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提升私校研發能量專案計畫-癌症的基礎及臨床研究--子計畫一:建立癌症研究的資料及統計中心(2/3)

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–子計畫依：建立癌症研究的資料及統計中心」

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摘要

本研究的主要目的在探討 1979 年到 1998 年間，台灣地區時空因子在台灣女性的乳癌發生率與死亡率上所扮演的角色。乳癌發生率和死亡率的資料是來自行政院衛生署。時空因子則包含了都市化程度、住宅地區、人口密度與醫療資源分配。結果顯示過去的 20 年間，台灣地區乳癌發生率增加的速度比乳癌死亡率的增加高出很多。大致來說，乳癌發生率在 45 歲到 49 歲間會有一個高峰出現，且在台灣地區 336 個鄉鎮區彼此間有很大的差異，並且與各地區乳癌死亡率有很強的相關性(r=0.37)。此外，乳癌發生率和死亡率也都與上述每一個時空因子有很強的相關性。因此，結論顯示時空因子在台灣女性的乳癌發生率與死亡率之變化，且環境因子在疾病的病源學上亦扮演重要的角色，本研究的結論適合用在癌症防治政策之參考。

關鍵字：時空因子，乳癌發生率，死亡率

Spatio-temporal Factors in Breast Cancer Incidence and Mortality in Taiwan, 1979-1998

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Abstract

Purpose The objective of this study was to investigate the roles of spatio-temporal factors in the incidence and mortality of breast cancer among Taiwanese women from 1979 to 1998.

Method Breast cancer incidence and mortality data were provided by Taiwan's Department of Health (DOH). The spatial factors included the degree of urbanization, areas of residence, density of population and allocation of medical resources.

Results The rate of increase in the incidence breast cancer over the 20-year period was much higher than that of breast cancer mortality. Overall, the incidence of breast cancer peaked in the 45 to 49 year age range. Breast cancer incidence in the 336 regions varied considerably and correlated strongly with mortality (r=0.37). Breast cancer incidence and mortality were strongly correlated with each of the four spatial factors.

Conclusion: The significant differences in breast cancer incidence and mortality based on spatio-temporal factors indicate that environmental factors play an important role in the etiology of this disease. The results of this study may be used as a reference in strategies aimed at preventing breast cancer.

Keywords: Spatio-temporal factors, breast cancer incidence, mortality

Breast cancer is the most common cause of cancer death in women worldwide. Rates varied about fivefold around the world, but they are increasing in districts that until recently had low rates of the disease [1]. In 2000, breast cancer mortality rate among women was 10.61 per 100,000 in Taiwan. There has been a steady rise in breast cancer incidence over the last twenty years which may reflect, in part, changes in lifestyle, such as diet and an increase in the use of tobacco products. In 1990, Taiwan's DOH implemented its first nationwide breast cancer screening program. Between 1999 and 2001, one million women aged over 35 years were given breast palpitations. The screening program included education about self-examination and the importance of early detection. Suspected positive cases were referred to local hospitals for diagnosis and treatment. This amplified the incidence rate in a short period of time but may cause a decline in the mortality of breast cancer in the long run. It has been found that mammography service screening substantially reduces mortality rates of breast cancer patients [2]. There was an upturn in breast cancer incidence for women aged 50-74 in the UK around 1990, and an examination of age-specific rates showed that this change was due largely to the implementation of screening by mammography from 1988 [3]. In Taiwan, such screening programs have not been comprehensively evaluated. Recent reports in Taiwan indicate that the age of onset of malignant breast cancer has become lower over the past few decades.

Family history of breast cancer is a well-known risk factor in early onset of this disease. In a population-based case-control study, a total of 4730 breast cancer patients were age- and residence-matched with 4688 controls. Family history of breast cancer, especially in an immediate relative, was found to be a significant factor, after adjusting for confounders [4]. The risk of developing breast cancer was 2.3 times higher in patients with a family history of breast cancer compared to those without family history of the disease [5]. The Collaborative Group on Hormonal Factors in Breast Cancer concluded that the lifetime excess incidence of breast cancer is 5.5% with one affected immediate relative and 13.3% for women with two [6]. Although family history most likely affects the incidence of breast cancer through genetic predisposition, various environmental factors may also play important roles. Breast cancer incidence has been positively associated with socioeconomic status across race/ethnicity, geography, and time [7,8]. During the 1990s, both incidence and mortality rates for breast cancer changed strikingly in several western countries. Similar changes have been observed when screening for breast cancer was introduced [9]. Currently, there are no available data in Taiwan on relationships between the incidence and mortality of breast cancer. Moreover, there are no data on the spatio-temporal factors that may affect the incidence and mortality of this disease in Taiwan. The findings of this study will be used to establish baseline data on breast cancer incidence and mortality in order to develop nationwide breast cancer prevention programs.

Methods

Data on the general population from 1979 to 1998 in Taiwan were provided by the Ministry of the Interior, while data on breast cancer cases and breast cancer deaths were provided by the Department of Health. Population data from 1996 were used as the standard to calculate the standardized incidence and mortality of breast cancer in each year. Standardized incidence and mortality in 336 townships from 1992 to 1996 were categorized into five levels (>80%, 60-80%, 40-60%, 20-40%, <20%), labeled as high risk, moderate high risk, moderate, moderate low risk and low risk. Urbanization data, residential data, and data regarding population density and medical resources (no. of medical staff) were provided by the Government Office of Statistics (Executive Yuan). The level of urbanization was classified into seven categories according to population density, social index, and economic status. In the current study three main categories of urbanization were used: metropolitan (high), suburban (moderate) and rural areas (low). Residential areas were classified into three categories: plains, mountains and outlying islands. The proportion of health care workers to the general population in a given area was calculated. These proportions were classified into high (top third), low (bottom third) and medium (middle third). The population density in each district was calculated in the same way. Age-adjusted incidence and mortality were graded into five levels. Breast cancer incidence was graded from 0-11.95, 11.95-15.95, 15.95-20.75, 20.75-27.24, 27.24-67.46 per 100,000 persons. Breast cancer mortality was graded from 0-3.93, 3.93-6.61, 6.61-8.41, 8.41-10.45, 10.45-26.25 per 100,000 persons.

The statistical model used was the proportional odds model

$$\log(ODD_{j(x)}) = \alpha_j + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k ,$$

where x meant spatial factors, j represented the mortality or incidence level , $j = 5,4,3,2$. Since the assumption of proportional odds holds (which was shown by the goodness-of-fit test for model fit), for any fixed j, the estimated odds that a spatial situation (denoted by A) is in the high risk direction rather than the low risk direction equals exp(β) times the estimated odds for the other spatial situation (denoted by B). For example, for the degree of urbanization, let x=A mean the moderately urbanized area, and x=B mean the low urbanized area. The odds ratio (OR) was calculated from these results as follows:

$$Odds\ Ratio = \frac{p_{5(x=A)} / (1 - p_{5(x=A)})}{p_{5(x=B)} / (1 - p_{5(x=B)})} = \frac{p_{4(x=A)} / (1 - p_{4(x=A)})}{p_{4(x=B)} / (1 - p_{4(x=B)})} = \frac{p_{3(x=A)} / (1 - p_{3(x=A)})}{p_{3(x=B)} / (1 - p_{3(x=B)})} = \frac{p_{2(x=A)} / (1 - p_{2(x=A)})}{p_{2(x=B)} / (1 - p_{2(x=B)})} .$$

An OR was over 1 meant that the population in the moderately urbanized area had a higher risk of developing breast cancer than the population in areas with a low level of urbanization. The same calculation method was used for the other spatial factors. Age standardized incidence and mortality were plotted for each year (1979 to 1998), for each age group, and for each birth cohort. Age standardized incidence and mortality of breast cancer in the 336 townships were calculated and classified into five categories and plotted on the map of Taiwan. The Pearson's correlation coefficient between incidence and mortality was calculated.

Results

Age standardized incidence and mortality of breast cancer in the 336 townships in Taiwan are shown in Figure 1. Breast cancer incidence and mortality were graded into five levels with the darkest areas indicating highest incidence and mortality. The darkest areas tend to coincide with the metropolitan regions, primarily in the north. Pearson's correlation coefficient between incidence and mortality of breast cancer was 0.37. Incidence was lowest in the east of Taiwan, although some areas with low breast cancer incidence had a high rate of mortality.

Figure 2 shows the trends in age-specific breast cancer incidence and mortality rates from 1979 to 1998. Incidence of breast cancer increases over time, with a sharp increase in 1990 which coincided with the implementation of a government-sponsored breast cancer screening program. However, the mortality rate increases only slightly (range from 5/100,000 persons to 10/100,000 persons). The peak in mortality rate occurred in 1997 and decreased gradually thereafter.

Figure 3 shows the trends in age-specific incidence and mortality rates of breast cancer by birth cohort (1902-1911, 1907-1916, …, 1942-1951). The incidence of breast cancer occurred at an earlier age and a higher rate in the younger generations.

The trends in age-specific incidence and mortality rates of breast cancer in three five-year periods (1982-1986, 1987-1991, 1992-1996) can be seen in Figure 4. There was a similar trend to that in Fig.3 with an increase of breast cancer mortality with age. The increase in incidence was highest in the most recent five-year time period (1992-1996), with a peak at the 45-49 year age group. Mortality rates increased in each of the three five-year time periods. The mortality rate was highest in women over 80 years of age. With the exception of women over the age of 80, the mortality rate in the most recent five-year period was consistently higher than in the other time periods. For all ages below 65, the incidence of breast cancer was higher than breast cancer mortality.

Table 1 shows the correlations of the five levels of breast cancer incidence and mortality with the spatial factors. Overall, there were significant correlations in the incidence and mortality of breast cancer between each of the spatial factors. A high degree of urbanization correlated positively with breast cancer incidence and mortality. There was an even spread in the levels of breast cancer incidence and mortality on the plains, but for the mountainous areas and outlying islands, there were negative correlations with breast cancer incidence and mortality. Population density correlated negatively with breast cancer incidence and mortality. Low population density correlated significantly with a high incidence of breast cancer, but breast cancer mortality was similar in area with a low population density. There was a positive correlation between the availability of medical resources and both breast cancer incidence and mortality.

The odds ratios of breast cancer incidence and mortality within the levels of each spatial factor can be seen in Table 2. There were dose-dependently significant correlations between the degree of urbanization and both breast cancer incidence and mortality. There was a significant difference between the plains region and the mountains region in breast cancer incidence and mortality, but there were no significant correlations among other topographical areas. Significant negative correlations between each of the levels of population density were found in breast cancer incidence, but for breast cancer mortality only areas of high and low population density correlated significantly. The OR (95% CI) in areas where medical resources were considered high was 3.8

(2.4 – 6.0) and 2.3 (1.4 – 3.6sd) for the incidence and mortality rates respectively, compared to the areas where medical resources were low.

Discussion

Our study has shown that breast cancer mortality is highest in urban areas, whereas other studies have shown that it is highly variable around the island as a whole. This may be due to the small number of breast cancer cases. Long-term monitoring of breast cancer mortality is required to identify trends in different parts of the country. In addition, cancer mapping, such as the "Geographic Information System" (GIS) can provide a dynamic exhibition of patterns and trends which yields information about the clustering and diffusion process in breast cancer mortality and incidence, as well their intercorrelations. The current study found that breast cancer mortality and incidence were highly correlated and have increased gradually over the past twenty years. This may be attributed to the introduction of the national cancer screening program in 1990 in Taiwan. Furthermore, dietary and lifestyle changes may have contributed to the increase in breast cancer mortality and incidence. Another important trend is the onset of breast cancer in women at considerably earlier ages over the past twenty years. As a result, the Department of Health in Taiwan may lower the age of breast cancer screening. Ongoing health awareness programs have also helped to catch breast cancer in its early stages in many women in Taiwan. Overall the incidence of various cancers increased from 10% to 30% but the cancer mortality rate remained approximately the same. This may be due to improved diagnosis and therapeutic advancements [10]. A study on the incidence and mortality of cancer in France from 1975 to 1995 found that mortality rates remained relatively even while incidence increased [11]. Moreover, mammography screening has been linked previously to breast cancer incidence increase in the United States, most notably the 4% annual increase after its widespread adoption in the 1980s [12]. Mammography utilization in Hawaii accounted for a 23% geographic fluctuation in overall breast cancer incidence in 1992-1993 and for a 36% fluctuation among women aged 50-64 years [13]. Our study witnessed a similar incremental increase in the incidence of breast cancer but just a minor increase in the mortality rate.

Cancer mapping studies have shown that the south-west of Taiwan has a clustering effect for certain cancers, such as cancers of the bladder, skin, liver and lung which have been attributed to arsenic in the groundwater. However, breast cancer incidence in this part of the country was no more significant than that in other areas. Factors other than lifestyle and diet that affect breast cancer incidence include pesticides, such as DDT which was used 50 years ago to eradicate malaria in Taiwan, and air pollutants, such as dioxin, from incinerators. The Taiwan EPA has recently reduced the maximum regulatory limit for dioxin in the air. Breast cancer incidence is generally much higher in highly urbanized areas. Breast cancer incidence rates are also reported to be higher in urban compared with rural areas in the Unites States. For Caucasian women, incidence rate ratios (IRRs) comparing the most urban areas with the most rural counties were 1.60 for situ and 1.18 for invasive cancers. For non-Caucasian women, IRR were 1.27 and 0.99, respectively [14]. This finding is consistent with those of Halls findings. We hypothesize that these urban women may have particularly benefited from the national screening program and had more exposure to certain risk factors. Previous studies [15,16]. have identified other factors associated with increased incidence of breast cancer, such as decreasing age of menarche, increasing age at first marriage, age at first birth, use of hormone replacement therapy, decreasing fertility rate and increasing adult height. These factors are related to the modern trend of urbanization. Significant period effect was observed on breast cancer incidence, although the cohort effect was marginal. The relative risks by birth cohort suggested a declining trend in younger birth cohorts [17]. Associations between community income and cancer incidence in North America were evaluated and it was found that breast cancer incidence was highest among the communities with the highest socioeconomic status, although the underlying mechanisms remain unclear. Over the years the cancer registry has developed comprehensive data on breast cancer [18]. The age-adjusted incidence rate was 25.1 per 10^5 person-years. Our study also pointed out that the age-specific incidence rates peaked at ages 45-49 years. The increase in breast cancer incidence rates was most striking among younger birth cohorts. In addition, breast cancer diagnostic techniques have improved considerably in the last ten years, as proven by follow-up biopsies in 80% of diagnoses [19]. This cancer registration can be used to correlate with environmental and ecological factors as well as personal risk factors, such as genetic predisposition, alcohol consumption and smoking habit [20]. Analyses of the significant associations are vital in the development of national cancer prevention programs. The trend in breast cancer incidence in the period 1989 -1998 in The Netherlands was found to have increased up to 1994 and stabilized at approximately116 per 10^5 person-years. This increase was mainly observed among women ages 50-69 years and for stage I cancer. Morality rates showed a slow and steady decrease over that period from 39.0 to 35.6 per 10^5 person-years [21]. The increase in the rate of incidence of breast cancer in Taiwan shows similarities to that found in The Netherlands, though this may be due to more successful nationwide screening programs [22]. It is expected that early detection would result in the decrease in the mortality rate of breast cancer sufferers. Screening also had indirect influences by raising an awareness of changes in detection and treatment. Due to the higher levels of availability of and accessibility to medical resources in urban areas, the rate of incidence and mortality is greater than in rural areas. Early detection may focus on precancerous lesions and thereby prevent the occurrence of invasive cancer.

In conclusion, the increase in of breast cancer incidence over the 20-year period covered in this study greatly outpaced that of breast cancer mortality. Overall, the peak of breast cancer incidence was in the age range of 45 to 49 years. Breast cancer incidence in the 336 townships of Taiwan varied considerably and correlated strongly with mortality (r=0.37). Breast cancer incidence and mortality were strongly correlated with each of the four spatial factors, including the degree of urbanization, areas of residence, density of population and allocation of medical resources. The significant differences in breast cancer incidence and mortality based on spatio-temporal factors indicate that environmental factors play an important role in the etiology of this disease.

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Table1 Correlations of the five levels of breast cancer incidence and mortality with the spatial factors(1992 to 1996)

Spatial factors	N	Rate of Incidence rate (%) Low	Mod Low	Mod	Mod high	High	#P r*	Rate of Mortality (%) Low	Mod Low	Mod	Mod high	High	#P r*
Degree of urbanization							<.0001						<.0001
Low	168	35.7	24.4	19.0	14.9	6.0	0.476	32.7	21.4	17.3	12.5	16.1	0.327
Moderate	143	7.7	20.3	23.8	27.3	21.0		10.5	23.1	24.5	25.9	16.1	
High	48	4.2	12.5	16.7	66.7	0.0		2.1	6.3	16.7	29.2	45.8	
Areas of residence							<.0001						<.0001
Outlying islands	9	22.2	44.4	11.1	11.1	11.1	0.273	44.4	11.1	22.2	0.0	22.2	0.204
Mountainous areas	29	65.5	13.8	10.3	6.9	3.4		58.6	10.3	10.3	6.9	13.8	
Plain areas	321	15.6	19.9	21.2	21.5	21.8		15.6	21.2	20.9	21.8	20.6	
Density of population													
Low	119	13.4	10.9	16.8	23.5	35.3	<.0001	12.6	18.5	21.0	21.8	26.1	<.0001
Moderate	120	14.2	23.3	23.3	22.5	16.7	−0.298	16.7	20.8	19.2	25.8	17.5	−0.194
High	120	31.7	25.8	20.0	14.2	8.3		30.0	20.8	20.0	12.5	16.7	
Allocation of medical resourcesx													
Low	119	23.5	26.9	22.7	19.3	7.6	<.0001	23.5	31.9	18.5	9.2	16.8	<.0001
Moderate	120	25.8	20.8	18.3	17.5	17.5	0.271	21.7	19.2	19.2	22.5	17.5	0.218
High	120	10.0	12.5	19.2	23.3	35.0		14.2	9.2	22.5	28.3	25.8	

#P：P value is according to chi-square tendency test

r*： r denotes Pearson’s correlation coefficient

Table2 Odds ratios (95%CI) of breast cancer incidence and mortality within levels of each spatial factor (1992 to 1996)

*P value is according to chi-square test

Spatial factor	Incidence rate		Mortality rate	
	Odds ratios (95%CI)	P*	Odds ratios (95%CI)	P*
Degree of urbanization				
Low	1	–	1	–
Moderate	2.9(1.9-4.5)	<.0001	2.0(1.3-3.0)	<.0001
High	22.4(11.2-45.0)	<.0001	6.1(3.4-11.2)	<.0001
Areas of residence				
Outlying islands	1	–		–
Mountainous areas	1.3(0.3-5.1)	0.002	0.4(0.1-1.9)	<.0001
Plain areas	3.4(1.0-11.8)	0.054	2.0(0.5-7.9)	0.318
Density of population				
Low	1	–	1	–
Moderate	0.4(0.3-0.7)	0.010	0.7(0.4-1.1)	0.105
High	0.2(0.1-0.4)	<.0001	0.5(0.3-0.8)	0.002
Allocation of medical resources				
Low	1	–	1	–
Moderate	1.4(0.9-2.2)	<.0001	1.3(0.8-2.0)	0.014
High	3.8(2.4-6.0)	<.0001	2.3(1.4-3.6)	0.001

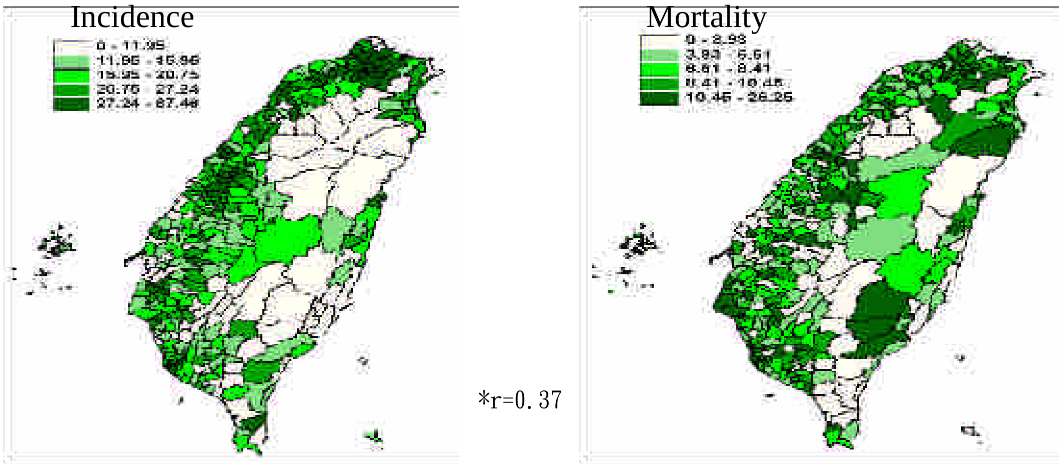

Figure 1 Age standardized incidence and mortality of breast cancer in the 336 townships in Taiwan.

*r：Pearson's correlation coefficient between incidence and mortality

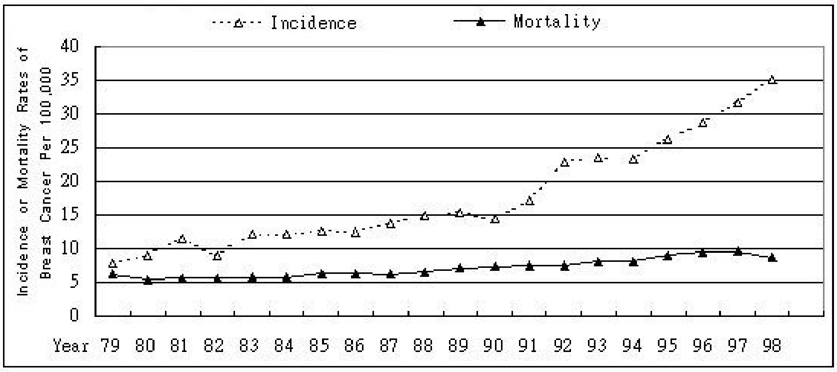

Figure 2 Trends in age-specific breast cancer incidence and mortality rates from 1980 to 1998.

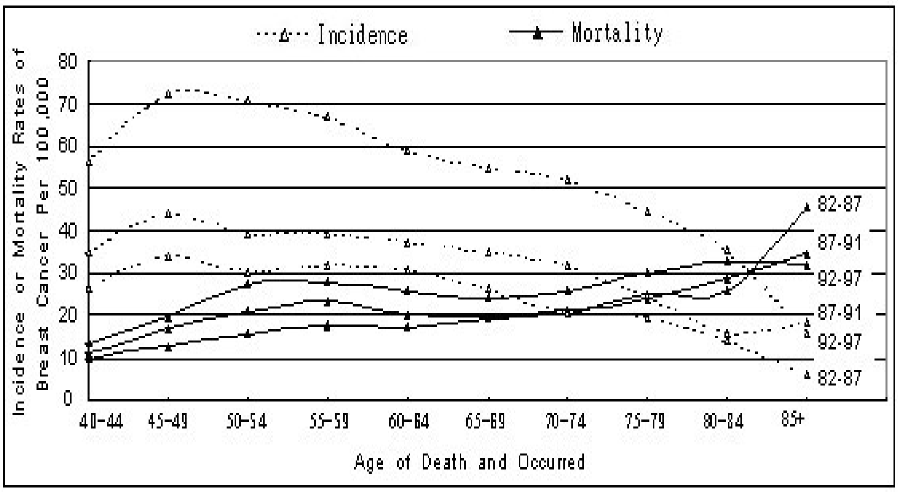

Figure 3 Trends in age-specific incidence and mortality rates of breast cancer by year of birt

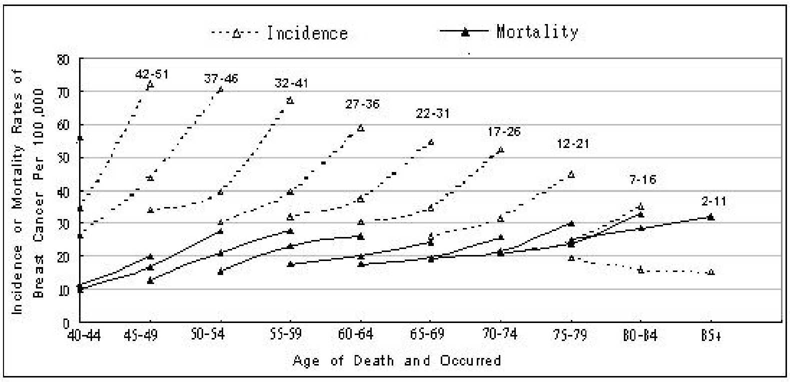

Figure 4 Trends in age-specific incidence and mortality rates of breast cancer in three five-year time periods.