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A plateau of breast cancer mortality in Poland – an impact of time periods or birth generations? A joinpoint regression and APC analysis of recent time trends

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Breast cancer is the major cause of cancer deaths in women worldwide. In Poland, breast cancer has been the most frequent cause of cancer deaths in females since 1976, when it overtook stomach cancer.

There were 1,587 deaths from breast cancer in Polish women in 1963. Over the next 3 decades the number of deaths caused by that cancer increased to 4,738 in 1996. Crude mortality rate from breast cancer in Poland increased from 10.0/10^5 in 1963 to 23.9/10^5 in 1996. Overall age-standardised mortality rate from breast cancer increased within the same time period from 9.4/10^5 to 16.2/10^5.

In all ages combined, an increasing trend of mortality has been observed within the entire time period (1963-1996), however a deceleration of mortality increase has been observed. Deceleration of the increase speed was observed in almost all age categories.

Deceleration of mortality increase or first signs of decline were observed previously in several Western European countries, United States, Canada, and Australia. It seems that the process of deceleration of mortality increase, which has begun in Western countries in the 1970s and 1980s, has appeared in Poland about one decade later. It is, however, still difficult to evaluate what are the main causes of that phenomenon, but it is most likely that several factors play a role simultaneously in that process.

Ograniczenie wzrostu umieralności z powodu nowotworów złośliwych piersi w Polsce – wpływ okresu czasu czy generacji urodzeniowych? Analiza trendów czasowych przy użyciu metod: „joinpoint regression" oraz „age-period-cohort model"

Nowotwory złośliwe piersi są najczęstrzą przyczyną zgonów na nowotwory wśród kobiet na świecie. W Polsce, rak piersi jest najczęstrzą przyczyną zgonów na nowotwory złośliwe u kobiet od 1976 roku, kiedy zajął miejsce nowotworów złośliwych żołądka jako najczęściej notowanego nowotworu.

W 1963 roku zanotowano u kobiet w Polsce 1587 zgonów z powodu raka piersi. W ciągu następnych trzech dziesięcioleci liczba zgonów z powodu tego nowotworu wzrosła do 4738 (w 1996 roku). „Surowy" współczynnik umieralności z powodu nowotworów złośliwych piersi wzrósł w Polsce w latach 1963-1996 z 10.0/10^5 do 23.9/10^5. Standaryzowany wg wieku współczynnik umieralności wzrósł w tym samym okresie z 9.4/10^5 to 16.2/10^5.

Jakkolwiek w całym analizowanym okresie (1963-1996) obserwowano wzrostowy trend umieralności na raka piersi ogółem (we wszystkich grupach wieku łącznie), to zanotowano również w tym czasie spadek tempa wzrostu. Zjawisko to odnotowano w niemal wszystkich kategoriach wiekowych.

Spadek tempa wzrostu umieralności na raka piersi lub pierwsze symptomy spadku częstości zgonów obserwowano wcześniej w wielu krajach Europy Zachodniej, Kanadzie, USA i Australii. Wydaje się, że proces spowolnienia wzrostu umieralności, który rozpoczął sie w krajach zachodnich w latach 70. i 80. pojawił się w Polsce około 10 lat później. Jest jednak trudno ocenić jednoznacznie jakie są główne przyczyny tego zjawiska. Analiza dostępnych danych wydaje się wskazywać, że wiele czynników odgrywa równocześnie rolę w tym procesie.

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Słowa kluczowe: nowotwory piersi, umieralność, regresja, modele, Polska, czynniki ryzyka, przeżycia

Introduction

Breast cancer is the major cause of cancer deaths in women worldwide, and the most frequently registered cancer in females. It has been estimated that in the year 2000 there were 373,000 breast cancer deaths worldwide (6.0% of all cancer deaths), and approximately 1,050,000 new breast cancer cases (10.4% of all new cancer cases) [1]. A prevalence of breast cancer in 2000 was estimated for 3,860,000 cases [1].

In Europe, the highest rates are observed in Western and Northern Europe, while the lowest rates dominate in Eastern and Southern Europe [2].

In Poland, breast cancer has been the most frequent cause of cancer deaths in females since 1976, when it overtook stomach cancer (3). The percentage of breast cancer deaths increased between 1963 and 1999 from 9% to 13% [3].

Few systematic analysis of breast cancer mortality in Poland have been published so far, covering the time period until the second half of 1980s [4, 5]. This paper aims to analyse time trends of breast cancer mortality in Poland using two methods, not previously used for Polish data: a joinpoint regression method and an age-period-cohort modelling method [6-9].

Material and methods

Mortality from malignant neoplasms of the breast were extracted from the World Health Organisation (WHO) Mortality Databank, by five-year age group, using the rubric 174 according to ICD-9 revision. Data were available for a 34 year period: 1963-1996. Corresponding population data, by age and calendar year, were also extracted.

To evaluate changes in time trends, age-standardised rates were calculated for all ages combined and for the following age groups: 20-29, 30-39, 40-49, 50-64, 65-74, and 75 and over, using the weights of the World Standard Population [10]. The joinpoint regression was then employed to estimate annual percentage change (EAPC) [6, 7]. For each EAPC estimate corresponding 95% confidence interval (95%CI) was also calculated

In order to fit „age-period-cohort" (APC) models, the data were grouped into periods of five years and approximate overlapping ten-year cohorts derived by subtracting the midpoint of the five-year age group from the midpoint of the period. The age range was restricted to persons dying of breast cancer at age of 20 to 74.

The APC statistical model provides a quantitative and comparable method of estimating trends over time, using a set of objective criteria to choose the best description of the data. Detailed description of the APC methodology has been published elsewhere [8, 9, 11].

The following hierarchy of models was fitted to the breast cancer mortality rates:

{1} Age;
{2} Age + (Period or Cohort) Drift;
{3a} Age + Drift + non-linear Period;
{3b} Age + Drift + non-linear Cohort;
{4} Age + Drift + non-linear Period + non-linear Cohort.

The relative contribution of each effect to the model was determined by comparing the change in the deviance and degrees of freedom in two sequentially fitted models with the appropriate chi-squared statistic. Hence, a comparison of model {2} with {1} provides a test for drift against the model of no temporal trend (model {1}); a comparison of model {3a} versus {2}, and model {3b} versus {2} tests for the effects of non-linear period and non-linear cohort, respectively. Comparing model {4} versus {3a} tests for the effects of non-linear cohort effects, adjusting for drift and non-linear period. Finally, the comparison of model {4} versus {3b} tests the effects of non-linear period, adjusting for drift and non-linear cohort.

Data on reproductive factors (i.e. number of children, fertility, age at childbearing) were retrieved from the on-line database of the Polish Central Statistical Office (GUS) (www.stat.gov.pl) [12]. Data on survival of breast cancer patients were derived from the EUROCARE-2 study [13].

Results

There were 1,587 deaths from breast cancer in Polish women in 1963. Over the next 3 decades the number of deaths caused by that cancer increased to 4,738 in 1996 (Table I). Crude mortality rate from breast cancer in Poland increased from $10.0/10^5$ in 1963 to $23.9/10^5$ in 1996. Overall age-standardised mortality rate from breast

Table I. Breast cancer mortality in Poland, 1963-1996

		Females	
Year	Number of deaths	Crude rate	Age-standardised rate
1963	1 587	10.0	9.4
1964	1 779	11.1	10.1
1965	1 938	12.0	10.8
1966	1 969	12.1	10.8
1967	2 149	13.1	11.4
1968	2 128	12.8	11.0
1969	2 303	13.8	11.9
1970	2 270	13.6	11.5
1971	2 380	14.1	11.8
1972	2 527	14.9	12.3
1973	2 669	15.6	12.6
1974	2 790	16.1	12.9
1975	2 895	16.5	13.2
1976	3 065	17.4	13.8
1977	3 049	17.1	13.5
1978	3 225	18.0	14.1
1979	3 264	18.0	14.1
1980	3 446	18.9	14.8
1981	3 599	19.6	15.1
1982	3 641	19.6	15.0
1983	3 664	19.6	14.8
1984	3 792	20.1	15.2
1985	3 795	19.9	15.1
1986	3 844	20.0	15.1
1987	3 905	20.2	15.1
1988	4 045	20.9	15.5
1989	4 097	21.1	15.5
1990	4 323	22.1	16.1
1991	4 198	21.4	15.5
1992	4 429	22.5	16.2
1993	4 381	22.2	15.7
1994	4 449	22.5	15.9
1995	4 665	23.6	16.3
1996	4 738	23.9	16.2

cancer increased within the same time period from 9.4/10^5 to 16.2/10^5 (Table I).

Joinpoint regression analysis

An analysis performed by joinpoint regression method showed deceleration of EAPC for all ages combined as well as in particular age categories (with an exception of the oldest age group 75 years and more). Time trends for all ages combined and for particular age categories (observed and fitted) are presented in Figures 1 and 2.

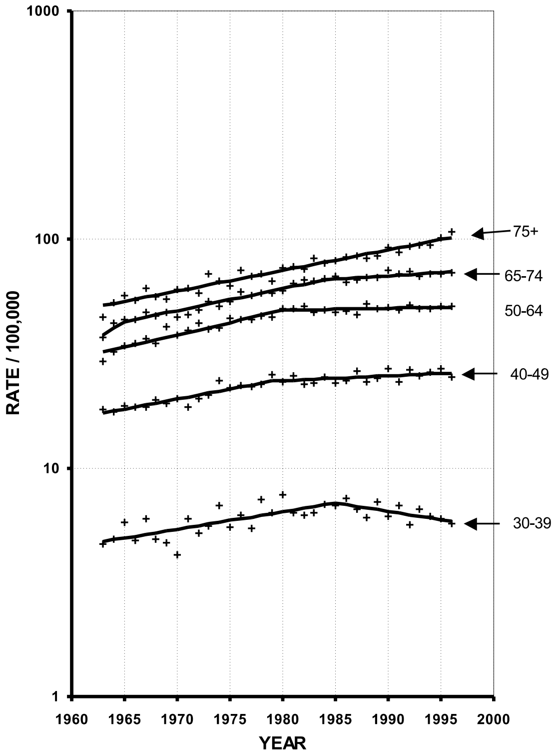

Figure 1. Breast cancer morality, Poland, by age groups, females, observed values (+) and jpinpoint regression (solid line)

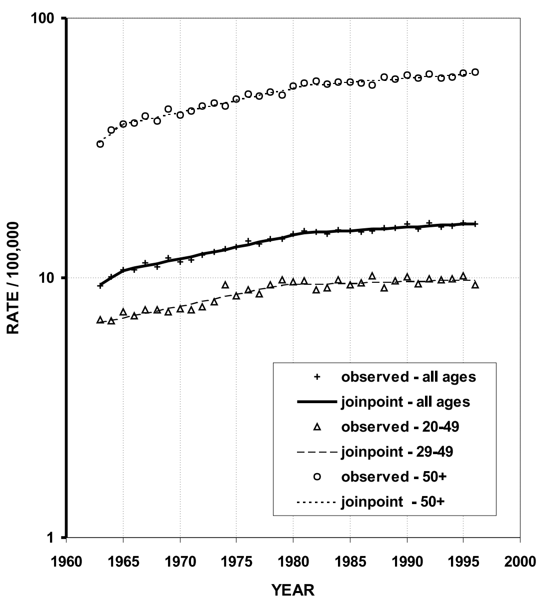

Figure 2. Breast cancer morality, Poland, all ages pre- (20-49) and postmenopausal (50+) females

In all ages combined, an increasing trend of mortality has been observed within the entire time period (1963-1996), however, a decreasing rate of mortality increase has been observed. In the period 1965-1980 mortality from breast cancer was increasing by 2.1% per year, while in the period 1981-1996 the EAPC was 0.6% (Table II). Similar changes were observed in middle-age and older women (between 45 and 74 years of age). In the age group 40-49 mortality was increasing by 2.0% per year in 1963-1978, and 0.5% in 1979-1996. In the age group 50-64 the EAPC was 2.5% in the years 1965-1979 and then dropped to 0.2% in the period 1980-1996. In older women aged 65-74 an EAPC of 2.2% was noted in 1965-1983 and 0.7% in 1984-1996 (Table II). There were no changes of the EAPC in the oldest age group (75+) – mortality in this age category was increasing at a rate of 2.1% per year within the entire analysed time period.

Table II. Changes in breast cancer mortality time trends, females, Poland 1963-1996 (joinpoint regression analysis)

	Females					
Age	Number of joinpoints	Year of joinpoint	Period	EAPC*	95%CI	
All	2		1963-1964	6.5	1.0	12.4
		1965	1965-1980	2.1	1.9	2.3
		1981	1981-1996	0.6	0.3	0.8
20-29	0		1963-1996	1.9	0.3	3.5
30-39	1		1963-1984	1.8	1.0	2.5
		1985	1985-1996	-1.7	-3.6	0.4
40-49	1		1963-1978	2.0	1.5	2.5
		1979	1979-1996	0.5	0.0	0.9
20-49	1		1963-1978	2.1	1.7	2.6
		1979	1979-1996	0.3	-0.1	0.7
50-64	1		1963-1979	2.5	2.1	2.9
		1980	1980-1996	0.2	-0.2	0.7
65-74	2		1963-1964	6.9	-3.6	18.5
		1965	1965-1983	2.2	1.9	2.6
		1984	1984-1996	0.7	0.0	1.3
75+	0		1963-1996	2.1	1.9	2.3
50-75+	2		1963-1964	8.5	0.9	16.7
		1965	1965-1980	2.2	1.9	2.5
		1981	1981-1996	0.7	0.4	1.0

* - Estimated Annual Percentage Change

The situation is somewhat different in young women (30-39 years of age). After an increase of mortality in 1960s, 1970s and first half of 1980s by 1.8% per year, there has been a decrease of mortality since 1985 (-1.7% per year in the period 1985-1996) (Table II).

Age-period-cohort modelling

Five types of models were fitted for females, starting from a simple "age" model to full "age+period+cohort" model. Table III shows deviance and number of degrees

Table III. Age-period-cohort (APC), breast cancer, females, Poland, 1967-1996

Model	Deviance	Number of df*	p-value	Difference of deviances	Difference in the number of df*	p-value (for difference between models)
AGE (A)	1028.5	45	0.000			
AGE+DRIFT (AD)	205.0	44	0.000	823.5	1	0.000
AGE+COHORT (DRIFT)(AC)	76.4	32	0.000	128.6	12	0.000
AGE+PERIOD (DRIFT) (AP)	106.4	40	0.000	98.6	4	0.000
AGE+PEROD+COHORT (APC)	27.0	28	0.518			
(a) Difference AP-APC				79.4	12	0.000
(b) Difference AC-APC				49.4	4	0,000

* - df - degrees of freedom

of freedom with corresponding p-values for each model fitted, as well as differences in deviance and degrees of freedom (and their statistical significance) between each two sequentially fitted models. It was found that the model, which fits the data best and reaches statistical significance, is full "age+period+cohort" model.

Based on the best fitting model changes in risk of breast cancer deaths were estimated. Table IV and Figure 3 show changes in relative risk (RR) by subsequent birth cohorts. The risk was increasing for all subsequent birth cohorts until the cohort born between 1945-1949 (given marked as 1947 in the table and graph). A first sign of a plateau was observed for the youngest birth cohort, 1950-1955. Table V and Figure 4 present changes in breast cancer risk by subsequent time period (taking period 1967-1971 as reference category, RR=1). Analysis showed that after an increase of risk in the first two 5-year time periods (1972-1976 and 1977-1981) by about 12%, a plateau of the RRs was observed within subsequent periods.

Table IV. Relative risk (RR) of breast cancer mortality, estimates for subsequent birth cohorts

Cohort	RR	Females 95%CI	
1897	0.70	0.62	0.79
1902	0.77	0.71	0.84
1907	0.81	0.76	0.87
1912	0.89	0.85	0.94
1917	0.95	0.92	0.99
1922	1.00	reference category	
1927	1.02	0.99	1.05
1932	1.05	1.01	1.10
1937	1.08	1.01	1.15
1942	1.13	1.04	1.22
1947	1.21	1.10	1.33
1952	1.20	1.07	1.35

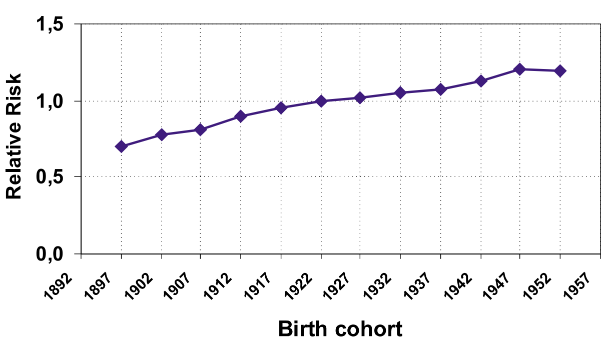

Figure 3. Relative risk for subsequent birth cohorts, breast, females, Poland

Table V. Relative risk (RR) of breast cancer mortality, estimates for subsequent time periods

Period	RR	Females 95%CI	
1967-1971	1.00	(reference category)	
1972-1976	1.06	1.03	1.10
1977-1981	1.12	1.07	1.17
1982-1986	1.12	1.05	1.19
1987-1991	1.11	1.02	1.20
1992-1996	1.10	1.00	1.21

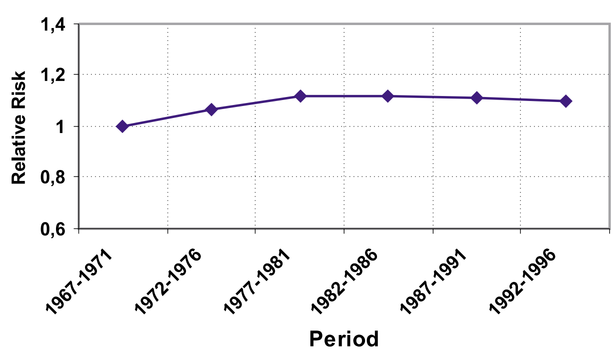

Figure 4. Relative risk by period of time, breast, females, Poland

Discussion

Breast cancers are derived from the epithelial cells that line the terminal duct lobular unit. An invasive breast cancer is one in which there is dissemination of cancer cells outside the basement membrane of the ducts and lobules into surrounding adjacent normal tissue [14]. Breast cancers were previously classified either as ductal or lobular types, since it was believed that ductal carcinomas arose from ducts and lobular carcinomas from lobules. It is known now that both invasive ductal and lobular breast cancers arise from the terminal duct lobular unit [14].

This paper aims to present changes in the mortality from breast cancer in Poland over the last three decades, and to analyse these changes in the light of the major breast cancer risk factors. The current analysis is based on the data until 1996 and employs two methodological approaches to evaluate changes in time trends and influence of period of time and birth cohort on the mortality rates. It was not possible to evaluate changes in mortality after 1996 since the quality of mortality data from Poland for the years 1997-1998 was insufficient [3].

During the last three decades breast cancer has become the most frequent cause of cancer deaths in Polish women. Between 1963 and 1996 the absolute number of deaths and age-standardised mortality rates increased by 198% and 72% respectively.

An increase in breast cancer mortality in Poland was previously reported by Staszewski [15]. Time trends of mortality from breast cancer in Poland were later discussed by Zatoński and Becker [4] and Zatoński [5], and breast cancer epidemiology in Poland was also described by Wronkowski et al. [16, 17]. It was pointed out by Zatoński [5] that after 1980 some deceleration of increase of mortality has taken place. Our analysis confirmed this observation and quantified the magnitude of that phenomenon (Table II, V). Moreover, if the estimation is done based upon the APC modelling, taking into account both linear and non-linear effect of period of time and birth cohort, no increase of risk has been observed for subsequent periods of time since 1977-1981. It was also previously pointed out that deceleration of mortality increase in time was accompanied by permanent increase of risk for subsequent birth generations [5]. Our analysis shows that risk was increasing until the birth cohort 1945-1949. For the youngest birth generation (1950-1954) a first sign of levelling off has been observed. Deceleration of the all-ages increase of mortality has been accompanied by first signs of decrease in young women (age 30-39), starting in mid 1980s. In general, in all age categories (with an exception of the youngest (aged 20-29) and elderly women aged 75 years or more) favourable changes have been observed: either slowing down of mortality increase (all ages combined and age groups between 40 and 74) or even decrease of mortality (age group 30-39).

Deceleration of mortality increase or first symptoms of decline were observed previously in several Western European countries, United States, Canada, and Australia [18]. It seems that the process of deceleration of mortality increase, which has begun in Western countries in the 1970s and 1980s, has appeared in Poland about one decade later.

Although the APC modelling shows statistical significance of both period and cohort in the full "age+period+cohort" model, an analysis of the relative contribution of them to the model indicates greater impact of period effect on mortality. However, some impact of cohort effect on the youngest age groups has also been observed.

There are several factors, both endo- and exogenous, which are known to affect risk of breast cancer in the population. These are factors such as: lifestyle (i.e. childbearing, breastfeeding, type of diet, obesity, use of alcohol and tobacco), hormonal status (influencing age at menarche and menstrual cycle, and determined by endogenous hormones, oral contraceptives use, and hormonal replacement therapy), anthropometric characteristic, radiation, and genetic predisposition [19, 20]. Finally, mortality from breast cancer may be influenced by prevention (e.g. chemoprevention using tamoxifen or raloxifene) and screening [21, 22].

Although several of those factors may be responsible for changes in breast cancer mortality in Poland, relatively little is known about their occurrence in the Polish population.

Population-based early detection has not been the reason for breast cancer mortality levelling off in Polish women observed since early 1980s, since such a programme did not exist in Poland in the 1970s and 1980s. Another possible responsible factor may be advances in treatment procedures, and the introduction of tamoxifen adjuvant therapy may well be among them. The effectiveness of tamoxifen in reducing mortality from breast cancer has been shown in several randomised clinical trials [23, 24]. The best effects were observed in ER-positive breast cancer patients [24]. High effectiveness of tamoxifen in preventing invasive breast cancers among women diagnosed with DCIS (ductal carcinoma *in situ*) has also been shown [25]. It has been estimated by Cuzick [26] that an overall reduction of breast cancer incidence as a result of tamoxifen administration may reach 40%. Although it is likely, that introduction of tamoxifen prevention and adjuvant therapy will affect future trends of breast cancer in Poland, no association can be established with past mortality trends of this disease.

There have been several studies showing relationship between several reproductive factors and risk of breast cancer incidence and mortality. It has been shown that risk of breast cancer is increasing with decreasing age at menarche, increasing age at first pregnancy, increasing age at menopause, and low parity [27, 28]. The data from Poland show that the average number of children born by Polish women aged 20-24 and 25-29 increased between 1970 and 1983 by approximately 15% in both age groups (Figure 5). However, after 1983 the average number of children born has been decreasing in all age categories, especially among women aged 20-24 (decrease by 57% between 1983 and 2000) (Figure 5) [12]. It should also be pointed out that in the 1970s and 1980s the average age of women at first birth increased, and, after a temporary decrease in the first half of 1990s, has continued to increase in the 2nd half of the 1990s (Figure 6). The fertility rate in Polish women was relatively stable in the 1970s, and has been consistently decreasing since the early the 1980s (Figure 6). Significant changes have taken

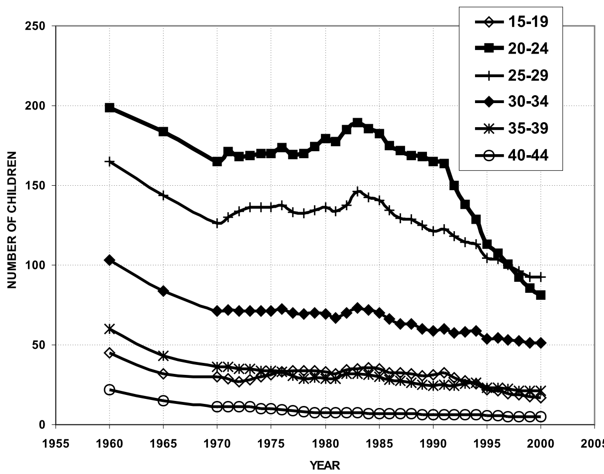

Figure 5. Number of live-born children by mothers' age groups, per 1000 women, Poland, 1960-2000

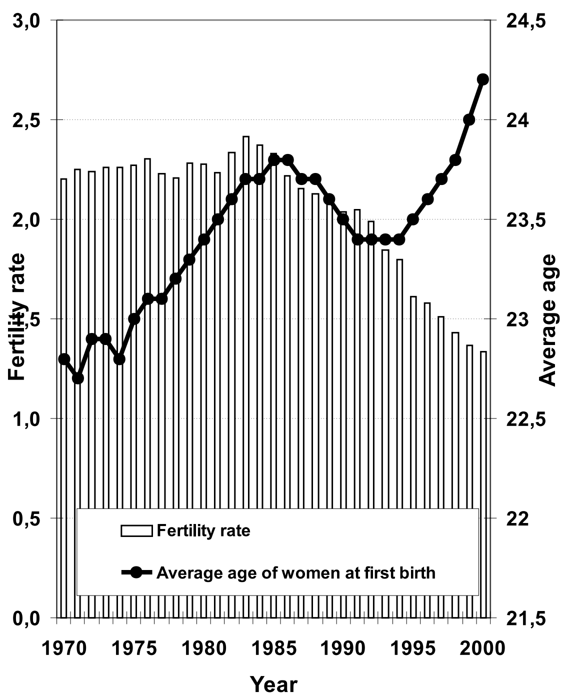

Figure 6. Fertility rate and average age at first birth in Polish women, 1970-2000

place also with regard to age at menarche in Polish girls after the Second World War. After a significant decrease of age at menarche observed until late 1970s, reverse trend has been noted in the 1980s and early 1990s [29, 30]. It does not seem that changes in reproductive factors alone might have a significant favourable impact on levelling off of the breast cancer mortality in Poland.

There are several life-style risk factors known or suspected to influence risk of breast cancer. Although several studies in the past suggested some association (both positive and negative) between exposure to tobacco smoke and breast cancer risk, no convincing evidences were found that both active and passive (second hand) tobacco smoking plays an important role in the risk of breast cancer [31-33]. However, epidemiological data concerning tobacco smoking and breast cancer are inconsistent [34, 35]. Since the relationship between smoking and breast cancer seems to be rather weak, it is unlikely that changes in tobacco smoking in Polish women has affected breast cancer mortality in the past.

Mortality from cancer is a function of two main factors: incidence rates and survival. Although incidence data for the whole of Poland in the past suffered from underreporting [3], data from some selected regional cancer registries suggest increasing trends in breast cancer incidence in the 1970s and 1980s [36]. On the other hand, EURACARE-2 data show that between the late 1970s and late 1980s a significant increase in breast cancer survival took place in Poland (Figure 7) [13]. The plateau in mortality from breast cancer observed in the 1980s and 1990s may be an outcome of increasing incidence and improving survival in Polish women.

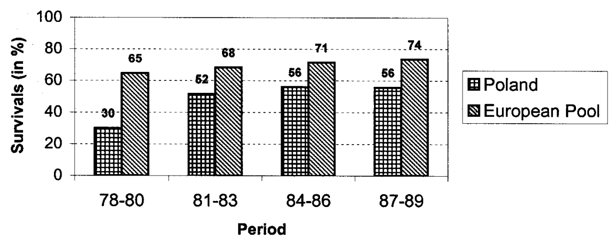

Figure 7. 5-year relative survivals in Poland and in Europe, breast cancer, females

Experiences from other countries (United Kingdom, Sweden, the Netherlands) show that one of the pathways to reduce mortality from breast cancer is mammography screening of healthy women in a given range of age. There is sufficient evidence that mammography screening can be efficient in women between 50 and 69 years of age [22]. However, there in not sufficient evidence that this type of screening may decrease mortality in women below 50 and over 69, and is not effective in women in high-risk groups (e.g. carriers of *BRCA1* and *BRCA2* mutations). It has been suggested by some authors that screening should be performed in women aged 40-50 every 2 years and each year in women over 50 [37], as well as in high-risk groups from age 35 every 12 months [38]. It seems that recent results from clinical trials and population-based screening programmes do not support such recommendations [22].

The phenomenon of a slowing down of increase of breast cancer mortality in Poland is difficult to be unequivocally explained in view of changes of known risk factors. It is most likely that several factors may play a role simultaneously. There is, however, a need for further studies to show which factors play a major role in that process.

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