Seasonal Changes in Cancer Mortality Rates among Cancer and Cardiovascular Patients in the Netherlands

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ABSTRACT

The burden of cancer, leading cause of death in developed countries, is increasing due to population aging and growth. In the general population there are higher mortality rates in winter than in summer. This study investigates seasonal changes in cancer mortalities (lung and breast cancer) in the Dutch population (1996-2016) and whether mortality in winter is correlated more with average temperatures, or more with influenza incidence. Results showed that temperature changes and higher influenza incidence in winter are associated with higher mortality rates. This was not seen in patients with lung and breast cancer, but it is important to address.

Keywords

Cancer mortality, Cardiovascular mortality, Seasonal Changes, Temperature, Influenza.

INTRODUCTION

Cancer, the leading cause of death in economically developed countries, has an increasing burden because of population aging and growth, as well as of various cancer-associated lifestyles (smoking, physical inactivity, "westernized" diet, etc.) [1]. Cancer incidence is determined by exposure to etiologic factors and by individual susceptibility, and may also be affected by earlier and better diagnosis. Cancer mortality is influenced by cancer incidence, genetic makeup, tumor characteristics, stage at diagnosis, and response to available treatment [2]. In the Netherlands, 45 790 people died from cancer in 2016, and this number has dramatically risen from 1996 to 2016 (increase of 16.4%) [3]. Cancer of the lung, stomach, colon, liver, and esophagus have been associated with the highest incidence worldwide, in addition to sex-specific malignancies of the female breast, uterine cervix, and male prostate [2].

It has been observed that in the general population there is a higher mortality rate in winter than in summer, possibly due to the characteristics of the weather. For example, a Finnish study reported that all major stroke subtypes occurred more frequently in autumn [4]. In addition, a Serbian study concluded that seasonal variations were most pronounced in mortality from cardiovascular and respiratory diseases, with the highest mortality rates recorded in February and March [5]. Furthermore, a Hungarian study showed that majority of deaths from cancers of female genital organs occurred in winter, and a significant seasonal pattern was revealed for deaths from breast cancer with a peak in January [6].

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SRC 2017, November 15, 2017, The Netherlands.

Severe infections have been associated with prolonged hospitalization and treatment delay, and are a major cause of mortality [7]. Infections in cancer patients can result from immunosuppression due to the treatment, or due to the malignancy itself. In contrast to hematological cancers, such as leukemia, breast cancers are not essentially linked to an immune deficit. Yet, limited data is available on the incidence of serious infections in cancer patients. One Swedish study assessed the risk and implications of serious infections in breast cancer patients by using registry-based data. In total, 720 breast cancer patients experienced an infection-related hospitalization during a median follow-up of 4.9 years [8]. Infections acquired by respiratory viruses, such as influenza, thus far have received little attention regarding cancer mortalities. Influenza viruses, due to their genotypic plasticity, cause yearly epidemics which result in significant clinical impacts [9].

In the Netherlands, lung cancer and breast cancer are two most prevalent cancer types, with a prevalence of 25 204 and 132 275 respectively in 2016 [10]. Despite therapeutic advances, little gain has been achieved in overall lung cancer survival over the past 30 years, with approximately 15% five-year survival rates for all stages [11]. The greatest risk factor for developing female breast cancer is aging. However, while incidence rates for most epithelial cancers rise steadily with aging, rates for female breast cancer increase rapidly until approximately age 50, and then rise more slowly.

The main purpose of this research is to investigate seasonal changes in cancer mortalities, specifically lung/trachea cancer and female breast cancer mortalities, in the Dutch population from 1996 to 2015. These results will be compared with the seasonal changes in mortality rates from the most common cardiovascular diseases. The hypothesis is that cancer mortality and cardiovascular disease mortality will be increased during the first and the fourth quarters of the years (which include the winter seasons). Furthermore, the goal will be to investigate whether mortality in the winter season is correlated more with the average temperatures, or more with the seasonal influenza incidence.

MATERIALS AND METHODS

Study population

Data was obtained from the open electronic database of the Central Bureau of Statistics (CBS) of the Netherlands [3]. The number of deaths from cancers and cardiovascular diseases were available from 1996 and were categorized in quarters of the year. The last quarter included was the third quarter of 2016. Both males and females were included in the analysis, as well as all age groups.

Average monthly temperature figures and the Hellmann Index were obtained from the Meteorological Institute of the Netherlands [12]. The Hellman index is a measure of the cold days during the period from November 1st of the previous year, to March 31st of a given year (thus in this research the number represented the cold days in the 1st and the 4th quarter of the years).

Data on influenza incidence was obtained from the European Center for Disease Prevention and Control (Influenza activity data in the Netherlands) [13]. Data was available only from the first quarter of 2009 until the third quarter of 2015.

Statistical Methods

To examine the seasonal trends occurring in mortality cases of lung/trachea cancer, breast cancer, diseases of the cardiovascular system, and total causes, line plots were constructed using IBM SPSS Software (version 23). For a more in-depth analysis, the variable periods was dummy coded. A means test was performed for each disease category in order to obtain the average difference in percentages between deaths in the winter and deaths in the summer.

Linear regression was performed to investigate the relationship between the average temperatures and all previously given variables. Also, the Hellmann index was analyzed in the same way. Furthermore, to investigate the influence of seasonal influenza on cancer mortality, again linear regression was performed. The missing data on influenza were ruled out, thus only the periods from 2009 until 2015 were used. 95% confidence intervals were calculated and *p*-values less than or equal to 0.05 were considered to be statistically significant. All these analyses were performed again using IBM SPSS Software.

RESULTS

Overall, there were 197 543, 69 729, 592 643, and 902 065 deaths from lung/trachea cancer, breast cancer, other malignant cancers, and cardiovascular diseases, respectively, in the Netherlands during the period 1996–2016. Most deaths occurred from cardiovascular diseases. Among the two major cancer types, most deaths resulted from lung/trachea cancer.

The average temperature measured during this period was M=9.9°C (SD=4.95). The highest average temperature was noticed in the third quarter of 2006 (18.6°C), and the lowest in the first quarter of 2013 (0.3°C). The average Hellmann index was M=45.02 (SD=40.08), meaning that on average, the temperatures in the Netherlands were normal during the past 20 years.

Investigation of Seasonal Trends

Mortality rates from lung/trachea cancer and breast cancer showed slight frequencies with positive peaks during the 1st and 4th quarters which represent the winter months, and negative peaks during the 3rd quarter which represents the summer months. Mortality rates from cardiovascular diseases and total mortality rates showed stronger frequencies, meaning that the correlation between these mortality rates and the change in seasons is stronger.

Four means tests were performed in order to obtain the average differences (in percentages) between the different disease categories in the winter and in the summer. The most obvious differences occurred within the mortality rates from cardiovascular diseases (an increase of 5.4% in the winter). The differences within mortality rates from lung/trachea cancer (an increase of 0.2% in the summer) and breast cancer (an increase of 0.6% in the summer) were not as big.

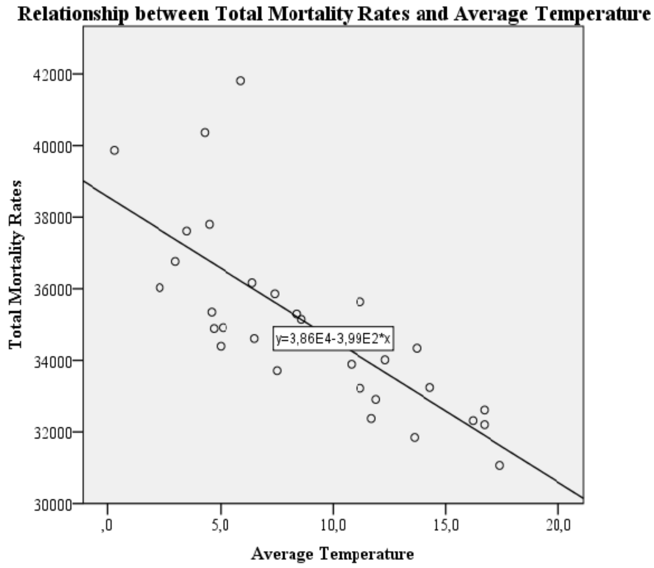
Investigation of Temperature Changes on Mortality Rates

Linear regression was performed to check the association between average temperature throughout the period from 1996-2016 and the mortality rates of the various causes. Association was checked between average temperature and mortality rates from: lung/trachea cancer, breast cancer, cardiovascular diseases, and all causes in total. Statistically significant associations were found among average temperature and mortality rates from lung/trachea cancer ($F(1,81)=3.67$; $p=0.05$), among average temperature and mortality rates from cardiovascular diseases ($F(1,81)=21.51$; $p<0.01$), and among average temperature and mortality rates from all causes ($F(1,81)=132.90$; $p<0.01$). The association among average temperature and mortality rates from breast cancer was found to be statistically insignificant ($F(1,81)=0.014$; $p=0.91$). Pearson correlation coefficients were calculated for each of the three significant associations. The correlation coefficients were negative, meaning that the lower the temperature, the higher the number of death cases from lung/trachea cancer, cardiovascular diseases and total all causes. To further investigate the influence of temperatures on mortality rates, the associations between the Hellmann index and the four different mortality rate types were investigated. However, these results were statistically insignificant.

Investigation of Influenza Occurrence on Mortality Rates

Linear regression was performed to check for a potential association between influenza incidence throughout the period from 2009 to 2015, and the mortality rates of the various causes. Association was checked for mortality rates from lung/trachea cancer, breast cancer, cardiovascular diseases, and all causes. Statistically significant results were observed for the association between influenza incidence and deaths from cardiovascular diseases ($F(1,25)=37.71$; $p<0.01$), and deaths from all causes ($F(1,25)=41,24$; $p<0.01$). The associations between influenza incidence and deaths from lung/trachea cancer ($F(1,25)=0.041$; $p=0.84$) and breast cancer ($F(1,25)=0.55$; $p=0.47$) were found to be statistically insignificant. The Pearson correlation coefficients for the statistically significant associations were positive, meaning that the higher the incidence of influenza in a certain period, the higher the total deaths and the deaths from cardiovascular diseases.

In order to compare the relationships between total mortality rates and both average temperatures and influenza incidence, linear regression was performed again for the average temperature, this time using the same period as the period available for the influenza incidence data (2009-2015), and the results were plotted on a scatterplot and compared (Fig. 1).



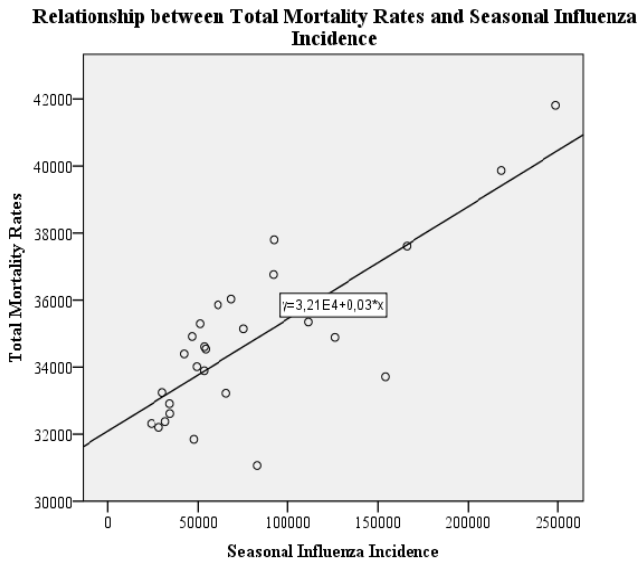


Figure 1. Comparison of the relationships between total mortality rates and average temperatures (top), and total mortality rates and influenza incidence (bottom).

DISCUSSION

Main Findings

This study had two main goals: (1) to investigate the potential relationships between seasonal changes, represented by changes in the average temperatures, and the changes in mortality rates from the two most common cancer types (breast cancer and lung cancer) and from cardiovascular diseases, and (2) to examine whether an association of influenza incidence with these mortality rates exists, and whether it is more or less significant. The results showed that a significant difference existed within the mortality rates from cardiovascular diseases (an increase of 5.4% mortality rate in the winter compared to the summer periods). A slight negative correlation was also seen within mortality rates from lung cancer. The most significant difference, however, was seen for total mortality rates; thus overall, most of the people died during the winter seasons. A significant seasonal pattern was not observed for breast cancer mortalities. These results might indicate that breast cancer and lung cancer patients mostly die from the burden of the cancer itself, rather than due to seasonal effects. The main cause of death in such cancers would therefore include metastases causing fatal hemorrhages, pulmonary thromboembolisms, hepatic failure, and failure of other organs [14, 15]. Furthermore, an association with the Hellmann index was not seen, indicating that extremely cold temperatures during the winter do not have a significant effect on mortality rates.

Significant associations were observed among influenza incidence and total mortality rates, and mortality rates from cardiovascular diseases. During the years, with a higher influenza incidence, more people died. Because influenza incidence peaks in the winter seasons, this supports the previous results. The associations with influenza were much stronger than the associations with the average temperature, meaning that, overall, seasonal influenza is likely to have a severe impact on mortality rates.

Limitations of this Study

The data for this study used to investigate seasonal changes was available from 1996-2016, while the data used for influenza incidence was only available from 2009-2015. Even though the time periods were matched in order to compare the two results, this time period was too short to observe any big effects of influenza incidence on mortality rates. Future research could try replicating this study by using a longer timeframe which would lead to much more reliable results.

This study used mostly linear regression to observe the results. A statistical test developed by Stolwijk et al. described seasonal patterns as one sine and one cosine function which can be incorporated into a regression model [16]. This might be a better way to investigate seasonal changes and improve the validity of the results. In this case this was not done because the IBM SPSS software does not allow manipulation of regression analysis outside of its built-in functions. Also, SPSS cannot handle longitudinal panel data.

Comparison with Other Studies

The results of this research are in line with other studies. A Norwegian study by Porojnicu et al. investigated the potential role of solar exposure on the survival of breast cancer patients. They showed that women who are diagnosed during the summer had about 25% better survival after standard treatment compared with women diagnosed during the winter. For women younger than 50 years, the benefit seemed to be even higher (40% better survival) [17]. Furthermore, the study by Hartai et al. showed a significant seasonality for overall deaths, with a peak in January and a large decrease in July [6].

Hematological Malignancies and Infection

The main risk factor for developing a serious infection in cancer patients is neutropenia. New therapeutic strategies have improved the long-term survival of cancer patients in recent years, but nevertheless, cytotoxic chemotherapy is the key therapeutic option, with neutropenia as its main complication. Patients with a hematological malignancy, such as leukemia, are especially vulnerable to infections because of their suppressed immune system, not only due to treatment, but due to the disease itself. Three possible mechanisms have been explained to have a role in the immunosuppression of leukemia: (1) inhibitory T-cell pathways (especially programmed death ligand 1/programmed death 1), (2) regulatory immune cells, and (3) metabolic enzymes, such as indoeamine-2,3-dioxygenase [18].

A study by Marin et al. aimed to identify factors which influence mortality in neutropenic patients with hematological malignancies. They showed that out of 602 episodes of bloodstream infections in neutropenic patients, 510 of them occurred in patients with hematological malignancies [19]. On the other hand, infections with influenza has not been investigated in this group of patients. The outcomes of this study showed that overall mortality is greatly correlated with influenza incidence in the winter periods. This might indirectly point out that morality rates of leukemia patients are greater in the winter months due to the higher incidence of influenza. Future research could potentially focus on this aspect.

CONCLUSION

The main finding of this study suggests that changes in temperatures and higher influenza incidences in the winter are associated with higher overall mortality rates. Although this was not specifically seen in patients with breast and lung cancer, it is important to address in the future. Indirectly, the study points out that other types of cancers, such as leukemia, which are associated with an extensively suppressed immune system, might have an increased mortality rate in winter seasons due to the incidence of influenza. Measures must be taken in order to reduce mortality rates associated with seasonal changes

ROLE OF THE STUDENT

Magdalena Shumanska was an undergraduate student at University College Roosevelt working under the supervision of Prof. Ger Rijkers when the research in this report was performed. Initially, the project was aimed at investigating the influence of seasonal influenza on mortality rates of patients suffering from leukemia; however, the data regarding this was not available in the open database of the CBS. Therefore, this more general project was performed. The research question was proposed by the supervisor, and the processing of the analysis, results, as well the formulation of the discussion, conclusions, and the writing were done by the student. The research was done in January-May 2017.

ACKNOWLEDGMENTS

I thank my supervisor, Prof. Ger Rijkers, who helped and provided useful comments on previous versions of this paper.

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