ORIGINAL RESEARCH

Future Patient Incidence in Hemato-Oncology: A Study Using Data from Cancer Registries in Japan

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Purpose: The distribution of patients with hematological malignancies is expected to change markedly in the future due to aging of the Japanese population. We assessed the expected incidence rates of leukemia, malignant lymphoma, and multiple myeloma using national population estimates and data from the Kanagawa Cancer Registry.

Patients and Methods: To evaluate the effects of community aging, we compared expected future incidences of hematological malignancies in Kanagawa with other three areas, namely the Yamagata, Osaka, and Nagasaki prefectures, which have different populations and predicted aging rates.

Results: The total number of patients newly diagnosed with hematological malignancy in Kanagawa in 2010 was 1970. This was predicted to increase to 2581 by 2025 and to 2712 by 2040. Trends were very similar for all three hematological malignancies. These incidence rates were predicted to increase continuously in patients aged ≥65 years from 2010 to 2040, with a 169% increase in leukemia, a 167% increase in malignant lymphoma, and a 169% increase in multiple myeloma. A continuous increase in the population aged ≥65 years was also noted in the other three prefectures.

Conclusion: The distribution demographic of patients with hematological malignancies is expected to change in the future as the number of elderly patients increases.

Keywords: leukemia, myeloma, lymphoma, aging, hematopoietic stem cell transplantation

Introduction

Japan is quickly developing an aging society, as are various other countries.[1] Advancing age is the most important risk factor for cancer,[2] and therefore, the number of cancer patients will rapidly increase in the future. Future predictions using simulation models have been conducted worldwide.[3–10] We recently predicted the future incidence of breast cancer[11] using data from the Kanagawa Cancer Registry,[12] 2010 census population data from the National Census, and estimated data for future populations up to 2040 from the National Institute of Population and Social Security Research.[2] We demonstrated that the future distribution of patients with breast cancer will drastically change, with the increasing number of elderly patients in urban areas. Kanagawa is the one of the biggest prefectures in Japan, which in 2010 had a population of 9,048,331 people. Thus, this prediction may be applied to many areas in Japan, and this change in distribution will induce a major shift in the demand for and supply of cancer medicine. These findings therefore suggest a great impact upon medical providers in the near future.

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Predicting the future incidence of hematological malignancies is significant because treatment options differ according to the type of malignancy, and the intensity of treatment is usually determined according to the patient's age. Highly intensive treatments require numerous medical resources, providers, and equipment types. Consequently, advance knowledge of which age groups and diseases are expected to increase in the future would be valuable for determining the required medical resources in the given geographies.

In this study, we investigated the future incidence of hematological diseases in Kanagawa and three other areas of Japan, viz., the Yamagata, Osaka, and Nagasaki prefectures, which have different demographic characteristics.

Patients and Methods
Data Collection

We conducted our analyses using a "simple model" (the mechanism of which we will explain further on), and an age-period-cohort model using the Nordpred package, which we also used in our previous study on breast cancer prediction.[11] Although the age-period-cohort model considers the effects of these three factors,[13] in this study, the period and cohort effects were probably overestimated.[11] In the cancer registries, the number of recorded cancer cases have appeared to increase due to the recent availability of more complete data; for example, the rate of "death certificate only" (DCO) cases in the Kanagawa Cancer Registry in 1990 was 33%, which improved to 18.2% in 2010, when the data collection criteria widened.

Therefore, we also used the simple 2010 model to evaluate the age effect in order to assess the validity of both models. Additionally, the Nordpred package does not provide a function for calculating confidence intervals; therefore, we utilized both models to afford greater accuracy to our findings.

Our data collection methods have been described elsewhere.[11] Briefly, we used the population-based cancer registry data for the Kanagawa prefecture (known as the Kanagawa Cancer Registry). Data were fully anonymized prior to our access. As in our previous study,[11] we used the observed data from 1995, 2000, 2005, and 2010. In 2010, the population of the Kanagawa prefecture was 9,048,331 people, and only Tokyo had a large population in Japan. All data from the Kanagawa Cancer Registry were retrieved from the database after obtaining permission from the Kanagawa prefecture in April 2016. The completeness of cancer registries was evaluated according to DCO, death certificate notification, and mortality/incidence ratios. This information is available on the National Cancer Center Japan website (https://ganjoho.jp/reg_stat/statistics/dl/statistics_p00.html).

Results are presented for the following cancer types, as defined by the International Classification of Diseases (10th edition): Hodgkin lymphoma (C81), follicular lymphoma (C82), non-follicular lymphoma (C83), mature T/natural killer-cell lymphomas (C84), other specified and unspecified types of non-Hodgkin lymphoma (C85), malignant immunoproliferative diseases and certain other B-cell lymphomas (C88), multiple myeloma and
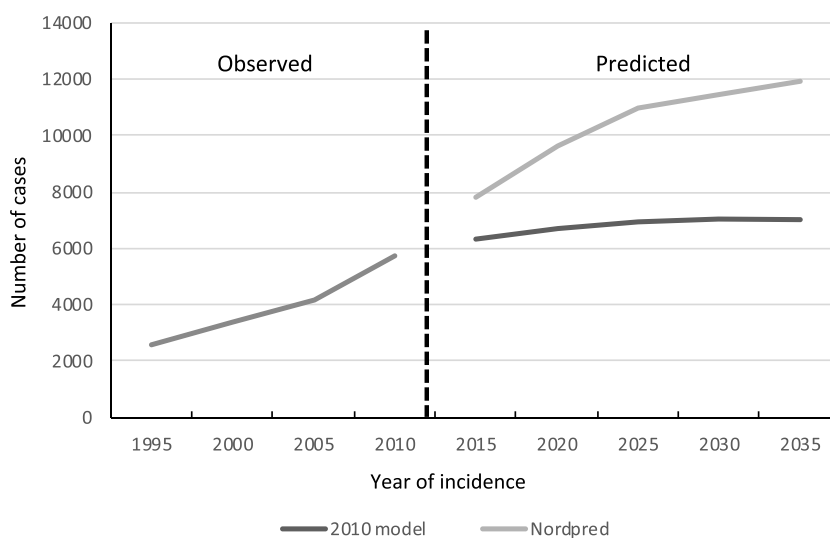

Figure 1 Predicted incidence of hematological malignancy in the Yamagata, Kanagawa, Osaka, and Nagasaki prefectures of Japan. The observed (1995–2010) and predicted (2015–2035) total incidences of hematological malignancy. The incidences were determined using the simple 2010 model and the Nordpred model.

malignant plasma cell neoplasms (C90), lymphoid leukemia (C91), myeloid leukemia (C92), monocytic leukemia (C93), other leukemias of specified cell type (C94), leukemia of unspecified cell type (C95), and other and unspecified malignant neoplasms of lymphoid and hematopoietic and related tissue (C96). Leukemia, malignant lymphoma, and multiple myeloma included codes C91–C95, C81–C85 and C96, and C88 and C90, respectively.

To estimate the expected incidence of cancer for the years 2015, 2020, 2025, 2030, and 2035, we used three databases. Data regarding newly diagnosed patients with hematological malignancy classified by sex and 16 age (at 5-year intervals up to 79 years and >85 years old) were retrieved from the Kanagawa Cancer Registry. Population data for 1995, 2000, 2005, and 2010 were retrieved from the National Census. Estimated data for 2015, 2020, 2025, 2030, and 2035 populations were retrieved from the National Institute of Population and Social Security Research.[14] Patients with hematological malignancy identified by DCO were excluded from the study because detailed information, such as incidence data and diagnosis date, was not obtained for these patients (Figure 1).

To compare the predicted values in Kanagawa with other areas in Japan with different geographic and demographic characteristics, including the rate of aging, we also used data from population-based cancer registries for the Yamagata, Osaka, and Nagasaki prefectures, with permission from each of these prefectures. The total populations of these prefectures, with populations of individuals aged ≥65 years (%) expressed in brackets, were estimated to be 1,168,924 (321,722 [27.6%]) for Yamagata; 9,048,331 (1,819,503 [20.2%]) for Kanagawa; 8,865,245 (1,962,748 [22.4%]) for Osaka; and 1,426,779 (369,290 [26.0%]) for Nagasaki.[15] The projected rates of the population of individuals aged ≥65 years for 2035 were 37.8%, 31.7%, 32.7%, and 37.7%, in the Yamagata, Kanagawa, Osaka, and Nagasaki prefectures, respectively. Age distribution data without standardization were used for analyses.

This study was approved by the Institutional Review Board of Kanagawa Cancer Center (28-Epidemiology-101).

Data Analysis

Data analysis was conducted as previously described.[11] Briefly, future estimates of the incidence rates of hematological malignancies were calculated by multiplying the 2010 incidence rates according to sex and the 16 age groups by the future populations according to sex and the 16 age groups. For example, the predicted incidence of hematological malignancies was calculated as follows:

$$
\begin{aligned}
\text{Predicted} \\
\text{incidence} \\
\text{of hmin} \\
2020
\end{aligned}
= \sum_{\substack{sex = woman, \\ man}}
\left\{
\begin{pmatrix} \text{the predicted} \\ \text{number of} \\ \text{individuals} \\ \text{by sex aged} \\ <85\,\text{years} \\ \text{in } 2020 \end{pmatrix}
\times \frac{\begin{pmatrix} \text{the incidence} \\ \text{of hm by sex in} \\ \text{those aged} \\ <85\,\text{years} \\ \text{in } 2010 \end{pmatrix}}{\begin{pmatrix} \text{the number of} \\ \text{residents by sex in} \\ \text{those aged} \\ <85\,\text{years} \\ \text{in } 2010 \end{pmatrix}}
\right.
$$

$$
\left.
+ \sum_{i=0}^{16} \begin{pmatrix} \text{the predicted} \\ \text{number of} \\ \text{residents} \\ \text{by sex in those} \\ \text{aged } 5i \text{ to } 5i+4 \\ \text{in } 2020 \end{pmatrix}
\times \frac{\begin{pmatrix} \text{the incidence} \\ \text{of hm by sex in} \\ \text{those aged} \\ 5i \text{ to } 5i+4 \\ \text{in } 2010 \end{pmatrix}}{\begin{pmatrix} \text{the number} \\ \text{of residents} \\ \text{by sex in those} \\ \text{aged } 5i \text{ to } 5i+4 \\ \text{in } 2010 \end{pmatrix}}
\right\}
$$

where *hm* represents hematological malignancies and *those aged* $5i$ *to* $5i+4$ represents a 5-year interval. We refer to this as the "simple 2010 model." We also used the Nordpred software package to perform sensitivity analysis. Nordpred is R-based software developed by the Cancer Registry of Norway, and uses an age-period-cohort model with Poisson regression:

$$ R_a^p = g\left(A_a + D \cdot p + P_p + C_c\right) $$

where g is a link function and R_a^p, D, A_a, P_p, and are defined as the incidence rates in the age group *a* and in the period *p*, common linear drift parameter, age component of the age group *a*, non-linear period component of the period *p*, and non-linear cohort component of the cohort *c*, respectively. We used two link functions: the exponential function, and for better predictions to level

off the exponential growth, the power 5 function, ie, $g(x) = x^5$ by Moller et al.[16]

Results

Estimation of Future Incidence

Trends for all three hematological malignancies in the Yamagata, Kanagawa, Osaka, and Nagasaki prefectures are shown in Figure 1. The total number of patients newly diagnosed with hematological malignancy in Kanagawa in 2010 was 1970, comprising 547 with leukemia, 1168 with malignant lymphoma, and 255 with multiple myeloma. The total number of patients newly diagnosed with hematological malignancy was predicted to increase to 2581 by 2025 and to 2712 by 2040. Trends were similar for all three hematological malignancies (Figure 2).

In the simple 2010 model, the incidence by age groups according to diseases, including malignant lymphoma, multiple myeloma, and leukemia, are shown in Table 1. The proportional incidence rates of the three hematological malignancies were predicted to increase continuously in patients aged ≥65 years, with a 169% increase for leukemia, a 167% increase for malignant lymphoma, and a 169% increase for multiple myeloma from 2010 to 2040 (Table 1). In the group of patients aged <65 years, incidence rates of these hematological malignancies were predicted to decrease (Table 1). The Nordpred-based sensitivity analysis predicted a similar trend in both groups, for people aged <65 years and those aged ≥65 years (Figure 3).

Comparison with the Other Prefectures

To evaluate the effect of community aging, we compared the predicted future incidences of hematologic malignancies in Kanagawa with those in the other three selected study areas with different populations and predicted aging rates. As the simple 2010 model demonstrates in Figure 4, continuous increase in incidences of patients aged ≥65 years in the other three prefectures was predicted. A higher rate of increase of patients aged ≥65 years was noted in the Kanagawa and Osaka prefectures, which have larger populations and lower aging rates compared with the Yamagata and Nagasaki prefectures, which have smaller populations and higher aging rates. The Nordpred-based sensitivity analysis predicted a similar trend, with the exception of Yamagata, where an extreme increase was predicted (Figure 4).

Discussion

The results of this study predict that the numbers of elderly patients with hematological malignances will increase and indicate that the distribution of patients will change in the future. This prediction may have a significant impact on future healthcare plans with regard to hematological malignancies.

We found that future incidence rates of hematological malignancies are expected to change. In this study, the number of patients with cancer onset aged ≥65 years is predicted to increase continuously until 2040 (Figure 3), whereas in patients aged <65 years, it is predicted to
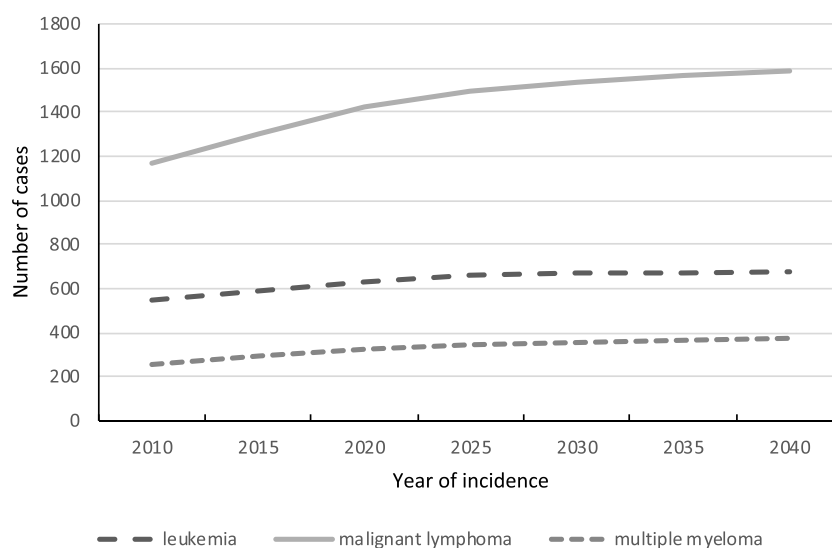

Figure 2 Predicted incidence of leukemia, malignant lymphoma, multiple myeloma, and leukemia in the Kanagawa prefecture, Japan. The observed (1995–2010) and predicted (2015–2035) incidences of malignant lymphoma, multiple myeloma, and leukemia. The incidences were determined using the simple 2010 model.

Table 1 Future Estimated Values Using 2010 Model

	Age Groups	Year						
		Future Estimated Values*						
		2010	2015	2020	2025	2030	2035	2040
Leukemia	≥65	100	122	137	147	153	159	169
	<65	100	95	95	96	95	89	80
	<60	100	98	100	98	93	84	78
	<40	100	92	84	78	74	71	67
Malignant lymphoma	≥65	100	122	137	144	150	157	167
	<65	100	94	96	102	103	97	86
	<60	100	101	107	109	104	91	84
	<40	100	89	81	77	74	70	66
Multiple myeloma	≥65	100	123	140	151	154	159	169
	<65	100	90	90	101	107	103	89
	<60	100	99	107	114	111	96	87
	<40	100	83	72	66	63	62	58

Note: *Future estimated values are presented as an index value, and they are expressed as the relative value compared with the 2010 incidence as a proportion of 100 by age.

decrease (simple 2010 model) or increase very little (Nordpred model) (Figure 4). The number of patients aged <65 years would extensively increase in Yamagata (Figure 4D). The transient increase from 2005 to 2010 was probably overestimated for the prediction after 2010. This indicates that predictions using the Nordpred model should be carefully interpreted when a transient increase or decrease is observed before the initial year of the predication due to overestimation.

This change is almost consistent with our future prediction for patients with breast cancer,[11] in which the aging "baby boom" generation (which includes individuals born during the first baby boom [1947–1949] after World War II) likely had a marked effect on the change in the distribution of patients. This group is a dominant demographic of the Japanese population, and the total number of baby boomers is estimated to be approximately 8,060,000.[17]

The predictions from the current study indicate that the demand for high-intensity treatments, such as allogeneic hematopoietic stem cell transplantation,[18] will decrease. The number of patients with leukemia aged <40 years, who are candidates for myeloablative transplantation, will decrease to 67% (76/113, simple 2010 model) from 2010 to 2040 (Table 1). The number of patients with leukemia aged <60 years, who are candidates for non-
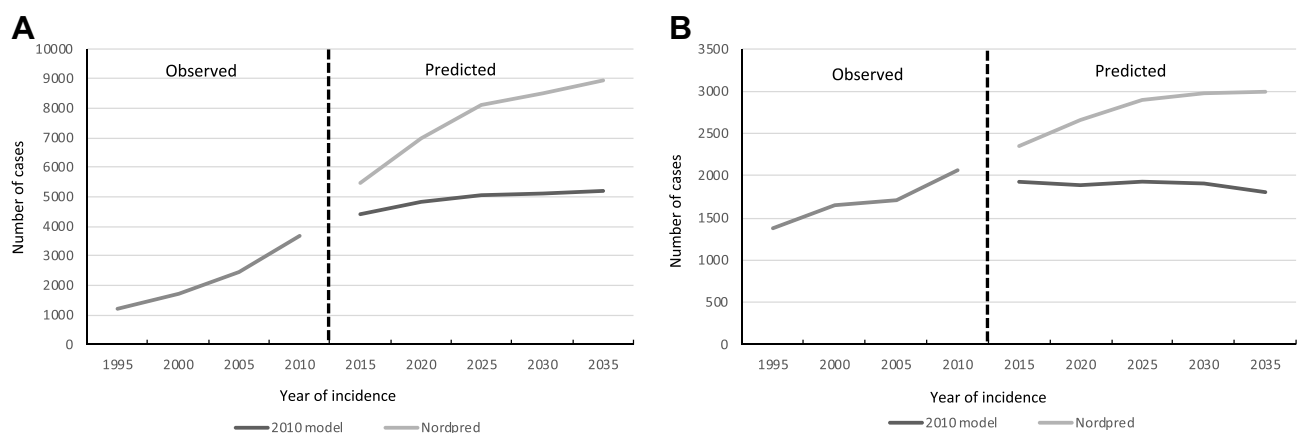

Figure 3 Predicted incidence of hematological malignancy according to the age groups in the Kanagawa prefecture, Japan. The observed (1995–2010) and predicted (2015–2035) total incidences of hematological malignancy in the people aged ≥65 years (**A**) and those aged <65 years (**B**). The incidences were determined using the simple 2010 model and the Nordpred model.
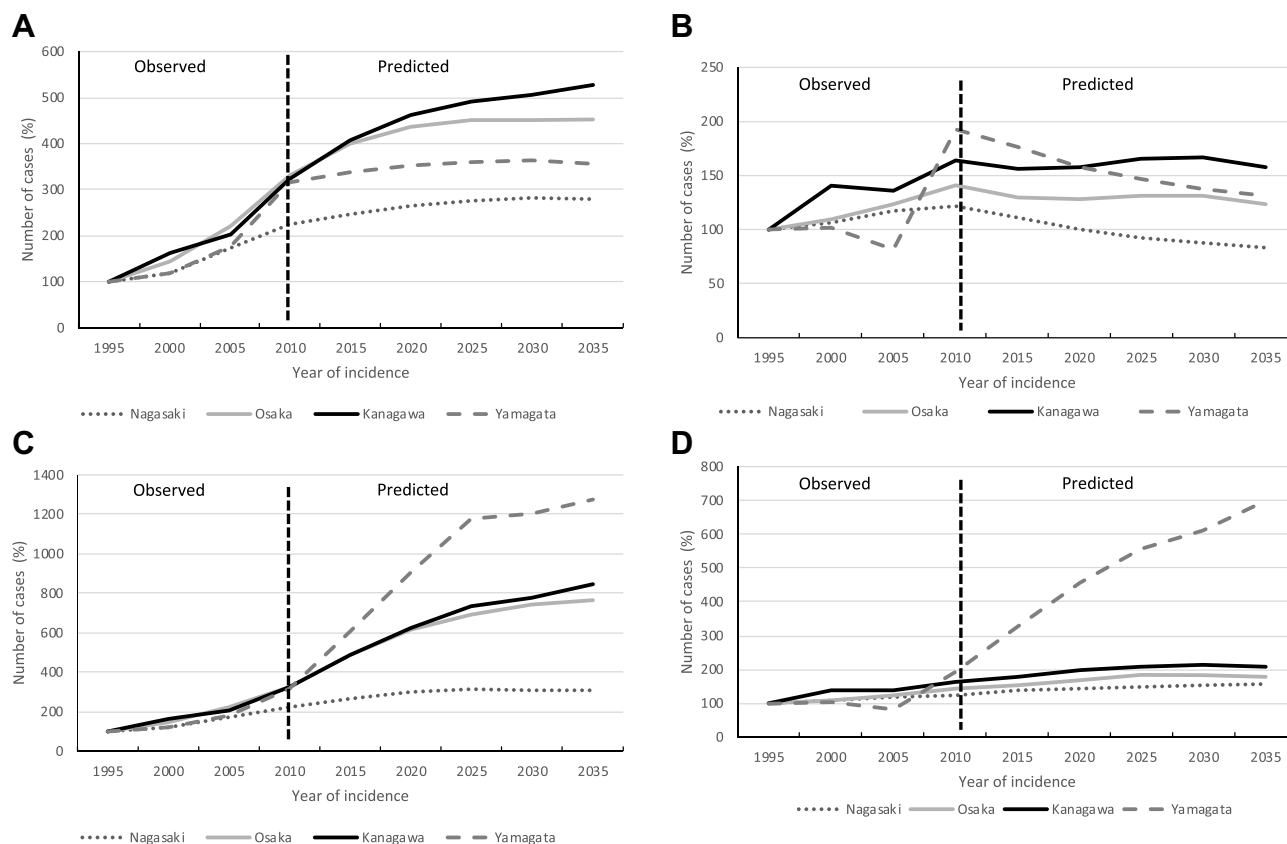
Figure 4 Predicted incidence of hematological malignancy in four prefectures in Japan. The observed (1995–2010) and predicted (2015–2035) total incidences of hematological malignancy are shown; (**A**) incidences using the simple 2010 model in people aged ≥65 years, (**B**) using the simple 2010 model in people aged <65 years, (**C**) using the Nordpred model in people aged ≥65 years, and (**D**) using the Nordpred model in people aged <65 years.

myeloablative transplantation, will decrease to 78% (177/ 227, simple 2010 model) (Table 1). Similarly, the number of candidates for autologous hematopoietic transplantation with malignant lymphoma and multiple myeloma will decrease. In contrast, the number of patients aged ≥65 years is expected to increase for all three diseases. In terms of therapeutic strategy for these patients, maintaining quality of life is often emphasized.[19] Therefore, in the near future, the role of intensive curative treatment will be lower and that of treatment focused on maintaining patients' quality of life will be higher. As the number of elderly patients with cancer continues to grow, clinicians are increasingly recognizing the necessity of performing clinical trials for this patient population. Clinical trials in geriatric hemato-oncology with endpoints for quality of life are needed.[20] Similarly, developing curative treatment with low intensity would be needed. Recent widespread hematopoietic stem cell transplantations, which usually use reduced intensity conditioning regimens, will be of significant importance in elderly care going forward.

The continuous future increase of patients aged ≥65 years is also predicted in the other prefectures with different population sizes and aging rates. Although data from the nationwide cancer database are not yet available for Japan, as it was founded only recently,[21] the same future trends were predicted in the groups with larger populations and lower aging rates, namely the Kanagawa and Osaka prefectures, as in the groups with smaller populations and higher aging rates, viz., the Yamagata and Nagasaki prefectures, indicating that this trend may be common to all of Japan's prefectures. Interestingly, the speed of increase differed, with a more rapid increase noted in metropolitan areas (namely the Kanagawa and Osaka prefectures) than in provincial areas, which is consistent with the findings of our previous study on breast cancer.[11] This indicates that a better supply of medical resources, especially those catering to elderly patients, will be needed in these metropolitan areas. It should be noted that sensitivity analysis using Nordpred demonstrated extreme future increase in patients aged ≥65 years, though this may be due to an

overestimation of the transient patient increase from 2005 to 2010 in Yamagata.

Although this study provided important information regarding future perspectives on hematological malignancies, one issue remains to be discussed. To estimate the future incidence according to each medical region, we multiplied the incidence rate for 2010 by the population. This estimation method, using the incidence data for a single year, can be applied to other municipalities, as our calculation did not consider the historical data of cancer incidence; however, unlike other methods, the impact of the cohort effect cannot be considered. As per the epidemiologic definition, a cohort effect occurs when different distributions of disease arise from a changing or new environmental cause that affects age groups in a different manner. Thus, a cohort effect is conceptualized as a period effect that is differentially experienced through age-specific exposure or susceptibility to said event or cause (eg, interaction or effect modification).[5,22] Only the effect of aging was considered in this study, yet this effect does not need to be considered in the prediction of hematological malignancies. Risk factors are unknown for most hematological diseases, as are effective prevention methods. Factors, except for age, may therefore be neglected or disregarded. To reduce the prospect of erroneous predictions as a result of inherently large random variation due to small numbers, models in Nordpred need at least 100 patients with cancer (all ages) per every 5-year period.[23] The numbers for leukemia, malignant lymphoma, and multiple myeloma in the Kanagawa Cancer Registry were not numerically strong. We therefore conducted the same evaluation and prediction using data from the other three prefectures to assess the results for the Kanagawa prefecture. In Japan, the nationwide cancer registry has recently been effected, and future estimations using large datasets from this resource are warranted.

Conclusion

In summary, the distribution of patients with hematological malignancies will change in the future: the number of elderly patients will increase, and the number of patients living in urban areas will increase. This prediction is likely to have a great impact on future healthcare plans.

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