluate the methods used and the results given, and decide whether a causal relationship seems a likely explanation for the results.

5.2 Examination Of Hypothesis

The main hypothesis of this study was to test the association between oral contraceptive use and breast cancer. The results showed were associated with oral contraceptive use and breast cancer the strength of association would increase oral contraceptive use

5.3 Comparison With Other Studies

5.3.1 Epidemiology of oral contraceptive use and breast cancer

The study design was an unmatched case - control study, and the instrument was a set of standard structured questionnaires used to determine the history of exposure to oral contraceptives.

The first phase of the analysis employed descriptive statistics which described both the cases and the controls of each variable. Mean, standard deviation, and percentage range, were used for categorical data. The odds ratio and 95 % confidence interval were analyzed simultaneously with the descriptive analysis to find out the magnitude of association of each variable with breast cancer.

In addition Chi-square and p-value were also calculated to determine whether the associations were significant or not. In instances where the all values were equal to five, two tailed Fisher's test was used.

All the variable which showed significant association with breast cancer were analyzed by multiple regression to adjust for the various confounding effects. Twenty-two of these factors are used in binary multiple regression analysis.

The variables which showed a significant associated with breast cancer were analysed by multiple logistic regression adjusted for the various confounding effects. The majority of all the cases at Siriraj Hospital, Ramathibodi Hospital, and Rajvithi Hospital were referral cases from health centers and various hospitals in Thailand, the fact that reduced generalizability of the sample population and was

considered one of the limitations of the study. The study findings revealed that the factors significantly associated with breast cancer were

Oral contraceptive use

The crude analysis result according to the study, it was also found that there was association between oral contraceptive use and breast cancer by crude OR but after adjusted by logistic regression analysis, the result showed there was no positive association between oral contraceptive use and breast cancer .The similar result was reported by the Sattin et al.(56), Thomas et al.(58), and Wingo et al.(60).

Age

It was the a well - known fact that increasing age has a relationship with breast cancer. The same result was reported by Furrival (76).

Lack of knowledge on breast self examination and no breast self examination

The not knowledge on breast self examination of breast cancer was found to have increased relationship with breast cancer and no the breast self examination was found to be related to breast cancer, the same result was reported by Kurioshi et al. (74) conducted a case control study to assess the contributions of BSE and mammography in Vermont in 355 patients with BSE incidentally; the BSE detected cancers were found significant.

Early menarche

There was statistically significant association between breast cancer. It was similar to the findings of the studies of Harris et al. (65), William (70), and Townsend (71).

Age when first married more than age 25

According to the study, there was statistically significant association between breast cancer .

Family history of breast cancer

According to the study finding, there was a relationship between family history and breast cancer after adjusting simultaneously all the other potential cofounders by logistic regression. The similar result was recorded in the studies by Harris et al. (65) and Tao (68).

History benign breast disease

The history benign breast disease found to have association breast cancer. The similar result was contrary to the previous studies of Herris et al. (65)conducted a study that history of breast cancer in first degree related of mother was increased (RR = 2.0) when comparison with no family history with breast cancer, WHO(66), and Tao et al.(68).

CHAPTER VI
CONCLUSION

6.1 Summary Of The Main Findings

During the study period from 1, July 2000 to 31, December 2000. A hospital based unmatched case control study. The study group consisted at Siriraj Hospital, Ramathibodi Hospital, and Rajvithi Hospital, were interviewed the 625 study in three of the most famous hospital in Bangkok.

The study group consisted of 250 cases. The majority of subject were registered at Siriraj Hospital 40% at Ramathibodi Hospital 32% and 28 % at Rajvithi Hospital. Data analysis showed that the two groups were comparable in general characteristics such as age group, ethnicity, place of birth, place of residence subject's income, history drink alcohol, not knowledge on breast self- examination with no breast self- examination, period for breast self examination, oral contraceptive use, duration of use oral contraceptive, early menarche, history of irregular menstruation ,hormone used after menopause, age when first married, age first pregnancy , family history of breast cancer, and history of breast cancer.

By mean of Parison Chi-square test and binary logistic regression of association, it was discovered that there was no association between breast cancer oral contraceptive use, duration of use oral contraceptive, age first pregnancy, history of irregular menstruation, hormone used after menopause .These association are non significant at 95% level of significant.

The associated factor from chi-square test are summarized and analysis by the method of binary multiple regression analysis. The factors consisted lack of knowledge on breast self- examination with no breast self- examination, age group, subject's income, early menarche, age when first married, family history of breast cancer, and history of breast cancer. Matched pair analysis and odd ratio were applied to prove the association. The found highly significant association with history benign breast disease (OR = 10.84, 95%CI = 1.53-76.56), and family history of breast cancer (OR = 68.09, 95% = 14.10-328.70).

The borderline significance were found with the following factors hormone used after menopause (OR = 0.07, 95%CI = 0.00-1.09).The three methods of analysis and quite the same results.

6.2 Recommendation on The Further Studies

Also, they should be given information to raise their awareness of the chance of breast cancer and the significance and benefits of early detection.

1. Other groups of women using oral contraceptive so that the finding can be generalized to a wider group of population.

2. Further studies should be conducted with other groups of women of risk of developing breast cancer such as those with immediate family member who have breast cancer.

3. Population –based multi-center case-control studies should also be conducted to represent other groups of population in the community.

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APPENDIX

QUESTIONNAIRE

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Instruction: Interviewer must explain this information to the patient before interviewing.

The objective of this study is to determine the environmental factors that may cause disease in human being. If the nature of disease and factors are know, it will give an advantage in prevention of that disease. Your answer will be useful in searching for causes of diseases, so will you please answer these questions truly ?

Date of interview ……/……./……

Hospital Number ……..

Place of admission …….

Part 1. Socio-demographic characteristics

1. How old are you?…… (Years)
2. Place of birth ……...
3. Present residence……..
4. Ethnicity

( ) Thai ( ) Muslim

( ) Christ ( ) Other

5. Religion

( ) Buddhism ( ) Muslim

( ) Christian ( ) Other

6. Marital Status

( ) Married

( ) Separate, Divorced

7. Education level

( ) Illiterate ( ) Primary school

( ) Secondary school ( ) Higher than secondary school

8. Occupation

( ) Government office

( ) Agriculture

( ) Wife house

( ) None

9. Your monthly income ……

Part 2. Information on health behavior

1. Your are smoking?

( ) Yes ( ) No

2. Your are alcohol drinking?

( ) Yes ( ) No

3. Do you know about knowledge on check breast for yourself?

( ) Yes ( ) No

4. Do you check breast for yourself?

( ) Yes ( ) No

Part 3. Information on menstrual history

1. Age at first menarche…….(years)

2. Do you have a regular menstruation?

( ) Regular ( ) Irregular

3. Do you have a menstruation?

( ) Yes ( ) No

4. Have you used any postmenopausal hormone?

( ) Yes ( ) No

Part 4. Used oral contraceptive

1. Have you used oral contraceptive?

( ) Yes ( ) No

2. First age used oral contraceptive……..years

3. Duration of used oral contraceptive ……years

4. Now do you use oral contraceptive?

( ) Yes ( ) No

Part 5. Married, fertility and history of mass on breast

1. Age at first married …….years.

2. Age at first pregnancy……..years.

3. Total number of pregnancy……..(Total abortion, fetal death)

Part 6. Family history

1. How about your mother

( ) Healthy

( ) Living with the disease ……..

( ) Died with the cause of…….

2. Do you have any relative got the breast cancer?

( ) Great grandparents

( ) Grand mother

( ) Aunt

( ) No ( ) Do not know

3. Have you history benign breast disease

( ) Yes

( ) No

แบบสอบถามสำหรับการวิจัย

ความสัมพันธ์ระหว่างการใช้ยาเม็ดคุมกำเนิดกับมะเร็งเต้านมในสตรี

วันที่สัมภาษณ์..... เดือน..... พ.ศ.....

HN.....

สถานที่สัมภาษณ์.....

ตอนที่ 1 ข้อมูลด้านประชากรและสังคม

1. ขณะนี้ท่านอายุเท่าไร..... ปี
2. จังหวัดที่ท่านเกิด.....
3. จังหวัดที่อยู่ปัจจุบัน.....
4. เชื้อชาติ

   ( ) ไทย ( ) มุสลิม ( ) จีน ( ) อื่นๆ.....
5. ศาสนา

   ( ) พุทธ ( ) อิสลาม ( ) คริสต์ ( ) อื่นๆ.....
6. สถานภาพสมรส

   ( ) คู่ ( ) หย่า, หม้าย
7. ระดับการศึกษา

   ( ) ไม่ได้เรียน ( ) ประถมศึกษา

   ( ) มัธยมศึกษา ( ) สูงกว่ามัธยมศึกษา
8. อาชีพ

   ( ) รับราชการ ( ) เกษตรกรรม

   ( ) แม่บ้าน ( ) ไม่มีอาชีพ

   ( ) อื่นๆ.....
9. รายได้เฉลี่ยต่อเดือน ..... บาท

ส่วนที่ 2 ข้อมูลพฤติกรรมอนามัย

1. ท่านเคยสูบบุหรี่หรือไม่

   ( ) เคย ( ) ไม่เคย

2. ท่านเคยดื่มสุราหรือไม่

   ( ) เคย ( ) ไม่เคย

3. ท่านมีความรู้เกี่ยวกับการตรวจเต้านมด้วยตนเองและตรวจด้วยตนเองหรือไม่

   ( ) มี ( ) ไม่มี

ส่วนที่ 3 ประวัติการมีประจำเดือน

1. ท่านมีประจำเดือนครั้งแรกเมื่ออายุ..... ปี
2. ประจำเดือนท่านมาสม่ำเสมอหรือไม่

   ( ) สม่ำเสมอ ( ) ไม่สม่ำเสมอ

3. ปัจจุบันท่านยังมีประจำเดือนอยู่หรือไม่

   ( ) มี ( ) ไม่มี ประจำเดือนหมดอายุเมื่ออายุ..... ปี

4. ถ้าเคย แพทย์เคยให้ยาปรับฮอร์โมนมารับประทานหรือไม่

   ( ) เคย ( ) ไม่เคย

ส่วนที่ 4 ประวัติการใช้ยาเม็ดคุมกำเนิด

1. ท่านเคยใช้ยาเม็ดคุมกำเนิดหรือไม่

   ( ) เคย ( ) ไม่เคย

2. อายุเมื่อเริ่มใช้ยาเม็ดคุมกำเนิด.....ปี
3. ระยะเวลาที่ใช้ยาเม็ดคุมกำเนิด.....ปี
4. ปัจจุบันท่านยังใช้ยาเม็ดคุมกำเนิดหรือไม่

   ( ) ใช้ ( ) ไม่ใช้

ส่วนที่ 5 ประวัติการสมรสและประวัติการตั้งครรภ์

1. ท่านแต่งงานครั้งแรกเมื่ออายุเท่าไร.....ปี
2. อายุเมื่อมีบุตรคนแรก.....ปี
3. ท่านตั้งครรภ์ทั้งหมดกี่ครั้ง

   ( ) ไม่เคยตั้งครรภ์ ( ) เคยตั้งครรภ์.....ครั้ง (นับรวมการแท้ง ตายคลอด)

4. จำนวนบุตรทั้งหมดของท่าน

( ) ไม่มีบุตร ( ) มีบุตร..... คน

ส่วนที่ 6 ประวัติครอบครัว

1. ปัจจุบันมารดาของท่านยังมีชีวิตอยู่หรือไม่

( ) ยังมีชีวิตอยู่และสบายดี

( ) ยังมีชีวิตอยู่แต่ป่วยด้วยโรค.....

( ) ถึงแก่กรรมด้วยโรค.....

2. ในเครือญาติของท่านมีใครเคยป่วยด้วยโรคมะเร็งเต้านมหรือไม่

( ) ไม่มี

( ) มี.....คน คือ.....

( ) ไม่ทราบ

3. ท่านมีประวัติมีก้อนที่เต้านมหรือไม่

( ) มี ( ) ไม่มี

BIOGRAPHY

NAME	Miss Wanvipa Umpan
DATE OF BIRTH	22 August, 1969
PALCE OF BIRTH	Ubonrachatani, Thailand
INSTITUTIONS ATTENED	Chiangmai nursing and midwifery, 1991-1992: Certificate of Midwifery and Nursing Rajabhat Institute Ubonrachatanee, 1993 – 1994: Bachelor of Science Sukhothaitamathirat University, 1997- 1998: Bachelor of Nursing Mahidol University, 1999-2003: Master of Science (Epidemiology)
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