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Role of Socioeconomic Status and Reproductive Factors in Breast Cancer

A Case-Control Study



ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the auditorium of Tampere School of
Public Health, Medisiinarinkatu 3, Tampere,
on May 19th, 2004, at 10 o'clock.

Acta Universitatis Tampereensis 1009

ACADEMIC DISSERTATION
University of Tampere, School of Public Health
Finland

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P.O. Box 617
33014 University of Tampere
Finland

Tel. +358 3 215 6055
Fax +358 3 215 7685
taju@uta.fi
<http://granum.uta.fi>

Cover design by
Juha Siro

Printed dissertation
Acta Universitatis Tamperensis 1009
ISBN 951-44-5969-5
ISSN 1455-1616

Electronic dissertation
Acta Electronica Universitatis Tamperensis 344
ISBN 951-44-5970-9
ISSN 1456-954X
<http://acta.uta.fi>

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2004

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ABBREVIATIONS

AAR	–	age adjusted incidence rate
CI	–	confidence interval
HBCR	–	hospital-based cancer registry
IRR	–	incidence rate ratio
IARC	–	International Agency for Research on Cancer
KMIO	–	Kidwai Memorial Institute of Oncology
NCRP	–	National Cancer Registry Programme
OR	–	odds ratio
p	–	probability
PBCR	–	population-based cancer registry
RR	–	relative risk
TR	–	truncated incidence rate
WHO	–	World Health Organization

1 INTRODUCTION

Breast cancer is predominantly a disease of women and has a major impact on the health of women. Globally breast cancer is the most frequent cancer among women accounting for 21% of all cancers in women and ranking third (9.8%) overall when both sexes were considered together (Parkin et al. 1999). It is the most common cancer among women in all the developed areas (except for Japan, where it ranks third), as well as in Northern Africa, South America, East, Southeast and Western Asia and Micronesia/Polynesia. The incidence rates of breast cancer are high in North America and Northern Europe, intermediate in southern Europe and South America and low in Asia and Africa. The age-standardized incidence rates of breast cancer per 100,000 women were over 100 in Montevideo, Uruguay in South America (114.9), among Non-Hispanic Whites in California, North America (109.6) and among Hawaiians, Hawaii in Oceania (101.3). The rate (age-standardized) of breast cancer in Finland was 72.4 per 100,000 women. The lowest incidence rate of breast cancer was seen in The Gambia in Africa (Parkin et al. 2002). Approximately 183,000 women (about 32% of all incident cancers in women) are diagnosed with invasive breast cancer each year in America and nearly 41,000 women die of the disease.

In American women, breast cancer is the most frequently diagnosed cancer and second leading cause of cancer death, second only to lung cancer. In women aged 40 to 55, breast cancer is the leading cause of all mortality. However, there has been a slight decline in breast cancer mortality overall, which can be attributed both to the success of early detection programmes and to advances in treatment, particularly development in systemic therapy (Winer et al. 2001).

Researchers have postulated that changes in the age of childbearing, alterations in the average ages of menopause and menarche, and/or the widespread use of oral contraceptives and hormone replacement therapy have contributed to the increasing incidence (Honig 1998). Although screening has become widely available, a relatively small percentage of the population takes advantage of it; only 15% of women over 50 years of age in North America were estimated to have had a mammogram in 1984.

The risk of developing breast cancer is age related. Breast cancer is uncommon before age 40; only 6.5% of all cases were diagnosed before age 39 (Miller et al. 1994). The risk increases sharply at age 40 and then continues to increase with a median age of breast cancer diagnosis of 64 years (Honig 1998). India is rapidly stepping towards industrialization vis a vis urbanization resulting in a change of life style factors, particularly an increase in age at marriage, delay in age at first birth, reduction in parity,

improved socioeconomic conditions etc. Estimates compiled from decennial census surveys indicate that for the whole of India age at marriage increased, on average, from 12.5 years (over the period 1921–31) to 17.2 years (over the period 1961–71). The mean age at marriage in greater Bombay (now Mumbai) for women was 18.5 years in 1960 and 20.1 years in 1965 (Jayant 1986). All these factors have possibly contributed to the gradual increase in the incidence of breast cancer in India.

Even though the rates of breast cancer were low in rural areas of India, the rates are higher in urban areas. Breast cancer is the leading site of cancer among women in Bombay (now Mumbai), Delhi, Bangalore and Bhopal and it ranks second at Madras (now Chennai) and Barshi. The age-adjusted rates of breast cancer in these centres were 30.8, 30.8, 25.2, 24.5, 26.7 and 8.1 per 100,000 women respectively during the period 1997–98. (NCRP 2002a).

The present study was undertaken in a southern State of India at Kidwai Memorial Institute of Oncology (A Regional Centre for Cancer Research and Treatment), Bangalore, Karnataka with an objective to study the socioeconomic status and reproductive factors associated with the risk of breast cancer.

2 REVIEW OF THE LITERATURE

2.1 Population characteristics of India

India is a vast country in Southern Asia with widely varying socio-cultural, religious and dietary practices. It is the second most populous country in the world next only to China. The country's population has grown from 238.4 million in 1901 to 1,027 million in 2001. The population has been steadily increasing since 1921. However since 1951, a rapid increase has been recorded in the annual growth rate (around 2 per cent). The total area of the country is 3.07 million sq. km with a population density of 324 inhabitants per sq. km.

The age-structure of India is typical of any developing country with nearly 39.6 per cent of population in the age group of 0–14 years, the corresponding figure being 21.7 per cent in the USA. The population above the age of 65 years in India accounted for 3.8 per cent as compared to 11.9 per cent in USA (UN 1985 and Health Information of India 1991).

Life expectancy is considered to be one of the best indicators of a country's level of development and the overall health status of its population. The average life expectancy in India has increased from 23.6 years to 58.1 years in males and from 23.9 years to 59.1 years in females compared for the period in 1901–1911 and 1986–1991 respectively (Health Information of India 1991).

Growing urbanization is a recent phenomenon in developing countries. The proportion of urban population in India has increased from 10.8 per cent in 1921 to 27.8 per cent in 2001. In other words, nearly about 285.4 million persons are living in urban areas as per the 2001 census figures. Thus, the majority of Indian population resides in rural areas where health facilities are far fewer compared to urban areas. The literacy rates in population aged 7 years and above according to the 2001 census were 65.4%. The literacy rate among males was higher (75.8%) compared to females (54.2%).

In India, the system of registration of vital events suffers from under reporting and under registration. Except in Greater Bombay (Mumbai) where the Coroner's Act is in force, obtaining reliable information on cause of death from the vital sources in rest of the country is very difficult. Information on cause of death collected from the medical records of a few selected major hospitals indicated that infectious and parasitic diseases and diseases of the circulatory and respiratory systems are the most common causes of death in India. The percentage of deaths caused by neoplasms is 4.3 and 4.1 among males and females respectively. The above information suffers from incomplete

reporting as the number of participating hospitals is not the same every year. In spite of sustained efforts, the improvement of the whole system of health information today in India is not at the expected level.

2.2 Karnataka at a glance

Historically, the borders of Karnataka (formerly State of Mysore) were subjected to repeated changes, but Karnataka as an administrative entity came into being during the seventh century when Pulikeshi II subdued the Ganga and the Kadamba rulers. After several centuries and numerous rulers, with the fall of Tippu Sultan in 1799, the princely State of Mysore came into existence and its borders remained unchanged until 1953. The latest change in the boundaries of the State took place under the State Recognition Act of 1956.

Physical Characteristics

Karnataka State is situated between 11 31' and 18 45' N latitude and 74 12' and 78 40' E Longitude. A greater part of Karnataka lies between 450 and 900 meters above sea level with the highest peak rising to 1,913 meters.

Physiographically, Karnataka State forms part of two well-defined macro regions of India: the Deccan Plateau and the coastal plains and islands. On the basis of the regional physiographic characteristics, the State can be divided into four regions: Northern Karnataka Plateau, Central Karnataka Plateau, Southern Karnataka Plateau and Karnataka Coastal Region.

Area and People

The total land area of Karnataka is 191,791 sq.kms. The State contains five percent of the population and six percent of the land area of India. The State has 27 Districts with 175 Taluks (Tehsils). For administrative purposes, the State is divided into four revenue divisions: Bangalore, Belgaum, Gulbarga and Mysore divisions. Bangalore, the capital city is situated in the Southeastern part of the State.

Many religions and sects have left their imprint on the socio-cultural lives of the people. Because of its geographic location, Karnataka became the meeting place of the northern and the southern cultural currents resulting in their synthesis there. In art, a

new Vesara style emerged out of the mingling of the Nagara and Dravida styles. In music both Hindustani and Karnatic styles flourished.

Kannada is predominantly spoken as the mother tongue. Tulu and Konkani are relatively more common in Dakshina Kannada and Konkani in Uttara Kannada. Telugu, Tamil, Hindi and Urdu are the other important languages. Sixty-nine percent of the population live in rural areas, compared to seventy four percent in the country as a whole.

2.3 Cancer registration system in India

Accurate information about the occurrence (incidence and mortality rates) and causes of cancer is essential in assessing the importance of the cancer problem in public health and in planning cancer control strategies. Although, cancer in India has been recognized since the Vedic times (ancient times), no nation-wide, accurate information on the magnitude of cancer was available till very recently (1982). It was only the Bombay Cancer Registry (a population-based cancer registry established in 1963) which used to provide reliable data on cancer and international comparisons for the entire country used to be based on this registry data. Since this registry covered only the Bombay metropolitan area and hence could not be used to extrapolate nation-wide estimates and also keeping in view of the paucity of reliable data in the country as a whole, the Indian Council of Medical Research (ICMR), initiated a network project, the National Cancer Registry Programme (NCRP) in 1982 to generate data on the extent/incidence of cancer in India by augmenting the Bombay Cancer Registry and establishing two more population-based cancer registries (PBCRs) at Kidwai Memorial Institute of Oncology, Bangalore and the Cancer Institute, Adyar, Madras (Chennai) and three hospital-based cancer registries (HBCRs) at the Postgraduate Institute of Medical Education and Research, Chandigarh, Assam Medical College, Dibrugarh and the Regional Cancer Centre, Thiruvananthapuram. In order to generate a large authentic database and for the better assessment of cancer patient care parameters including diagnosis, extent of disease, treatment modalities and their outcome, follow-up details for survival studies, it was soon realised that there was a need for the expansion of a few more registries, and thus the ICMR decided to add three more HBCRs at Bangalore, Bombay (Mumbai) and Madras (Chennai) in 1984, where the PBCRs were in operation. Later on three more PBCRs were established, one at the Rotary Cancer Hospital, Delhi and a special registry at the Gandhi Medical College, Bhopal in 1986 following the worst chemical disaster and a rural registry at Barshi in Maharashtra State in 1987. Currently, the network of NCRP consists of six PBCRs (including the rural-based registry at Barshi) and five

HBCRs (the hospital-based cancer registry established in 1982, at the Postgraduate Institute of Medical Education and Research, Chandigarh ceased its operations from 1990 due to administrative reasons). The coverage of cancer registration by the NCRP for urban population in the country is 16.4 percent and that of rural population is 0.06 percent. Total population coverage is only 4.2 percent.

The main objectives of the NCRP were;

1. To generate authentic data on the magnitude of the cancer problem
2. To conduct/undertake epidemiological investigations and advise control measures
3. To promote human resource development in cancer epidemiology.

2.4 Magnitude of cancer problem

2.4.1 The global scene

The global cancer burden in terms of the annual incidence rates and numbers of new cases of 25 different cancers has been estimated for the year 1990 in 23 areas of the world by Parkin et al. (1999). According to these estimates, the total number of new cancer cases (excluding non-melanoma skin cancer) was 8.1 million, just over half of which occur in the developing countries. Of the total 8.1 million new cases, 4.3 million were men and 3.8 million were women with a male to female sex ratio of 1:0.88. Out of these 3.8 million (3,789,800 cases) cases in women, 1.88 million cases were estimated to be from developed regions and 1.91 million cases were from developing regions.

Cancer of the lung was the most predominant site of cancer in the world in 1990 with 1.04 million new cases, and accounted for 17.9% of all cancers in men and 7.0% of all cancers in women together accounting for 12.8% of all cancers in both sexes. These estimates represent an increase of 16% over 1985 estimates with an increase of 14% in men and 21% in women. The age-standardized rates in men ranged from 2.2/100,000 in Western Africa to 75.9/100,000 in Eastern Europe. In women, incidence was comparatively lower with a highest estimated rate of 32.9/100,000 in North America.

Stomach cancer was the second most common cancer in men and accounted for about 12% of all cancers in men. Among women it ranks fourth, accounting for about 8% of all cancers in women. Together in men and women stomach cancer accounted for 10% of the global burden. Thirty-eight percent of these cases occur in China, where stomach cancer remains most common in both sexes, as was the case in Eastern Asia. The age standardized incidence rates were highest in Japan 77.9/100,000 in men and

33.3/100,000 in women and low in East and North Africa, North America and Southeast Asia.

Breast cancer was the commonest cancer among women globally, accounting for 21% of all cancers in women. The total number of new cases was estimated to be 795,600 in 1990, and ranked third overall when both sexes were considered together. The age standardized incidence rates were high in North America (86.3/100,000) and low in China (11.8/100,000).

Colorectal cancer was the second commonest malignancy in women next to breast cancer and accounted for 10% of all cancers in women globally. It ranked third in men with 9.4% of all cancers in men. But when the cancers were classified in developed and developing regions, colorectal cancers were the second most common cancers in developed countries. The age standardized incidence rates in men in developed countries ranges from 25.3/100,000 in Eastern Europe to 45.8/100,000 in Australia/New Zealand, whereas in developing countries the rates ranged from 27.2/100,000 in men to 24.4/100,000 in women in Temperate South America.

As per the estimates of cancer incidence and mortality there were an estimated 2.6 million new cases of cancer in Europe in 1995, representing over 1 quarter of the world burden of cancer. The overall incidence rate in men was highest in the Western European countries at 420.9 per 100,000 with only Austria having a rate under 400. Eastern European men had the second highest rate of cancer (414.2) with extremely high rates being observed in Hungary (566.6) and in the Czech Republic (480.5). The lowest male all-cancer rate by area was observed in the Northern European countries with fairly low rates seen in Sweden (356.6) and UK (377.8). In contrast to men, the highest rates in women were observed in Northern Europe (315.9) and were particularly high in Denmark (396.2) and the other Nordic countries except in Finland. Lung cancer with an estimated 377,000 cases was the most common cancer in Europe in 1995, rates were particularly high in much of Eastern Europe reflecting the current and past tobacco and smoking habits of many inhabitants. Together with cancers of the colon and rectum (334,000), and female breast (321,000), the three cancers represented approximately 40% of new cases in Europe. In men the most common primary sites of all cancer cases were lung (22%), colon and rectum (12%) and prostate (11%) and in females breast (26%), colon and rectum (14%) stomach (7%). Lung cancer was the most common cause of death from cancer in men (29%) and breast cancer was the common cause of death in females (17%) (Bray et al. 2002).

2.4.2 *The Indian scene*

Since the establishment of a cancer registration system in India on a national basis by the Indian Council of Medical Research in 1982, authentic information on the extent of the cancer problem has been available. The population based cancer registries (PBCRs) established in the country provide data on the extent of the cancer problem in the community in terms of rates, whereas the hospital-based cancer registries (HBCRs) provide data on the magnitude, various types of cancers, stage of the disease, treatment modalities, outcome and on follow-up information of a given hospital / region.

Cancer cases in PBCRs

Six PBCRs are functioning in the country (including one rural-based registry at Barshi) under the National Cancer Registry Programme (NCRP) project at Bangalore, Mumbai (Bombay), Chennai (Madras), Delhi, Bhopal and Barshi. The first three registries were started in 1982 (except the PBCR at Mumbai (Bombay), which was started in 1963 but included under the network of NCRP in 1982) and the registries at Delhi and Bhopal were established in 1986. For the first time a population-based rural cancer registry was also started by the Indian Council of Medical Research in the subsequent year (1987) in Barshi at Sollapur district in the State of Maharashtra. The PBCRs at Bangalore, Mumbai (Bombay), Chennai (Madras) and Delhi are based at the Regional Cancer Centres. The Bhopal Registry is based at Gandhi Medical College, Bhopal. The area and the population covered by these registries are given in Table 1.

Table 1: Area and Population covered by Indian PBCRs (1997–98).

Registry	Area (sq.kms)	Population (Millions)
Bangalore	276.4	5.16
Barshi *	3713.4	0.50
Bhopal	284.9	1.32
Chennai (Madras)	170.0	4.09
Delhi	685.3	11.24
Mumbai (Bombay)	603.0	11.21

* Rural-based

Source: NCRP 2002a.

These registries record more than 22,850 incident cases of cancers annually. The highest numbers of cancers are recorded by the Mumbai (Bombay) Cancer Registry, followed by Delhi, Chennai (Madras), Bangalore, Bhopal and Barshi. The age-adjusted (world population) incidence rates for all types of cancers in different urban centres of India are shown in Table-2. The rates were higher in both sexes at Delhi, the capital city of the country, compared to other urban centres. Further, the rates among females in all the centres (except in Bhopal) were higher than in males.

Compared to the rates of urban centres the age-adjusted (world population) incidence rates of cancer in the rural registry at Barshi were much lower (43.9/100,000 in males and 51.7/100,000 in females). When the rates of the Indian cancer registries are compared with the rates of Western registries, Connecticut (White) and Birmingham exhibit age-adjusted rates of more than two and half times those reported by Indian registries. The age-adjusted incidence rates for all types cancers for all age groups reported from Finland were 305.6/100,000 in males and 252.3/100,000 in females (Parkin et al. 1997).

The age-adjusted rates for females in India are lower than those reported in Cali (Colombia), Connecticut (White), Oxford, Finland and Japan. The truncated rates also showed that there is variation in the cancer incidence rates in males (rates varying between 186.1 and 222.1 per 100,000) and in females (rates varying between 242.7 and 332.4 per 100,000) in these truncated age groups of 35–64 years in the Indian registries (NCRP 1995).

Comparison between the incidence of a disease in different places and at different times is always difficult, particularly if the disease is one that requires a high standard of medical intervention before it can be diagnosed and which varies sharply in incidence with age. In these circumstances, comparisons can lead to conclusions that are highly misleading, unless the limitations of the figures are appreciated, as India lacks a nationwide cancer registration system and at present only about 4.2% of the total population is covered by the existing population based cancer registries.

Table 2. Age-adjusted incidence rates (AAR) per 100,000 persons of all cancers in different registries during 1997–98.

Registry	Males	Females
Bangalore	91.9	114.8
Barshi *	43.9	51.7
Bhopal	116.7	108.7
Chennai (Madras)	111.3	125.2
Delhi	120.9	134.8
Mumbai (Bombay)	117.3	127.9

* Rural-based

Source: NCRP 2002a.

Common cancers among females in PBCRs

Cancer of the breast, which was the second leading site of cancer all these years at Bangalore, replaced cancer of the cervix during the period 1997–98 and it is now the most common site of cancer among females. The same change has been observed in Bhopal. At Mumbai (Bombay) and Delhi breast cancer continues to be the leading site. In Chennai (Madras), cancer of the cervix continues to be the leading site, but the gap in the relative proportions of cervical and breast cancers has narrowed. In the rural-based cancer registry at Bharshi, cancer of the cervix is the predominant site of cancer followed by breast cancer. Oral cavity cancers, cancer of the oesophagus, ovary and stomach are the other common cancers in females with varying proportions. Gall bladder was the fourth leading site of cancer among Delhi females. (NCRP 2002a).

Cancer cases in HBCRs

Five hospital-based cancer registries are functioning under the National Cancer Registry Programme of ICMR at Tata Memorial Hospital, Mumbai (Bombay), Kidwai Memorial Institute of Oncology, Bangalore, Adyar Cancer Institute, Chennai (Madras), Regional Cancer Centre, Thiruvananthapuram, and Assam Medical College, Dibrugarh.

During the five year period 1994–1998 a total number of 179,969 cases of cancer were registered at these five hospital-based cancer registries with Tata Memorial Hospital, Mumbai (Bombay) accounting for more than 42% and Kidwai Memorial Institute of Oncology, Bangalore about 20% of the total cases. The number of cases registered at these hospital-based cancer registries by sex is shown in Table 3.

Table 3. Number of cancer cases by sex, sex ratio percent and relative proportion of cancers at different HBCRs 1994–1998.

Centre	Male	Female	Total	M to F Ratio (%)	Relative proportion of all cancer cases
Bangalore	15926	18552	34478	86	19.2
Chennai (Madras)	13413	15581	28994	86	16.1
Dibrugarh	2645	1498	4143	177	2.3
Mumbai (Bombay)	43006	33722	76728	128	42.6
Thiruvananthapuram	18978	16648	35626	114	19.8
TOTAL	93968	86001	179969	109	100.0

Source: NCRP 2002b.

Common cancers among females in HBCRs

Cancer of the cervix was the leading site of cancer in all centres, accounting for 17.4 percent of cancers in females in Dibrugarh, and for 42.2 percent of cancers in Chennai (Madras). Cancer of the female breast was the second leading site at Mumbai (Bombay) (23.0%), Thiruvananthapuram (21.7%), Chennai (Madras) (15.8%) and Chandigarh (15.3%). Cancer of the oral cavity in Bangalore (13.1%) and oesophagus at Dibrugarh (13.5%) were the second most frequent cancers. If the ranking is considered based on individual site i.e. without grouping of oral cavity sites (gum, floor of mouth and other mouth) breast cancer ranks number two at Bangalore.

2.5 Descriptive epidemiology of breast cancer

Breast cancer continues to be a major public health problem in all the developed countries and the incidence rates are rising even in the developing countries. The estimated number of new breast cancer cases in 1990 was 795,600, of which 471,500 cases were from developed regions and 324,100 cases were from developing regions. Breast cancer was by far the most frequent cancer among women and accounted for 21% of all cancer in women and ranked third overall when both sexes were considered together. It is the most common cancer among women in all the developed regions (except for Japan, where it was the third ranking cancer after stomach and colo-rectal cancer), as well as in northern Africa, South America, East, Southeast and Western Asia and Micronesia/ Polynesia. The estimated number of breast cancer cases in 1990 was about 11% more than the estimated numbers (719,000) in 1985. The age-standardized incidence was highest in North America (86.3 per 100,000) and lowest in China (11.8 per 100,000) (Parkin et al. 1999). The incidence rates of breast cancer in 23 areas of the world during 1990 are shown in Table 4.

Table 4. The standardized incidence rates of breast cancer for the year 1990 in 23 areas of the world.

Area	Rate/100,000
1. Eastern Africa	18.6
2. Central Africa	13.6
3. Northern Africa	25.0
4. Southern Africa	31.5
5. Western Africa	19.0
6. Caribbean	33.5
7. Central America	25.5
8. South America (Temperate)	69.1
9. South America (Tropical)	39.1
10. North America	86.3
11. Eastern Asia: China	11.8
12. Eastern Asia: Japan	28.6
13. Eastern Asia: Other	17.8
14. South Eastern Asia	22.5
15. South Central Asia	21.2
16. Western Asia	24.3
17. Eastern Europe	36.0
18. Northern Europe	68.3
19. Southern Europe	49.5
20. Western Europe	67.3
21. Australia/New Zealand	71.7
22. Melanesia	23.9
23. Micronesia/Polynesia	51.7
Developed countries	56.4
Developing countries	20.4
ALL AREAS	33.0

Source: Parkin et al. (1999).

Breast cancer has a major impact on the health of a woman. Approximately 183,000 women are diagnosed with invasive breast cancer each year and nearly 41,000 women die of breast cancer in the United States. In American women, breast cancer was the most frequently diagnosed cancer and the second leading cause of cancer death (Winer et al. 2001).

Breast cancer trends in the United States have shown increasing rates of new cases with a sharp rise in the 1980's because of the increased use of mammography. Over the past 30 years, specifically in the decades from 1970–1990, breast cancer patients have increased by 117%, whereas deaths have increased by nearly 50%. These increases were partly due to increase in the population of older women and increase in the average length of life, in addition to screening programmes. Regarding age specific trends, the increase in the incidence rate was nearly 40% for women aged 65 years and older, whereas the increase was less than 5% for women younger than 50 years. Based on the trends to date, there is every reason to believe that the burden of breast cancer will

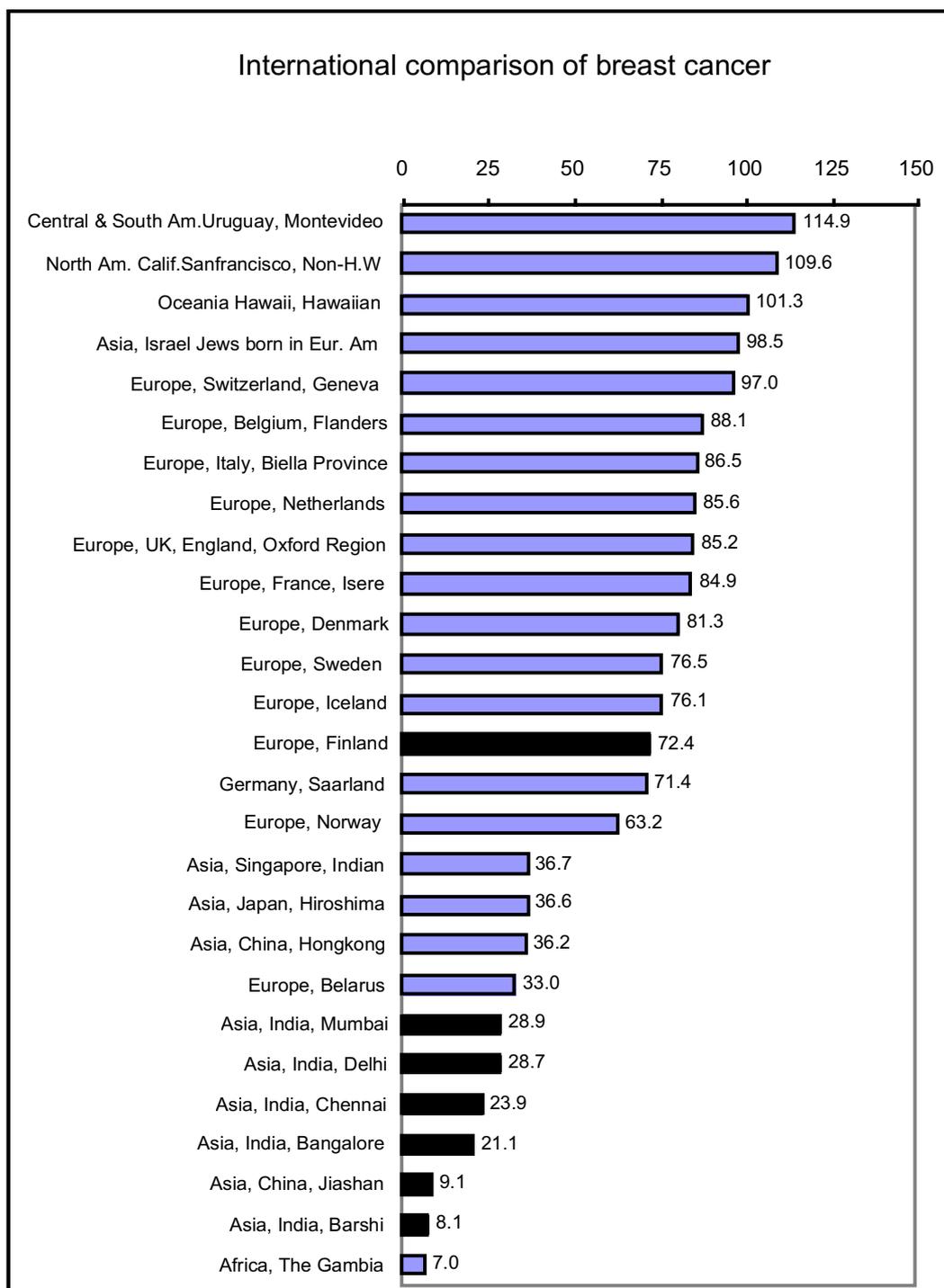
continue to grow not only in terms of the absolute numbers of cases but also in terms of incidence and mortality rates (Sondik 1994).

Among the European countries, the highest age-adjusted incidence rate of 97.0 per 100,000 women during the period 1993–97 was reported from Geneva, Switzerland and the lowest rate of 33.0 per 100,000 women from Belarus. The age-adjusted incidence rate of breast cancer in Finland during this period was 72.4 per 100,000 women (Parkin et al. 2002). Trends in the incidence of and mortality from breast cancer results from a variety of influences: the changing profile and risk factors in the population (e.g. decreasing fertility and increasing height and weight), earlier diagnosis including screening programmes or simply better health awareness. Several European countries introduced screening programmes for the early detection of breast cancer in the late 1980s. Incidence rates of breast cancer are lower in Estonia and Slovakia than in other countries with age standardized rates reaching 100/100,000 women in 1990s. Mortality rates are low (consistently below 50 per 100,000 women) in Finland, Sweden, Czech Republic, Estonia, France, Italy, Norway, Slovakia, Slovenia and Spain. (Botha et al. 2003).

2.5.1 International variation in the incidence of breast cancer

The incidence and mortality rates of breast cancer have been highest in North America and Northern Europe, intermediate in Southern Europe and Latin America, and lowest in Asia and Africa. The age-adjusted (world population) annual incidence rate of breast cancer per 100,000 women during the period 1993–1997 has varied between 7.0 from the Gambia (Africa) as the lowest rate, and 114.9 from Montevideo, Uruguay (South America) as the highest rate across the world (Parkin et al. 2002).

The rates of breast cancer in different countries/regions are shown in Figure -1.



* Rate per 100,000 women

Source: Parkin et al. (2002): Cancer Incidence in Five Continents, Vol.VIII, IARC, Sc.Publ.No.155, Lyon, France

Figure 1. International comparison of age-adjusted incidence rates* (AAR) of female breast cancer: 1993–1997.

In recent years, steep increases in breast cancer incidence and mortality rates have been reported in several Asian and Central European countries. Jayant (1986) reported that the incidence of breast cancer has increased over the last 20 years in Mumbai (Bombay), India and the increasing trend appears to continue. Similar increases in the age-adjusted incidence rates of female breast cancer in Mumbai, India were observed by Yeole et al. (1990). An increasing trend of breast cancer and decreasing trend of cervical cancer in all most all the registry areas in India were observed (NCRP 2002a).

International differences in breast cancer incidence have been hypothesized to be partially related to variation in such factors as body weight, some aspect of diet, hormone levels and reproductive characteristics, especially age at menarche and possibly menstrual cycle length, parity and lactation (Kelsey and Horn-Ross 1993) in addition to the environmental changes within a country.

2.5.2 Breast cancer incidence in India

According to the predictions made by Yeole (1997), there would be 66,833 female breast cancer cases in India in the year 2001 and this was the most frequent site of cancer among urban females accounting for about 25% of all female cancers. However, among rural females cancer of the cervix would be the most frequent cancer, accounting for about 32%.

Among the cancer registries established under the National Cancer Registry Programme of Indian Council of Medical Research cancer of the breast in females was the first leading site of cancer at Bangalore, Bhopal, Delhi and Mumbai (Bombay) with age-adjusted incidence rates of 25.2, 24.5, 30.8 and 30.8 per 100,000 women respectively during the period 1997–98. In Chennai (Madras) it ranks second next to cancer of the cervix but the incidence of breast cancer is showing an increasing trend over the years. In the rural registry at Barshi the incidence rate of breast cancer is lower (8.1/100,000 women) compared to the urban registries. A tendency of breast cancer to rise over time has been observed in all the urban registries. Cancer of the cervix was the leading site of cancer in women till the late 1960's at Mumbai (Bombay), but rate of breast cancer has started to rise the last two to three decades. A gradual increase in the rates of breast cancer in other urban registries has been observed from middle of the 1990's in contrast to cervical cancer, the rates of which are gradually but notably declining.

The lifetime (0–74 years) risk of developing breast cancer at Bangalore was 2.5%, Barshi – 1.0%, Bhopal – 2.1%, Chennai (Madras) – 2.4%, Delhi – 3.0% and Mumbai (Bombay) – 3.4% (NCRP 2001). Similar risk estimates according to the data of the

Surveillance, Epidemiology and End Results (SEER) Programme indicate that white women in the United States have a 13.1% life time risk of developing breast cancer; where as African American women have a 9.6% life time risk (Winer et al. 2001).

2.6 Risk factors for breast cancer

The risk of developing breast cancer is associated with several factors such as increasing age, family history, exposure to female reproductive hormones (both endogenous and exogenous), dietary factors, benign breast disease and environmental factors. Age plays a major role in breast cancer risk. In women under 30 years of age, breast cancer is very uncommon, but with increasing age the incidence of breast cancer also increases. The age-specific incidence of breast cancer increases steeply with age until menopause. After menopause, although the incidence continues to increase, the rate of increase decreases to approximately one-sixth of that seen in the pre-menopausal period (Winer et al. 2001), suggesting that ovarian activity plays a major role in the aetiology of breast cancer. Epidemiologic studies have shown that late age at menopause increases the risk of breast cancer. The development of breast cancer in many women appears to be related to female reproductive hormones. Epidemiological studies have consistently identified a number of breast cancer risk factors, each of which is associated with increased exposure to endogenous estrogens. Early age at menarche (Schatzkin et al. 1987, Yuan et al. 1988), nulliparity or late age at first birth (Ewertz et al. 1990) and late age at menopause (Kelsey et al. 1993, Talamini et al. 1996) increase the risk of developing breast cancer. In postmenopausal women, obesity and postmenopausal hormone therapy, both of which are positively correlated with plasma estrogen levels and plasma estradiol levels, are associated with increased risk of breast cancer (Winer et al. 2001).

The relative risk of developing breast cancer for a woman with natural menopause before the age of 45 years is one-half that of a woman whose menopause occurs after the age of 55 years (Winer et al. 2001). High social status, comprising higher education (Hakama et al. 1982), higher income (Madigan et al. 1995), urban living etc. are shown to be risk factors of breast cancer.

Migrant studies have shown that women who migrate from countries with low incidence rates to countries of high incidence rates tend to develop breast cancer at the rate comparable to that of the country of adoption and not at the rate of their country of origin (Lilienfeld et al. 1972) suggesting that environmental factors play an important role.

2.6.1 Socioeconomic status

Several epidemiological studies have indicated a positive association between breast cancer and socioeconomic status (Talamini et al. 1984, Vagero and Persson 1986, Rimpela and Pukkala 1987 and Ewertz 1988b). Some investigators measured the socioeconomic status by educational level (Lilienfeld et al. 1972) by income (Zippin and Petrakis 1971) by social class (Campbell 1972) and some by the highest level of education attained and occupational history (Van Loon et al. 1994).

In a multi-centre case control study carried out in Italy to evaluate the occurrence of breast cancer in women of different social class and residential history, Barbone et al. (1996) found that, compared to housewives, managers and professionals had a 1.7 fold increased risk of developing breast cancer, whereas the relative risk was 0.7 and 0.6 respectively in auxiliaries and manual workers. The risk of breast cancer also increased with increasing social level of the husband's occupation and subjects' number of years of schooling. Pukkala (1995) in a survey of 109,000 cancer cases among Finns of working age observed that the incidence of breast cancer was about 2-fold higher among women of higher social class compared with those of lower social class in Finland and that this difference in the incidence rate was attributed to early age at menarche and late age at menopause among women of higher social class. Madigan et al. (1995) found in a cohort study that women with higher income had an elevated risk of breast cancer compared with women of lower income. Regarding population attributable risk estimates, higher income contributed about 19% of the breast cancer cases in the United States. Cusimano et al. (1989) reported that women of higher socioeconomic status (class 1 vs. class 4) had a 3-fold risk of developing breast cancer. Monthly family income was independently associated with the increased risk of breast cancer (OR 1.69; 95% CI 1.18–2.42) and being a housewife (OR 2.86; 95% CI 1.83–4.47) (Gomes et al. 1995). In a study on "The effect of social class based on occupation on survival of female breast cancer patients", Karjalainen and Pukkala (1990) reported that those in the lowest social class had about 1.3 times higher relative excess risk of dying than those in the highest social class.

Some studies did not find a positive association between socioeconomic status and risk of developing breast cancer (Van Loon et al. 1994) and socioeconomic status per se is not a risk factor for breast cancer. It may play an important role in conjunction with other aetiological factors such as education, marital status, age at marriage, age at childbirth and parity (Wynder et al. 1960, Shapiro et al. 1968).

2.6.2 *Area of living*

The rates of breast cancer are higher among women living in urban areas than in rural areas. Hakama et al. (1982) reported that the incidence rates of breast and cervical cancer were high in an urban environment with a high standard of living. The individuals with high risk of breast cancer were of high socioeconomic status and were well educated, whereas cervical cancer was common among women of low socioeconomic status and with less education. The difference in the degree of urbanization does not explain the variation in breast cancer incidence among countries (Gajalakshmi 1997).

2.7 Reproductive factors

The importance of menstrual and reproductive factors (age at menopause, age at first birth, parity, age at and type of menopause) as determinants of a woman's risk of breast cancer is well established (MacMahon et al. 1970a, Henderson et al. 1985, Kelsey et al. 1993). These factors have been found to be important in high-risk Western populations (Kvale 1992) and in low-risk Asian groups (Tao et al. 1988, Yuan et al. 1988, Wang et al. 1992) although the magnitude of risks and the relative importance of specific factors have varied between studies.

2.7.1 *Age at menarche*

Early age at menarche has been found to be one of the important determinants in the aetiology of breast cancer. Many epidemiologic studies have suggested that the younger a woman's age at menarche the higher her risk of breast cancer (Wynder et al. 1960, Henderson et al. 1974, Choi et al. 1978, Schatzkin et al. 1987, Kvale and Heuch 1988, Hsieh et al. 1990, Kelsey et al. 1993, Decarli et al. 1996, McCredie et al. 1998, Gao et al. 2000). A reduction of 4–5% in the risk of breast cancer per year of delay in the age at menarche was reported by Kvale and Heuch (1988) and Decarli et al. (1996). This reduction in the risk of breast cancer decreased even further to 20–30% for women with the onset of menstruation at or after 15 years of age compared with those with earlier menarche (Negri et al. 1988) or with age at menarche of 12 years or younger (Brinton et al. 1988). Nagata et al. (1995) from a meta-analysis of eight case control studies from Japan reported an odds ratio (OR) of 0.7 (95% CI 0.6–0.8) for women with onset of menstruation after age 16 compared to those before age 14. Early age at menarche increases the risk of breast cancer during both premenopausal (Staszewski 1971,

Stavraky and Emmons 1974) and perimenopausal years (Wynder et al. 1978) more than in the postmenopausal period. Ewertz (1988a) observed decreasing risk with increasing age at menarche in premenopausal women. From a large international multicentre case-control study consisting of 3,993 breast cancer cases and 11,783 controls, Hsieh et al. (1990) found that age at menarche was a risk factor among both pre- and postmenopausal women, and the risk of breast cancer reduced by about 10% (95% CI 6–15%) for each two years delay in onset of menstruation. In a study to examine whether age at menarche is causally involved in the aetiology of breast cancer or serves as a correlate with other early life exposures, Magnusson et al. (1999) observed a statistically significant negative association between increasing age at menarche and breast cancer risk in women born before 1925 but not after, suggesting the fact that some evidence of a role of environmental correlates of early menarche in the aetiology of breast cancer and underlining the importance of childbirth especially early in life in the prevention of breast cancer.

From a population-based case-control study among Chinese women in urban Shanghai, Gao et al. (2000) observed that early age at menarche was associated with increased risk of breast cancer among both pre- and postmenopausal women. Clavel-Chapelon and the E3N-Epic group (2002) using the data on 1,718 breast cancer cases obtained from a large sample of around 100,000 French women participating in the E3N cohort study reported that the overall risk of breast cancer increased with decreasing age at menarche. The study revealed that age at menarche had an effect on pre-menopausal breast cancer risk, with a decrease in risk with an increasing age of 7% per year ($p < 0.05$), compared to those who had their first menstrual period at 11 or before, women experiencing menarche at 15 or after had an RR of 0.66 (95% CI 0.5–1.0) in the premenopausal group. Since menarche at a young age is associated with earlier onset of regular menstrual cycles, early exposure to the hormonal milieu associated with regular ovulatory menstrual cycles may be an important aetiological factor (Kelsey et al. 1993). Women with early menarche do not have a longer duration of exposure to anovular cycles than do those whose menarche is delayed, and that variation in the duration of exposure to post-menarcheal anovular cycles does not explain the association of breast cancer risk with early age at menarche (MacMahon et al. 1988b).

Some authors, however, did not find early age at menarche to be a risk factor for breast cancer (Paymaster and Gangadharan 1972, Soini 1977, Tao et al. 1988, Gajalakshmi and Shanta 1991, Gomes et al. 1995 and Talamini et al. 1996).

2.7.2 Marital status and age at marriage

The risk of breast cancer was higher among never-married women than ever-married women (Fraumeni et al. 1969, Talamini et al. 1984, Brignone et al. 1987). A relative risk of 3.1 for single women was reported by Paymaster and Gangadharan (1972) compared with married women. Single women were found to be at a more than 5-fold significant risk of breast cancer compared with married women in both pre and postmenopausal groups (Gajalakshmi and Shanta 1991). Rao et al. (1994) found a risk of 2.3 for unmarried women compared with married women. Compared with ever-married women, never-married women in the premenopausal group were at slightly higher risk of breast cancer (OR 1.97) than in the postmenopausal group (OR 1.56) (Brignone et al. 1987).

Apart from marital status, age at marriage was found to be an important factor in the aetiology of breast cancer. A two and a half-fold risk was reported by Rao et al. (1994), for women who married at the age of 30 years and above compared with women who married at the age of 14 years or below. Gajalakshmi and Shanta (1991) from a hospital-based case-control study in Madras (now Chennai), India reported that, compared to women who married before the age of 15, women who married at the age of 18–20 years had a risk of 1.9 (95% CI 1.1–3.2) and women who married at the age of 20 years and above had nearly two and a half-fold risk (OR 2.4; 95 % CI 1.3–4.4) in the premenopausal group and the respective risks in the postmenopausal groups were 3.1 (95% CI 1.9–5.0) and 3.8 (95% CI 2.1–6.8).

Though an increased risk of breast cancer among never-married women compared with ever-married women was reported, the findings of the studies reported from India were not based on multivariate analysis.

2.7.3 Age at first birth

The importance of age at first birth as a risk factor was first established by MacMahon et al. (1970a) from a large international case control study. Since then, many epidemiologic studies have revealed that on average, the younger a woman is when she has her first full-term pregnancy, the lower is her risk of breast cancer (Paffenbarger et al. 1980, Lubin et al. 1982, Helmrich et al. 1983, Schatzkin et al. 1987, Yuan et al. 1988, Negri et al. 1988, Layde et al. 1989, Leon 1989, Kelsey et al. 1993, Romieu et al. 1996, Lambe et al. 1996, Decarli et al. 1996, Hinkula et al. 2001, Palmer et al. 2003). The age at which a woman gave birth to her first live child is predictive of breast cancer

risk and the maternal age at first birth explains the protective effect of parity (MacMahon et al. 1970a).

Women who gave birth to their first child after age 30 have a higher risk of breast cancer compared to nulliparous women (Tulinius et al. 1978, Brinton et al. 1983, Negri et al. 1988, Layde et al. 1989). A two to five-fold excess risk was reported by several studies for women with a birth after age 25 to 30 years compared to those with a birth prior to age 18 to 20 years (Brinton et al. 1983, Negri et al. 1988, Wang et al. 1992, Nagata et al. 1995). The possible explanation for the high risk in women who have their first full-term pregnancy after age 30 could be that a full term pregnancy at an early age may reduce the likelihood of tumour initiation while a full-term pregnancy at a later age may promote the growth of existing tumour cells (MacMahon et al. 1970a).

In a meta-analysis of eight population-based studies (three cohort and five case – control) from the Nordic countries Ewertz et al. (1990) observed a significant increasing trend in risk with increasing age at first childbirth. An increased risk of 40% was found for women who had their first birth after the age of 35 years compared to those with a first birth before the age of 20 years. The risk was much higher (OR 3.6; 95% CI 2.2–5.8) among premenopausal women than postmenopausal women (OR 1.3; 95% CI 1.0–1.7) for those whose age at first birth was above 31 years compared to those with birth prior to 20 years (Talamini et al. 1996).

From a case-control study carried out in India, Gajalakshmi and Shanta (1991) found a relative risk of 2.6 and 5.6 among premenopausal and postmenopausal women respectively when the age at first childbirth was above 25 years compared to below 17 years. Gao et al. (2000) also found that late age at first live birth was associated with increased risk of breast cancer among both pre and postmenopausal women. A cohort study by Clavel-Chapelon and the E3N-Epic Group (2002) found that the age at first full-term pregnancy had an effect on both pre- and postmenopausal breast cancer risk with significant tests showing increasing risk per year of increasing age ($p = 0.001$ and $p < 0.05$ respectively). A full-term pregnancy above the age 30 carried a risk of 1.63 (95% CI 1.12–2.38) and 1.35 (95% CI 1.02–1.78) in the pre and postmenopausal group respectively. In a nationwide cohort study of women with at least five births (grand multiparas) carried out in Finland, Hinkula et al. (2001) observed that increase in the age at first birth from less than 20 years to 30+ years nearly doubled the risk.

Late age at first birth was a risk factor for breast cancer especially among younger women and is significantly stronger for those diagnosed with breast cancer at younger age, below 55 ($p=0.002$) (Weiss et al. 1996) compared to over 55 (Tulinius et al. 1990). Palmer et al. (2003) from a cohort study carried out among African – American women in U.S. observed that late age (above 29 years) at first birth compared with early age (less than 20 years) was a risk factor for breast cancer among younger women of age

below 45 years (Incidence Rate Ratio (IRR) 2.5; 95% CI 1.1–5.8) and the risk was not elevated among older women of age 45 years and above (IRR 0.7; 95% CI 0.4–1.4).

However, a few studies found no significant association between age at first birth and the risk of breast cancer (Adami et al. 1980, Meirik et al. 1986, Alexander et al. 1987, Kvale and Heuch 1987, Ewertz and Duffy 1988, Adami et al. 1990, McCredie et al. 1998)

Interval between menarche and first birth longer than 14 years was found to have a significantly higher risk of breast cancer in women older than 61 years (RR 2.4; 95% CI 1.3–4.4) (De Stavola et al. 1993). A similar study from India by Gajalakshmi and Shanta (1991) revealed a three-fold risk (RR 3.1; 95% CI 1.4–6.7 and RR 3.3; 95% CI 1.5–7.3) among pre and postmenopausal groups respectively when the interval between age at first birth and menarche was > 12 years relative to an interval of < 4 years.

2.7.4 Parity

Women with high parity were found to be at reduced risk of breast cancer compared to women with low parity (Hakama et al. 1979, Layde et al. 1989, Ewertz et al. 1990, Lambe et al. 1996, Wu et al. 1996, Magnusson et al. 1999, Hinkula et al. 2001). Nulliparous women are at increased risk for breast cancer compared with parous women, with estimates of protection for parous women from the risk of breast cancer ranging between 10% to 32% (Paymaster and Gangadharan 1972, Henderson et al. 1974, Lubin et al. 1982, Ewertz and Duffy 1988, Leon 1989, Ewertz et al. 1990, Tulinius et al. 1990, Gajalakshmi and Shanta 1991, Rao et al. 1994, Gomes et al. 1995, Nagata et al. 1995, Lambe et al. 1996, McCredie et al. 1998, Gao et al. 2000). The risk of breast cancer in nulliparous women under age 45 was 3 times that for parous women in the same age group, and women over 44 years of age with a parity greater than 4 had a risk of breast cancer of 0.3 compared to women of the same age but with a parity of 1–4 (Rosero-Bixby et al. 1987). Breast cancer risk showed a statistically significant decline with increasing parity even after adjustment for age at first birth. Further births subsequent to the first have an independent effect on breast cancer (Leon 1989).

In a meta-analysis of three cohort and five case-control studies from the Nordic countries, Ewertz et al. (1990) found that nulliparous women had 30% higher risk of breast cancer compared with parous women and the risk reduced by about 16% for every two births. Persisting protective effect of parity was noted even after adjusting for age at first birth and vice-versa indicating that, both these factors have an independent effect on breast cancer risk. A 40–50 % reduction in the risk among multiparous women with 3 or more pregnancies compared to nulliparous women was reported by Rao et al.

(1994). Nagata et al. (1995) from a meta-analysis found that parous women with 3 or more births had a 32% diminished risk (OR 0.7; 95% CI 0.5–0.9) compared with nulliparous women, independent of age at first childbirth. The effect of parity was determined by the age of occurrence of various births (Decarli et al. 1996).

A strong trend of decreasing breast cancer risk with increasing parity (OR 0.85; 95% CI 0.80–0.90) per borne child was observed in women aged between 50 and 74 years by Magnusson et al. (1999). In a nationwide cohort study of women with at least 5 births (grand multiparas) conducted in Finland, Hinkula et al. (2001) found that parity of fifth child onwards was an independent and powerful protective factor for breast cancer risk. Clavel-Chapelon and the E3N-Epic Group (2002) found this protective effect of high parity only for postmenopausal breast cancer risk (p for trend test= 0.001), with point estimates of 0.79 (0.60–1.04), 0.69 (0.54–0.88), 0.66 (0.51–0.85) and 0.64 (0.48–0.86) associated to one, two, three and four or more full-term pregnancies.

The Collaborative Group on Hormonal Factors in Breast Cancer (2002) in a collaborative reanalysis of individual data from 47 epidemiological studies observed a reduced risk of 7.0% (95% CI 5.0–9.0, $p < 0.0001$) for each birth. Parity was found to have a dual association with breast cancer risk among the African-American women (Palmer et al. 2003). Compared with primiparity, high parity was associated with an increased risk of breast cancer among women younger than 45 years (Incidence Rate Ratio (IRR) for 4 or more births was 2.4, 95% CI 1.1–5.1) and a decreased risk among women aged 45 years and older (IRR 0.5; 95% CI 0.3–0.9).

A few authors (Yuan et al. 1988, Adami et al. 1990), however, found no association between parity and risk of breast cancer.

2.7.5 Age at last birth

MacMahon et al. (1970a) from an international collaborative study of breast cancer observed that births after the first have relatively little influence on breast cancer risk, and the relationship between breast cancer risk and parity results primarily from the fact that age at first birth and ultimate total parity are highly correlated. Further, it was also noted that age at first confinement is a much more important factor than total parity; indeed, the latter probably has no association with breast cancer risk except through its association with age at first birth. Compared to nulliparous women the breast cancer odds ratio for uniparous women who had their child before age 25 was 0.62 and ratio for biparous women who had both their children under that age was 0.18 (MacMahon et al. 1982a). Trichopoulos et al. (1983) observed a 0.9% increase of risk for every year of increase in age at any (and every) birth (95% CI 0.04–1.5%). Births after the first do

exert an independent effect on breast cancer risk which, given the distribution of births by age of the mother in the population studied, is one of increasing protection with increasing number of births (Leon 1989).

Negri et al. (1990), using pooled data from two hospital-based case-control studies in Italy to study the role of age at first and at second births on subsequent breast cancer risk, observed that the results for age at first and second birth were similar in the two studies pooled. A significant interaction with age was observed in relation to age at first and second birth. In younger women (below age 50) a strong and direct association with age at first birth was found, while no apparent protection was conveyed by earlier second birth. Among older women (aged 50 or over), there was no apparent relationship with age at first birth after allowance for age at second, but the role of age at second birth was independent and statistically significant, suggesting the fact that, age at second birth has an independent and significant role in biparous women after allowance for age at first birth and indicated that, after reciprocal allowance, the role of first and second birth was not apparently different. Age at the time of birth of the second child was a determinant of that effect among women who had only two children.

In a study conducted to detect a transient increase in risk of breast cancer following childbirth in Swedish women, Leon et al. (1995) reported that within three years of their last childbirth, women had an estimated rate of breast cancer of 1.2 (1.0–1.4) times that of women whose last birth was 10 or more years earlier after adjustment for parity and age at first birth.

Lambe et al. (1996) observed a small increase of risk of marginal statistical significance (OR 1.1; 95% CI 1.0–1.1) for every five-year increase in age at last birth. Age at subsequent births has an independent, though smaller effect on breast carcinogenesis with an estimated 0.7% increase of risk per each year of delay (Decarli et al. 1996).

2.7.6 Lactation

The quest to identify the association between lactation and risk of breast cancer dates back to the 1920's. Lane Claypan (1926), proposed that, 'the breast which has never been called upon for normal function is certainly more liable to become cancerous. An association of lactation and risk of breast cancer has long been postulated, but uncertainty remains'.

Some studies have found a protective effect between lactation and breast cancer (Lubin et al. 1982, Tao et al. 1988, Yuan et al. 1988, Layde et al. 1989, Yoo et al. 1992,

Brinton et al. 1995, Katsouyanni et al. 1996, Romieu et al. 1996, Yang et al. 1997, Enger et al. 1997, Gao et al. 2000).

From a population-based case-control study, Lubin et al. (1982) found breastfeeding to be an apparent protective factor for the risk of breast cancer independent of age at first birth and parity. Premenopausal women had a consistently stronger reduction in breast cancer risk associated with breastfeeding independent of age, parity and age at first full term pregnancy than postmenopausal women (McTiernan and Thomas 1986). Yoo et al. (1992) also made a similar observation that the risk was lowest among premenopausal women who had ever lactated for 7–9 months (adj. OR 0.39; 95% CI 0.15–0.97) compared with parous women who had never breastfed.

In China, where more than half of the women breastfeed for at least 3 years, a 64% reduction in risk was found among mainly premenopausal women who breastfed for at least 10 years compared with women who never breastfed (Tao et al. 1988). Women who had lactated for 6–9 years and more than 9 years had relative risks of 0.35 and 0.37 respectively (Yuan et al. 1988). Romieu et al. (1996) from a case-control study found that parous women who had ever lactated had a reduction in breast cancer risk (age adjusted odds ratio (OR) 0.39; 95% CI 0.25–0.62) compared with parous women who had never breastfed. Breast cancer risk tended to fall amongst parous women with increasing duration of breastfeeding and the association was most apparent in the youngest women, while women over 40 years at diagnosis showed no clear negative trend (McCredie et al. 1998).

In a meta-analysis to evaluate the relation between breastfeeding and breast cancer, Bernier et al. (2000) found a slight but significant decreased risk of breast cancer in ever breastfeeding, compared with never breastfeeding parous women, and this decrease was more pronounced in non-menopausal women at the time of diagnosis of breast cancer and in long-term breastfeeding women.

A significant 4.3% (95% CI 2.9–5.8, $p < 0.0001$) reduction in the breast cancer risk for every 12 months of breastfeeding was reported from a collaborative reanalysis of 47 epidemiological studies in 30 countries by the Collaborative Group on Hormonal Factors in Breast Cancer (2002). The group also noted that the size of the decline in the relative risk of breast cancer associated with breastfeeding did not differ significantly for women in developed countries and developing countries and did not vary significantly by menopausal status, ethnic origin, the number of births a woman had, her age when her first child was born, age at diagnosis, education, country, mother or sister with breast cancer, age at menarche, height, weight, body mass index (BMI), previous use of hormonal contraceptives, alcohol consumption and tobacco consumption.

Several studies have found a negative relationship between lactation and risk of breast cancer independent of age at first birth (MacMahon et al. 1970b), parity

(MacMahon et al. 1982a, Layde et al. 1989, Yoo et al. 1992, Gomes et al. 1995, Negri et al. 1996, Magnusson et al. 1999) and duration of breastfeeding (Thomas et al. 1993). Stuver et al. (1997) in a reanalysis of the 1960's data of MacMahon and colleagues observed no significant effect of lactation either for premenopausal or postmenopausal women from the high, moderate or low risk areas. Examination of cumulative duration of lactation did not support an inverse association between breast cancer and increased length of total breastfeeding. Though breastfeeding appeared to be a protective factor it was of small magnitude compared with other known risk factors for breast cancer Bernier et al. (2000).

2.7.7 Age at menopause

A large number of epidemiologic studies have suggested that age at menopause is an important determinant in breast cancer. Late age at menopause was found to be associated with an increased risk of breast cancer (Lubin et al. 1982, Kelsey and Hildreth 1983, Schatzkin et al. 1987, Tao et al. 1988, Negri et al. 1988, Hsieh et al. 1990, Talamini et al. 1996, Fioretti et al. 1999). Gao et al. (2000) reported that late age at menopause was a risk factor only among postmenopausal women.

The increased risk associated with late age at natural menopause among postmenopausal women was not found until after age 65, suggesting that the effect of age at menopause was not seen for 10–20 years after menopause (Alexander and Robert 1987). A relative risk of about 1.4 was found in those women who were in the still menstruating age-groups compared with those no longer menstruating. This elevation in risk, as suggested by the above authors, indicates that existing tumours may have an increased growth rate at the time of menopause. In other words, relative to postmenopausal women of the same age, tumours in women who are still being exposed to premenopausal levels of sex hormones may be growing faster.

Negri et al. (1988) reported a relative risk of 0.7 for women whose age at menopause was below 45 years compared to those women whose age at menopause occurred at age 50 years and above, and this trend in risk was found to be statistically significant in all the three models studied i.e., (i) excluding parity, (ii) excluding age at first live birth, and (iii) including all variables, but excluding nulliparous women. In a cohort study conducted in Norway, Kvale and Heuch (1988) observed that, for each year of increase in age at menopause, the risk of breast cancer increased by 3–6% and the protection effect of early menopause was strongest for breast cancer diagnosed in patients 80 years of age or older. A more than two-fold risk (OR: 2.16) was found for women whose menopause occurred after age 50 compared to menopause before age 45

(Tao et al. 1988). For every 5 year difference in age at menopause the risk for breast cancer changes by about 17% Hsieh et al. (1990).

Magnusson et al. (1999) in a population-based case-control study including 3,016 women aged 50 to 74 years with invasive breast cancer and 3,263 controls of similar age found no association between menopausal symptoms and risk of breast cancer.

The increased risk associated with early age at menarche and late age at menopause possibly implies that the longer the exposure to sex hormones during the reproductive years, the higher the risk of breast cancer (Henderson et al. 1985). It is possible that the two factors, early age at menarche and late age at menopause are independent risk factors for breast cancer. It would be difficult to separate their independent effects from the effect of total number of years of menstrual activity, since the total number of years depends on age at menarche and menopause.

2.7.8 Hormone replacement therapy and risk of breast cancer

The effect of exogenous hormones, in the form of hormone replacement therapy and oral contraceptives, on breast cancer risk has been studied extensively. In a collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer the Collaborative Group on Hormonal Factors in Breast Cancer (1997) demonstrated that the relative risk of having breast cancer diagnosed increased by a factor of 1.02 (95% CI 1.01–1.04) for each year of use among current users of hormone replacement therapy or those who ceased use 1–4 years previously and the relative risk was 1.35 (95% CI 1.21–1.49) for women who had used hormone replacement therapy for 5 years or more. It was also noted from the study that this increase was comparable with effect on breast cancer of delaying menopause, since among never-users of hormone replacement therapy the relative risk of breast cancer increased by a factor of 1.03 (95% CI 1.02–1.03) for each year older at menopause, 5 or more years after cessation of hormone replacement therapy use, there was no significant excess of breast cancer overall or with respect to duration of use. This finding is consistent with studies demonstrating that postmenopausal women with higher concentrations of endogenous estrogen levels have a greater risk of developing breast cancer than women with lower estrogen levels (Hankinson et al. 1998). More recent studies have found statistically significant increases in risk in women taking both estrogen and progestin compared with those taking estrogen alone for hormone replacement (Ross et al. 2000)

2.7.9 Oral contraceptives and breast cancer risk

The use of oestrogens and progestagens for contraception has revolutionized the reproductive life of millions of women since the 1960's. So far there is no consistent evidence to suggest that use of oral contraceptives increases the risk of breast cancer for older women. An increased risk of breast cancer was noted in women of all ages who had used oral contraceptives within the past year but not to a greater extent in women near the age of menopause than in younger women. Relative risks did not increase with the duration of oral contraceptives use after age 45 in either pre or postmenopausal women. This suggests that there is no enhancement in the risk of breast cancer with the use of oral contraceptives by a greater amount when taken around the time of menopause than when taken at other times (Thomas and Noonan 1991).

In a meta-analysis, the Collaborative Group on Hormonal Factors in Breast Cancer (1996), based on 54 epidemiological studies worldwide, reported that women who are currently taking combined oral contraceptives are at a slightly increased risk of breast cancer relative to never users and that this risk decreases after stopping use. Moreover, no increase in the relative risk was found 10 years after cessation of oral contraceptive use.

Among BRCA 2 mutation carriers ever use of oral contraceptives was not associated with an increased risk of breast cancer. For BRCA 1 mutation carriers, ever use of oral contraceptives was associated with a modestly increased risk of breast cancer. Among BRCA 1 mutation carriers, women who used oral contraceptives before age 30 or women who used oral contraceptives for 5 or more years may have an increased risk of early-onset breast cancer. (Narod et al. 2002)

In a cohort study carried out in Sweden, Olsson et al. (2003) reported that longer use of hormone replacement therapy containing progestins significantly elevated breast cancer risk, whereas estradiol use did not. Continued use of progestins rendered the highest risks. The yearly risk of breast cancer for long-term users of progestins was of the magnitude of 50% the risk of BRCA 1 mutation carrier.

In a large Norwegian cohort study, Dumeaux et al. (2003) found that the risk of breast cancer increased by 25% for ever use of oral contraceptives and that the risk increased with increasing duration of use. No association between time since last use and breast cancer risk was observed after stratification of duration of use. The increased risk of breast cancer related to oral contraceptive formulations may mostly be due to the estrogen component. Althuis et al. (2003) found that women who recently used oral contraceptives containing more than 35 mg of ethinyl oestradiol per pill were at increased risk of breast cancer compared to users of lower dose preparations when compared to never-users. This relationship was more marked among women younger

than 35 years of age, where risks associated with high and low-dose ethinyl oestradiol use were of over 3-fold and about 2-fold respectively. Current use of oral contraceptives was associated with more than 2-fold risk of lobular carcinoma and there was a significant trend of increased risk of breast cancer with more recent use (Newcomer et al. (2003).

Some studies found no significant association between use of oral contraceptives and risk of breast cancer (Vessey et al. 1989, Rosenberg et al. 1992, Tavani et al. 1993, Paul et al. 1995).

2.7.10 Abortion and risk of breast cancer

Many studies have been carried out to assess the risk of breast cancer in relation to spontaneous and or induced abortions. Regardless of whether spontaneous and induced abortions are considered separately or in combination, some studies have shown positive association (Pike et al. 1981, Ewertz and Duffy 1988, Howe et al. 1989, Daling et al. 1996). Some have shown inverse associations (Paffenbarger et al. 1980, Vessey et al. 1989).

Kvale et al. (1987) in a cohort study from Norway observed only a borderline significant risk among those women who reported at least one abortion compared to those who did not, but no trend was found according to the number of abortions. A moderate risk of breast cancer was found for first trimester induced abortion, especially if the abortion occurred before a first full-term pregnancy (Pike et al. 1981, Daling et al. 1996). Lipworth et al. (1995), found that parous women who experienced an induced abortion prior to their first full-term pregnancy had a significant two-fold increased risk of breast cancer. An induced abortion after a full-term pregnancy appeared to be related to a 60% increase in breast cancer risk among parous women, while spontaneous abortion did not materially affect risk.

Some studies found no association between risk of breast cancer and history of either induced abortions (Lubin et al. 1982, Helmrich et al. 1983, Parazzini et al. 1991, Talamini et al. 1996 and Tavani et al. 1996) or spontaneous abortions (Clavel-Chapelon and the E3N-Epic Group 2002, Erlandsson et al. 2003). Paoletti et al. (2003) from the E3N cohort study reported no relationship between breast cancer and induced abortion but an association with spontaneous abortions is possible and may depend on menopausal status. The study revealed that in premenopause the risk decreased with increasing number of spontaneous abortions, where as it increased after menopause.

It is difficult to reach definite conclusions from these studies because of the inconsistencies of results and the inaccuracies in reporting of both spontaneous and induced abortions.

2.8 Other risk factors

2.8.1 Religion

India is a vast country with widely varying social, cultural, religious and dietary practices, and each of these factors differs depending on the religion. The major religion is Hinduism followed by Islam, Christianity and others (among them Jains, Buddhists, Sindhis, Sikhs, Neobuddhists, Parsi etc). Such kinds of religions probably cannot be found in any other countries of the world. In one of the studies carried out in greater Bombay (Mumbai) by Jussawalla et al. (1981), it is reported that the risk of developing breast cancer is high in Parsi women as compared to Christian, Muslim and Hindu women, and this fact may be due to a higher proportion of Parsi women remaining unmarried, their higher age at marriage, late age at first pregnancy, broad spacing of pregnancies and smaller number of pregnancies, in addition to better socioeconomic conditions (Paymaster and Gangadharan 1972) and leading a more westernized lifestyle (Jayant 1986).

Egan et al. (1996), from a population-based case-control study, found that the relative risk of breast cancer was much higher for Jewish women with a first degree relative who had breast cancer than in women of other religions, suggesting that certain groups of Jewish women have a higher than expected rate of mutation in the breast cancer gene BRCA1.

2.8.2 Eating habits

Various studies have shown that diets high in fat, particularly polyunsaturated, have enhanced the production of tumours in animals challenged with chemical carcinogens. Other studies have found an apparent contradiction of no difference in the incidence of breast cancer with varying levels of serum cholesterol as measured decades earlier (Graham et al. 1982). More frequent consumption of beef, pork and sweet desserts was associated with an elevated risk of breast cancer, increased risks were also noted for use of butter at the table and for frying with butter or margarine, as opposed to vegetable oils (Lubin et al. 1981). Breast cancer development was related to a diet rich in meat, fat

and sugar, and that some protection against cancer may be afforded by a reduction in these dietary components and an increase in cereal consumption (Ingram 1981).

Studies carried out on diet and breast cancer have yielded inconsistent results regarding the association between dietary fat intake and risk of breast cancer. Vatten et al. (1990) found a positive association between frequency of overall meat intake and breast cancer risk. Women who had a main meal with meat 5 times or more per week were found to have about two fold risk compared with women who had two meat dinners or less per week, but there was an inverse relation with the frequency of main meals containing fish in poached form. A significantly elevated risk of breast cancer with high intake of total fat and saturated fat among postmenopausal women and a protective effect of fruits, vegetables and vitamin C was observed in a meta-analysis by Howe et al. (1990).

Reduction in risk of breast cancer associated with high intake of milk and green-yellow vegetables (green leafy vegetables, carrots and pumpkins) was observed among both pre and postmenopausal Japanese women by Hirose et al. (2003). Consumption of fish 5 or more times a week compared to fewer than 3 times per month and increased intake of fruits showed a significantly reduced risk for postmenopausal women in this population. In a population case-control study to investigate the associations of breast cancer risk with vegetables, fruits and related micronutrient intake among Chinese women, Malin et al. (2003) found no association between breast cancer risk and total vegetable intake. However, the risk of breast cancer declined with increasing intake of dark yellow-orange vegetables. Intake of fruits, except watermelons and apples was inversely associated with breast cancer risk.

A few studies have reported no association of dietary fat in the aetiology of breast cancer (Willet et al. 1987, Rohan et al. 1988).

Many epidemiological studies have been carried out to investigate the relationship between breast cancer and the consumption of alcohol and/or tobacco. The published results from these studies have generally suggested that women who generally consume alcohol may be at a slightly increased risk of breast cancer, but the findings reported for tobacco are inconsistent. Alcohol and tobacco consumption are known to be associated one with another and published results have not always allowed adequately for possible confounding between these exposures.

In a meta-analysis of 53 epidemiological studies, Beral and the Collaborative Group on Hormonal Factors in Breast Cancer (2002) found that, compared with women who reported drinking no alcohol, the relative risk of breast cancer was 1.32 ($p < 0.00001$) for an intake of 35–44 g per day alcohol, and 1.46 ($p < 0.00001$) for 45 g of alcohol or more per day. The relative risk of breast cancer increased by 7.1% ($p < 0.00001$) for each additional 10 g per day intake of alcohol. This increase was the

same in ever-smokers and never-smokers (7.1% per 10 g per day in each group). In contrast, when analysis was restricted to women with breast cancer and controls who reported drinking no alcohol, smoking was not associated with breast cancer. In developing countries, where alcohol consumption among controls averaged only 0.4 g per day, alcohol would have a negligible effect on the incidence of breast cancer. The findings of the above study suggest that smoking has little or no independent effect on the risk of developing breast cancer. The effect of alcohol on breast cancer needs to be interpreted in the context of its beneficial effects, in moderation, on cardio-vascular disease and its harmful effects on cirrhosis and cancers of the mouth, larynx, oesophagus and liver.

2.8.3 Family history of breast cancer

Many epidemiologic studies have suggested that a family history of breast cancer increases a woman's risk of developing breast cancer (Lubin et al. 1982, Yoo et al. 1992, DeStavola et al. 1993, Madigan et al. 1995, Romieu et al. 1996, Weiss et al. 1996, Yang et al. 1997) and the extent of risk varies according to the nature of the family history, type of relative affected, age at which relative developed breast cancer and the number of relatives affected and may vary according to the age of the individual (Pharoah et al. 1997). The risk was greater if the relative had breast cancer while premenopausal than if she had breast cancer while postmenopausal (Romieu et al. 1996) and higher if the relative had bilateral breast cancer than if she had unilateral disease (Ottman et al. 1986).

Madigan et al. (1995) from a cohort study observed more than two and a half times risk (RR 2.6; 95% CI 1.7–3.9) of breast cancer among women with a history of breast cancer in a first degree relative and suggested that according to the population attributable risk estimates, 9.1% of the breast cancer cases in the United States were accounted for through family history of breast cancer compared with women with no family history of breast cancer. A risk of 2.7 (95% CI 2.2–3.3) in those with one first-degree relative affected and a risk of 2.8 (95% CI 1.3–5.7) in those with two or more affected relatives was reported by Parazzini et al. (1993). From a case-control study in Brazil, Gomes et al. (1995) observed that women with a history of breast cancer among first degree family relatives (mothers, sisters or daughters) was independently associated with an increased risk (OR 9.35; 95% CI 3.22–27.14) of breast cancer.

Claus et al. (1990) from a large population-based case-control study reported that among relatives of cases, a significant increase in the risk of breast cancer was associated with decreasing age at onset of the case and with having an additional

relative affected with breast cancer. The hazard ratio for the mother of a case with breast cancer diagnosed at 50 years of age was 1.7 (95% CI 1.4–2.0) compared with 2.7 (95% CI 2.2–3.2) and 4.3 (95% CI 3.3–5.6) for the mother of a case whose diagnosis occurred at 40 and 30 years of age respectively. The hazard ratio for the sister of a case with an unaffected mother and at least one affected sister was 5.9 (95% CI 3.9–8.9) when the case was diagnosed at age 50, compared with 9.4 (95% CI 6.2–14.4) and 15.1 (95% CI 9.4–24.3) when the case was diagnosed at 40 and 30 years of age respectively. The hazard ratio for the sister of a case with both unaffected mother and at least one affected sister apart from the case was 17.1 (95% CI 9.4–31.3) when the case was diagnosed at age 50 years, compared with 27.5 and 44.2 when the case was diagnosed at 40 and 30 years of age respectively. No effect of case's menopausal status and bilaterality was found, suggesting that, in addition to a positive family history, age at onset is the strongest indicator of a possible genetic subtype of breast cancer in these populations. In a study carried out by Dite et al. (2003), extensive BRCA 1 and BRCA 2 mutation testing was carried out for 788 case patients diagnosed before age 40 years, including manual sequencing of DNA from 72 patients with two or more affected relatives. It was reported that cumulative risks of breast cancer to age 50 years in the sisters, mothers and aunts of the case patients respectively were 6, 3 and 2 times the population risk if the case patient was younger than age 40 years at diagnosis, but were considerably lower if the case patient was older at diagnosis. When relatives of the case patients with BRCA 1 or BRCA 2 mutations were excluded, these risks fell at most, by 20%. Sister and aunts but not mothers who had an additional first-degree relative with breast cancer were at increased risk and the risk was greater when that relative was younger at diagnosis. Hazard ratios were 10.7 (95% CI 4.2–26.8) for sisters and 4.2 (2.2–8.1) for aunts, if the relative was aged 40 years at diagnosis. Less than one third of the excess of breast cancer in relatives of case patients diagnosed before age 40 years that are attributable to familial factors are BRCA 1 or BRCA 2 related. The above results indicate that mutations in genes other than BRCA 1 and BRCA 2 may be associated with a high risk of breast cancer, especially in young women. Brignone et al. (1987) reported that family history was not a risk factor for breast cancer in a Southern European population.

2.8.4 Obesity

The association between body mass index (BMI) and risk of breast cancer has been examined in numerous studies. Body mass index is calculated as weight in kilograms divided by square of height in meters (kg/m^2). Some studies have found a positive association between body mass index and risk of breast cancer among postmenopausal

women (DeWaard 1975, Choi et al. 1978, Hsieh et al. 1990, Franceschi et al. 1996, Shu et al. 2001). A lower risk of breast cancer in women with high body mass index was reported among premenopausal women by London et al. (1989), Ursin et al. (1995) Franceschi et al. (1996) whereas some studies found no association (Adami et al. 1977, Wynder et al. 1978, Negri et al. 1988, Lund 1991).

Hsieh et al. (1990) in an international multi-centre case-control study found that height and obesity (measured through the weight/height sq. index) were independent risk factors for breast cancer among postmenopausal women but not pre menopausal women. A 12% higher risk of breast cancer (95% CI 3–21%) was observed among postmenopausal women taller by 10 cm, and those women (postmenopausal) of average height (approximately 158 cm) had an 11% higher risk of breast cancer, when they were heavier by 10 kg (i.e. more obese by 4 kg/m²). In a population-based case-control study to investigate the relation between body size and breast cancer risk among black women and white women, Hall et al. (2000) found that among premenopausal women body mass index (kg/m²) was inversely associated with breast cancer (OR 0.46; 95% CI 0.26–0.80) for whites but not for blacks. No association was observed among postmenopausal women. But higher waist/hip ratio adjusted for body mass index, increased risk for all women. Shu et al. (2001), who examined the association of body size and fat distribution with the risk of breast cancer among Chinese women, reported that even in a relatively thin Chinese population, weight gain and height are related to an increased risk of postmenopausal breast cancer, while central fat distribution was associated with premenopausal breast cancer. Jonsson et al. (2003) reported that overweight at age 25 was associated with decreased risk of breast cancer (RR 0.51; 95% CI: 0.33–0.78) and increased risk of breast cancer was found in only older women (\geq 70 years).

Body mass index, adjusted for life time exercise, was strongly associated with breast cancer risk among women with a positive family history of breast cancer (p-trend <0.0001), but only weakly associated among women with no family history (p-trend=0.08; homogeneity of trends p=0.0005) (Carpenter et al. 2003). It is suggested that general weight control (Shu et al. 2001) and avoidance of abdominal obesity (Connolly et al. 2002) may reduce the risk of breast cancer. Further age is an important effect modifier of cancer risk associated with obesity and obesity and overweight in young adult life may also affect cancer risk later in life (Jonsson et al. 2003).

3 AIMS OF THE STUDY

India is rapidly moving towards industrialization, resulting in a change of lifestyle factors such as improved socioeconomic conditions, higher education, increase in age at marriage, delay in age at first birth, reduction in parity etc., and probably all these factors have contributed to the gradual rise in the incidence of breast cancer in the country.

Two broad areas that are linked with the risk of the breast cancer are:

1. Increase in standard of living resulting in improved socioeconomic status
2. Reproductive and hormonal factors which are closely linked.

In a developing country environment much less is known about the risks of breast cancer. In order to examine whether the standard of living and hormonal or reproductive factors in a developing country enhance the risk of breast cancer, the aims of the study were to examine:

1. The role of socioeconomic status
2. The role of reproductive and hormonal factors in relation to the risk of the breast cancer.

However, these are not independent of each other but rather, standard of living and other environmental factors affect marital practice and other reproductive factors and hence also the hormonal bias. Therefore the study aims to also examine

3. The interrelationship of socioeconomic status and reproductive factors.

4 MATERIAL AND METHODS

4.1 Study area

The study was conducted in a cancer centre at Kidwai Memorial Institute of Oncology (KMIO) located in Bangalore, the capital city of the State of Karnataka in southern India. Karnataka had a population of 52.7 million as of the 2001 census and that of Bangalore city population 5.7 million. The State of Karnataka has been divided into four regions, the coastal region, the malnad (hilly area), the northern plains and, the southern plains. For administrative convenience, it was further divided into 27 districts and Bangalore is one among these districts. The male to female sex ratio of the state is 1:0.9 and the literacy rate is about 67%. The ratio of urban population to the total population is 30 per cent.

The KMIO is a comprehensive centre for cancer research and treatment in the State, and is one of the seventeen Regional Cancer Centres in India. The Institute has bed strength of 429, apart from a Dharmashala – Ambulatory Patient Home, which provides accommodation for 250 patients along with their attendant relatives. The Institute offers all modalities of cancer directed treatment: surgery, radiotherapy, chemotherapy and hormone therapy with a multidisciplinary team approach. Since the centre is located in the extreme south of the State, patients from all over the State and also from the adjoining areas of the neighbouring states of Tamilnadu, Andhra Pradesh and other regions also seek cancer care from this Institute. Annually over 12,000 new cases are registered of which about 70% would be confirmed to have cancer. The male to female sex ratio of the patients was 1: 1.2. Microscopic confirmation of the diagnosis accounts for about 93% of all cancer sites in males and 95% of all cancer sites in females.

4.2 Cancer registration at KMIO

The Institute has both a hospital-based cancer registry (established since the inception of the Institute in 1973) and a population-based cancer registry established in 1982 under the network project of the National Cancer Registry Programme of the Indian Council of Medical Research. Later, in the year 1984, the hospital-based cancer registry was included under the National Cancer Registry Programme.

The main task of the hospital-based cancer registry is to maintain detailed information about each and every patient registered in the Institute. Over 250,000 patients' records are maintained since the inception of the Institute (1973). Patients attending KMIO are registered only once and records are updated as and when patients attend the centre for their follow-up treatment.

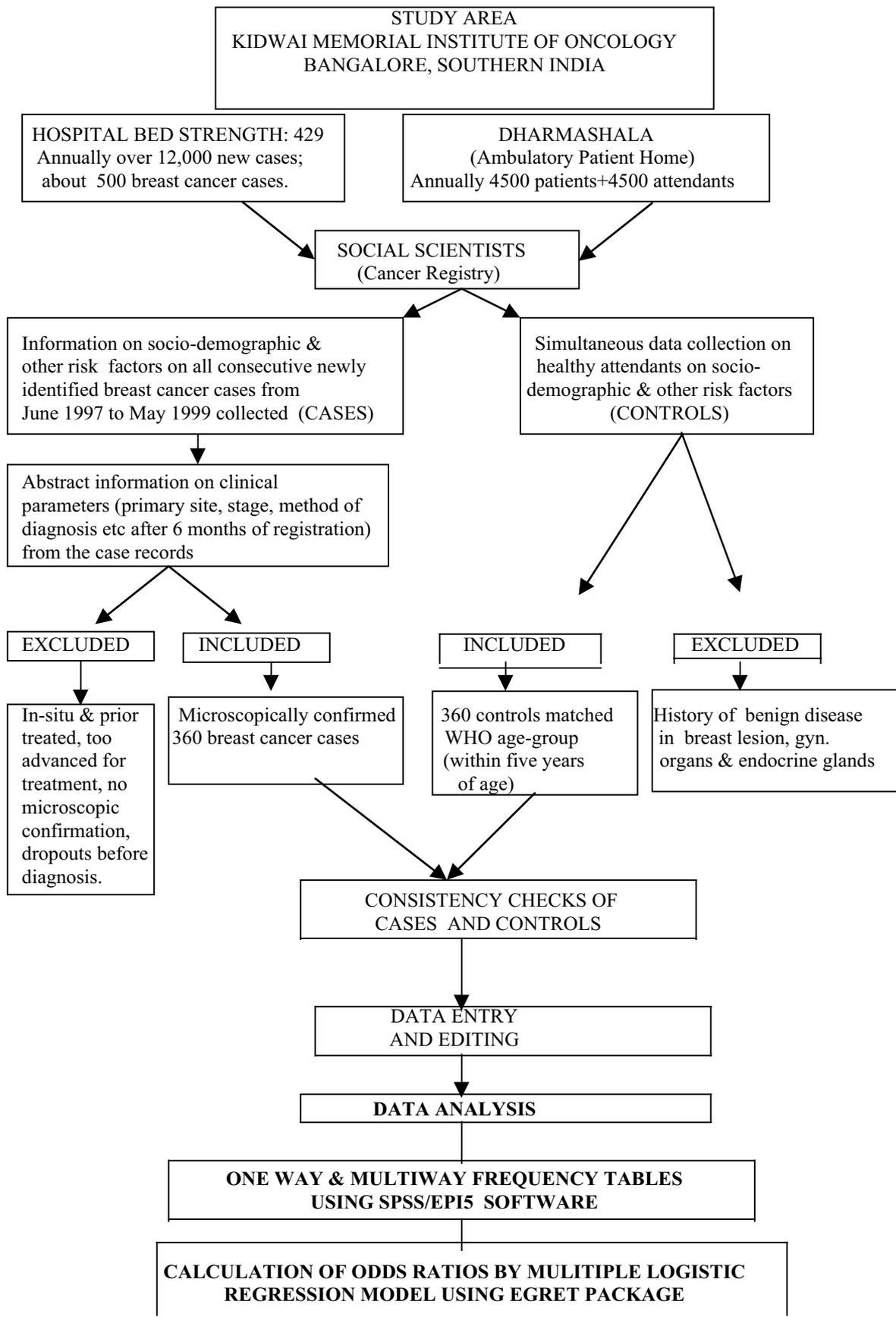
The registry staff, soon after the registration of a patient and before sending the patient to any of the out-patient department, collects information on identification and sociodemographic items such as hospital / registration number, name, address (permanent and local), age, sex, marital status, mother tongue, educational level, religion, race etc, in a structured questionnaire and after six months of registration, the case records of these patients are obtained from the medical records to the registry to abstract information on clinical items such as method of diagnosis, site of tumour, histological diagnosis, stage of the disease, treatment particulars, discharge status etc.

The population-based cancer registry covers a population of 5.7 million in an area of 191 sq. kms of the Bangalore Urban Agglomeration. About 65% of the cases registered in the population-based cancer registry are from KMIO alone.

4.3 Study design

The study was planned and conducted as a prospective hospital based case-control study. The information on exposure factors was collected from all the suspected cases of breast cancer during the first presentation of the patient at the time of registration and simultaneously from the attendants of cancer patients staying at Dharmashala-Ambulatory Patient Home. Among the suspected cases, those cases confirmed microscopically to have malignancy were included in the study, as per the inclusion criteria with one control per case matched for age (within the WHO age group of 5 years).

FLOW CHART OF THE STUDY DESIGN



4.4 Selection of cases and controls

A total number of 360 consecutive, newly identified breast cancer cases registered at Kidwai Memorial Institute of Oncology from June 1997 to May 1999 formed the case series. Cases confirmed either by histology, cytology or both were included in the study. Even though about 500 cases of breast cancer cases are registered at this Institute annually, the cases with a history of previous treatment before registration at KMIO were excluded for the reason that, economically better-off patients would have gone to private hospitals for treatment where the cost of treatment was higher and thereby uniformity of cases for comparison with the controls would have been lost and assessment of actual date of diagnosis would be difficult. In-situ carcinoma of the breast, cases with advanced disease and cases with non-microscopic diagnosis, were also excluded.

Controls were selected from among the attendants of the cancer patients staying at the Dharmashala- Ambulatory Patient Home a unique project of its kind in the country. This place provides an accommodation for 250 ambulatory cancer patients who require prolonged and continuous cancer care and who could not get an inpatient bed in the Institute during their visit to the hospital. One attendant (normally a close relative of the patient) is also permitted to stay with the patient in the Dharmashala during the course of treatment of these patients. Of the female attendants staying at Dharmashala 360 women were selected after ascertaining (orally) that these women do not have any disease in the breasts, gynaecological organs or endocrine glands. Matching was done for age. From the pool of controls, a control was selected to match with the age of a case. In the event of non-availability of a particular age-matched control with that of age of the case, matching was done within plus or minus 5 years WHO age-group. The elected attendant (control) was unrelated to the matched case.

4.5 Data collection

Kidwai Memorial Institute of Oncology is a comprehensive and regional centre for cancer research and treatment and has a bed strength of 429. All patients either with a definite diagnosis of cancer or suspected cases of cancer are registered on recommendation by the General Duty Doctor (GDD) who examines the patients, and a unique hospital number is assigned to every patient. The Assistant Social Scientists of the cancer registry interviews all these registered patients prior to their detailed examination at the out-patient departments and collect information in the core proforma devised uniformly for cancer registry purposes. For the purpose of the present study, a

separate questionnaire was devised by the author based on a preliminary review of the literature with regard to the risk factors of breast cancer. This questionnaire was tested by interviewing 25 patients with breast cancer and an equal number of controls. As obtaining information on body mass index, particularly from the controls, was found to be difficult, this item was dropped, and a final questionnaire containing the following information was used in the study.

- Registration number
- Whether case or control
- Name and address
- Age
- Mother tongue
- Religion
- Education
- Area of living
- Economic status
- Occupation
- Total number of members in the family
- Eating habits
- Marital status
- Duration of marital life
- Age at menarche
- Menstruation cycles
- Age at marriage
- Number of pregnancies
- Number of live births
- Number of children alive
- Age at first birth
- Age at last birth
- Lactation history
- Menopausal status and age at menopause
- Use of birth control measures
- Duration of oral contraceptive use
- Family history of cancer: site of cancer in the relatives, relationship of the affected person (first or second degree relatives)
- Age at diagnosis of the cancer affected member of the family
- Method of diagnosis
- Histological type of tumour
- Stage of disease
- Previous history of treatment prior to registration at Kidwai Memorial Institute of Oncology

Two Assistant Social Scientists working in the registry were given two weeks' training to collect information for the present study and were not informed about the aims and objectives of the study. Socio-demographic and on exposure factor information from both cases and controls were obtained by these Assistant Social Scientists using the structured questionnaire by the personal interview method. On clinical parameters the required information was abstracted from the medical case records. The quality of information obtained/abstracted was checked by the author. About 25% of the completed questionnaires were picked randomly and checked against the records of the patients as a quality check of the information collected and errors (if any) were pointed out to the abstractors. Finally the data collected by the Assistant Social Scientists was checked for its completeness and consistency checks and coding of data were performed by the author.

4.6 Data analysis

The final data after consistency checks were entered into the computer in Dbase III using the programme, which was developed to enter the data item by item. Range checks were carried out after completion of the data entry.

SPSS (PC version 4.0) and EPI5 statistical software were used for generating one-way and multi-way frequency tables. Multiple logistic regression methods were employed using epidemiological graphics, estimation and testing package (EGRET) version 0.25.1; Epixact, version 0.03 (EGRET 1990) for estimating the odds ratios.

4.7 Case-control studies

The case-control study, also commonly called a retrospective study, follows a paradigm that proceeds from effect to cause. In a case-control study, individuals with a particular condition or disease (the cases) are selected for comparison with a series of individuals in whom the condition or disease is absent (the controls). Cases and controls are compared with respect to existing or past attributes or exposures thought to be relevant to the development of the condition or disease studied.

At times a distinction is made between the sources from which cases and controls are selected. In a population-based case-control study, all cases of the disease studied occurring within a defined geographical area during a specified period of time are ascertained, often through a disease registry or hospital network. The entire case series or a random sample of it is selected for study. Controls are selected by taking a

probability sample of individuals free of the study disease in the geographical area from which the cases arose. In a hospital-based case-control study, all cases of the study disease admitted to a single hospital or network of hospitals are ascertained during a specified period of time. The entire case series or a random sample of it is selected for study. In the hospitals from which the cases originated, controls are selected from individuals admitted for conditions other than the study disease (Schlesselman 1982).

Advantages and disadvantages of the case-control method:

Advantages:

1. They are well suited to the study of rare disease or those with long latency.
2. Case-control studies are relatively quick to mount and conduct.
3. Relatively in-expensive.
4. Requires comparatively few subjects.
5. Existing records can occasionally be used.
6. No risk to subjects.
7. Allows study of multiple potential causes of a disease.

Disadvantages:

1. Relies on recall or records for information on past exposures.
2. Validation of information is difficult or sometimes impossible.
3. Control of extraneous variables may be incomplete.
4. Selection of appropriate comparison group may be difficult.
5. Rates of disease in exposed and unexposed individuals cannot be determined.
6. Method relatively unfamiliar to medical community and difficult to explain.

The procedure suggested for analysing the case-control study data by Breslow and Day (1980) was followed. The most suitable statistical model for making inferences about the odds ratio with matched or very finely stratified data is to determine the conditional probability of the number of exposed cases in each stratum, assuming that the marginal totals of that stratum are fixed. For tables in which these are zero marginal totals, i.e. for the extreme tables in which either both or neither the case nor control are exposed to the risk factor, this conditional distribution assigns a probability of one to the observed outcome and hence contributes no information about the odds ratio. The statistical analysis uses just the discordant pairs, in which only the case or only the control is exposed. Thus the odds ratio estimation is done by obtaining the ratio of the two types of discordant pairs, namely the ratio of number of pairs where the case is exposed and control is not exposed to number of pairs where the case is not exposed and control is exposed. A technique to control for confounding in a matched analysis is to model the effects of the confounding variables in a multivariate equation which also includes the exposure of interest. For each variable in the model (e.g. age at menarche) a parameter estimator (β) and a standard error of the estimate (s.e) were obtained.

Hierarchical models were compared using the difference in deviances and in degrees of freedom. The difference in the deviances with its defined degrees of freedom expresses how significantly, using the Chi-square distribution, a newly fitted variable explains the outcome, the risk of breast cancer. An odds ratio [$OR = \exp(\beta)$] representing the relative risks and the 95% confidence intervals for them was calculated from the parameter estimates (β) and their standard error (s.e). Factors other than the exposure factor of interest were first fitted into the model. After looking for confounding factors, the exposure factors of interest were added to the model.

4.8 Parameters for evaluation

4.8.1 Socioeconomic status and standard of living

In the present study, three parameters: (i) Educational level, (ii) Economic or income level and (iii) Area of living were included under socioeconomic status.

Educational level

According to the existing education system in the country, the educational levels have been categorized into four groups depending on the number of years of schooling.

- (a). Illiterates (no schooling at all)
- (b). Primary (Up to 4 years of schooling)
- (c). Secondary (5–10 years of schooling)
- (d). College (11–15 or more years of schooling)

Economic or income level

Economic or income level based on the income has been classified into three groups, which has been adopted at KMIO and other government funded hospitals for the purpose of levying of charges for the investigation of disease and treatment.

- (a). Lower income (an income of Rs. below 1500 per month)
- (b). Middle income (income between Rs.1500–4500 per month)
- (c). Higher income (income of more than Rs.4500 per month)

Area of living

Area of living has been classified into two groups – namely urban and rural. As per the definition of Census Department, Government of India, an area is considered as urban, if

- (i). A city has a minimum population of 5,000.
- (ii). At least 75% of the male working population engaged in non-agricultural activities.
- (iii). Population density of at least 400 persons per sq.km.

Rural refers to / is defined as a revenue village which has a definite surveyed boundary.

4.8.2 Reproductive and hormonal factors

Information on the following reproductive variables was collected as continuous variables (as answered by cases and controls) and later categorised for analysis purpose.

- *Age at menarche*
- *Marital status and age at marriage*
- *Age at first birth*
- *Interval between menarche and first birth (computed)*
- *Parity*
- *Age at last birth*
- *Lactation*
- *Duration of lactation*
- *Menopausal status**
- *Age at menopause*

* Women were classified as premenopausal if they were still having their menstrual periods or if their periods had stopped within 6 months prior to diagnosis of breast cancer (in respect of cases and in respect of controls at the time of interview) and as postmenopausal if the menstrual periods had stopped for 6 or more months prior to diagnosis or at the time of interview in respect of cases and controls respectively.

In addition to the above, three more factors – religion, eating habits and family history were considered individually for evaluation.

4.8.3 Religion

India is a vast country with many religions and within these religions there are many castes and or sub-castes. However, the three major religions viz: (i) Hinduism (ii) Islam and (iii) Christianity were considered for the study and the rest were included under 'others'.

4.8.4 Eating habits

Eating habit has been classified into two categories: (1) Vegetarian and (2) Non-vegetarian.

Cases and controls were classified as vegetarians if they consumed a purely vegetarian diet consisting mainly of cereals like rice, wheat, ragi, milk and grain legumes particularly known as pulses as the staple food items in addition to root vegetables and green leaf vegetables.

Cases and controls were classified as non-vegetarians if they consumed non-vegetarian food which includes chicken, fish, meat, pork, beef and eggs as their diet irrespective of frequency of intake of these items which ranged from daily to once monthly. This category of non-vegetarians also consumed vegetarian food, in other words, this category was a mixed group.

4.8.5 Family history of cancer

Information on family history of cancer (including breast cancer) was collected from the cases and controls during the personal interview. This was oral information furnished by the cases and controls and no records were verified.

5 RESULTS

A total number of 1,606 cases was registered with suspected and or with a definite diagnosis of breast cancer at Kidwai Memorial Institute of Oncology during the period from June 1997 to May 1999, of which 360 cases of breast cancer confirmed microscopically were included in the study and 1,246 cases were excluded. The details of cases excluded and the clinical profile of the cases included in the study are shown in Tables 5 and 6 respectively.

The age at diagnosis of breast cancer cases included in the study is shown in Table 7. Since the controls were matched for age (WHO age group of ± 5 years) it follows the same age groups as that of cases.

The average (\pm Sd) age at diagnosis of breast cancer cases was 45.2 (± 10.3) years and the average (\pm Sd) age of controls was 44.8 (± 10.5) years.

Table 5. Details of cases excluded from the study.

Reasons for exclusion	
History of previous treatment	825
Benign lesions	260
Dropouts before diagnosis	103
Too advanced disease	30
Non microscopic confirmation	25
In-situ carcinoma	3
Total	1246

Table 6. The clinical profile of the cases .

	#	%
Microscopic diagnosis		
Primary Histology	264	73
Secondary Histology	4	1
Cytology	92	26
Total	360	100
Morphology		
Adenocarcinoma, Nos	1	0.2
Carcinoma, Nos	9	2.4
Comedocarcinoma, Nos	1	0.4
Cribriform	2	0.6
Cystosarcoma Phyllodes	9	2.6
Infiltrating Duct Carcinoma	310	86.1
Lobular Carcinoma	10	2.8
Medullary Carcinoma	5	1.3
Mucinous Adenocarcinoma	8	2.3
Neoplasm, Malignant	4	1.1
Tubular Adenocarcinoma	1	0.2
Total	360	100
Extent of disease		
Localised	40	11
Regional	247	69
Distant	73	20
Total	360	100
Laterality		
Right	167	46.40
Left	183	50.80
Bilateral	10	2.80
Total	360	100

Table 7. Age at diagnosis of breast cancer cases by 5 year age group .

Age groups	#	%
< 20	1	0.3
20–24	5	1.4
25–29	12	3.3
30–34	35	9.7
35–39	54	15.0
40–44	51	14.2
45–49	61	16.9
50–54	65	18.1
55–59	34	9.4
60–64	26	7.2
65–69	14	3.9
70 +	2	0.6
Total	360	100

5.1 Analysis of risk factors for breast cancer

The association between breast cancer and the following variables were studied

1. Socioeconomic status
2. Reproductive and hormonal factors
3. Other risk factors
 - 3.1. Religion
 - 3.2. Eating habits and
 - 3.3. Family history of cancer

Even though evaluation of other risk factors i.e., religion, eating habits and family history of cancer were not included under the objectives of the study, the risk if any, associated with breast cancer was studied.

5.2 Results of univariate analysis of risk factors

5.2.1 Socioeconomic status and risk of breast cancer

The odds ratios (ORs) for factors related to socioeconomic status—comprising educational level, economic status and area of living are shown in Table 8. The univariate analysis of the socioeconomic factors as regards standard of living revealed that the risk of breast cancer increased significantly with the increase in educational level by over four-fold, particularly for women with educational levels of secondary and college level compared with illiterate women. Similarly, women with higher income had about three-fold risk of developing breast cancer compared to women with lower income. Women residing in urban areas were found to be at over two-fold higher risk of breast cancer compared to women residing in rural areas.

Table 8. Odds ratios (ORs) and 95% confidence intervals (95% CI) of breast cancer by socioeconomic status (standard of living).

Factor	Case	Control	OR	95% CI
Educational level				
Illiterate	153	215	1.00*	–
Primary	57	71	1.24	0.82–1.87
Secondary	119	58	4.09	2.56–6.53
College	31	16	4.15	1.99–8.68
Economic status				
Lower	143	177	1.00*	–
Middle	106	129	1.07	0.76–1.51
Higher	111	54	3.06	1.95–4.82
Area of living				
Rural	208	250	1.00*	–
Urban	152	110	2.05	1.41–2.99

* Reference category

5.2.2 Reproductive factors and risk of breast cancer

A non-significant reduction of the risk of developing breast cancer was observed among women whose age at menarche was 13 years and 14 years compared with women whose age at menarche was at 12 years or less. Among women whose age at menarche was at 15 years, the risk did not alter materially. However, the risk was found to be slightly higher (non-significant) among women whose age at menarche was 16 years and above. Compared with women who ever-married, women who had never-married had a significant ten-fold risk of developing breast cancer and those who married after the age of 18 years had a significantly elevated risk compared with those who married at the age of 18 years or below (Table 9).

Table 9. Odds ratios (ORs) and 95% of confidence intervals (95% CI) of breast cancer by reproductive factors.

Factor	Case	Control	OR	95% CI
Age at menarche (years)				
≤ 12	76	71	1.00*	–
13	96	106	0.84	0.55–1.28
14	109	117	0.87	0.57–1.32
15	45	42	0.99	0.58–1.71
≥ 16	34	24	1.33	0.72–2.48
Marital status				
Ever-married	349	358	1.00*	–
Never-married	11	2	10.00	1.28–78.12
Age at marriage (years)				
≤ 18	222	257	1.00*	–
> 18	127	101	1.48	1.05–2.09
Age at first childbirth (years)				
< 20	147	197	1.00*	–
20–24	130	103	1.89	1.30–2.73
25–29	37	37	1.64	0.92–2.93
≥ 30	14	4	4.75	1.47–15.34
Interval between menarche and first childbirth (years)				
≤ 2	31	51	1.00*	–
3–4	74	84	1.45	0.81–2.58
5–6	71	79	1.52	0.86–2.69
> 6	152	127	2.10	1.21–3.64
Parity				
Parous	328	341	1.00*	–
Nulliparous	21	17	1.31	0.68–2.52
Number of children				
>6	24	37	1.00*	–
5–6	53	69	1.21	0.65–2.23
3–4	135	138	1.56	0.88–2.75
1–2	116	97	1.92	1.06–3.47
Nulliparous	21	17	2.14	0.92–4.96
Age at last birth (years)				
< 20	17	14	1.00*	–
20–24	62	68	0.70	0.30–1.61
25–29	115	124	0.81	0.37–1.78
30–34	95	86	0.94	0.42–2.09
> 35	39	49	0.68	0.29–1.59
Lactation				
Yes	320	336	1.00*	–
No	8	5	1.75	0.51–5.98
Duration of lactation (months)				
> 18	122	116	1.00*	–
13–18	70	101	0.69	0.46–1.04
6–12	98	116	0.74	0.50–1.08
< 6	30	3	11.26	2.64–48.01
Menopausal status				
Premenopausal	187	198	1.00*	–
Postmenopausal	173	162	1.41	0.86–2.31
Age at menopause (years)				
< 50	132	125	1.00*	–
> 50	41	37	1.19	0.67–2.13

* Reference category

Age at first childbirth was found to be associated with the risk of breast cancer. Elevated risk of breast cancer was observed as the age at first childbirth was delayed. Compared to women whose age at first childbirth was below 20 years, women whose age at first childbirth occurred between 20–24 years, 25–29 years and 30 years or more had a risk of 1.9, 1.6 and 4.8 respectively.

The risk of developing breast cancer was found to increase as the interval between menarche and first childbirth increased. The risk was more than double among those women whose interval between menarche and first childbirth was more than six years, compared with women whose interval was less than or equal to 2 years.

Nulliparous women were found to be at an increased risk (non-significant) by about 30% compared with parous women. Women with a parity of 1–2, had a significantly elevated risk of breast cancer (OR 1.92; 95% CI 1.06–3.47) compared with women of parity of more than six. Nulliparous women were at over two-fold risk compared with parous women of more than six children. Age at last birth did not indicate any risk or protection in this study.

Women with history of no lactation were at higher risk compared to those who have lactated. Duration of breastfeeding appeared to be a significant risk factor for breast cancer. Compared with women who have breastfed their children for more than 18 months, women who have breastfed for less than six months were at significantly higher risk (RR 11.3; 95% CI 2.6–48.0). Further, a decreasing trend of risk was observed as the duration of breastfeeding increased. Postmenopausal women had about 40% higher risk of breast cancer compared with premenopausal women (non-significant). Women who attained menopause naturally at 50 years of age and above were at slightly elevated risk (non-significant) of breast cancer compared with women who attained menopause at less than 50 years of age.

5.2.3 *Other risk factors*

Among the women of three major religious groups, a significantly higher risk of developing breast cancer was seen among Christians (OR 2.60; 95% CI 0.99–6.85) and Muslims (OR 1.7; 95% CI 1.01–2.74) compared with Hindus (Table 10).

In the present study, eating habits were categorized into two groups i) vegetarian and ii) non vegetarian. Surprisingly, women under the non-vegetarian category had a protection for breast cancer risk by 36% (Table 10).

Though a two-fold risk of breast cancer was seen among women with family history of breast cancer, it did not attain statistical significance.

Table 10. Odds ratios (ORs) and 95% confidence intervals (95% CI) of breast cancer by religion, eating habits and family history of breast cancer.

Factor	Case	Control	OR	95% CI
Religion				
Hindu	301	323	1.00*	–
Muslim	43	28	1.67	1.01–2.74
Christian	14	6	2.60	0.99–6.85
Others	2	3	0.73	0.12–4.44
Eating habits				
Vegetarian	85	57	1.00*	–
Non-Vegetarian (mixed)	275	303	0.64	0.45–0.91
Family history of breast cancer				
No	346	353	1.00*	–
Yes	14	7	2.00	0.81–4.96

* Reference category

5.3 Results of multivariate analysis of risk factors

The risk of developing breast cancer increased as the level of education increased, even after adjusting for the potential confounding factors. Women with the educational levels of secondary and college level showed elevated risks of 3.1 (95% CI 1.83–5.38) and 2.5 (95% CI 1.02–6.09) respectively when compared with women of illiterate level. Higher economic status, though a risk factor for breast cancer, it did not attain the statistical significance which was there in the univariate analysis. Women of higher economic status had one and a half fold risk of breast cancer compared with women of lower economic status. The two-fold statistically significant elevated risk of breast cancer found in the univariate analysis among women who lived in the urban areas compared with women living in rural areas was slightly reduced to one and a half-fold risk, but was of marginal significance when adjusted for other socioeconomic and reproductive factors (Table 11).

Table 11. Adjusted odds ratios (adj.ORs) with 95% confidence intervals (95% CI) for breast cancer by educational level, economic status and area of living.

Factor	Univariate Odds ratio	95% CI	Adjusted odds ratio #	95% CI
Educational level				
Illiterate	1.00*	–	1.00*	–
Primary	1.24	0.82–1.87	1.05	0.67–1.64
Secondary	4.09	2.56–6.53	3.14	1.83–5.38
College and above	4.15	1.99–8.68	2.49	1.02–6.09
Economic status				
Lower	1.00*	–	1.00*	–
Middle	1.07	0.76–1.51	0.79	0.53–1.16
Higher	3.06	1.95–4.82	1.46	0.83–2.58
Area of living				
Rural	1.00*	–	1.00*	–
Urban	2.05	1.41–2.99	1.47	0.95–2.26

* Reference category

Odds ratios adjusted for religion, reproductive factors, family history of breast cancer and other variables in the above table.

Age at menarche did not emerge as a risk factor for breast cancer in the multivariate model. However, compared with women whose age at menarche was at 12 years or below, women with menarche at age 13 and above were found to be at decreased risk of breast cancer (non-significant) (Table 12).

Never-married women had over eight-fold risk (non-significant) of developing breast cancer compared with ever-married women. Age at marriage did not indicate any association. The significant one and a half-fold risk observed in the univariate analysis for women who married after the age of 18 years compared with women who married at the age of 18 or under disappeared in the multivariate model. Compared with women whose age at first birth was under 20 years, a more than two-fold risk (non-significant) was noted among women whose age at first childbirth 30 years or more and a statistically significant increased risk was found among women whose age at first childbirth was between 20–24 years of age (RR 1.7; 95% CI 1.01–2.77). The risk observed in the univariate analysis for women whose interval between menarche and age at first birth exceeded six years disappeared when adjusted for confounding factors.

Compared with parous women, nulliparous women had a two-fold (non-significant) risk of developing breast cancer. The significant risk found in the univariate analysis for women with a parity of 1–2 children compared with women with a parity of more than 6 children disappeared when adjusted for potential confounding factors. Although, an approximately 3-fold risk for nulliparous women was observed compared with women of parity of more than 6 children, this risk was not significant. Age at last birth did not indicate any risk for breast cancer. Women who had not lactated were at increased risk compared with those who had lactated. Duration of breastfeeding was found to be a strong risk factor. Compared with women who breastfed for more than eighteen months, a significantly more than eight fold risk (RR 8.6; 95% CI 1.92–38.49) was found among women who had breastfed for less than six months and women who breastfed for 13–18 were found to be at 37% reduced risk (significant) of breast cancer, even after adjusting for socioeconomic and other reproductive factors. It was also observed that as the duration of breastfeeding increased, the risk of breast cancer decreased. Compared to premenopausal women, postmenopausal women had an increased risk for breast cancer. Age at menopause (natural) was not found to be associated with the risk of breast cancer when studied for below 50 years vs. 50 years or more (Table 12).

Table 12. Adjusted odds ratios (adj.ORs) with 95% confidence intervals (95% CI) for breast cancer by reproductive factors.

Factor	Univariate odds ratio	95% CI	Adjusted [#] odds ratio	95% CI
Age at menarche (years)				
≤ 12	1.00*	–	1.00*	–
13	0.84	0.55–1.28	0.78	0.49–1.25
14	0.87	0.57–1.32	0.67	0.42–1.08
15	0.99	0.58–1.71	0.85	0.47–1.57
≥ 16	1.33	0.72–2.48	0.80	0.40–1.59
Marital status				
Ever- married	1.00*	–	1.00*	–
Never- married	10.00	1.28–78.12	8.74	0.40–189.80
Age at marriage (years)				
≤ 18	1.00*	–	1.00*	–
> 18	1.48	1.05–2.09	0.89	0.54–1.46
Age at first childbirth (years)				
< 20	1.00*	–	1.00*	–
20–24	1.89	1.30–2.73	1.67	1.01– 2.77
25–29	1.64	0.92–2.93	1.09	0.45– 2.67
≥ 30	4.75	1.47–15.34	2.32	0.54–10.01
Interval between menarche and first child- birth (years)				
≤2	1.00*	–	1.00*	–
3–4	1.45	0.81–2.58	1.21	0.65–2.25
5–6	1.52	0.86–2.69	1.11	0.58–2.12
>6	2.10	1.21–3.64	0.99	0.43–2.31
Parity				
Parous	1.00*	–	1.00*	–
Nulliparous	1.31	0.68–2.52	2.14	0.44–10.44
Number of children				
> 6	1.00*	–	1.00*	–
5–6	1.21	0.65–2.23	1.19	0.61–2.33
3–4	1.56	0.88–2.75	1.30	0.64–2.62
1–2	1.92	1.06–3.47	1.12	0.48–2.61
Nulliparous	2.14	0.92–4.96	2.96	0.48–18.37
Age at last birth(years)				
≤ 19	1.00*	–	1.00*	–
20–24	0.70	0.30–1.61	0.65	0.26–1.63
25–29	0.80	0.37–1.78	0.65	0.25–1.69
30–34	0.94	0.42–2.09	0.78	0.28–2.19
≥ 35	0.68	0.29–1.59	0.61	0.18–2.10
Lactation				
Yes	1.00*	–	1.00*	–
No	1.75	0.51–5.98	1.75	0.45–6.86
Duration of lactation (months)				
> 18	1.00*	–	1.00*	–
13–18	0.69	0.46 – 1.04	0.63	0.41–0.98
6–12	0.74	0.50 – 1.08	0.67	0.44–1.03
< 6	11.26	2.64–48.01	8.59	1.92–38.49
Menopausal status:				
Premenopausal	1.00*	–	1.00*	–
Postmenopausal	1.41	0.86–2.31	1.58	0.91–2.72
Age at menopause (years)				
< 50	1.00*	–	1.00*	–
≥ 50	1.19	0.67–2.13	1.04	0.51–2.15

* Reference Category

Odds ratios adjusted for educational level, economic status, age at marriage, area of living, family history of breast cancer and variables in the above table.

Among the three major religious groups – Hindus, Muslims and Christians, the risk of developing breast cancer was high among Muslims (RR 1.9; 95% CI 1.07–3.42) compared with women of Hindu religion. A statistically non-significant elevated risk was also observed among Christians. Compared with women who consumed only vegetarian food, a 15% reduced risk (non-significant) was found in women who consumed vegetarian plus non-vegetarian food.

The two-fold risk observed in univariate analysis with the family history of breast cancer was reduced by about 80% when adjusted for potential confounding variables. However, a 20% enhanced risk (non-significant) was found among women with a family history of breast cancer (Table 13).

Table 13. Adjusted odds ratios (adj.ORs) with 95% confidence intervals (95% CI) for breast cancer by religion, eating habits and family history of breast cancer.

Factor	Univariate Odds ratio	95% CI	Adjusted Odds ratio #	95% CI
Religion				
Hindu	1.00*	–	1.00*	–
Muslim	1.67	1.01–2.74	1.92	1.07–3.42
Christian	2.60	0.99–6.85	1.63	0.56–4.74
Other	0.73	0.12–4.44	0.86	0.13–5.72
Eating habit				
Vegetarian	1.00*	–	1.00*	–
Non-vegetarian	0.64	0.45–0.91	0.85	0.57–1.28
Family history of breast cancer				
No	1.00*	–	1.00*	–
Yes	2.00	0.81–4.96	1.21	0.45–3.26

* Reference Category

Odds ratios adjusted for educational level, economic status, area of living, reproductive factors and variables in the above table.

6 DISCUSSION

The present study was carried out at Kidwai Memorial Institute of Oncology, which is a regional centre for cancer research and treatment in the State of Karnataka. In view of the facilities available for the diagnosis and treatment of cancer at the Institute, patients hail from all over Karnataka and also from adjoining states. Annually about 12,000 new cases are registered as new cases and about 68–70 percent of these are confirmed to be cancer cases.

Among the confirmed cancers, the proportion of female cancers is high with a male–female sex ratio of 1:1.2. Cancer of the breast, which was the second or third leading site of cancer among all cancers in women in the PBCRs India / Bangalore until 2–3 decades ago, has now become the first leading site of cancer at Bangalore, Bhopal, Mumbai (Bombay) and Delhi, while it was the second most common cancer in Chennai (Madras) and Barshi (NCRP 2002a). Breast cancer is the second commonest site of cancer among women at the hospital-based cancer registry of Kidwai Memorial Institute of Oncology (NCRP 2002b) and accounted for over 14 percent of all female cancers. Hence in order to ascertain whether the established risk factors do play an important role in the aetiology of breast cancer, an attempt was made to study them through a hospital-based case-control study. Though case-control studies are well suited for the study of rare diseases, relatively inexpensive (unlike cohort studies) and quick to mount and conduct, the main problems one has to deal with are; obtaining accurate information on past exposures since case-control studies proceeds from effect to cause (reducing recall bias) and selection of suitable comparison group (controls) apart from validation of information and total control of extraneous variables.

Healthy attendants of cancer patients without any history of breast disease, gynaecological disorders or endocrine glands were used as controls, as these persons are readily available easily at Dharmashala- Ambulatory Patient Home within the hospital campus. As all the cancer patients coming to the hospital could not get inpatient beds immediately on arrival, they would be provided free accommodation and free food facilities at Dharmashala so that they undergo their treatment on and out-patient basis. One attendant for each patient is permitted to stay to take care of the patient's needs.

Some bias in using such controls cannot be ruled out, particularly with respect to socioeconomic status, because normally patients with lower economic status would be willing to stay at Dharmashala and so also the attendants. Since the area of living and socio-economic status were not matched, the possibility of having compared an urban case with a rural control and vice versa could not be ruled out; eventhough an attempt was made in analysis by adjusting these factors, the possibility of bias remains. Since

the pairing identity was not retained, this might have affected the results, especially when matched analysis was carried out, where the matched pairs that are concordant in outcome are excluded from the analysis and the risk estimates are based solely on discordant pairs and these numbers of concordant and discordant pairs would be different if the matched pairs are different. Breslow and Day (1980) stated that “ in the case of children and young adults a very close match is indicated because experiences change rapidly at these ages and because a discrepancy of a given magnitude, say one year, is a relatively greater proportion of the lifespan than it is in the middle or old age”. As breast cancer is common in middle and older ages, the effect of difference in age (matched) between case and a control of few pairs will have negligible impact on the results.

Selection bias was reduced to the maximum extent since clear inclusion and exclusion criteria are defined. All new consecutive cases without any history of prior cancer directed therapy at the time of registration at KMIO were included in the study so as to have comparability of cases and controls, particularly with respect to socioeconomic status, since patients with the financial means could go to private hospitals where the cost of treatment is fairly high compared to the cost of treatment at KMIO.

The information was collected both from cases and controls by two trained Assistant Social Scientists working in the Cancer Registry on the first presentation of patients and simultaneously from the controls through personal interview. Later the cases confirmed microscopically as breast cancer were included as cases for the study. Neither the objective nor the hypothesis of the study was revealed to the Assistant Social Scientists to avoid interviewer bias. All possible efforts were made to obtain correct and reliable information for the study, in spite of which one cannot rule out the differential recall of exposure, especially on parameters like age at menarche, age at first birth, duration of breast feeding, age at menopause etc. Another problem in the Indian set-up is obtaining information on exact income. This is very difficult unless the case or control is an employee of a governmental/non-governmental agency or factory. This is more so in hospitals like KMIO, which is a government hospital where charges for diagnosis and treatment are based purely on the income categories. However, maximum effort was taken to obtain relatively accurate income data by posing several cross-questions. Since income group and educational levels can be considered as indirect indicators of social status factors, these variables were included in the multivariate analysis to control for their confounding effect.

As some of the risk factors show very little variation in India, information on factors such as body mass index, smoking, alcohol and dietary pattern were not collected since collecting information on body mass index from the controls was

difficult and women are generally lean. Smoking and alcohol habits are very rare and even negligible among the women of this region and even if there are very few women with these habits, the risk of breast cancer associated with either smoking independently or with alcohol is very slight (Collaborative Group on Hormonal Factors in Breast Cancer 2002). Information on dietary pattern was not collected as assessment of actual quantity and the type of food consumed individually would be very difficult to obtain, since the majority of the families still live in joint families. Very few subjects and controls used oral contraceptives and this variable as such was not included in the analysis. Further, the majority of women do not reveal the truth with regard to abortion as a matter of reticence, obtaining information on actual number of abortions is difficult. As such this factor was not considered for the study and hence parity has been selected in the discussion and not the number of pregnancies.

6.1 Socioeconomic status

The socioeconomic status in terms of standard of living in the present study was evaluated based on educational level, economic/income level (assessed by occupation and area of living). The findings of the study revealed that the risk of breast cancer increased as the level of education increased. Compared with women of illiterate level, women with educational levels of secondary education, college and above had a more than four-fold statistically significant risk of developing breast cancer in the univariate analysis. When the potential risk factors were controlled for the risk of breast cancer, though reduced to over 3-fold and two and a half-fold respectively for women with the educational levels of secondary and college and above, the risk was significant. Women with higher economic status are found to be at an elevated risk of breast cancer compared with women of lower economic status. The three-fold risk observed among women of higher income status compared with women of lower income status in the univariate analysis decreased to about one and a half-fold after adjusting for all possible confounding factors and the risk was significant. As mentioned earlier, in spite of the interviewers' efforts to elicit the true income of the patient, deliberate falsification of income by the subjects cannot be ruled out. The main reason for this is to get the treatment either free or at a lower cost at the Institute since charges for treatment are based on income categories. As the main occupation of subjects and controls was that of being housewives in addition to agriculture, they are mainly dependent on the income of their spouse (which is in general a reality factor in India), the role of occupation (in terms of social status) and the risk of breast cancer could not be estimated even though some studies indicated an association of occupation with breast cancer (Talamini et al.

1984, Madigan et al. 1995, D'Avanzo and LaVecchia 1995). As far as the area of living is considered, women who lived in urban areas are at increased risk of breast cancer compared to women living in rural areas. The significant two-fold risk observed for women living in urban areas in univariate analysis has reduced to over one and a half-fold risk when adjusted for economic status (OR 1.60; 95% CI 1.07–2.41) and when adjusted for education (OR 1.56; 95% CI 1.02–2.37). However, though similar risk estimates were found for these urban women when adjusted for reproductive factors, the risk was not significant.

To summarise, the findings of the present study indicated a positive association between socioeconomic status vis a vis standard of living and risk of breast cancer. These results are consistent with studies reported by Barbone et al. (1996) who found that education as measured by the number of years of schooling was directly associated with breast cancer besides being correlated with occupation (Madigan et al. 1995, D'Avanzo and LaVecchia 1995) and with that of Paymaster and Gangadharan (1972) of India.

6.2 Reproductive factors

6.2.1 Age at menarche

Early age at menarche is reported to be associated with an increased risk of breast cancer. A significant reduction in the risk of breast cancer in the range of 30–36% was found for women with onset of menstruation after age 15 or 16 compared to those of age 11 or before (Nagata et al. 1995, Gao et al. 2000, Clavel-Chapelon and the E3N-Epic Group 2002). Several studies carried out in the high risk populations found no association between age at menarche and risk of breast cancer (Adami et al. 1978, Brignone et al. 1987, East-European Study Group of Breast Cancer Epidemiology 1990, Talamini et al. 1996). Magnusson et al. (1999) found a statistically significant negative association between increasing age at menarche and breast cancer risk in women born before 1925 but not after.

The results of the present study showed a 33% non-significant increased risk of developing breast cancer among women whose age at menarche was 16 years or more compared with women whose age at menarche was at 12 years or less in the univariate analysis. After adjustment for socioeconomic variables and other reproductive factors, the increased risk found among women whose age at menarche occurred at age 16 disappeared and non-significant reduction in the risk of breast cancer was observed among women whose menarche occurred at age 13 years or more compared with

women whose menarche was at 12 years or less. These findings are consistent with the studies carried out in India by Paymaster and Gangadharan (1972), Gajalakshmi and Shanta (1991) and Rao et al. (1994) and with several studies carried out in the high risk populations by Wynder et al. (1960), Salber et al. (1969), Lin et al. (1970), Adami et al. 1978, MacMahon et al. 1982b, East-European Study Group of Breast Cancer Epidemiology 1990, Magnusson et al. 1999), the negative findings of this study may be partly due to inaccuracies encountered in the reporting of menstrual histories, especially the imprecise recall of the actual age of menarche by elderly women apart from lower educational level. In addition age at menarche is influenced by childhood nutritional status and also by socioeconomic conditions.

6.2.2 Marital status and age at marriage

Several epidemiologic studies have reported that the risk of breast cancer is higher among single women than married women (Fraumeni et al. 1969, Paymaster and Gangadharan 1972, Brignone et al. 1987, Ewertz 1988b).

The results of the present study revealed that, compared with women who ever-married, women who never-married were at significantly ten-fold elevated risk of breast cancer in the univariate analysis. But when adjusted for socioeconomic and reproductive variables, though a more than eight-fold risk was found, it was not statistically significant. This was probably because only eleven cases and two controls were unmarried in the entire series. Similarly, when age at marriage was considered, a significant one and half-fold risk was found for women who married at the age of 18 years or under compared with women who married after age 18. This excess risk was diminished when adjusted for potential confounding factors. These findings are consistent with other studies carried out in India by Gajalakshmi and Shanta (1991) and Rao et al. (1994) -the results of which are based on univariate analysis.

6.2.3 Age at first birth

The age at which a woman gave birth to her first live child is predictive of breast cancer risk and the risk increased with age at first birth. Women having a first childbirth over the age of 35 had an elevated risk compared with nulliparous women (MacMahon et al. 1970a). A consistent finding reported from many epidemiologic studies was that the younger a woman is when she has her first childbirth, the lower is her risk of breast cancer (Paffenbarger et al. 1980, Lubin et al. 1982, Helmrich et al. 1983, Schatzkin et al. 1987, Yuan et al. 1988, Negri et al. 1988, Tao et al. 1988, Leon 1989, Wang et al.

1992, Hinkula et al. 2001, Palmer et al. 2003). An excess risk ranged from 2–5 fold or increase in risk by 3–5% per year of delay in age at first birth for women with a birth after 30 compared to those with a birth prior to 18 has been reported by several studies (Brinton et al. 1983, Trichopoulos et al. 1983, Nagata et al. 1995, Decarli et al. 1996, Lambe et al. 1996, Hinkula et al. 2001).

Some studies however, found no positive association between age at first birth and the risk of breast cancer (Adami et al. 1978, Choi et al. 1978, Adami et al. 1980, Meirik et al. 1986, Rosero-Bixby et al. 1987, Kvale and Heuch 1987, Ewertz and Duffy 1988, McCredie et al. 1998).

The results of the present study showed that, compared to women with a birth prior to age 20, women with a birth at age 30 or after were at nearly five-fold significant risk (unadjusted) of breast cancer and women whose age at first birth was in the age interval 20–24 years were also found to be at nearly two-fold risk (significant) of breast cancer. Among women whose age at first birth was in the age interval 25–29, although they had an increased risk (OR 1.64) it did not attain statistical significance. These findings of the present study are consistent with the findings of studies carried out in India by Gajalakshmi and Shanta (1991) and Rao et al. (1994), which were based on univariate analysis. After the control of potential confounding factors, the increased risk found in the univariate analysis among women whose age at first birth was at age 30 or after has reduced by 50 per cent (adj.OR 2.32) and the risk became non-significant, but women whose age at first birth was in the age-interval 20-24 years were at significantly increased risk of breast cancer compared to women whose age at first birth was before age 20. When the stepwise logistic regression model was fitted, the elevated risk found among women whose age at first birth was in the ageinterval 20–24 years compared with women whose age at first birth was before age 20, remained almost unaltered and significant independent of socioeconomic, other reproductive variables but, among women whose age at first birth was at age 30 or after, the risk was not significant when the socioeconomic and reproductive variables were adjusted, except for economic status. In other words, a risk of 3.79 (95 % CI 1.15–12.50) was found for women whose age at first birth was 30 or later compared with women with a birth before age 20. No significant risk was found for women with age at first birth in the age interval 25–29 years. These results are consistent with the findings of Gajalakshmi (1997) and studies carried out by (Gao et al. 2000, Hinkula et al. 2001, Clavel-Chapelon and the E3N-Epic Group 2002).

Interval between menarche and first birth

Brignone et al. (1987) reported over five-fold significant risk of developing breast cancer among premenopausal women when the interval between menarche and first birth was more than 20 years compared with less than six years and the risk among postmenopausal women was slightly more than two-fold when the interval between menarche and first birth was 16–20 years compared with less than six years. Gajalakshmi and Shanta (1991) reported a three-fold risk in both pre- and postmenopausal groups when the interval between menarche and age at first birth was more than 12 years compared with less than 4 years and these risk estimates were based on univariate analysis but matched for age, socioeconomic class and menopausal status.

In the present study, an over two-fold risk (OR 2.1) of developing breast cancer was found among women whose interval between menarche and first birth exceeded 6 years compared with women whose interval was 2 years or less in the univariate analysis. In the multivariate analysis, this excess risk disappeared. These results are consistent with the results reported from India (Gajalakshmi and Shanta 1991), which are based on univariate analysis.

6.2.4 Parity

Low parity was found to be significantly associated with an increased risk of breast cancer (Kvale et al. 1987, Negri et al. 1988, Ewertz et al. 1990, Gomes et al. 1995, Romieu et al. 1996, Magnusson et al. 1999). Nulliparity was associated with an increased risk of 27–30% compared with parous women (Ewertz et al. 1990, McCredie et al. 1998) and for every two births; the risk was reduced by about 16% (Ewertz et al. 1990). In a nationwide cohort study of women with at least five births (grand multiparas) Hinkula et al. (2001) reported that the incidence of breast cancer was low in the grand multiparas cohort. A protective effect of high parity was found only for postmenopausal women to Clavel-Chapelon and the E3N-Epic Group (2002).

A few studies carried out in India have revealed a significant protective effect of parity and risk of breast cancer. Paymaster and Gangadharan (1972) reported relative risks of about 2-fold for women with ≤ 3 or fewer pregnancies compared with women with more than 3 pregnancies. Rao et al. (1994) found that multiparous women with 3 or 4 pregnancies had a 40–50% reduction in the risk of breast cancer compared with nulliparous women. Gajalakshmi and Shanta (1991), in a case-control study observed that nulliparous women had a higher risk relative to women with more than four

children and a three fold risk relative to all parous women in the premenopausal group but on the contrary, the risk in nulliparous women was not significantly different from unity when compared to women with more than four children or all parous women among the postmenopausal women.

The findings of the present study suggest that the risk of breast cancer diminished by about 35% for every additional two births in the univariate analysis. Compared to women with a parity of more than 6 children, women who had only 1–2 children are at about two-fold risk (significant) of breast cancer and women with no children (nulliparous) are at more than two-fold risk of marginal significance. But when the effect of potential confounding factors was controlled for in the multivariate analysis, the risk of parity per se disappeared except that nulliparous women showed a three-fold non-significant risk compared to women with parity of more than 6 children. These results are consistent with those reported from India (Gajalakshmi and Shanta 1991, and Rao et al. 1994) which were based on univariate analyses. Results by menopausal status would have provided some clue regarding the increase or decrease in risk associated with parity, since some studies reported a protective effect of high parity only for postmenopausal women (Clavel-Chapelon and the E3N-Epic Group 2002). In view of the small numbers, the results were not analysed by menopausal status in the present study.

6.2.5 Age at last birth

Births after the first have relatively little influence on breast cancer risk, and the relationship between breast cancer risk and parity results primarily from the fact that age at first birth and ultimate total parity are highly correlated (MacMahon et al. 1970a). Age at first confinement is a much more important factor than the total parity; indeed the latter probably has no association with breast cancer risk except through its association with age at first birth.

From a pooled data of two hospital-based case-control studies in Italy to study the role of age at first and second birth on subsequent breast cancer risk, Negri et al. (1990) observed no difference in the risk estimates for age at first and second births in the two studies pooled. A significant interaction with age was observed in relation to age at first and second birth. In younger women (below age 50) a strong and direct association with age at first birth was found, while no apparent protection was conveyed by earlier second births. Among older women (aged 50 or over), there was no apparent relationship with age at first birth after allowance for age at second birth, but the role of age at second birth was independent and statistically significant.

In the present study age at last birth did not emerge as a risk factor either in the univariate or multivariate analysis and these findings are partly consistent with the findings reported from the high-risk population. (MacMahon et al. 1970a, Negri et al. 1990).

6.2.6 Lactation

Several studies carried out around the world have reported lactation as a protective factor for breast cancer (Lubin et al. 1982, Tao et al. 1988, Yaun et al. 1988, Layde et al. 1989, Land et al. 1994, Romieu et al. 1996, the Collaborative Group on Hormonal Factors in Breast Cancer 2002). The duration of lactation is one of the important factors in the risk of breast cancer. Yuan et al. (1988) reported that women who had breastfed for 73 to 108 months and 109 and more months had an adjusted odds ratio of 0.35 and 0.07 respectively. This protective effect of duration of lactation was observed mainly among premenopausal women (Tao et al. 1988, Katsouyanni et al. 1996) and a considerable reduction in risk among women who began to breastfeed at younger age, but other timing parameters (i.e. interval since first or last breastfeeding) were not predictive of risk (Brinton et al. 1995).

Some studies, however, found no association between lactation and risk of breast cancer (Rosero-Bixby et al. 1987, Brignone et al. 1987, London et al. 1990, Gomes et al. 1995, Negri et al. 1996, Stuver et al. 1997, Magnusson et al. 1999). The findings of the present study revealed that among parous women a non-significantly elevated risk of about two-fold was found for women who never lactated compared with women who had ever lactated both in the univariate and multivariate analyses. However when the duration of lactation was studied, compared with women who had breastfed for more than 18 months, women who breastfed for less than 6 months had a more than 11-fold significant risk of developing breast cancer in the univariate analysis. When adjusted for socioeconomic and other reproductive variables, it was found that compared to women who breastfed for more than 18 months, women who breastfed for less than six months were at significantly more than 8-fold risk of breast cancer and women who breastfed for 13–18 months were at significantly 40% reduced risk. A reduced risk of about 30% was also observed among women who breastfed for 6–12 months (marginal significance) compared with women who breastfed for less than 6 months. These findings are consistent with the results of several studies (Tao et al. 1988, Yuan et al. 1988, Land et al. 1994, Romieu et al. 1996, Katsouyanni et al. 1996) and with that of the results reported by the Collaborative Group on Hormonal Factors in Breast Cancer (2002). Among a few studies carried out in India, history of lactation and duration of

breastfeeding with the risk of breast cancer have not been studied in detail except for one study by Rao et al. (1994), who reported that although there was an elevated risk for women who never lactated, the risk was not significant.

To summarise, breastfeeding for longer duration provides protection from breast cancer in this population.

The variations in the magnitude of risks between lactation and breast cancer reported across the studies and negative associations reported may be due to varied methodologies in reporting the history of lactation, in addition to the fact that comparison of a history of ever vs. never breastfeeding may be too crude an indicator and that it may be more important to demonstrate a dose-response relationship in making causal inferences. It is generally true that women who start their families at a young age have larger families and more breastfeeding experience than those who are older at first pregnancy. It appears therefore that the association between age at first birth and duration of lactation accounts for the apparent decrease in risk associated with breastfeeding. This particular notion is true at least in this part of the world, where normally women get married at an early age and breastfeeding is also common.

6.2.7 Age at menopause

Late age at menopause has been shown to be a risk factor for breast cancer by many studies (Paffenbarger et al. 1980, Helmrich et al. 1983, Lipnick et al. 1984, Schatzkin et al. 1987, Kvale and Heuch 1988, Tao et al. 1988, Hsieh et al. 1990,

Talamini et al. 1996, Gao et al. 2000). The protective effect was more evident among women who attained menopause at age 45 or below compared with women who attained menopause after 55 years (Tricopolous et al. 1972, Hsieh et al. 1990). An increase in risk of 3–6% for each year of increase in age at menopause was observed in a Norwegian cohort study by Kvale and Heuch 1988 and the protective effect of early menopause was strongest for breast cancer diagnosed in patients 80 years of age or older.

Some studies have found no association between age at menopause and risk of breast cancer (Adami et al. 1978, Brignone et al. 1987, Cusimano et al. 1989, McCredie et al. 1998, Magnusson et al. 1999).

In the present study, although an elevated risk of 1.4 and 1.6 was found for postmenopausal women compared with premenopausal women in the univariate and multivariate analyses the risk was not significant. When the age at menopause was studied (less than 50 years vs more than 50 years), the risk estimates remained close to unity. These results are consistent with the findings reported by Adami et al. (1978),

McCredie et al. (1998), Magnusson et al. (1999). Though a three-fold risk was found by Gajalakshmi and Shanta (1991) among women whose age at menopause was 44–49 years compared to women who attained menopause before the age of 41 years, these results were based on univariate analysis.

There is nevertheless some evidence that surgical menopause provides protection against cancer (Trichopoulos et al. 1972), the protective effect was greatest for women who had induction of menopause below 35 years but was also in evidence for those who had surgery up to 50 years and persisted beyond age 70. It has been suggested that this effect is limited to women in whom hysterectomy was accompanied by oophorectomy, but it is very uncommon among women of this region to opt for any kind of artificial menopause and as such this information was not included in the questionnaire. Thus the effect of artificial menopause on the risk of breast cancer was not studied.

6.3 Other risk factors

6.3.1 Religion

India is a secular country with varying social religions and dietary practices. Such kinds of religions/castes may well not exist in any other countries in the world. The three major religions in India are Hinduism, Islam and Christianity.

The findings of the present study revealed that, compared with women of Hindu religion, women belonging to the Muslim and Christian religions were found to be at elevated risk of breast cancer. A significant risk of about two-fold and more than two-fold risk of breast cancer was found among women belonging to the Muslim and Christian religions respectively in the univariate analysis. After adjustment for socio-economic, reproductive and eating habit variables, the risk found among women of Muslim religion was slightly elevated and was significant, but among women of Christian religion, the risk of 2.6 found in the univariate analysis decreased to 1.6 and this risk was non-significant. However, in view of the small numbers of women belonging to the Christian religion (14 cases and 6 controls), the results are to be viewed with caution.

The higher risk of breast cancer among Muslim women may be due to their life style factors, particularly consumption of fatty food compared with Hindu women. Christians do consume fatty food but the majority of Christians are converts from Hinduism who normally belong to the poorer section and consumption of fatty food as such is quite small among Christians in India. Although higher incidence rates of breast cancer were reported by Paymaster and Gangadharan (1972) among Parsi women

compared with other religions – Hindus, Muslims, Christians and Jews, in the present study neither the cases nor the controls belonged to the Parsi community and the majority of Parsi population live in Mumbai (Bombay).

Egan et al. (1996) in a population based case-control study reported that the risk of breast cancer was much higher for Jewish women with a first degree relative who had breast cancer and the effect of family history was greater in Jewish women than in women of other religions, suggesting that certain groups of Jewish women have a higher than expected rate of mutation in the breast cancer gene BRCA1.

6.3.2 Eating habits

The eating habits in India differs markedly from religion to religion within the country, between one sect of people to other sects within the same religion. Some sects of people in a religion do not consume non-vegetarian food (eg. Brahmins, Lingayats) according to their religious customs. Muslims do not consume pork. Further, as the majority of Indian families still live in a joint family set-up, assessment of actual quantity of either fruits, vegetables, fats or even consumption of individual quantities of meat, pork, fish or beef is extremely difficult. As such the data is analysed based on only two categories – (1) vegetarians and (2) non-vegetarians. The non-vegetarians are the mixed group of vegetarian and non-vegetarians and hence the protective effect found for the non-vegetarian group in this study has to be viewed and interpreted carefully.

6.3.3 Family history

Many epidemiologic studies have suggested that a family history of breast cancer increases a woman's chance of developing breast cancer (Lubin et al. 1982, Tao et al. 1988, Yoo et al. 1992, Kelsey et al. 1993, Gomes et al. 1995, Madigan et al. 1995, Weiss et al. 1996). Having a history of breast cancer among first degree female relatives (mothers, sisters or daughters) was independently associated with an increased risk of breast cancer (Parazzini et al. 1993, Gomes et al. 1995) and the risk reported by several authors ranged 2–9 fold. The risk associated with a positive family history was higher if the relative was also young at the time of diagnosis (Calle et al. 1993). The risk of breast cancer with a family history of breast cancer in a first degree relative was stronger for premenopausal women than for postmenopausal women (Romieu et al. 1996).

In the present study, although a 2-fold risk in the univariate analysis was found for women with the family history of breast cancer, the risk was not significant. This 2-fold

risk was reduced to 1.2 in the multivariate analysis and even this risk did not attain statistical significance. The elevated risk observed in this study may be related to environmental factors, yet the role of genetic factors cannot be ruled out. Since there were only 14 cases and 7 controls in the series with family history of breast cancer no definite conclusion could be drawn on the risk of breast cancer with regard to family history of breast cancer.

7 SUMMARY

The incidence rates of breast cancer among females are showing a rising trend in all the urban registries of India. Breast cancer is the first leading site of cancer in 4 out of the 5 urban registries – Bangalore, Mumbai (Bombay), Delhi and Bhopal. In Chennai (Madras) it is the second leading site of cancer but a tendency of breast cancer to rise over time has been observed. In the hospital based cancer registry at Kidwai Memorial Institute of Oncology (A Regional Center for Cancer Research and Treatment) about 500 cases of breast cancer are registered annually. In order to study the role of socioeconomic status vis a vis standard of living, reproductive factors and risk of breast cancer a hospital-based case – control study was undertaken. 360 cases of breast cancer confirmed microscopically (excluding cases with prior history of treatment, those too advanced for treatment, non-microscopic confirmation, dropouts before diagnosis and in-situ carcinomas) and an equal number of controls without a history of any disease in the breast, gynecological organs or endocrine glands matched for age (plus or minus 5 years in the WHO age group) formed the subjects of the study. The results are reported based on univariate (unadjusted) and multivariate (conditional logistic regression model) odds ratios after adjusting for socioeconomic, reproductive and other risk factors. The major findings of the study are:

- The risk of breast cancer increased as the level of education increased. Compared to illiterate women (no schooling) women with secondary education (up to 10 years of schooling) had a significantly more than three-fold risk (adj. OR 3.14, unadj. OR 4.09) and women with an educational level of college and above (11–15 or more years of schooling) had a two and a half-fold (adj. OR 2.49, unadj. OR 4.15) significant risk of developing breast cancer.
- Women with higher income are at an elevated risk (adj. OR 1.46, unadj. OR 3.06) compared with women with lower income.
- Compared to women living in rural areas, women living in urban areas appeared to be at increased risk. (adj. OR 1.47, unadj. OR 2.05)
- Among the three major religions – Hinduism, Islam and Christianity Muslims were found to be at an elevated risk (adj. OR 1.92; unadj. OR 1.67) of developing breast cancer (significant) followed by Christians (adj. OR 1.63, unadj. OR 2.60) compared with Hindus.
- Compared with ever-married women, never-married women are at increased risk (adj. OR 8.74, unadj. OR 10.00) of developing breast cancer. Nulliparous women had a two-fold risk (adj. OR 2.14, unadj. OR 1.31) of

developing breast cancer compared with parous women. Compared with parous women with more than six children, the risk among nulliparous women was found to be about three-fold (adj. OR 2.96, unadj. OR 2.14).

- Women who delayed their first childbirth were at elevated risk of developing breast cancer. Compared with women whose age at first childbirth was below 20 years, women whose age at first childbirth was above 30 years were at more than two-fold risk (adj. OR 2.32, unadj. OR 4.75) and women whose age at first childbirth was between 20–24 years were at almost two-fold risk (adj. OR 1.67, unadj. OR 1.89) of developing breast cancer.
- The risk of developing breast cancer was found to be high in women who had never lactated (adj. OR 1.75, unadj. OR 1.75) compared with ever lactated. Breastfeeding for a longer duration emerged as an apparent protective factor for the risk of breast cancer independent of age at first birth, parity and other potential confounding factors. Compared with women who breastfed for more than 18 months women who breastfed for less than 6 months are at significantly more than eight-fold risk (adj. OR 8.59, unadj. OR 11.26). Ultimately it may be that breastfeeding accounted for much of the effect due to parity in this study. This is what relatively consistent in other studies as well.
- Postmenopausal women are at an elevated risk compared to premenopausal women (adj. OR 1.58, unadj. OR 1.41).
- Age at menarche, parity, age at last birth and age at menopause appear to have no association with the risk of breast cancer in the present study.
- Family history was rare in this material and most of the effects could be accounted for by socioeconomic status, hence genetic inheritance in the aetiology of breast cancer appears to be not of importance in India, at least given the current distribution of risk factors. This may change if the environment changes and gene expression changes.

8 ACKNOWLEDGEMENTS

This study was carried out at the hospital-based cancer registry of Kidwai Memorial Institute of Oncology, Bangalore, India and at the Tampere School of Public Health, Tampere, Finland. I am very grateful to the Cancer Society of Finland and the Government of Finland for providing me with the opportunity to complete the postgraduate programme at the University of Tampere through financial and educational support. I sincerely thank Prof. Matti Hakama D.Sc., Tampere School of Public Health, Tampere, Finland and Dr. Usha K.Luthra, MD, Ph.D, former Additional Director-General, Indian Council of Medical Research, India for having initiated this fellowship programme in the early 90's as part of the Human Resource Development Programme in India.

I am indebtedly grateful to Prof. Matti Hakama D.Sc., for giving me the opportunity to carry out the doctoral work under his guidance and I can never forget the moral support, valuable guidance and encouragement that I had from him during my stay in Tampere, Finland and during his visits to India, in addition to the excellent teaching.

I would like to express my sincere gratitude to Dr. N. Anantha, MD, DMRT, and the former Director, Kidwai Memorial Institute of Oncology for permitting me to take up this fellowship programme at Tampere School of Public Health, Tampere, Finland.

I sincerely thank Dr. P.S. Prabhakarn MS, Director, Kidwai Memorial Institute of Oncology for the support and encouragement given to me in completing this task.

I thank my colleagues Dr C. Ramesh, Mr. D.J. Jayaram, Mrs. B.J. Kumudhini, Mrs. A.K. Jyothi, Mr. K. Venkatesh and other colleagues in the Department of Biostatistics and Cancer Registry for their skilful support rendered to me in completing this assignment.

I sincerely thank the Director General, Indian Council of Medical Research for the continuous encouragement provided to the Registry staff as part of Human Resource Development.

I am extremely grateful to Dr. Arja Rimpelä, Dr. Iiro Kilpikari, Prof. Pekka Laippala, Prof. Lyly Teppo, Dr. Suri Virtanen, Mr. Esa Läärä, Dr. Timo Hakulinen, Mrs. Heini Huhtala, Mrs. Anna Koivisto and all the other teachers for their excellent teaching, kindness and love showered on me. My special thanks to Dr. Joakim Dillner, who was kind enough to introduce me to fascinating Stockholm, Sweden and for his hospitality. I sincerely thank Prof. Anssi Auvinen, and Mrs. Catarina Ståhle-Nieminen

for the hospitality they rendered on my arrival to Tampere for the second time. I thank Mrs. Virginia Mattila from the language centre of the University of Tampere for suggesting the language correction prior to manuscript printing and Mrs. Marita Hallila for her quick and excellent editing in effecting the corrections.

I am thankful to Dr. Jaakko Kaprio, MD, Ph.D, Professor of Genetic Epidemiology, Department of Public Health, University of Helsinki, Finland and Dr. Riitta-Sisko Koskela, Docent in Epidemiology, University of Tampere, Finland for reviewing my manuscript and in particular Prof. Jaakko Kaprio for the pains he has taken in the thorough review of the manuscript and for his valuable guidance and suggestions which helped to enhance the standard of the manuscript.

I thank my fellow students, who always encouraged me wholeheartedly and provided moral and social support, particularly Mrs. Tiina Salminen, Dr. Merja Viikki, Mr. Juozas Kurtinaitis and Mr. Ravi Shankar. I also thank Mr. Mahender Reddy Nandi Konda and Mr. Hariharan Ramalingam the two Indian friends working at Nokia Research Centre for their social support extended to me during my stay in Tampere, Finland.

I place on record my deepest gratitude to my parents for their blessings and constant encouragement. I will be failing in my duty if I do not express my gratitude to my wife, Rama, who met with a bus accident and survived by the grace of God three years prior to my fellowship assignment, my daughter Anitha who got married just before my taking up of fellowship assignment, Mr. Srinivas, my son-in-law who has taken care of my family in my absence, to my son Anand and my sisters and brothers-in-law, without whose encouragement concentration on studies at Tampere, Finland would have been difficult. Last but not the least, I would like to thank all my friends for their support extended to my family in my absence and encouragement given to me. I finally thank all those who have supported me directly or indirectly in this endeavour.

K.RAMACHANDRA REDDY

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