REVIEW OF LITERATURE
A review of earlier reports helps in identifying the conceptual methodological issues relevant to the present study. This would enable the researcher to collect information and subject them to sound reasoning and meaningful interpretation. Hence the relevant references in connection with the present study were reviewed and critiqued with relevant data extracted. Keeping in view the objectives of the study, the reviews were presented under the following headings:

2.1 Indian pesticide scenario
2.2 Perceptions of farmers and consumers to pesticide use
2.3 Health hazards of pesticide use
2.4 Cancer incidence and mortality
2.5 Breast cancer and risk factors
   2.5.1 Risk factors of breast cancer
2.6 Pesticide correlates of cancer
   2.6.1 Pesticide correlates of breast cancer
   2.6.2 In vivo studies of pesticide exposures

2.1 Indian pesticide scenario:

Adulteration (PFA) Act, 1954, under the Ministry of Health & Family Welfare has laid down standards for different food products as well as provisions for their storage, distribution and sale. The Maximum Residue Limits (MRLs) for different pesticides are regulated through this PFA Act.

In 2005, a Central Sector Scheme for Monitoring of Pesticide Residues at the national level has been approved in order to ascertain the prevalence of pesticide residues at farm gate and market yards to enable remedial measures to be undertaken as required. Under this, 21 laboratories under various Ministries/Departments were
provided with equipments to undertake analysis of pesticide residues in vegetables, water, meat & meat products, and marine products.

Out of the total agrochemical market in India (which varies between 4000 and 4500 crore rupees), approximately 1200 crores worth of pesticides is of counterfeit or spurious chemicals every year, as per industry’s own estimates. The industry also admits that in 2000-01, in India, crop loss amounts due to pests was about 60,000 crores of rupees despite plant protection measures. These losses are from 25% of its arable area (FICCI (2006)).

Ghodake et al, (1973) made a simple economic analysis of pesticide use in cotton in Haryana at regional research station IARI and observed that pesticide was highly productive inputs and their recommendations based on the maximization of physical product were improper.

Subba Rao et al, (1987) highlighted the indiscriminate use of conventional insecticides as well as synthetic pyrethroids by cotton farmers in Guntur district of Andhra Pradesh.

Kumari Beena et al, (2003) in a study, tested vegetable samples and reported 100% contaminated with low but measurable amounts of pesticide residues. Among the four major chemical groups, residue levels of organophosphorous insecticides were highest followed by carbonates, synthetic pyrethroids and organochlorines. About 32% of the samples showed contamination with organophosphorous and carbamate insecticides above their respective MRL values.

Pesticide, Residues & Regulation in India (2007) reported that the highest level of DDT residues found was 2.2 mg/kg. The proportion of the samples with residues above the tolerance limit was maximum in Maharastra (74%) followed by
Gujarat (70%), Andhra Pradesh (57%), Himachal Pradesh (56%) and Punjab (51%). In the remaining states, this proportion was less than 10%. Data on 186 samples of 20 commercial brands of infant formulae showed the presence of residues of DDT and HCH isomers in about 70 and 94% of the samples with their maximum level of 4.3 and 5.7 mg/kg (fat basis) respectively.

2.2 Perceptions of farmers and consumers to pesticide use:

Sahabat (1984) studied with the use of pesticides in Malaysia and reported that almost three-quarters of pesticide users had no knowledge of the danger of pesticide use, and the problem was observed with the inadequate controls and safety measures regulating their use. A similar attempt was made by Jeyaratnam (1990); Ngowi (2002); Wilson (2002) on a limited scale in some developing countries to value the health damage due to pesticide exposure.

World Health Organization estimated, that pesticides cause 30,000 cases of poisoning and 2,20,000 deaths annually across the globe, the majority of those were reported from developing countries and these numbers, even more alarmingly, show a rising trend (WHO (1990); DTE (2001); Rosenstock et al, (1991); Pimental (1992); Kishi et al, (1995); WRI (1998). While indiscriminate use and unscientific handling of toxic chemicals were very common, the extent, severity and frequency of associated health problems are often unknown.

Gandhi and Patel (1997) stated that farmers’ awareness regarding the ill-effects of pesticides on water and air were very limited.

Chitra grace et al, (2000) observed that the use of pesticides in agriculture sector poses a serious environmental and public health problem, and emphasized the
need for creating more awareness among the farmers and authorities in enforcing and ensuring the use of protective gear while handling pesticides.

International Labour Organization (ILO) (2000) estimated that half of the world labour force was employed in agriculture and around 1.3 billion workers are engaged in agricultural production worldwide and also stated that hazards associated with agriculture are, however, more pronounced in the less developed countries as there is much greater labour participation in the agriculture sector (around 60%, against 10% in developed nations).

Hurtig et al, (2003) developed a structural questionnaire focusing on socio-demographic characteristics, knowledge and experience of adverse health effects related to pesticide use, details of work practices, and an inventory of pesticides used on the farm in the Amazon basin of Ecuador where Pesticide use is one of the most significant occupational exposures for agricultural workers and they concluded that training and educational campaigns on pesticide use should be encouraged for this cohort suggesting alternative methods of pest control.

Konradsen et al, (2003) emphasized substitution of pesticides with safe and cost-effective alternatives and immediate phasing out of the WHO Classes I and II pesticides through national policies and enforcement.

Susmita and Mainul (2005) conducted a survey on agricultural farmers and the survey results highlighted the necessity for policymakers to design effective and targeted outreach programs that deal specifically with pesticide risk, safe handling, and averting behavior. Ideally, the approach would be participatory in nature to address key informational gaps, as well as increasing a farmers' awareness retention.
William et al, (2006) studied the Farmer perceptions and pesticide use practices in vegetable production in Ghana and advocated the introduction of well-targeted training programmes for farmers for the safe use of pesticides to avert pesticide poisoning.

Suleisin and Ismet (2007) studied and analysed that adoption of pesticide practices was influenced more by characteristics such as age, fruit growing experience and education. Thus the perception on the harmful effects of the pesticides is not fully reflected in practices and that attitudes and practices are inconsistent with each other. Various precautions need to be taken in order to bring about a consistency between the farmers’ existing environmental awareness and their behaviour.

Atreya (2008) conducted household surveys in rural Nepal and assessed the magnitude of exposure to insecticides and fungicides that significantly influenced the occurrence of acute symptoms among individuals who apply pesticides compared to individuals in the same household who are not directly exposed. This study suggested that there are acute health impacts of pesticide use; however, because of the low level of the health costs, farm workers may underestimate the effects of pesticides on the human being, and thus they may continue to use pesticides without any safety precautions.

Dikshit (2008) reported the consumption of pesticide for different crops;

- Cotton consumed 55 percent of total pesticides in India while the total area under cotton was only 5 per cent.
- Similarly in the case of paddy, 17 percent of the pesticides were consumed, while the total area under paddy was 24 per cent.
- In the case of fruits and vegetables the usage was 13 per cent of total production and the area was only 3 per cent of the total cultivated area.
Gupta et al., (2008) studied the Consumers Perception on Pesticide residue and their management in vegetables in the city area of Varanasi district and opined that safer measures to be taken for vegetables contaminated to make safer to eat with the proper decontamination of fruits and vegetables prior to their consumption.

Obopile et al., (2008) studied the Vegetable farmers’ knowledge and perceptions of pests, diseases and pest management practices by interviewing the growers and observed that about 98% of farmers relied heavily on the use of synthetic pesticides to control these pests and their decision to apply pesticides was mostly on noticing the presence of a pest or disease. Also suggested an integrated pest management programme to reduce over reliance on pesticides.

Juthathip and Genesh (2009) conducted studies to investigate pesticide use and prevention practices of tangerine growers in Fang district, Chiang Mai province in Northern Thailand and observed that only 36% of the participants pursued the recommended prevention practices every time they used pesticides. They emphasised that the farmers rather believed in their experiences and those of their neighbours. Education, training and research into harmful effects and the health and environmental costs of pesticide use are needed.

Remor et al., (2009) conducted a study to evaluate the effects of exposure to complex mixtures of pesticides in farm workers from two communities from Rio Grande do Sul, Brazil and reported a significant decrease in the butyrylcholinesterase (BChE) and aminolevulinic acid dehydratase (ALA-D) activities in farm workers (n=37) relative to the control group (n=20) (P< or =0.05 and P< or =0.001, respectively). The study suggests that the use of PPE seems to be important in the prevention of contamination, as suggested by BChE levels and Comet assay results.
Christos and Eleftherohorinos (2011) studied the adverse effects of pesticide use on the environment (water, soil and air contamination from leaching, runoff, and spray drift, as well as the detrimental effects on wildlife, fish, plants, and other non-target organisms) and reported that many of these effects depend on the toxicity of the pesticide, the measures taken during its application, the dosage applied, the adsorption on soil colloids, the weather conditions prevailing after application, and how long the pesticide persists in the environment.

2.3 Health hazards of pesticide use:

Both media and scientific attention to pesticide use and its effects gained momentum in India only very recently.

Rachel Carson (1962) an American courageous woman and scientist, wrote down her nature observation and pointed out sudden dying of birds caused by indiscriminate spraying of pesticides (DDT). Her book, “Silent Spring”, became a landmark. It changed the existing view on pesticides and has stimulated public concern on pesticides and their impact on health and the environment. Silent Spring facilitated the ban of the DDT in 1972 in the United States.

Brown and Chow (1975) from Ontario obtained paired samples of adipose tissue and blood from autopsies on accident victims residing in Norfolk County and 52 blood samples from persons engaged in the agricultural application of DDT in the country and 315 from residents of Holland Marsh were analysed for total DDT and reported mean values of total DDT for adipose tissue and blood were 5.83 and 0.032 ppm respectively. There was a statistically significant correlation between total DDT in fat and blood, mean value for total DDT in human blood samples was 0.032 ppm in
Norfolk County and 0.016 ppm in Holland Marsh and in 26 persons exposed during formulation of DDT preparations was 0.063 ppm.

Kannan et al, (1980) detected Methly parathion, Fenitrothion, Malathion and endosulfan in various parts of rice plant using Gas Liquid Chromatography and reported that these pesticide residue levels in the leaves were above environment protection agency tolerance limits even after 15 days and the same trend was reported on whole grain, dehusked grain and hay immediately after harvest.

Brahmaprakash Sethunathan (1987) and Gangamma and Satyanarayana (1991) reported the presence of pesticide residues in soil, water bodies, air, food materials and the bodies of living beings, and stated that pesticide residues in food in India, especially vegetables, are the highest in the world. This is mainly due to the unregulated use of pesticides.

Mencher (1991) examined the problems of pesticide usage in Indian rice growing regions, which pose a serious threat to the health of rural people and health hazards were analysed and it was denoted that organophosphates remain in the human blood system for six to nine weeks. Constant exposure to pesticides will result in a build-up of these chemicals in the blood.

Kanja et al, (1992) analysed a total of 41 samples of maternal blood, milk subcutaneous fat and umbilical cord blood of mothers giving birth by caesarean operation at Kenyatta National Hospital in Nairobi in 1986 and reported contaminants like pp’ DDT (100%), pp’ DDE (100%), op’ DDT (59%), dieldrin (27%), transnonachlor (15%), β-HCH (12%) and lindane (2%) of all the samples analysed and also reported that the mean level (mg/kg fat) of t-DDT was 5.9 in
subcutaneous fat, 4.86 in mother’s milk, 2.75 in maternal serum and 1.9 in umbilical
cord serum.

Frank et al, (1993) collected 750 whole blood samples from residents of large
and medium to small urban centers across Ontario and analysed for pesticide residues
in foods consumed by Ontario residents during 1986-87 on the food basis and
detected pesticide residues which showed a mean concentration of PCBs up to 9.2
mg/kg and DDE up to 3.7 mg/kg which was higher than the range of dietary levels of
PCBs and DDE ranged from 0.1-3.0 mg/kg and 0.05 - 0.77 mg/kg respectively.

Dua et al, (1996) in a case study of two groups analysed for HCH and DDT
contamination in whole blood and found mean HCH and DDT contents in whole
blood of general population of 37 males not involved in spraying from district
Hardwar, UP were 21.50 mg/l and 20.79 mg/l respectively and 47 samples from the
occupationally exposed persons, involved in spraying operation of HCH and DDT for
the control of mosquitoes and flies, was 68.0 mg/l and DDT was 58.43 mg/l i.e. 3.1
times and 2.8 times more as compared to general population.

Veeraiah and Durga Prasad (1996) conducted a study on six drinking water
pond samples of 7 villages of Guntur District, Andhra Pradesh for organochlorine
residues and detected the presence of OC residues like α, γ, β HCH, DDT, DDE,
DDD and also showed that higher quantities of HCH isomers recorded are attributed
to their greater water solubility, in comparison, concentrations of DDT group residues
are somewhat lower reflecting their poor water solubility. The study also observed
that the long term hazard of the DDT group is much more because they are
hydrophobic and are bioaccumulated to a greater extent.
Puri (1998) in his study observed that chemical pesticide residues have often been detected in food grains, vegetables, fruits, oils, cattle feed and fodder in most parts of the country and stated about 72 per cent of food samples in India have shown the presence of pesticide residues within tolerance levels while in 28 per cent samples they were above the tolerance level as compared to 1.25 per cent globally. As a consequence, India accounts for one-third of the total pesticide poisoning cases in the world.

Waliszewski et al., (2000) in a study from Veracruz, Mexico collected maternal adipose tissue, maternal blood serum from 64 volunteer mothers and analysed for organochlorine pesticide residues- HCB, α, β, γ, δ- HCH, aldrin, dieldrin, heptachlor, heptachlor epoxide, pp’-DDT, op’-DDT, pp’- DDD, α, β, endosulfan, endosulfan sulfate, chlordane, and methoxychlor and detected t-HCH in maternal adipose tissue, maternal serum was 0.17 and 0.22 mg/kg on fat basis, t-DDT was 5.851, 5.226 mg/Kg and hexachloro benzene was 0.065 and 0.18 mg/kg

The investigations were carried out on the occurrence of pesticide residues in 68 surface and ground water sources by Bratanova and Vassilev (2001) reported residues of 15 pesticides have been found in 19 % of the examined 176 water samples and observed atrazine, 13 % and lindane, 10%. The contamination levels ranged from 0,01 to 0,1 µg/l for atrazine and from 0,01 to 0,06 µg/l for lindane pesticides, due to unregulated storage and disposal of pesticides.

Meijer et al., (2001) reported concentrations typically ranging from 0.1 to 10 ng/g of soil (dry weight), with γ-hexachlorocyclohexane (γ-HCH), dieldrin, and p,p’-DDE consistently having the highest concentrations and observed the trends in the Broadbalk background soils are largely consistent with usage patterns, with peak concentrations occurring in the 1960’s for DDT’s and between the 1960’s and the
1980s for the other OC’s were as in the Luddington control and sludge-amended soils, several of the OC’s showed a significant decline in concentrations from the late 1960s to 1990, with half-lives ranging from ~7 years (α-HCH) to ~25 years (dieldrin).

Mohammad et al, (2001) in his study on school children in Peninsular Malaysia and collected 577 whole blood samples for pesticide residue analysis and detected 11 organochlorine and 2 organophosphorus pesticides, this revealed the presence of pesticide residues in blood at nanogram per gram - aldrin, nd-47.6; dieldrin, nd; endrin, nd; alpha-endosulfan, nd-0.6; beta-endosulfan, nd; endosulfan sulfate, nd; heptachlor, nd- 3.8; lindane, nd-5.7; p,p’-DDT, nd-3.4; o,p’-DDE, nd-1.4; p,p’-DDE, nd; chlorpyrifos, nd-10.3; diazinon, nd-103.0.

Amaral Mendes (2002) reported that some of environmental chemicals such as pesticides and industrial chemicals acts as Endocrine disruptors (EDs) by mimicking the effect of endogenous hormones and disrupting the normal functioning of the endocrine system and can modulate both the endocrine and immune systems resulting in alteration of homeostasis, reproduction, development and behaviour. He also emphasised the most significant pathological effects, on the male reproductive tract, female gynecological system, human fertility, thyroid function and the central nervous system.

Curl (2003); Lu (2005) in their studies found those shifting children’s diets from conventional foods to organic foods, by direct substitution of conventional foods, leads to a reduction of organophosphate pesticides in urine. This suggests that foods are a key source of exposure to some pesticides.

Rashmi Sanghi et al, (2003) reported HCH isomers; endosulfan, malathion, chlorpyrifos, and methyl-parathion were monitored in human milk samples from
Bhopal, Madhya Pradesh. The endosulfan concentrations were highest and exceeded the S-HCH, chlorpyrifos, and malathion concentrations by 3.5-, 1.5-, and 8.4-fold, respectively.

Soares et al, (2003) conducted a study of 1,064 rural workers from 1991 to 2000 of nine counties in Minas Gerais State and characterized the rural work process based on the land tenure structure of farm operations, and work practices related to pesticide (carbamates/organophosphates) use and poisoning. The study assessed the high level of health risk associated with pesticide use among these rural workers.

Whyatt et al, (2003) in a study in the USA reported seven pesticides, in 48-83% of plasma samples (range, 1-270 pg/g) the organophosphates chlorpyrifos and diazinon, carbamates bendiocarb and 2- isoproxyphenol (metabolite of propoxur) and fungicides- dicloran, phthalimide (metabolite of folpet and captan) and tetrahydrophthalimide (metabolite of captan and captafol) and observed high correlated (p<0.001) between samples.

Prenatal organophosphate pesticide residues in maternal or umbilical cord blood was reported by Whyatt et al, (2003); Bradman and Whyatt (2005); Needham (2005); Eaton et al, (2008); Neta et al, (2010). In all these studies they analysed organophosphate pesticide levels in blood allowed for direct measurement of parent compounds rather than metabolites and may more accurately represent the dose that reaches the target tissue whereas chlorpyrifos and diazinon are lipophilic so the portion of the compound that partitions into body fat may be eliminated more slowly and indicated levels in blood may represent a steady state concentration.

Waliszewski et al, (2004) analysed for HCB, b-HCH, pp’- DDE, op’- DDT and pp’- DDT and results were statistically compared for mean and standard deviation
for all organochlorine pesticides between both sample groups indicating significant higher values of serum lipids vs. adipose lipids expressed as mg/kg on lipid basis (HCB 0.178 vs. 0.055, b- HCH 0.504 vs. 0.216, pp’ DDE 2.789 vs. 1.063, op’- DDT 0.130 vs. 0.062, pp’ DDT 0.340 vs. 0.585 and t- DDT – 3.258 vs. 1.706).

Mancini et al, (2005) documented the serious consequences of pesticide use for the health of farmers, particularly women field helpers because of female tasks such as mixing concentrated chemicals and refilling spraying tanks were as hazardous as a direct pesticide application. He assessed acute pesticide poisoning among farmers in three villages in India.

Hawkes & Ruel (2006) reported that agricultural producers, systems and outputs are associated with human health through a complex set of factors including environmental change, exposure to a variety of natural and human-origin stressors, social position, changing behaviour, occupation, and access to services (including health and social security).

Subramaniam et al, (2006) observed high concentrations of both BHC & DDE in the serum samples of the people who had direct exposure to the pesticides, namely agriculturalists and public health workers with few exceptions. The pesticide residue concentration in serum ranges from 0.006 to 0.130 ppm for BHC and 0.002 to 0.033 ppm for DDE. This study reveals that the presence of these banned pesticides in human serum.

Chen Xuehui (2007) reported the residues of OC pesticides (DDT, DDE, DDD and HCH) in human adipose tissues and found significantly (p<0.05) correlated between subcutaneous and visceral adipose tissues in patients with endometrial cancer.
of the uterus, reflecting the impact of OC pesticides on the etiology of this disease, which was hormonal-related pathology.

Curwin et al, (2007) studied 47 fathers, 48 mothers and 117 children of Iowa farm and non-farm households and reported geometric mean (GM) level of the urine metabolite of atrazine, chlorpyrifos were significantly higher in households compared with those from non-farm households, but metolachlor and glyphosate levels were similar between the two groups.

Haozheng Wang et al, (2007) observed that the total concentrations of OCPs varied from 3.06 to 23.24 ng g\(^{-1}\). \(\sum\text{HCH (}\alpha\text{-HCH, }\beta\text{-HCH, }\delta\text{-HCH, }\gamma\text{-HCH), }\sum\text{DDT (p, }p'\text{-DDE, p, }p'\text{-DDD, o, }p'\text{-DDT, p, }p'\text{-DDT) and }\sum\text{Cyclodiene (Heptachlor, Aldrin, Heptachlor epoxide, Dieldrin, Endrin) ranged from 1.86 to 21.48, 0.5 to 2.81 and 0.56 to 1.53 ng g}^{-1}, \text{respectively, in three rivers in Daliaohe River watershed (Hunhe River, Taizihe River and Daliaohe River).}\)

Sanborn et al, (2007) reported that there is a strong evidence of association with pesticide exposure for all neurological outcomes, genotoxicity, and 4 of 6 reproductive effects: birth defects, fetal death, altered growth, and other outcomes and also reported that exposure to pesticides generally doubled the level of genetic damage as measured by chromosome aberrations in lymphocytes; dermatologies effects of pesticides were higher among those who had high exposure to pesticides on the job.

Tan et al, (2008) analysed maternal adipose tissue samples for the presence of persistent organic pollutants (POP’s), polychlorinated biphenyls (PCB’s) and polybrominated biphenyl ethers (PBDE’s) and elucidated the relationship between concentrations of POPs in adipose tissues and donors' characteristics and reported that
food consumption played the most significant role in accounting for levels of POPs in adipose tissue probably due to an alteration in lipid metabolism.

Abhilash and Nandita Singh (2009) reported that exposure to pesticides both occupationally and environmental causes a range of human health problems, such as increasingly linked to immune suppression, hormone disruption, diminished intelligence, reproductive abnormalities and cancer.

Javed et al, (2009) determined occupational exposure to a complex mixture of pesticides results in a significant increase of DNA damage in farmers chronically exposed to pesticides in open fields. Statistically significant difference (P < 0.001) in DNA damage of exposed individuals (mean 6 S.D 14.80 6 3.04 ml) was observed when compared with control group (6.54 6 1.73 ml) as studied on the basis of comet tail length.

Lorenz (2009) reported that the pesticides sprayed onto food, especially fruits and vegetables, can enter the human body through inhalation of aerosols, dust and vapour that contain pesticides; through oral exposure by consuming food and water; and through dermal exposure by direct contact of pesticides with skin and these chemicals bioaccumulate in the body and causes serious health problems over time.

Ranga Rao et al, (2009) investigated pesticide residues in vegetables and reported the residues of monocrotophos and endosulfan below the maximum residue limit (MRL) in 59 vegetable samples, while the residues of chlorpyrifos were above the MRL in 4 samples and cypermethrin in 2 samples. The presence of pesticide residues in water samples were below MRLs.

Charan et al, (2010) reported that about 40.11% of total analysed samples were contaminated with different pesticide residues, among which 35.62% of total
contaminated samples were exceeded the maximum residue limit (MRL) values in vegetable samples.


Rahul Pathak et al, (2010) observed a positive correlation between maternal blood levels of β-HCH and MDA (r = .78), β-HCH and GSH (r = .65), γ-HCH and MDA (r = .89), γ-HCH and GSH (r = .74) and α-endosulfan and MDA (r = .54) in preterm delivery cases and found significant correlations between cord blood levels of β-HCH and MDA (r = .59), β-HCH and GSH (r = .69), γ-HCH and MDA (r = .62) and α-endosulfan and MDA (r = .54) by concluding that higher levels of some of the organochlorine pesticide residues may be associated with preterm delivery and increased oxidative stress.

Balabanic et al, (2011) reported that a substantial number of environmental pollutants, such as polychlorinated biphenyls, dioxins, polycyclic aromatic hydrocarbons (PAHs), phthalates, bisphenol A, pesticides, alkylphenols and heavy metals (arsenic, cadmium, lead, mercury), have been shown to disrupt endocrine functions and may cause breast cancer.

Kumar et al, (2012) reported concentration of total organochlorine pesticides (OCPs) (Aldrin, dieldrin, heptachlor and lindane pesticides) in selected root and leaf vegetables was ranged between, <0.01-6.00 ng/g, with an average of 2.16±0.21 ng/g (wet wt.) and revealed that selected vegetables had residue levels, much below the recommended maximum residue limits (MRLs) set by the European Commission and Indian government.
2.4 Cancer incidence and mortality:

Cancer is a very complex disease with a long time lag between initiation and the onset of symptoms. Cancer is the second most common cause of death worldwide. The incidence of cancer varies strikingly according to the varied regional habits and environmental conditions.

Reports of the International Agency for Research on Cancer reports indicated that lung cancer was the most frequent, accounting for 12 per cent cancer cases worldwide. In the developed countries, the commonest cancer site i.e., lung (15%), followed by colon and rectum (13%), breast (12%) and stomach (9%). On the other hand, stomach cancer ranked first in developing countries (11%) followed by lung (9%) and cervical cancer (9%). The frequency of breast cancer (298,000) in developing nations was less than that of oral cancer (301,000), which comprised of 4th most groups of neoplasm (8%) (Parkin et al., 1993).

Krishnaswamy and Prasad (1998) reported that a nationwide increase of 5.5 per cent in males and 4.9 per cent in females for cancer at all sites between 1982-1989. In men lung cancer was leading (12.6/100,000) followed by a mouth (12.4), pharynx (10.2) and esophagus (9.4), while among women cervical cancer was the most common (27.6) followed by breast (25.9) and mouth (7.5). In males 24 per cent decrease in cancer related to tobacco, namely oral and pharyngeal, while the increase (16%) in cancers related to smoking such as lung was observed from 1982-89. Among the females the decreasing trends were seen for mouth (37%), pharynx (15%) and stomach (38%) whereas increased trends were seen for breast (16%) and ovary (21.5%) cancer.
Hortobagyi *et al.*, (2005) reported that Breast cancer is the most common type of cancer and the most common cause of cancer-related mortality among women worldwide. However, the burden is not evenly distributed, and according to the best available data, there are large variations in the incidence, mortality, and survival between different countries and regions and within specific regions.

In India officially over half a million deaths were recorded due to cancer during 2011 – 5.35 lakhs as against 5.14 lakh in 2009 and 5.24 lakh during 2010. In the state of Uttar Pradesh recorded 89,224 deaths due to cancer, while Maharashtra saw 50,989 fatalities. According to the Union health ministry there were about 28 lakh cases of cancer at any given point of time in India, with 10 lakh new cases being reported annually. According to World Health Organization (WHO, 2010), the estimated cancer deaths in India were projected to increase to 7 lakh by 2015.

Jemal *et al.*, (2011) reported that about 12.7 million cancer cases and 7.6 million cancer deaths are estimated in 2008; of these, 56% of the cases and 64% of the deaths occurred in the economically developing world. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths. Lung cancer is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths.

According to Rebecca *et al.*, (2011) Breast cancer is now also the leading cause of cancer death among females in economically developing countries, a shift from the previous decade during which the most common cause of cancer death was cervical cancer. Further, the mortality burden of lung cancer among females in developing countries is as high as the burden for cervical cancer, with each accounting for 11% of the total female cancer deaths. Although overall cancer incidence rates in the
developing world are half those seen in the developed world in both sexes, the overall cancer mortality rates are generally similar.

2.5 Breast cancer and risk factors:

Breast cancer is a cancer that starts in the cells of the breast in women and men. Generally it refers to a malignancy in women that arises from the terminal ductal-lobular units of epithelial tissue, which in the mature breast represent 10% of the total volume (WHO (2010)).

There are many ways that breast cancer can develop, but most of the time it starts in the breast ducts. Several studies have suggested that there is a continuum of events linking benign breast disease with breast cancer development (Black et al, (1972); Rywlin (1984); Dupont and Page (1985); Bodian (1993); Cheryl M Taylor (2007).

The rising global incidence, morbidity and mortality from breast cancer have led to intensified efforts in the search for etiological factors of the disease. Risk factors that modulate the development of breast cancer are age, race, ethnicity, geographic location (country of origin), socioeconomic status, reproductive events, exogenous hormones, lifestyle risk factors (alcohol, diet, obesity and physical activity), familial history of breast cancer, mammographic density, history of benign breast disease, ionizing radiation, bone density, height, breast feeding and chemopreventive agents (Dumitrescu & Cotarla (2005); Hortobagyi et al, (2005). On the other, multiple analysis of Yavari et al, (2005) indicated that never married, post menopause, age at first live birth, number of live births, the use of oral contraceptive pills, and history of chest X-rays between adolescence and 30 yrs of age, were significantly associated with breast cancer. Variables such as early age at menarche,
abortion, breastfeeding and its duration were not significant risk factors (Parvez et al, 2001).

2.5.1 Risk factors of breast cancer:

a. Age: The strongest risk factor for breast cancer (after gender) is age: the older the woman, the higher her risk. The incidence of breast cancer increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically (Nelson et al, (2012); Van Ravesteyn et al, (2012).

b. Geographical variation: The incidence of breast cancer varies with the locality. Geographical differences in incidence have helped to discover the role of different etiological factors in the pathogenesis of disease, also in Central Asia (Moore et al, (2009); (2010). The inhabitants of Asia are taken ill of the disease 5-10 times less than residents of North America and Western Europe. These differences cannot be explained by genetic factors, because the risk of breast cancer among the natives of Asia, living in developed countries, the same as that of the indigenous people of the same countries. But the natives of Asia, living in developed countries differ significantly from the residents of Asia (Moore and Sobue (2010); Liao et al, (2011).

c. Reproductive history: Now-a-days women are at increased risk of breast cancer due to the fact that women have fewer children and a limited duration of breastfeeding.

i. Age at menarche: Early age at menarche has been consistently associated with an increased risk of breast cancer. Average age of menarche fell from around 16-17 years in the mid 19th century (Tanner, 1973) to 12-13 today (Maruti et al, (2008); Howard et al, (2009); Kerlikowske et al, (2010).
ii. **Age at first birth:** The younger the woman is when she begins childbearing, the lower her risk of breast cancer. The relative risk of developing breast cancer increases by 3% for each year of delay (Butt et al., 2012). For example, a woman who has her first baby at age 28 would have a 3% lower risk of breast cancer than a woman who had her first baby at 29, all other factors being equal.

iii. **Parity:** The effect of parity on reducing the risk of breast cancer has long been recognized. In the 18th century Bernado Ramazzini (1633-1714) reported the highest rate of breast cancer in nuns compared with married women and speculated that this might be associated with their lack of children. In one meta-analysis nulliparity was associated with a 30% increase in risk compared with parous women. The higher the number of full-term pregnancies, the greater the protection. There is a reduction in risk of 7% for each birth after the first, in the absence of breastfeeding (Butt et al., 2012).

iv. **Breastfeeding:** Women who breastfeed reduce their risk compared with women who do not breastfeed. The longer a woman breastfeeds, the greater the protection: risk is reduced by 4.3% for each year a woman breastfeeds (Parkin, 2011).

v. **Age at menopause:** Late menopause increases the risk of breast cancer (Parsa and Parsa, 2009). For each year menopause is delayed, there is an approximate 3% increase in breast cancer risk (Michels et al., 2007). Postmenopausal women have a lower risk of breast cancer compared to premenopausal women of the same age. This is true for both natural menopause and menopause induced through surgery (Michels et al., 2007).
d. Exogenous Hormones:

i. The Pill: The use of oral contraceptives (OCs) slightly increases the risk of breast cancer in current and recent users, but there is no significant excess risk ten or more years after stopping use (Parkin (2011)). These estimates are based on a collaborative analysis of 54 studies in 25 countries, with data on over 50,000 women with breast cancer. Cancers diagnosed in women who have used OC tend to be less clinically advanced than those detected in never-users. OC users are generally younger women whose breast cancer risk is comparatively low, so the small excess risk in current users will result in a relatively small number of additional cases.

ii. Hormone Replacement Therapy (HRT): HRT use increases the risk of breast cancer and reduces the sensitivity of mammography (Parkin (2011); Bilyalova et al, (2012). The risk of breast cancer for current or recent users of HRT increases by 2% per year of use. For women who had used it for at least five years (average 11 years) the risk increase was 35%. (Parkin (2011). The effect is substantially greater for estrogen-progestagen combinations than for estrogen only HRT. Risk increases with duration of use: the risk for current users of estrogen-progestagen combinations for 10 or more years was 2.31 compared to 1.74 for 1-4 years of use (Zota et al, (2010).

e. Endogenous hormones:

Higher levels of endogenous hormones have long been hypothesized to increase breast cancer risk. A pooled analysis of nine prospective cohort studies found a statistically significant increased risk of breast cancer in postmenopausal women with higher levels of sex hormones (Key et al, (2010); Bilyalova et al, (2012). The risk was approximately double for women whose oestradiol levels were in the top
quintile compared with women whose oestradiol levels were in the bottom quintile. Evidence for premenopausal women is inconclusive.

f. Personal history: Today women are at increased risk of breast cancer due to their personal history which is considered as non-communicable risk factors.

g. Bodyweight: Overweight and obesity, as measured by a high body mass index (BMI), moderately increases the risk of postmenopausal breast cancer and is one of the few modifiable risk factors for breast cancer (Reeves (2007); Parkin and Boyd (2011). After the menopause, when the ovaries stop producing oestrogen, adipose tissue is the primary source of endogenous oestrogen so obese and overweight women are exposed to higher levels of oestrogen. Obesity is also associated with lower levels of sex hormone-binding globulin (SHBG) which increases the amount of bio-available oestradiol (Parkin and Boyd (2011).

h. Height: Reeves (2007); Parkin and Boyd (2011) reported that taller women have an increased risk of breast cancer. There was an approximate increase in relative risk of 7% for each additional 5 cm in height for postmenopausal women and 2% for premenopausal women (Green et al, (2011).

<table>
<thead>
<tr>
<th>Sl.No.</th>
<th>Body Mass Index (BMI)</th>
<th>Presumptive Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;</td>
<td>Chronic Energy Deficiency (CED)</td>
</tr>
<tr>
<td>2</td>
<td>16.0-17.0</td>
<td>CED</td>
</tr>
<tr>
<td>3</td>
<td>17.0-18.5</td>
<td>CED</td>
</tr>
<tr>
<td>4</td>
<td>18.5-20.0</td>
<td>Low</td>
</tr>
<tr>
<td>5</td>
<td>20.0-25.0</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>25.0-30.0</td>
<td>Obese Grade 1</td>
</tr>
<tr>
<td>7</td>
<td>&gt;</td>
<td>Obese Grade 2</td>
</tr>
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</table>

Key: Body Mass Index is calculated as the weight in kilograms divided by the square of the height in metres.

i. Diet: A diet high in fat has been positively associated with breast cancer in international correlation studies (Inumaru et al, (2012). Overall, the evidence suggests
a fat intake, particularly animal fat, may cause a small increased risk of breast cancer but probably does not play as large a role as was once thought.

**j. Alcohol intake:** A significant association between alcohol intake and breast cancer was observed with an increase in risk of 7% for each additional 10 grams of alcohol/day consumed (Allen *et al.*, (2009); Parkin (2011). Around 4% of breast cancers in women in developed countries may be attributed to alcohol. Although alcohol and tobacco smoking are closely related social habits, there was no direct association between tobacco and breast cancer (Luo *et al.*, (2011).

**k. Family history of breast cancer:** A woman with one affected first degree relative (mother or sister) has approximately double the risk of breast cancer of a woman with no family history of the disease; if two (or more) relatives are affected, her risk increases further (Balmana *et al.*, (2011). However, over 85% of women who have a close relative with breast cancer will never develop the disease, and more than 85% of women with breast cancer have no family history of it (Inumaru *et al.*, (2012). In developed countries it is estimated that hereditary factors contribute around a quarter of inter-individual differences in susceptibility to breast cancer, while environmental and lifestyle factors contribute the remaining three-quarters (Inumaru *et al.*, (2012). Small proportions of women have a particularly strong family history of breast cancer and are at very high risk. Mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 account for the majority of families with four or more affected members and 2-5% of all breast cancers (Balmana *et al.*, (2011). Women carrying such a mutation have a 50-80% chance of developing the disease. Since breast cancer affects one woman in nine there will be many women who have a mother or sister with the disease. But only if there are several family members with early onset breast cancer is
there a likelihood of a significant inherited predisposition to the disease (Balmana et al., 2011).

1. Environmental chemicals and breast cancer: Many environmental chemicals are metabolized in the body to reactive intermediates that readily react with DNA to form modified bases known as adducts, while other compounds mimic the biological function of estrogen. Because environmental chemicals tend to accumulate in human tissues and have carcinogenic and/or estrogenic properties, there is heightened interest in determining whether environmental chemicals increase risk for endocrine-related cancers, including breast cancer (Weyandt et al., 2008).

2.6 Pesticide correlates of cancer:

Buckley et al., (1989) reported that the risk estimates for parental pesticide exposure were substantially increased for children under age 6 at diagnosis (OR for prolonged exposure to either parent = 11.4; trend, $P = 0.003$) and for those with myelomonocytic and monocytic subtypes (OR, 13.6; trend, $P = 0.007$). This data provide further evidence for a role of occupational risk factors in the etiology of childhood cancer.


Bhatnagar et al., (2004) analysed human blood samples from 18 male healthy volunteers of Ahmedabad (urban) area and the results showed the presence of pp’ DDE, op’- DDT, pp’ DDD, pp’ DDT and t-DDT at an average value of 20.85, 1.15,
2.03, 9.28 and 32.61 mg/l in serum samples, the concentration of α, β, γ and δ HCH in serum samples was 4.49, 35.06, 1.69 mg/l and 41.23 mg/l. Hexachlorobenzene was present in 7 samples at an average concentration of 0.2 mg/l respectively.

Flower et al, (2004) examined childhood cancer risk and associations with parental pesticide application in a prospective study via questionnaires of pesticide applicators in Iowa and North Carolina and analysed results by logistic regression to explore associations between self-reported parental pesticide application practices and childhood cancer risk and reported the increase risk of cancer among children whose fathers did not use chemically resistant gloves [odds ratio (OR) = 1.98; 95% CI, 1.05-3.76] compared with children whose fathers used gloves. This study says that farm exposures including pesticides may play a role in the etiology of childhood lymphoma.

Mike Howsam et al, (2004) measured concentrations in serum of several organochlorines by gas chromatography and assessed point mutations in K-ras and p53 genes in tissue samples by polymerase chain reaction/single-strand conformation polymorphism and assessed the expression of p53 protein and reported elevated risk of colorectal cancer associated with higher serum concentrations of mono-ortho polychlorinated biphenyl (PCB) congeners 28 and 118.

Freeman et al, (2005) explored a possible association of diazinon exposure with cancer risk in the Agricultural Health Study, among 4,961 applicators and reported that using diazinon, 301 incident cancer cases were diagnosed during the follow-up period ending December 2002 compared with 968 cases among 18,145 participants who reported no use. Poisson regression was used to calculate rate ratios and 95% confidence intervals and observed significant increased trend for lung cancer and leukemia.
Roos et al, (2005) reported that toxic equivalency quotient (TEQ), a summed metric that weights congeners by their dioxin-like potency, was associated with non-Hodgkin's lymphoma, with a 35% increased risk.

Nickerson (2006) reported that levels of POPs such as organochlorines are known to increase with age and exposure suggesting bioaccumulation in tissues which may suggest increased levels of certain toxicants in adults and cause human cancers.

Alexander (2007) observed that the farmers using 2, 4, 5-TP on their farms had high levels of the pesticide in their urine samples soon after the chemical had been applied to the fields and given the evidence of increased susceptibility of children and young adolescents to the carcinogenic effects of chemicals.

Bonner et al, (2007) investigated associations between malathion exposure and cancer among 19,717 pesticide applicators enrolled in the Agricultural Health Study between 1993 and 1997 and reported rate ratios and 95% confidence intervals using Poisson regression, adjusting for potential confounders and found no association with all cancers combined.

Luccio-Camelo and Prins (2011) identified broad classes of androgen disrupting molecules that include organochlorine pesticides, industrial chemicals, and plasticizers with the capacity to ligand the androgen receptor which act as anti-androgens with documented in vivo evidence for male reproductive tract perturbations.

2.6.1 Pesticide correlates of breast cancer:

Baker and Wilkinson (1990) reported that chlorinated pesticides, particularly DDT, may have oestrogenic activity, as the chemical structures of DDT and 17 β oestradiol were very similar and interact with the oestrogen receptor or associated
enzymes, with high affinity, and thus, potentially interfere with the hormone-responsive mechanisms of the reproductive system. The levels of DDT and its analogues have been identified in the serum, adipose and breast milk of women (owing to its lipophilic nature), and have been implicated in increasing the risk of cancers of the reproductive system, especially breast cancer.

Aronson et al, (2000) evaluated that the association between breast cancer risk and breast adipose tissue concentrations of several organochlorines in Ontario, Canada and reported that the biopsy tissue of 217 cases and 213 benign controls frequency matched by study site and age in 5-year groups was analysed for 14 polychlorinated biphenyl (PCB) congeners, total PCBs, and 10 other organochlorines. Multiple logistic regressions were used to assess the magnitude of risk and showed clear associations with breast cancer risk.

Stellman et al, (2000) assessed a possible etiological role of organochlorine compounds in breast cancer development on Long Island, a high-risk region of New York State, concentrations of organochlorine pesticides and polychlorinated biphenyls (PCBs) were measured in the adipose tissue of 232 women with breast cancer and 323 hospital controls admitted to surgery for benign breast disease or non-breast-related conditions. The relative abundance of individual pesticide species and PCB congeners was similar in cases and controls.

Key et al, (2001) and Brekelmans (2003) established that determinants of breast cancer include age, relative body weight, change in weight over time, the number and timing of reproductive events and lactation, exogenous and endogenous hormone concentrations and metabolism, history of benign breast disease, exposure to radiation, alcohol consumption, and family history of breast cancer.
Charlier et al, (2002) reported high mean levels of total DDT and HCB in breast cancer patients than for controls. These results add to the growing evidence that certain persistent pollutants might occur in higher concentrations in blood samples from breast cancer patients than controls.

Abdalla et al, (2003) analysed the association between pesticide exposure and risk of breast cancer mortality in three areas: Greenville, Corinth and Yazoo, and reported that the total number of acres planted was positive and significantly associated with female breast cancer mortality rate, and these associations differed by race and type of crop.

Krippel et al, (2003) reported the role of vascular endothelial growth factor (VEGF) gene which was associated with VEGF plasma level polymorphism for breast cancer risk. The study revealed that the VEGF genotype in 500 women with breast cancer and 500 sex- and age-matched healthy control subjects. Additionally, they determined VEGF plasma levels in 21 nonsmoking post-menopausal controls; carriers of a 936T allele had significantly lower levels (median 23 pg/ml; range 6-50 pg/ml) than noncarriers (37; 21-387; p = 0.034), and concluded that carriers of a VEGF 936T-allele were at decreased risk for breast cancer.

Jesus et al, (2004) stated that the total effective xenoestrogen burden (TEXB-alpha) was a risk factor for breast cancer over and above the risk potentially linked to specific pesticides (p,p-DDE (1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene), aldrin, endosulfan ether and lindane) and found an increased risk for breast cancer in the leaner women, especially in the leaner postmenopausal subgroup, related to the TEXB-alpha.

CDC (2005); EWG (2005); Mills (2005); Engel (2005) stated that the widespread use of pesticides on food crops was a significant source of exposure to
endocrine-disrupting compounds and carcinogens linked to breast cancer and reported greatest concern include atrazine, an endocrine-disrupting compound; heptachlor, an insecticide that was banned from production in 1988 and from use in 1993, but persists in soil and in humans; dieldrin and Aldrin, related pesticides that are endocrine disruptors; and several other pesticides that have been linked to breast cancer in agricultural workers.

Engel et al, (2005) found evidence of increased incidence of breast cancer in women using 2, 4, 5 trichlorophenoxypropionic acid (2, 4, 5-TP) and incidence was also modestly elevated in women whose homes were closest to areas of pesticide application.

Lu et al, (2005) reported that VEGF over-expression has been associated with advanced stage and poor survival of several cancers and suggested that VEGF polymorphisms may be a significant genetic marker for breast cancer prognosis.

Mills (2005) in a study noted that the risk of breast cancer was associated with the use of chlordane, malathion and 2, 4-D chemicals were higher in young women and in those with early-onset breast cancer than in unexposed women.

Nielsen et al, (2005) examined associations between organochlorines and the development of breast cancer in a large prospective study using stored adipose tissue and reported that the inverse association for estrogen receptor–negative breast cancer was unclear.

Jennifer A Rusiecki et al, (2005) correlated organochlorine concentrations in different biological media. Gas-liquid chromatography determined serum, breast adipose, and gluteal adipose tissue levels of dichloro diphenyl dichloroethane, β-benzene hexachloride, and polychlorinated biphenyl (PCB) congeners, PCB-153 and
PCB-180. The study found strong correlations among the three biological media which showed a combination of both recent and past exposures, which have metabolized slowly and may still persist.

Susan et al, (2006) observed pesticide exposures in relation to breast cancer primarily in occupational studies, by using unconditional logistic regression was used to calculate odds ratios and 95% confidence intervals. Breast cancer risk was associated with ever lifetime residential pesticide use (odds ratio ¼ 1.39, 95% confidence interval: 1.15, 1.68).

Cohn et al, (2007) conducted a prospective, nested case-control study with a median time to diagnosis of 17 years using blood samples obtained from young women during 1959-1967. Subjects were members of the Child Health and Development Studies, Oakland, California, who provided blood samples 1-3 days after giving birth (mean age, 26 years) and reported that the cases (n = 129) developed breast cancer before the age of 50 years by assaying serum was assayed for p, p’-DDT, the active ingredient of DDT; o, p’-DDT, a low concentration contaminant; and p, p’-DDE, the most abundant p, p’-DDT metabolite and reported high levels of serum p, p’-DDT, predicted a statistically significant 5-fold increased risk of breast cancer among women who were born after 1931.

Rudel et al, (2007) studied 216 chemical carcinogens (industrial chemicals, chlorinated solvents, products of combustion, pesticides, dyes, radiation, drinking water disinfection byproducts, pharmaceuticals and hormones, natural products, and research chemicals) in animal studies and reported all of the chemicals were mutagenic and most caused tumors in multiple organs and species, suggesting a need to strenmutagenicmicals testing and risk assessment as tools for breast cancer prevention.
Teitelbaum et al. (2007) in a case-control study of 1,508 women newly diagnosed with breast cancer between August 1996 and July 1997 and 1,556 randomly selected, age-frequency-matched controls and reported the association between reported lifetime residential pesticide use and breast cancer risk among women living on Long Island, New York by using an in-person, interviewer-administered questionnaire and by applying unconditional logistic regression was used to calculate odds ratios and 95% confidence intervals and stated that the breast cancer risk was associated with ever lifetime residential pesticide use (odds ratio = 1.39, 95% confidence interval: 1.15, 1.68). This study suggests that self-reported use of residential pesticides may increase breast cancer risk.

Santamaria-Ulloa Carolina (2009) conducted ecological study tests whether the Breast Cancer incidence in Costa Rica is related to pesticide environmental exposure (PEE) and reported that PEE had a statistically significant direct association with Breast Cancer for women 45 yrs+. The corresponding incidence rate ratio for PEE was 1.29 for women 45+. PEE was significant in some rural and agricultural areas of the country, after controlling for other risk factors.

Govind Pandey (2010) studied the relevance between environmental and food contaminants, including therapeutic agents (e.g., antibiotics, antihypertensive drugs, etc.) and oestrogenic endocrine disruptors (xenoestrogens or xenobiotic chemicals) and development of cancer and reported that several compounds present as dietary components or contaminants or formed during food processing has influence on cancer development, and may play a role in cancer risk by interfering with the physiological functions of oestrogens by binding to oestrogen receptors; interact with steroid hormone binding proteins; inhibit oestrogen synthesis; and overall can interact with enzyme systems to modulate the oestrogen metabolism.
Shakeel et al, (2010) correlated the differences in the levels of pesticides like dichlorodiphenyltrichloroethane (DDT), Dichloro Diphenyl Dichloro Ethylene (DDE), Poly Chlorinated Biphenyls (PCB), Hexachlorobenzene (HCB) and Hexa Chlorocyclo Hexane (HCH) and their effect for the development of breast cancer between developed and developing countries.

Makris (2011) evaluated structural and/or functional integrity of the mammary gland (MG) across life stages to assess developmental, reproductive, and carcinogenic risk for environmental chemicals and recommended to enhance mammary gland assessment in guideline toxicology studies.

Rudel et al, (2011) in a case study in Oakland, California, USA and presented a comprehensive review of hormone and chemical effects on mammary gland and reported that the effects on mammary gland dehormonalnt are not limited to estrogenic endocrine disruptors but the effects induced by diverse chemicals.

Anita Iversen et al, (2012) studied on 203 healthy premenopausal women aged 25–35 yr in the Norwegian from 2000-2002 to determine whether common polymorphisms in CYP17, in combination with metabolic risk factors and concluded that modification of metabolic risk factors may have significant implications for the prevention of breast cancer in women with the minor allele of CYP17 rs2486758.

2.6.2 In vivo studies of pesticide exposures:

Ito et al, (1973a); (1973b); Hanada et al, (1973); Puatanachokchai et al, (2006) demonstrated dose- and time-dependency of the effects of HCH and concluded that alpha-HCH causes tumours in rats and mice by consistent dose-dependent increases in tumor formation in which multiple dose levels were evaluated.
Bennett and Davis (2002) observed that the bioassays have identified 42 chemicals that induce tumors in the rodent mammary gland. The physical and chemical characteristics of the carcinogens vary, but epoxides (including chemicals metabolized to epoxides) and nitro-containing compounds are associated with increased breast cancer risk. They also reported that several carcinogen exposures are associated with breast tumor induction in both humans and rodents including radiation, diethylstilbestrol, and estrogens. These studies demonstrate that route, timing and frequency of exposure, and genetic factors contribute to the overall susceptibility to breast cancer development.

Mathur et al, (2002) reported a positive association between levels of alpha-HCH in the blood and breast cancer in a single age category of women and did not account for several potential confounders, including the presence of other organochlorine pesticides and body fat levels (a parameter which is associated with both breast cancer risk and the body burden of lipophilic chemicals such as alpha-HCH).

Kim (2004b); (2010) reported that rodents are particularly susceptible to chemically induced cancers, making them a good system for studying the cellular and intercellular processes involved in the initiation and progression of mammary tumours due to their shorter life span and comparable profile of development make mice and rats good models for studying the effects of early exposure to environmental toxicants on susceptibility to tumour development.

Warren et al, (2004) reported the effects of in utero exposure to environmental toxicants and potential interaction with postnatal genistein, gross enlargement of thoracic mammary glands and reported mild histological changes in the mammary glands of rats exposed to the mixture in utero while pronounced ductal hyperplasia,
lactational changes, and fibrosis were observed in mammary glands from the genistein group and were more prominent in the mix gemstone group. The mammary glands of the control group were histologically normal.

Sukhdeep et al., (2005) evaluated and reported the toxic effects of three organophosphates; monocrotophos, dimethoate and methyl parathion on female rat reproduction and reported cellular and molecular level degenerative changes in the ovaries as evidenced by a significant decrease in the concentration of cytoplasmic as well as membrane bound proteins, total lipids, phospholipids and cholesterol.

In 2006 Assessment of Lindane and Other Hexachlorocyclohexane Isomers (USEPA (2006), completed as part of the Reregistration Eligibility Decision (RED) for Lindane, EPA established chronic oral RfDs for alpha-HCH of 0.001 mg/kg-day and 0.008 mg/kg-day. Agency for toxic substances and Disease registry (ATSDR) (2005) established a chronic oral MRL for alpha-HCH of 0.008 mg/kg-day. The non-cancer RfDs and MRL are all based on hepatotoxicity.

Animal models have also been important in profiling changes in gene expression associated with the development of breast cancer (Shoushtari (2007); Drost (2009) as well as some of the interactions between genetic and environmental factors in altering risk for breast cancer (Zarbl (2007).

Zarbl (2007) studied different exposures and described the changes in specific gene activities and studied the relationships between these genetic changes and health outcomes with various environmental chemicals in animal models. Another controversy related to the use of rodents for testing human health effects of exposure to endocrine-disrupting compounds (EDCs), including risk of breast cancer, comes from recognition that not all rodents are equally sensitive to the hormone-disrupting effects of EDCs and stated that the strains of rats with low estrogen-receptor levels are
relatively unresponsive to EDCs like BPA in terms of later effects on reproductive and developmental processes (Gray (2010); Ryan (2009); vom Saal (2010)).

Lokesh et al, (2009) stated that the polymorphism not only triggers the beginning of tumor but also make hearse conditions for therapy. Further in recent year 2010, Milan reported that SNPs in the VEGF promoter led to efficacy and toxicity to the anti-VEGF antibody bevacizumab in breast cancer. The promoter region was completely sequenced for the VEGF and found 74% genetic variations.

Atef (2010) evaluated the influence of α-lipoic acid treatment in rats exposed to malathion pretreatment with α-lipoic acid significantly attenuated the physiological and histopathological alterations induced by malathion and reported significant increase in activities of serum glutamic oxaloacetic acid transaminase (GOT), glutamic pyruvic acid transaminase (GPT), alkaline phosphatase (ALP), and acid phosphatase (ACP), and the values of creatinine, urea, and uric acid, while the values of total protein and total albumin were significantly decreased in rats exposed to malathion, even reported that administration of malathion for one month resulted in damage of liver and kidney structures.

White et al, (2011) demonstrated persistent effects of perfluorooctanoic acid (PFOA) in drinking water on mouse mammary gland development at exposures lower than in some contaminated drinking water supplies and reported that Gestational PFOA exposure induced delays in mammary gland development and/or lactational differentiation across three generations, and stated that the Chronic, low-dose lactationalre in drinking water was also sufficient to alter mammary morphological development in mice, at concentrations approximating those found in contaminated human water supplies.