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Lifestyle changes during adolescence and risk of breast cancer: an ecologic study of the effect of World War II in Norway

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There are biologic reasons to believe that the period between thelarche and the first full-term pregnancy is a particularly sensitive period in a woman's life regarding the development of breast cancer. In this ecologic study, data provided by the Norwegian Cancer Registry were analyzed to compare risk of breast cancer among women who experienced this sensitive period before, during, or after World War II. An ordinary age-cohort model and a model where the cohort was described by exposure by calendar period and sensitivity to this exposure at different ages, were fitted to the data. The incidence of breast cancer was lower than expected among women who experienced puberty during the war. The estimated configuration of the exposure variable showed an increase in exposure up to the start of WWII to twice the level in 1916, dropped by 13 percent during the war, and increased again after the war. The level in 1975 was approximately 2.7 times higher than the level in 1916. The results indicate that one or more lifestyle factors that changed among adolescent women during the war, influenced their risk of breast cancer. Dietary intake of energy, fat, meat, milk, fish, fresh vegetables, and potatoes, in addition to physical activity level and height, are important factors to consider in relation to breast cancer risk. *Cancer Causes and Control*, 1996, 7, 507-512

Key words: Breast cancer, diet, height, Norway, physical activity, World War II.

Introduction

There are biologic reasons to believe that the period between the beginning of breast development at puberty (thelarche) and the first full-term pregnancy is a particularly sensitive period in a woman's life regarding the development of breast cancer. During this period, there is a high mitotic activity in the breast cells. Such an increase in the number of cells may require a reduced activity of the cells' control mechanisms.[1] The largest excess risk of breast cancer following the atomic bomb explosions in Japan was seen among survivors who were between 10 and 20 years of age at the time of bombing.[2] At the first full-term pregnancy, there is a differentiation of the terminal end buds in the breast into secretory units.[3] These secretory units have a reduced proliferative activity, a longer cell cycle and more efficient DNA repair capacity. Thus, the most sensitive period of breast cells may end at the first full-term pregnancy. The importance of this period in life has been supported by modelling studies carried out by Moolgavkar *et al.*[1]

The highest incidence rates of breast cancer are found in the United States and the western part of Europe.[4] Correlation and migrant studies have focused on the Western lifestyle as unfavorable and migrant studies suggest that the risk is determined principally by the influence during adolescence and young adulthood.[5] Among environmental factors, diet is thought to be an

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important determinant of breast cancer. Doll and Peto[6] estimated that 50 percent of the variation in breast cancer among countries could be related to diet. A diet characterized by a high intake of fat and meat,[7] and low in fruit, vegetables, and grains that provide insoluble fiber and antioxidants [8,9] may increase the risk of breast cancer. The correlation with breast cancer risk is particularly high for fat.[7] The lack of association between fat consumption and breast cancer found in most prospective studies[10-14] possibly could be due to dietary assessment at ages other than the most sensitive period. During World War II, substantial reduction in energy, fat, meat, and milk consumption, and increase in fish, fresh vegetables, and potato consumption took place in Norway and may have influenced the occurrence of breast cancer. Stature is related to nutritional factors and is associated positively with risk of breast cancer.[15] Those who experienced the war as adolescent girls had a lower stature compared with adolescent girls prior to and after the war years.[16] Further, there was an increase in physical activity level which may relate favorably to breast cancer risk.[17]

The Norwegian Cancer Registry provided data to compare risk of breast cancer among women who experienced the sensitive period before, during, or after World War II and to propose the configuration of an exposure variable by time. By an age-cohort model and a model which described the cohort by an exposure/sensitivity approach, the hypotheses that lifestyle changes during World War II decreased the risk of breast cancer, was examined.

Material and methods

Norway has a total population of almost 4.5 million. In this study, all women born between 1903-53, and between 30 and 59 years of age in the observation period 1956-92, were included. Altogether, 20,111 women with breast cancer were included in the study, with a total of 23,365,000 person-years (PY).

The population-based Cancer Registry of Norway started its registrations in 1952. According to Norwegian law, all cases of cancer must be reported to the Registry. The report, in addition to stating residence at time of diagnosis and the person's unique 11-digit identification number, includes diagnosis, stage of cancer at time of diagnosis, histologic findings, and the basis for the diagnosis. For breast cancer, the Registry is regarded as close to complete, and 97 percent of the cases are verified histologically. The analyses were carried out using two models. The first model was an ordinary age-cohort model. The second was an extension of the first model in that we tried to model in more detail the birth cohort effect. This was done by attributing an exposure for each calendar year to each birth cohort. In addition, it was assumed that the sensitivity to this exposure was highest in the beginning of puberty and gradually decreased towards the first full-term pregnancy. An acceptable goodness of fit of the second model would provide further support for our hypothesis of a sensitive period with regard to later risk of breast cancer. The fitting of the second model also would provide an estimate of the configuration of the exposure variable and hence give us an idea of how factors that influence breast cancer risk may have changed by calendar year. Estimation and testing were carried out using the GLIM 3.77 statistical program.[18]

First model: age-period-cohort model

The population was divided into three-year age groups (30-32, . . ., 57-59) and three- year birth cohorts (1903-05, . . ., 1951-53) covering the period of diagnosis 1956-92. Let D_{ij} be the number of observed cases in age group i, birth cohort j, and let N_{ij} be the number of PYs at risk. Dij is assumed to be Poisson distributed with mean $\exp(\xi + \alpha_i + \beta_j + \pi_k + \log [N_{ij}])$, where ξ is the constant term, α_i is the effect of age, β_j of birth cohort, and π_k of period. Since the period of diagnosis was given by birth cohort and age at diagnosis, and both these last two variables were expressed in three-year age groups, the periods of diagnosis overlapped. An acceptable goodness of fit, appraised by the deviance, was achieved by including the variables age and birth cohort only, while the model that included age and period of diagnosis only did not give an acceptable goodness of fit even when the data were organized in 'clean' three-year partitions. Therefore, the final version of the first model is expressed by describing the mean as $\exp(\xi + \alpha_i + \beta_j + \log [N_{ij}])$, where the data were organized with 'clean' three-year groups of age and birth cohort.

Second model: an exposure/sensitivity approach

In the second model, we assumed the existence of an exposure variable that is important for later developing breast cancer. The exposure variable, $\theta(t)$, for calendar year t, was defined as three straight lines where $\mu_{(1,2,3)}$ is the intercept and $\nu_{(1,3)}$ the-slope of the line which corresponds to the yearly change. The exposure variable may be thought of as a single exposure factor or as an expression of several factors:

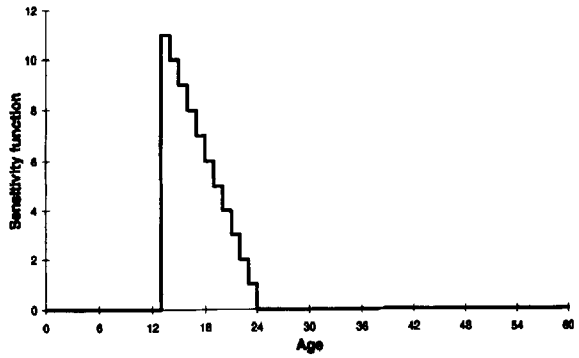
$$\theta(t) = \begin{cases} \mu_1 + \nu_1 \times t & \text{for } t = 1903,1904, \ldots,1939 \text{ (before WWII)} \\ \mu_2 & \text{for } t = 1940,1941, \ldots,1945 \text{ (during WWII)} \\ \mu_3 + \nu_3 \times t & \text{for } t = 1946,1947, \ldots,1975 \text{ (after WWII).} \end{cases}$$

Further, the second model was based on the assumptions that the sensitive period starts at age 13, representing age of thelarche and ends at 23, representing age of first full-term pregnancy. The sensitivity by age, $\tau(s)$, in relation to the exposure variable, was defined as:

$$t(s) = \begin{cases} 0 & \text{if } s < 13 \text{ years} \\ 24\text{-}s & \text{if } s = 13,14,\ldots,23 \text{ years} \\ 0 & \text{if } s > 23 \text{ years,} \end{cases}$$

implying that the exposure variable was of no importance if the woman was exposed before the age of 13 or after the age of 23. The most sensitive age was assumed to be 13 years, and subsequent to age 13, the sensitivity was assumed to decrease linearly towards zero at age 23 (Figure 1).

Figure 1. The assumed relationship between the sensitivity function and breast cancer development and age.



The assumptions about the form of exposure and sensitivity were connected to the cohort parameter, γ_j, by:

$$\gamma_j = \sum_{t=1900+3_j}^{1902+3_j} \sum_{s=1}^{59} \theta(t+s)\tau(s).$$

D_{ij} was assumed to be Poisson distributed with mean $\exp(\xi + \alpha_i + \gamma_j + \log[N_{ij}])$.

Results

Based on the ordinary age-cohort model, estimated incidence curves by birth cohort for different age groups at diagnosis were plotted (Figure 2). For the oldest birth cohorts (1903 to 1917), there was a marked incidence increase by birth cohort. For later birth cohorts, up to 1932, the incidence rate levelled off with a small increase for the first cohorts and a small decrease for the latest cohorts. These women were between eight and 27 years of age during WWII. For women born between 1933-44, a strong increase by time again was observed with a tendency to level off for cohorts born after WWII.

Figure 3 shows the estimated exposure variable, when fitting the second model to breast cancer incidence. The exposure variable increased up to the start of WWII to a level about twice the exposure level in 1916. During the war, the estimated exposure level dropped by 13 percent compared with the level just before the war. After the war, the exposure increased again, but the yearly increase (the slope) was now somewhat smaller. The estimated exposure level in 1975 was approximately 2.7 times higher than the level in 1916.

Figure 4, corresponding to Figure 2, shows the estimated incidence of breast cancer by age and birth cohort, but based on assumptions about exposure and sensitivity (second model). The incidence, as estimated by the two models, did not differ very much, but the levelling off

Figure 2. The estimated incidence of breast cancer in Norwegian women by age at diagnoses and birth cohort (the first model: age and birth cohort model).

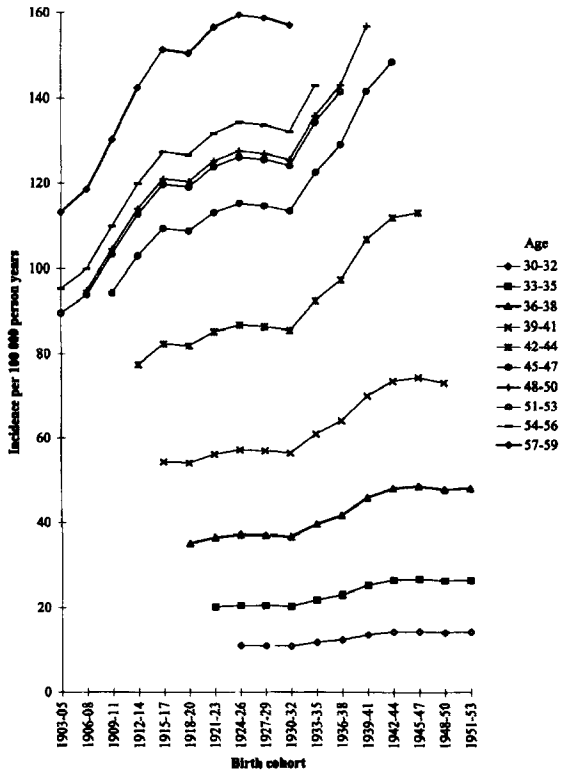


Figure 3. Estimated exposure variable for breast cancer by calendar year (Year 1916 = 100).

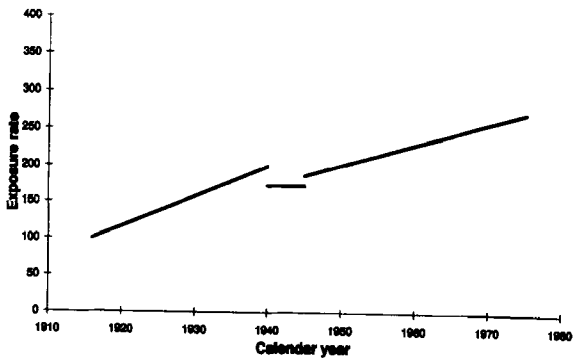
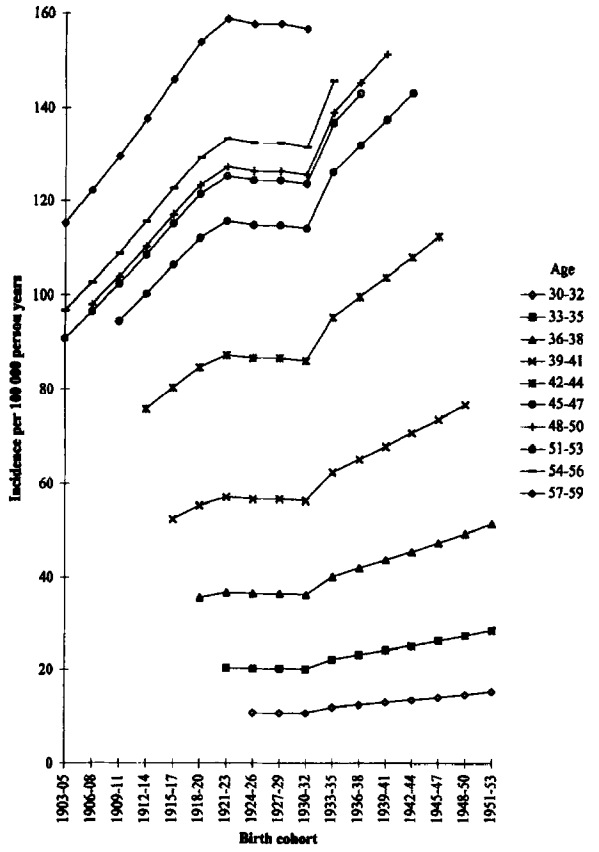


Figure 4. The estimated incidence of breast cancer in Norwegian women by age at diagnoses and birth cohort (the second model based on assumption about exposure and sensitivity for the exposure).



may have started some cohorts later in the second model.

When fitting the two models to the incidence of breast cancer, we achieved a deviance of 113.7 with 88 degrees of freedom (d.f.) for the first model, and a deviance of 125.7 with 99 d.f. for the second. An inspection of the standardized residuals revealed no particular pattern to indicate that the models did not present an acceptable description of the observed incidence (data not shown). We conclude that both models gave an acceptable goodness of fit, and that the second model was as good as the age-cohort model in terms of goodness of fit.

Discussion

This study shows that age at diagnosis and a simple description of an exposure variable that acts during adolescence are elements of a possible model for explaining variation in breast cancer incidence in Norway. The configuration of the estimated exposure indicated that one or more factors that influence risk of later developing breast cancer changed during the war. If these factors could be identified and changed among girls from the time their breasts begin to grow until the age of first full-term pregnancy, then their risk of breast cancer might be significantly reduced.

A major factor which changed during World War II in Norway was diet, on which the following discussion focuses and for which documented information was available. There were probably geographic differences within the country, in that urban areas generally were affected more than rural areas. Since we do not know the habitation history of each woman, this could not be accounted for. One important dietary change was a decrease in daily energy intake by 22 percent during the war.[19] The main reason for the reduction in calories was the reduced intake of fat. It is known that caloric restriction inhibits the development of neoplasm in rodents [20] and may also apply to humans.[21]

Short stature may be an indicator of caloric restriction in early life.[22] Changes in energy intake thus may be reflected in the height curves. Micozzi [23] found mean adult height and breast cancer incidence in 30 countries to be highly correlated (correlation coefficient = 0.8). Norwegian data [17] have demonstrated a positive association between height in adult life and incidence of breast cancer. Vatten and Kvinnsland[24] indicated in a later study that this association was most pronounced among the birth cohorts 1929-32. In this context, the study by Brundtland *et al* [16] is relevant. They reported height and weight of school children in Oslo (the capital of Norway) during 1920-80. The mean height of 13 year-old girls increased from 145.6 cm in 1920 to 155.0 cm in 1940. This corresponds to a yearly increase of 0.48 cm, assuming the increase was linear. In 1945, the mean height was 154.2 cm. After the war, the mean height increased again and was 158.7 cm in 1975 corresponding to a yearly increase of 0.12 cm. The same picture was seen for every year of age (from eight to 13 years).

The supply of meat and meat products increased up to the war, and then dropped substantially during the war. The consumption of fish and fish products remained almost constant before the war and were more than doubled during the war.[25] Fewer milk products were consumed during the war, but more fresh vegetables, including Swedish turnips and potatoes, were consumed. Strøm[25] found that the consumption of vitamins was satisfactory, but pointed out that the intake differed widely among families and probably some families had less than the requisite amount. This applied particularly to vitamin A. Dietary fiber intake was greater during the war due to larger intake of potatoes, bread, oats, and a higher extraction rate of flour.[26] Several nutrient stimulants like tobacco, coffee, tea, and some types of alcohol could not be imported by Norway during the war. None of the stimulants, except alcohol, are accepted risk factors for breast cancer. Some private alcohol production was maintained or even increased, but consumption of alcohol among

teenage women was almost nonexistent before, during, and for a long time after the war ended.

It also has been pointed out, but not documented, that the level of physical activity increased, especially among the urban population. A high level of physical activity may reduce the risk of breast cancer.[27] If physical activity was of importance, then our data indicate a need to look for evidence of high physical activity during puberty. It has been shown previously that pre-menarcheal girls with high level of physical activity may experience a delay in the onset of menses.[15] However, the age of menarche did not change to any extent during the war.[28] Thus, the explanation of a lower breast cancer incidence among those in puberty during the war did not seem to be a shorter period of sensitivity as a result of more physical exercise.

Information about the age at thelarche was not available and therefore the age at menarche was the best indicative measure for the variable. In Norway, the median age of menarche varied between 13 and 14 years of age in the calendar periods studied. Therefore, 13 years of age was chosen as the lower limit for the sensitive period. Since the present study is an ecologic study, it was natural to use the median age of first full-term pregnancy as an endpoint. The median age was about 23 years for the birth cohorts 1935 to 1953 in Norway.[29] We have no documentation for the mean age of first full-term pregnancy for the cohorts 1903 to 1934, but do not believe it deviated very much from 23. The risk of breast cancer by age at first full-term pregnancy is found to be almost linear from age 15 to age 30.[30] This observation shows that the upper age for the sensitive period varies among females. Our choice of 23 years as the upper age is a simplification of the real-life situation, but a reasonable choice in an ecologic study. In order not to make the models too complicated, we have chosen not to include any other information on the childbearing pattern than mean age at first delivery. In a previous ecologic study,[31] we indicated that changes in the childbearing pattern among women aged 15 to 49 years could account for 15 percent of the increase in incidence of breast cancer from 1955 to 1984.

In conclusion, the results indicate that one or more environmental factors that influence the risk of breast cancer changed during the war. Dietary reduction in energy, fat, meat, and milk consumption, and increase in fish, fresh vegetables, and potato consumption, in addition to an increase in physical activity level are important factors to consider. In discussion of future studies as well as previous studies, dietary habits during adolescence should be taken into account.

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