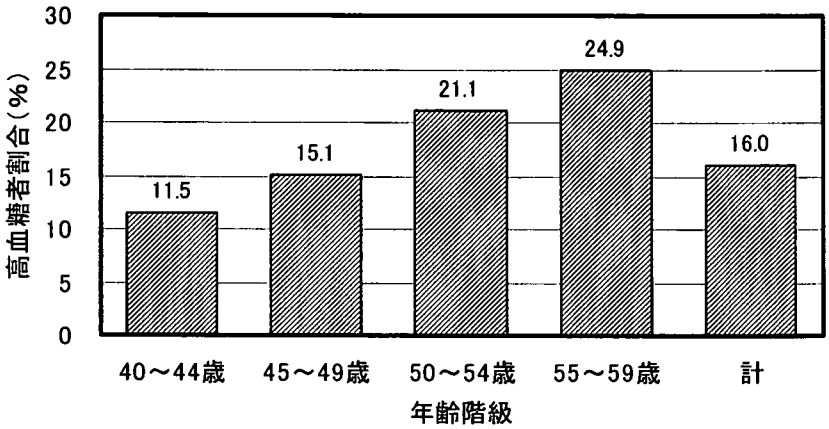

図5　年齢階級別の高血糖者割合

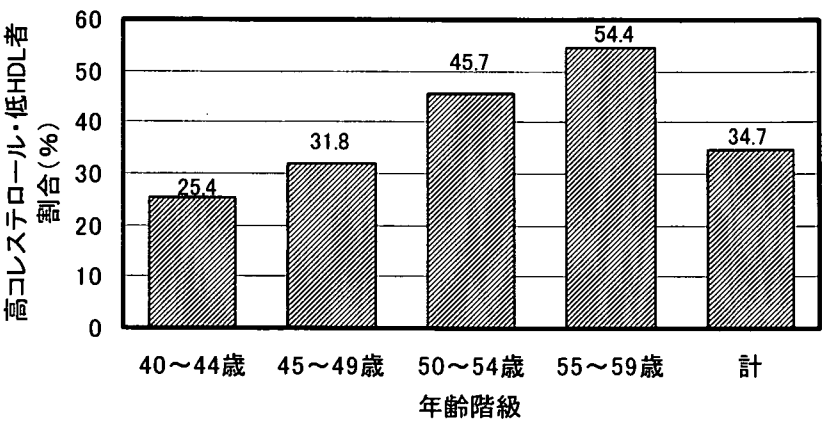

図6　年齢階級別の高コレステロール・低HDL者の割合

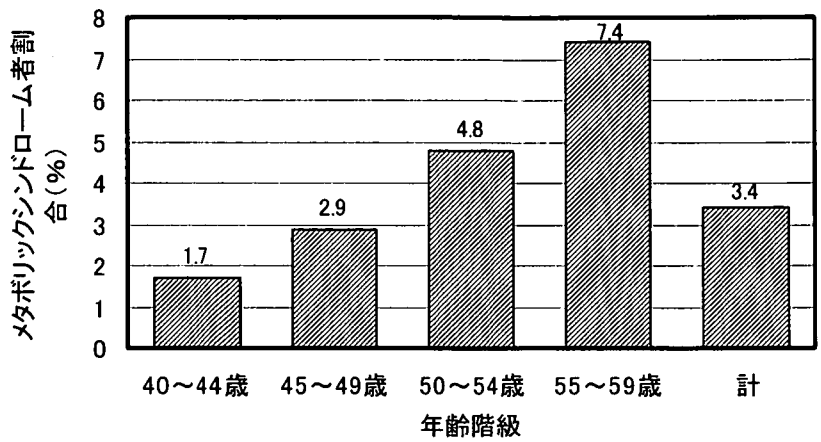

図7　年齢階級別のMet-s割合

表1　年齢階級別にみたMet-sの構成状況およびMet-s分布

	40～44歳（3499名）	45～49歳（3048名）	50～54歳（2252名）	55～59歳（848名）	計（9647名）
腹囲80cm以上者割合（%）	7.2	10.8	12.1	15.7	10.2
高血圧者割合（%）[1)]	12.3	61.8	34.2	43.0	22.6
高血糖者割合（%）[2)]	11.5	15.1	21.1	24.9	16.0
高コレステロール・低HDL者割合（%）[3)]	25.4	31.8	45.7	54.4	34.7
メタボリックシンドローム者割合（%）	1.7	2.9	4.8	7.4	3.4

1) 高血圧者：SBP≧130mmHg and/or DBP≧85mmHg
2) 高血糖者：空腹時血糖値≧100mg/dl
3)高コレステロール・低HDL者：血清総コレステロール値≧220mg/dl and/or HDLコレステロール値≦40mg/dl

F. 資料

学会発表　抄録

女性看護職の生活習慣の再現性に関する検討

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【目的】長期的にみた女性の生活習慣の安定性と変化の状況、および生活習慣の変化と妊娠、閉経といったリプロダクティブヘルスに関する経験との関連を明らかにする。

【対象】「群馬ナースヘルス研究（GNHS)」は、女性に特徴的な生活習慣・保健医療習慣およびその健康への影響について検討することを目的に、群馬県看護協会の協力をうけて、群馬県内の 20 歳以上の女性看護職を対象に 1999 年から開始された前向きコホート研究であり、2 年ごとの追跡調査を実施している。GNHS では 1748 人にベースライン調査を行い、そのうち 931 人に追跡調査の承諾が得られた。今回はコホートメンバーのうち、ベースライン(1999 年)、2 年目(2001 年)、4 年目(2003 年)調査のすべてに回答がある 450 人を分析対象とした。

【方法】喫煙習慣(現在喫煙の有無)、飲酒頻度(飲まない～毎日の 7 分類)、食品摂取頻度(摂らない～毎日の 5 分類)について、2 年ごとの調査における回答の一致性を検討する。また年齢、妊娠歴の有無、閉経状況による生活習慣の変化を検討する。

【結果】1.現在喫煙者率は 1999 年 15%、2001 年 13%、2003 年 11%であった。1999 年-2001 年の間の喫煙習慣の一致率は 95%、カッパ係数は 0.79 であった。喫煙習慣の変化では、やめた人が 3%、吸い始めた人が 2%であった。過去 2 年間に妊娠を経験した人では喫煙習慣の一致率(92%)、カッパ係数(0.57)ともやや低い傾向であった。2. 飲酒および食品摂取頻度について 2001 年-2003 年の回答の再現性をスピアマン相関係数により検討した結果、飲酒 0.82、牛乳・乳製品 0.55、豆腐 0.56、納豆 0.59、みそ汁 0.71、朝食 0.67 であった。過去 2 年間に妊娠を経験した人では飲酒 0.64、牛乳・乳製品 0.46、豆腐 0.54、納豆 0.35、みそ汁 0.63、朝食 0.47 であった。牛乳、豆腐、納豆は 2 年間で摂取頻度が有意に増加しており、年齢別には 30 歳代以上の人で有意な増加がみられた。3.閉経状況は生活習慣の変化と顕著な関連がみられなかった。

【考察】喫煙、飲酒は、比較的変化しにくい生活習慣であることが確認された。しかし妊娠を経験した人では一致率がやや低く、妊娠は喫煙・飲酒習慣の変化に影響する要因であることが明らかになった。みそ汁は他の食品に比べて変化しにくい項目であった。30 歳代

以上の女性では牛乳、豆腐、納豆の摂取頻度が有意に増加している傾向がみられ、今後の摂取傾向を健康への影響とあわせて観察していく必要がある。

Industrial Health 2007, 45, 679–686 **Original Article**

Design of the Japan Nurses' Health Study: A Prospective Occupational Cohort Study of Women's Health in Japan

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Abstract: The Japan Nurses' Health Study (JNHS) is a prospective occupational cohort study investigating the effects of lifestyle and healthcare practices on women's health. It was initiated in 2001, with a six-year entry period and a proposed ten-year follow-up. Participants comprise female registered nurses, licensed practical nurses, public health nurses, and midwives, aged 25 yr or over at the baseline survey. Participants were recruited in cooperation with the Japanese Nursing Association and the Japan Menopause Society. A self-administered baseline questionnaire was distributed, requesting demographic information, lifestyle factors, pharmaceutical drug use, physical condition, reproductive health, and disease history. A total of 49,914 women from all 47 prefectures in Japan responded to the baseline survey. Among them, approximately 18,000 agreed to be followed-up, and returned signed informed-consent sheets, together with their completed baseline questionnaires. Changes in lifestyle, healthcare, incidence of disease, and health outcomes over time will now be studied. The cohort receives annual JNHS newsletters and biennial follow-up questionnaires by mail.

Key words: Study design, Cohort study, Women's health, Questionnaire, Nurses, Smoking

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Introduction

Relatively few biomedical and epidemiological investigations have targeted women, although many gender-specific issues are associated with women's occupational health. Some large-scale prospective cohort studies focused on women's health between the 1970s and 1990s such as the Nurses' Health Study-I and -II[1, 2], the Women's Health Initiative Study[3], and the Million Women Study[4]. These investigations evaluated the effects of gender-specific and non-specific exposure issues such as exogenous hormones and cigarette smoke, respectively. Although these studies highlighted important women's health issues, many controversial issues remain, such as the use of hormone replacement therapy to prevent cardiovascular disease among postmenopausal women. Despite decades of evidence from observational epidemiological studies[5], clinical trials in the Women's Health Initiative Study generated adverse results[6]. Such diversity indicates that the effectiveness of various healthcares might differ among various populations.

Epidemiological studies that provide comparable evidence of women's health have not been implemented in Japan. An epidemiological study is needed for Japanese women who may have a different lifestyle, working environment, and healthcare practice from women in other countries. We designed a prospective occupational cohort study of Japanese women based on the design of the Nurses' Health Study (NHS) that has contributed the most to women's health worldwide. We confirmed the feasibility of the research strategy in the 1999 Gunma Pilot Study[7], and we initiated the Japan Nurses' Health Study (JNHS) in 2001. This paper describes the design of the JNHS and results obtained during the recruitment phase.

Subjects and Methods

Study design and purposes

The Japan Nurses' Health Study (JNHS), the Epidemiological Study of Lifestyle and Women's Health, is a prospective occupational cohort study that investigates the health of Japanese women. The study was initiated in 2001 and consists mainly of a cross-sectional baseline survey and longitudinal follow-up. The entry and follow-up periods are six and ten years, respectively. The primary purposes of the JNHS are to describe the status of lifestyle, healthcare practice, and physical status of Japanese women, to estimate the effects of those factors on their health, and to establish evidence regarding the risk-benefits of long-term administration of women-specific health management such as exogenous hormones use. The secondary purposes of the study are to investigate occupational health among Japanese nurses, and to evaluate the effects of shift work and work related stress on women's health.

Recruitment

In order to protect personal information of their members, the Japanese Nursing Association would not permit detailed sampling based on a register of nurses, as had been employed in the American NHS. Given these conditions, we announced recruitment to the study at conferences of the Japanese Nursing Association and the Japan Menopause Society, by advertisements in newsletters sent to members of the Japanese Nursing Association, by invitation letters to nurses in the health/medical institutes in cooperation with the prefectural Nursing Associations, and by invitation from the JNHS Recruitment Committee (see Appendix). Interested medical institutes or individual nurses requested baseline questionnaire sets from the JNHS coordination center by application postcard, facsimile, e-mail, or telephone. At some nurses' conferences and hospitals, we distributed the baseline questionnaire sets directly to individual nurses.

Inclusion criteria

The study population was designed for female registered nurses, licensed practical nurses, public health nurses, and/or midwives, who were at least 30 yr of age and resident in Japan at the baseline survey. The age limit was reduced to 25 yr in 2005. Although the participants were all licensed to practice nursing in Japan, they were not necessarily working full-time in this role.

Baseline survey

The baseline questionnaire was distributed with an invitation letter, photographs of female hormonal drugs, and a stamped self-addressed envelope. Respondents completed their questionnaires, sealed the envelope, and mailed them back to the JNHS coordination center. Respondents who agreed to be followed-up for ten years provided their name and address, signed the informed consent sheet, and returned the information with their completed baseline questionnaire.

The questionnaire addressed personal information and occupation (birth date, birth place, marital status, education, nursing qualification, employment position, place of employment, history of shift work), physical indicators (current weight, weight at birth, weight at age 18, height, blood pressure, total serum cholesterol, HDL-cholesterol, FBS, HbA1c), periodical medical examination (breast cancer

mammography and self-examination, stomach cancer, uterine cervical cancer, endometrial cancer), habit and lifestyle (smoking, alcohol consumption, physical exercise, food), history of reproductive health (menarche, sterility, pregnancy, pregnancy-induced toxemia, childbirth, menstrual cycle, menopause), use of female hormone agents (oral contraceptives, hormone replacement therapy, with drug identification from photographs), other drugs and supplements, medical history and family history of diseases (hypertension, diabetes, hypercholesterolemia, myocardial infarction, angina pectoris, stroke, transient cerebral ischemia, endometriosis, uterine myoma, cervical carcinoma, uterine cervical cancer, endometrial cancer, ovarian cancer, breast cancer, gastric cancer, colon-rectal cancer, osteoporosis), and so on.

Follow-up study

Participants to be followed-up for ten years comprised those who provided written informed consent and who legibly registered their name and personal correspondence address. They were then mailed the annual JNHS newsletter and biennial follow-up questionnaires. This newsletter updates participants on the progress of the study and includes new information about women's health. Each follow-up questionnaire inquired about changes in lifestyle, healthcare practice, incidence of disease, and health over the past two years. Participants who had changed their name or address during the follow-up notified the JNHS coordination center of such using a sealed, stamped, self-addressed postcard. Maintaining a response rate in each follow-up survey is important. Individuals who did not respond to the first mailed questionnaire received a second mailing within 6 months. Subsequently, we mailed a third and fourth questionnaire to those who still did not respond. If the JNHS coordination center could not contact the participants by mail, the JNHS Follow-up Committee confirmed the migration and a new address with the resident registry of the corresponding local district and sent a questionnaire to the new address. The JNHS Follow-up Committee confirms any deaths through death certificates retrieved from the National Vital Statistics.

Endpoints of the follow-up study

Primary endpoints of the follow-up study are the incidence of breast cancer, endometrial cancer, ovarian cancer, colon-rectal cancer, myocardial infarction, angina pectoris, stroke, gallstone disease, and lung embolism according to participant self-reports. All-cause death, death from cancers (breast, uterine cervical, endometrial, colon-rectal, stomach, gallbladder, and lung), and death from cardiovascular diseases (myocardial infarction, coronary heart disease, subarachnoid hemorrhage, cerebral infarction, cerebral hemorrhage) identified by the death certificates from the National Vital Statistics are also primary endpoints. Secondary endpoints are self-reported diabetes, bone fracture, other cancers, endometriosis, uterine myoma, benign breast tumor, venous thrombosis, arterial thrombosis of the lower limbs, hypertension, and hypercholesterolemia. We also investigated the incidence of diseases such as osteoporosis, intestinal polyp, cataract, rheumatoid arthritis, connective tissue disease, hepatitis, thyroid disease, and systemic lupus erythematosus.

Sample size and statistical power

The sample size of the baseline survey was established at 50,000 women as described below. The statistical power was updated using the interim results of the cumulative incidence of target diseases in the baseline survey and has been presented elsewhere[8]. Assuming 0.0015/person-years as the incidence of target health events (breast cancer or endometrial cancer), ten years as average follow-up duration, 20% as the exposure proportion of study population, 1.3 as the relative risk, two-tailed alpha=0.05, and beta=0.20, then the follow-up study population should comprise 39,750 women. We estimated the proportion of followed-up women as 80% of the baseline survey participants. Consequently, the sample size was set at 50,000 for the baseline survey.

Ethics, confidentiality and data management

This project proceeded in accordance with international guidelines of Good Epidemiology Practice[9] and Japanese Ethical Guidelines for Epidemiological Research[10]. Institutional review boards of the Gunma University and the National Institute of Public Health reviewed and approved the study protocol. The JNHS Study Monitoring Committee that is independent of the JNHS research group also reviewed the research strategy and periodically monitors the study procedure (see Appendix). Participants were informed of the purposes and procedures of the study in the invitation letter at the time of the baseline survey. All the signed consent sheets sent to the JNHS coordination center were filed. Any participant can withdraw from the study at any time during the follow-up period by sending written notice to the coordination center. Completed questionnaires and personal information such as name and address are securely stored at the JNHS Coordination and Data Center and confidentially handled only by the JNHS personnel designated by the principal investigator. The

data for statistical analysis are stored by trained staff in electronic files using a double-entry system, and are separate from the personal information files. Only a number identifies the participants in the data files used for statistical analysis. Range, logical, and missing checks are performed using the software SAS, according to the data management manuals prepared by the JNHS Data Management and Analysis Committee. If the automated check flags inconsistent information, the data are manually verified by trained data entry staff at the JNHS Data Center.

Validation of self-reported illnesses

The endpoints of the follow-up study are primarily self-reported illness and health events. We send confirmation questionnaires for selected diseases to women who report such in the follow-up questionnaires to determine details of diagnosis and treatment. The JNHS Validation Study Committee then seeks written permission from the participants to review medical records for specific diseases or to ask their attending physician about the diagnosis and administered treatment. The JNHS Validation Study Committee provides sub-study protocols and confirmation questionnaires for selected diseases.

Study organization

The JNHS was initiated in collaboration with the Japan Menopause Society, and a principal investigator with a Steering Committee administers the study (See Fig. 1). The organization presently (2007) comprises one center and six committees. An ad hoc Protocol Review Committee was struck during the protocol development phase. The Coordination and Data Center is located at the Epidemiological Research Office, School of Health Sciences, Gunma University. The Data Management and Analysis Committee control the data management procedure with study coordinators, data entry staff, and data analysts to ensure the data quality. The Follow-up Committee searches for missing women during the follow-up period by confirming the resident registry of the corresponding local district and mortality in the National Vital Statistics. The Validation Study Committee validates self-reported illness and exposure, and finalizes the incidence of diseases as endpoints of the follow-up study. The Nurses Committee supervises the recruitment and counsels about the development of questionnaires, especially from the viewpoint of the occupational health of nurses. Our recruitment committee cooperated with the 47 prefectural Nursing Associations and with recruitment advisers from the Japan Menopause Society for eight

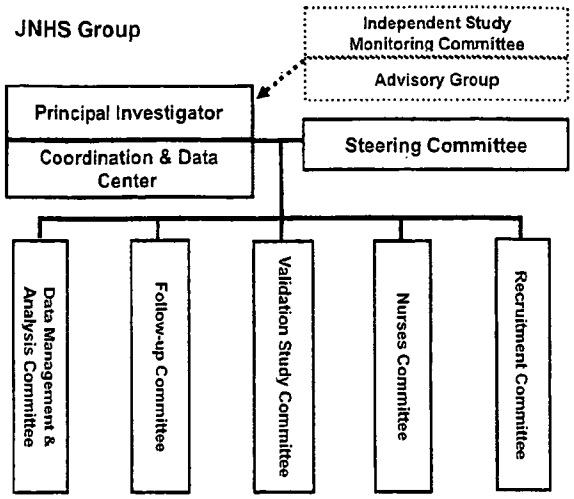

Fig. 1. Organization of the JNHS Group.

geographic regions to invite nurses to participate in the study. Independently of the study organization, the Study Monitoring Committee periodically monitors the study process, having a similar task force to the Data and Safety Monitoring Committee in mega clinical trials. We also have advisory group of researchers at the Harvard School of Public Health that has run a Nurses' Health Study[1, 2] for 30 yr.

Results

Recruitment of nurses

Subject recruitment including the collection of baseline questionnaires began in November 2001 and was completed in March 2007. A total of 49,914 women had responded to the baseline survey from all 47 prefectures in Japan by March 2007. We cannot characterize the response rate in a general sense, because the precise source population of the study is indefinable. Nevertheless, these 49,914 responses represent 45.4% of 110,000 copies of the baseline questionnaire that were actually printed and mailed from the JNHS Study coordination center, that is, 8.6% of 579,665 members of the Japan Nursing Association (Year 2005), or 0.104% of all 47.8 million Japanese females in the general population aged over 25 yr. Data entry of the baseline questionnaire, confirmation of signed acceptance of follow-up study, and mailing JNHS newsletter and follow-up questionnaires are currently in progress. Approximately 18,000 women provided written informed consent. Figure 2 shows the proportion of women registered by August 2006 compared with the female population aged

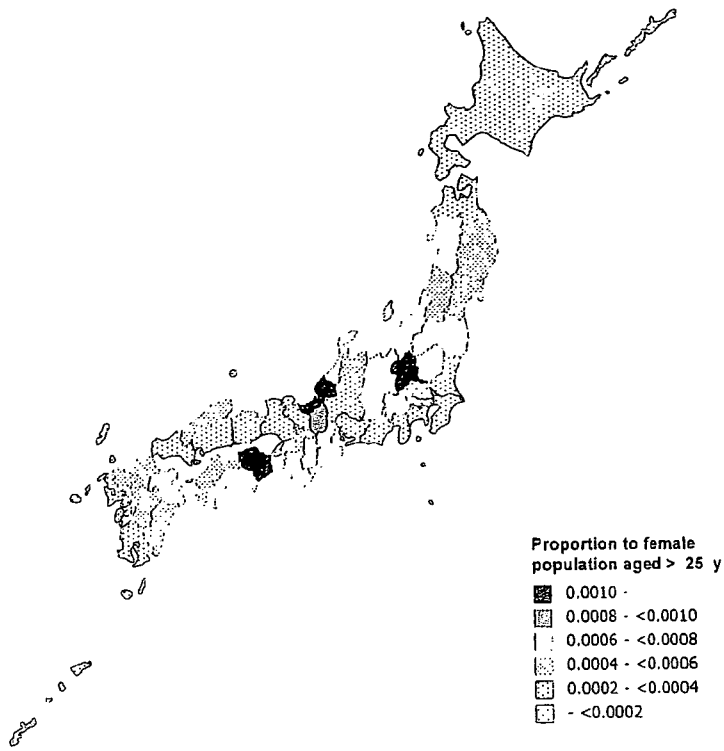

Fig. 2. Proportion of participants registered for the Follow-up Study before August 2006 compared to the female population aged >25 yr (including Gunma Pilot Study participants in Gunma Prefecture).

over 25 in each prefecture.

Interim analysis of participant characteristics

Table 1 briefly summaries the characteristics of the respondents sent the baseline questionnaire by March 2006 including age at the baseline survey, nursing certification, history of shift work, and of smoking. The proportions of age groups of the women were 30's, 42.9%; 40's, 40.0%, and 50's, 16.4%. Only a few women were aged <30 or 60+ yr. Most women (80%) functioned as registered nurses and had worked rotating night shift work, and 16.9% women were current smokers.

Discussion

The JNHS is the first nationwide prospective cohort study to focus on the health of Japanese women. Since healthcare, such as the administration of female hormone agents at each stage of life and reproductive health problems are gender-specific, the JNHS will provide valuable epidemiological evidence of the risk-benefits of lifestyle and healthcare among Japanese women. The Gunma Pilot Study has already examined the feasibility of a prospective study of Japanese nurses using a self-administered questionnaire[6]. The nature of the study design has the following potential limitations. For example, nurses represent a unique occupational population that might be relatively healthier, physically more active at work, and have more understanding about health than the general female population. Nurses who voluntarily agree to long-term participation might be healthier than those who do not. Consequently, the prevalence of lifestyle exposure, healthcare practice, or disease among the JNHS population may not necessarily be generalized to other populations. However, the association between lifestyle/healthcare factors and health outcome obtained by comparing women who have been exposed or not to such factors in JNHS population would be applicable to the general female population of Japan, because the observed association does not depend on the prevalence of exposure.

Most primary endpoints of the study rely profoundly on self-reporting of the participants, which is another limitation. Nurses were preferred as the study population because they report medical information more accurately than broader

Table 1. Characteristics of 48,158 respondents to the baseline survey before March 2006

Characteristics	Number of women	Percentage
Age at the baseline survey (yr)		
–29	562	1.2
30–34	10,813	22.5
35–39	9,855	20.5
40–44	9,406	19.5
45–49	7,916	16.4
50–54	5,756	12.0
55–59	2,129	4.4
60+	386	0.8
Missing	1,335	2.8
Nursing qualification		
Registered nurse	39,132	81.3
Licensed practical nurse	5,006	10.4
Public health nurse	900	1.9
Midwife	2,736	5.7
Unknown	384	0.8
Shift work history (yr)		
Never	8,602	17.9
1–2	1,341	2.8
3–5	2,657	5.5
6–9	6,092	12.7
10–14	10,353	21.5
15–19	7,958	16.5
20+	9,933	20.6
Unknown	1,222	2.5
Smoking history		
Never	33,656	69.9
Current smoker	8,136	16.9
Ex-smoker	5,427	11.3
Unknown	939	1.9

samples of women[1]. They are more familiar with medical terms and more easily understand questions about diseases in the JNHS questionnaires. Moreover, for most diseases, self-reported information will be confirmed with additional questionnaires and medical records by the sub-studies implemented by the JNHS Validation Study Committee. The JNHS Follow-up Committee will confirm deaths using data from the National Vital Statistics. Such activities of the JNHS group will preserve the accuracy of the self-reported illness in the study.

Nurses should also report accurate exposure information of lifestyle and healthcare. For example, the general female population may not easily identify their administered pharmaceutical drugs in a community-based survey. However, nurses can readily identify drugs used for oral contraceptives or hormone replacement therapy, and the list of female hormonal agents with photographs should support the accuracy of the answers in the JNHS baseline survey. The study design of prospective observation should help to avoid recall bias and misclassification of exposure to various factors. The frequent observation of exposure by biennial questionnaires in the follow-up study and the inconsistency examination will reduce the misclassification of exposure to elements that could affect health. Compared with traditional community-based cohort studies in Japan, the JNHS is characterized by comprising only women aged from 25 to > 60 yr from a geographic area that encompasses all 47 prefectures of Japan. The JNHS should generate comprehensive current and useful information about the status of women's health in Japan.

Acknowledgements

We appreciate the support and cooperation of all Japanese nurses who are currently participating in our study, the Japanese Nursing Association, and the Japan Menopause Society for their cooperation with the study. We also thank Drs. Shuku Fujimaki, Takami Maeno, Yasuki Kobayashi, Seiichiro Yamamoto, Satoshi Nakai, Ami Yamada, Yoshikazu Kitahara, Bunpei Ishizuka, and Hiroaki Ohta for help during development of the study protocol. The baseline survey was supported in part by a Grant-in-Aid for Scientific Research (B: 14370133, 18390195) from the Japan Society for the Promotion of Science, and by the grants from the Japan Menopause Society.

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APPENDIX: The JNHS Investigators (2007)

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Original Article

Prevalence of Diseases and Statistical Power of the Japan Nurses' Health Study

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Abstract: **The Japan Nurses' Health Study (JNHS) is a long-term, large-scale cohort study investigating the effects of various lifestyle factors and healthcare habits on the health of Japanese women. Based on currently limited statistical data regarding the incidence of disease among Japanese women, our initial sample size was tentatively set at 50,000 during the design phase. The actual number of women who agreed to participate in follow-up surveys was approximately 18,000. Taking into account the actual sample size and new information on disease frequency obtained during the baseline component, we established the prevalence of past diagnoses of target diseases, predicted their incidence, and calculated the statistical power for JNHS follow-up surveys. For all diseases except ovarian cancer, the prevalence of a past diagnosis increased markedly with age, and incidence rates could be predicted based on the degree of increase in prevalence between two adjacent 5-yr age groups. The predicted incidence rate for uterine myoma, hypercholesterolemia, and hypertension was ≥3.0 (per 1,000 women, per year), while the rate of thyroid disease, hepatitis, gallstone disease, and benign breast tumor was predicted to be ≥1.0. For these diseases, the statistical power to detect risk factors with a relative risk of 1.5 or more within ten years, was 70% or higher.**

Key words: Cohort Study, Women's Health, Nurses, Incidence rate, Statistical power

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Introduction

Many large-scale epidemiological studies of women's health have been conducted in various parts of the world, such as the Nurses' Health Study (NHS)[1, 2], the Iowa Women's Health Study[3], the Women's Health Initiative Study(WHI)[4], the Women's Health Study[5], the Million Women Study(MWS)[6], the Australian Longitudinal Study on Women's Health[7], and the Shanghai Women's Health Study[8]. Nevertheless, large-scale research of this nature has been comparatively rare in Japan. Among those investigations previously conducted, the NHS incorporates a unique occupational cohort and observes lifestyle and health events by biennial questionnaires. Although the NHS has greatly contributed to women's health worldwide by reporting the findings on oral contraceptives, postmenopausal use of hormones, smoking, food and shift work[1], the findings cannot necessarily be generalized for Japanese women. Japanese women may have a different lifestyle, working environment, and healthcare practice from women in western countries, and as such, it is important to consider cultural and biological interactions during women's health studies[9].

The Japan Nurses' Health Study (JNHS), was designed to be comparable with the NHS, and is a large-scale epidemiological cohort study investigating women's lifestyle habits and health, that is planned to follow female nurses aged 25 yr and over for at least ten years[10]. The objectives of the JNHS are to monitor the occurrence of various diseases prospectively, including female-specific diseases, and to assess the effects of various lifestyle factors and healthcare habits on the health of Japanese women. The JNHS consists mainly of a cross-sectional baseline survey and longitudinal follow-up surveys. The baseline survey was completed in 2007, during which responses were received from 49,914 women from 47 prefectures all over Japan. Among the respondents, approximately 18,000 women agreed to participate in the follow-up surveys.

Calculating the sample size of a study population is indispensable for clinical trials. Even in an observational epidemiological study, it is essential that the study protocol describes sample size and adequate statistical power. For example, the Women's Health Initiative (WHI) study described its statistical power calculations for an observational study as well as for clinical trials conducted by the WHI[4]. If an association between a lifestyle factor and a disease truly exists, the possibility to detect statistical significance of the association greatly depends on the strength of the association and incidence rates of this disease in the population. Nevertheless, we were unable to find any reliable statistical data on the incidence rate of diseases among Japanese women, except for population-based cancer registries[12]. The initial sample size of the JNHS baseline survey was tentatively set at 50,000 based on the population-based cancer registries, i.e. the incidence rates of breast cancer and endometrial cancer in the Japanese general female population at the study design phase. Therefore, it is important to examine the statistical power for long-term studies, based on more reliable information of the JNHS population which may be obtained after initiation of the study. For example, in a paper describing the design of the Million Women's Study[6], it was reported that the statistical power was updated during the study entry period. These revisions were based on information obtained from new studies indicating that mortality in women taking hormonal agents is likely to be 20% lower than that of the general female population.

In the JNHS, it was considered essential to examine the statistical power of follow-up surveys, as the actual sample size of participants, who consented to the follow-up, was approximately 18,000. The present study investigated the prevalence of a past diagnosis of various diseases among 5-yr age groups based on the JNHS cross-sectional baseline survey. We also predicted the incidence rates of these diseases, and examined the statistical power to detect risk factors for diseases in the JNHS.

Materials and Methods

The present study analyzed data obtained from a total of 44,139 women who participated in the JNHS cross-sectional baseline survey in 2001–2004. These women were divided into 5-yr age groups as follows: 30–34 yr (n=10,471); 35–39 yr (n=9,466); 40–44 yr (n=9,060); 45–49 yr (n=7,572); 50–54 yr (n=5,542); and 55–59 yr (n=2,018). The study design of the JNHS and characteristics of the respondents at the baseline survey have been described in detail elsewhere[10]. The following diseases were studied: hypertension, myocardial infarction, angina pectoris, subarachnoid hemorrhage, cerebral hemorrhage, cerebral infarction, transient ischemic attack, vein thrombosis/pulmonary embolism, artery thrombosis of lower limbs, diabetes mellitus, thyroid disease, hypercholesterolemia, gallstone disease, hepatitis, endometriosis, uterine myoma, uterine cervical cancer, endometrial cancer, ovarian cancer, benign breast tumor, breast cancer, stomach cancer, colorectal cancer, and osteoporosis.

The prevalence of a past diagnosis, which refers to the

proportion of women who had been diagnosed at the time of the baseline survey, was calculated for each of these diseases. The Cochran-Armitage test for trend was used to examine whether the prevalence of past diagnosis increased monotonously with age among the six 5-yr age groups. Analyses were performed on Statistical Analysis System Software (Ver 8, SAS Institute, Cary, NC), and the level of significance was set at a two-sided 5%. When the prevalence of past diagnosis of a disease increased monotonously with age, it was assumed that women developed the disease between adjacent age groups, and the incidence rate of the disease was predicted based on the degree of increase between the two adjacent age groups. For example, for one 5-yr age group (i) and the next 5-yr age group (i+1), the incidence rate of a rare disease between the two groups was calculated using the following formula:

$$I_{i\to i+1} = \frac{(P_{i+1} - P_i)}{(AGE_{i+1} - AGE_i)}$$

where, N_i and N_{i+1} represent the numbers of subjects, D_i and D_{i+1} are the numbers of individuals diagnosed with the disease, P_i and P_{i+1} are the prevalence of past diagnosis ($P_i=D_i/N_i$), and AGE_i and AGE_{i+1} are the average ages.

i = 1: 30–34 yr
2: 35–39 yr
3: 40–44 yr
4: 45–49 yr
5: 50–54 yr
6: 55–59 yr

As shown by the following formula, the inverse of the variance in each incidence rate between two adjacent age groups (e.g., between 30–34-yr-olds and 35–39-yr-olds) was weighed in order to calculate the overall incidence rate from 30–59 yr of age, I, for each disease.

$$I = \frac{\sum_{i=1}^{3} I_{i\to i+1} \times w_i}{\sum_{i=1}^{3} w_i}, \qquad w_i = \frac{(AGE_{i+1} - AGE_i)^2}{\{\frac{P_i(1-P_i)}{n_i} + \frac{P_{i+1}(1-P_{i+1})}{n_{i+1}}\}}$$

We also examined how many years of follow-up would be needed in the JNHS in order to detect the statistical significance of an association. When observing the occurrence of a disease by following 18,000 participants while setting the level of significance (two-sided α) at 5% and the proportion of exposure to a specific factor among the survey participants (exposed group) at 20%, statistical power ($1-\beta$) was calculated with the minimum relative risks of 1.5 and 2.5 to be detected at 2, 4, 6 and 10 yr after the baseline survey, according to the following formula[11]:

$$z_{1-\beta} = \frac{\sqrt{n/(1+K)} \times |p_0(1-R)| - z_{1-\alpha/2} \times \sqrt{(1+1/K)U(1-U)}}{\sqrt{p_0R(1-Rp_0) + p_0(1-p_0)/K}}$$

where, $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ refer to the unit normal deviates corresponding to level of significance (α), and statistical power ($1-\beta$); n is the sample size (18,000); R is the minimum relative risk to be detected; K is the ratio of the sample size of the unexposed to that of exposed groups (4, because the proportion of participants who had ever used female hormone agents (oral contraceptives and/or postmenopausal use of hormones) was about 20% at the baseline survey); I is the predicted overall incidence rate of each disease among the surveyed population; and p_0 is the cumulative incidence rate of each disease up to "y" years among the unexposed group.

$$p_0 = 1 - \exp\left\{-I \times \frac{(K+1)}{(K+R)} \times y\right\}$$

$$U = \frac{Kp_0 + p_0R}{K+1}$$

Results

Prevalence of a past diagnosis and the predicted incidence rate of each disease

The prevalence of a past diagnosis of uterine myoma, hypercholesterolemia, endometriosis and hypertension exceeded 5% (Table 1). Because the weight of young participants was relatively high in the baseline survey, the prevalence of past diagnosis of gynecological diseases that are often seen in women aged 30–34 yr was high. As the results of the Cochran-Armitage test for trend, the prevalence of past diagnosis of all diseases increased monotonously according to age, excluding ovarian cancer. This tendency was particularly marked for hypercholesterolemia, uterine myoma, diabetes, gallstone disease, hepatitis, osteoporosis, angina pectoris, and hypertension. Figure 1 shows the prevalence of past diagnosis for the three most frequent diseases among 55–59-yr-old women (i.e., hypercholesterolemia, hypertension, and uterine myoma) for each 5-yr age group. The prevalence of past diagnosis increased markedly with age, thus suggesting disease occurrence. Based on the degree of increase in the prevalence of past diagnosis between two adjacent 5-yr age groups, overall incidence rates were predicted from 30 to 59 yr of age. The predicted overall incidence rate was ≥3.0 (per 1,000 women per year) for uterine myoma, hypercholesterolemia, and hypertension, and ≥1.0 for thyroid disease, hepatitis, gallstone disease, and benign breast tumor (Table 2). Among all age groups, the

Table 1. Prevalence of a past diagnosis of each disease by age group during the baseline survey

		Prevalence of past diagnosis						Cochran-Armitage test	
	Total n=44,129	30–34 yr n=10,471	35–39 yr n=9,466	40–44 yr n=9,060	45–49 yr n=7,572	50–54 yr n=5,542	55–59 yr n=2,018	χ^2 value	*p* value
Hypertension	5.06%	0.48%	1.50%	3.26%	7.45%	13.86%	20.47%	222.27	<0.001
Myocardial infarction	0.06%	0.00%	0.02%	0.03%	0.09%	0.20%	0.25%	33.31	<0.001
Angina pectoris	0.52%	0.07%	0.18%	0.26%	0.66%	1.44%	2.58%	260.38	<0.001
Subarachnoid hemorrhage	0.10%	0.03%	0.05%	0.09%	0.11%	0.20%	0.50%	29.93	<0.001
Cerebral hemorrhage	0.06%	0.03%	0.03%	0.07%	0.08%	0.13%	0.10%	6.97	0.008
Cerebral infarction	0.20%	0.07%	0.03%	0.14%	0.22%	0.54%	0.84%	77.08	<0.001
Transient ischemic attack	0.45%	0.18%	0.24%	0.39%	0.58%	0.70%	1.88%	91.41	<0.001
Vein thrombosis/pulmonary embolism	0.28%	0.13%	0.20%	0.36%	0.37%	0.40%	0.40%	15.31	<0.001
Artery thrombosis of lower limbs	0.17%	0.10%	0.10%	0.13%	0.28%	0.29%	0.30%	16.12	<0.001
Diabetes mellitus	1.17%	0.17%	0.38%	0.86%	1.68%	2.87%	4.91%	475.86	<0.001
Thyroid disease	4.22%	2.32%	3.32%	4.69%	5.53%	5.94%	6.54%	209.55	<0.001
Hypercholesterolemia	8.23%	2.66%	4.05%	6.36%	9.60%	19.29%	29.68%	2358.86	<0.001
Gallstone disease	2.08%	0.46%	1.24%	2.25%	3.08%	3.88%	5.00%	378.50	<0.001
Hepatitis	3.40%	1.62%	2.22%	3.29%	4.38%	6.17%	7.28%	374.66	<0.001
Endometriosis	5.29%	4.18%	4.85%	5.70%	6.50%	5.65%	5.70%	37.35	<0.001
Uterine myoma	10.08%	2.67%	6.24%	10.58%	15.65%	18.82%	19.33%	1672.37	<0.001
Uterine cervical cancer	0.91%	0.59%	0.92%	1.05%	1.11%	0.96%	0.94%	8.68	0.003
Endometrial cancer	0.16%	0.03%	0.12%	0.11%	0.25%	0.16%	0.84%	41.52	<0.001
Ovarian cancer	0.20%	0.11%	0.22%	0.20%	0.34%	0.16%	0.20%	3.03	0.082
Benign breast tumor	3.48%	2.23%	3.12%	3.63%	4.70%	4.19%	4.36%	81.51	<0.001
Breast cancer	0.77%	0.16%	0.32%	0.68%	1.23%	1.68%	2.23%	206.00	<0.001
Stomach cancer	0.39%	0.06%	0.17%	0.43%	0.54%	0.96%	0.89%	99.18	<0.001
Colorectal cancer	0.22%	0.00%	0.05%	0.12%	0.36%	0.69%	0.79%	116.30	<0.001
Osteoporosis	0.93%	0.32%	0.36%	0.65%	0.82%	2.24%	4.81%	335.94	<0.001

predicted incidence rate of gynecological diseases such as uterine myoma, endometriosis, uterine cervical cancer, and benign breast tumor increased from the 30's to the early 40's, while the incidence of so-called 'lifestyle-related' diseases such as hypertension, angina pectoris, cerebral infarction, diabetes, hypercholesterolemia, and osteoporosis increased from the late 40's to the 50's.

Calculation of the statistical power to detect a risk factor for a particular disease

Table 3 shows the statistical power for diseases listed in decreasing order of the predicted incidence rate in relation to the follow-up period. When following 18,000 women aged 30–59 yr, the statistical power for uterine myoma (7.72/1,000 women per year) after 2 yr of follow-up was 81% with a relative risk of 1.5 or more. With regard to other diseases, the statistical power exceeded 70% after 4 yr for hypercholesterolemia and hypertension, after 6 yr for thyroid disease, after 8 yr for hepatitis and gallstone disease, and after 10 yr for benign breast tumor. For diseases where the statistical power did not reach 70% after 10 yr of follow-up

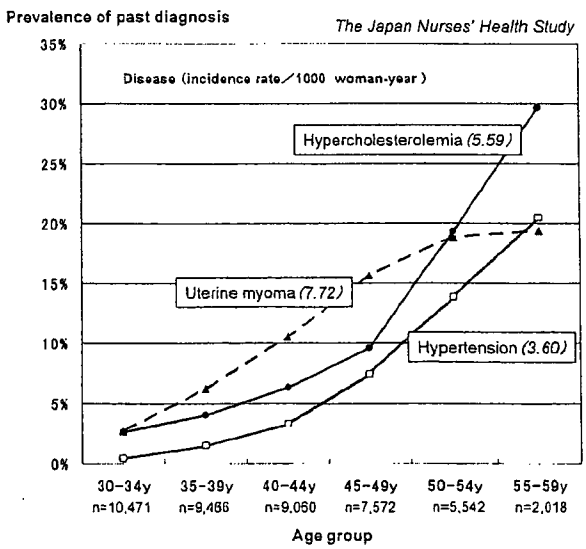

Fig. 1. Prevalence of a past-diagnosis in the female nurse population.

Table 2. Predicted incidence rate of each disease by age group

	Overall incidence rate (95% confidence interval)	Predicted incidence rate* 30–34 yr ~ 35–39 yr	35–39 yr ~ 40–44 yr	40–44 yr ~ 45–49 yr	45–49 yr ~ 50–54 yr	50–54 yr ~ 55–59 yr
Hypertension	3.60 (3.17, 4.04)	2.06	3.54	8.39	13.31	13.33
Myocardial infarction	0.05 (0.00, 0.10)	0.04	0.02	0.12	0.22	0.10
Angina pectoris	0.35 (0.20, 0.50)	0.23	0.17	0.79	1.63	2.29
Subarachnoid hemorrhage	0.07 (0.00, 0.15)	0.05	0.07	0.03	0.19	0.60
Cerebral hemorrhage	0.03 (0.00, 0.10)	0.01	0.07	0.03	0.10	−0.05
Cerebral infarction	0.08 (0.00, 0.17)	−0.07	0.23	0.16	0.66	0.61
Transient ischemic attack	0.27 (0.09, 0.44)	0.12	0.29	0.39	0.25	2.38
Vein thrombosis/pulmonary embolism	0.14 (0.00, 0.29)	0.14	0.33	0.01	0.06	0.00
Artery thrombosis of lower limbs	0.07 (0.00, 0.18)	0.00	0.08	0.29	0.02	0.02
Diabetes mellitus	0.82 (0.59, 1.05)	0.42	0.97	1.63	2.48	4.11
Thyroid disease	1.96 (1.38, 2.54)	2.01	2.77	1.69	0.84	1.22
Hypercholesterolemia	5.59 (4.90, 6.27)	2.78	4.65	6.49	20.12	20.97
Gallstone disease	1.72 (1.35, 2.09)	1.57	2.05	1.65	1.67	2.27
Hepatitis	1.91 (1.41, 2.41)	1.20	2.16	2.19	3.71	2.25
Endometriosis	0.93 (0.28, 1.59)	1.34	1.70	1.60	−1.77	0.10
Uterine myoma	7.72 (6.92, 8.53)	7.19	8.74	10.13	6.58	1.02
Uterine cervical cancer	0.25 (0.00, 0.54)	0.66	0.26	0.12	−0.32	−0.03
Endometrial cancer	0.12 (0.02, 0.22)	0.18	−0.01	0.28	−0.18	1.37
Ovarian cancer	0.07 (0.00, 0.20)	0.24	−0.05	0.29	−0.38	0.07
Benign breast tumor	1.18 (0.65, 1.72)	1.78	1.04	2.14	−1.07	0.35
Breast cancer	0.56 (0.35, 0.77)	0.31	0.74	1.09	0.93	1.11
Stomach cancer	0.31 (0.17, 0.46)	0.23	0.53	0.22	0.86	−0.13
Colorectal cancer	0.15 (0.07, 0.23)	0.11	0.14	0.47	0.68	0.22
Osteoporosis	0.50 (0.28, 0.72)	0.07	0.59	0.34	2.95	5.18

*: per 1,000 women per year.

A negative value for the incidence rate means that the prevalence of a past diagnosis of one 5-yr age group was higher than that of the next 5-yr age group.

with a relative risk of 1.5 or more, the statistical power was recalculated with a relative risk of 2.5 or more. The statistical power exceeded 70% after 4 yr for endometriosis, diabetes, and breast cancer, after 6 yr for osteoporosis; after 8 yr for angina pectoris and stomach cancer, and after 10 yr for transient ischemic attack and uterine cervical cancer.

Discussion

The present study identified marked increases with age in the prevalence of past diagnosis for all diseases, excluding ovarian cancer. We proposed a simple method for predicting an incidence rate based on the degree of age-related increase in the prevalence of past diagnosis. The incidence rate of each disease was also predicted. Nevertheless, there are several assumptions and limitations associated with the prediction of incidence rates. Firstly, we assumed the lack of a cohort effect on disease occurrence. In other words, we assumed that the disease incidence rate among 5-yr age groups was the same for all cohorts. While it is possible that changes in lifestyle habits bring about systemic changes in disease occurrence among cohorts, this point was not taken into account. For example, it is uncertain whether an observed increase in the prevalence of hepatitis is affected by aging, such as the duration of occupational hazard exposure, or by a cohort effect. The incidence rates of gynecological diseases such as endometriosis, benign breast tumor, ovarian cancer and endometrial cancer between 45–49-yr-old and 50–54 yr-old were negative in value (Table 2). This might be influenced by a cohort effect related to reproductive health.

Secondly, data from women who died due to diseases were not included in the JNHS. The prevalence of past diagnosis of ovarian cancer was highest among women aged 45–49 yr, and did not indicate a monotonous statistical increase (Table 1). This might be influenced by a higher fatality rate of ovarian cancer compared with that of uterine cervical cancer or endometrial cancer. Thirdly, most participants were working. They had past diagnoses of diseases but were

Table 3. Calculated statistical power for each disease in the Japan Nurses' Health Study

Minimum relative risk to be detected = 1.5

	Overall incidence rate (per 1,000 women, per year)	Statistical power (%) Years after the baseline survey				
		2 yr	4 yr	6 yr	8 yr	10 yr
Uterine myoma	7.72	81	98	100	100	100
Hypercholesterolemia	5.59	68	92	99	100	100
Hypertension	3.60	51	78	92	97	99
Thyroid disease	1.96	32	54	70	82	89
Hepatitis	1.91	31	53	69	81	88
Gallstone disease	1.72	29	49	65	77	85
Benign breast tumor	1.18	22	37	50	61	71
Endometriosis	0.93	19	31	42	52	61
Diabetes mellitus	0.82	17	28	38	47	56
Breast cancer	0.56	14	21	29	35	42
Osteoporosis	0.50	13	20	26	32	38
Angina pectoris	0.35	11	16	20	25	29
Stomach cancer	0.31	10	15	19	23	27
Transient ischemic attack	0.27	9	13	17	21	24
Uterine cervical cancer	0.25	9	13	16	20	23
Colorectal cancer	0.15	7	10	12	14	16
Vein thrombosis/pulmonary embolism	0.14	7	10	12	14	16
Endometrial cancer	0.12	7	9	11	13	14
Cerebral infarction	0.08	6	7	9	10	11
Subarachnoid hemorrhage	0.07	6	7	8	10	11
Artery thrombosis of lower limbs	0.07	6	7	8	10	11
Ovarian cancer	0.07	6	7	8	10	11
Myocardial infarction	0.05	6	6	7	8	9
Cerebral hemorrhage	0.03	5	6	7	7	7

Alpha = 0.05 (two-tailed), total sample size =18,000, unexposed-exposed ratio = 4:1.

Minimum relative risk to be detected = 2.5

	Overall incidence rate (per 1,000 women, per year)	Statistical power (%) Years after the baseline survey				
		2 yr	4 yr	6 yr	8 yr	10 yr
Endometriosis	0.93	63	88	97	99	100
Diabetes mellitus	0.82	58	84	95	98	100
Breast cancer	0.56	45	71	85	93	97
Osteoporosis	0.50	42	66	81	90	95
Angina pectoris	0.35	32	53	68	79	87
Stomach cancer	0.31	30	49	64	75	83
Transient ischemic attack	0.27	27	44	57	69	77
Uterine cervical cancer	0.25	26	42	56	67	75
Colorectal cancer	0.15	19	29	39	47	55
Vein thrombosis/pulmonary embolism	0.14	18	28	38	46	54
Endometrial cancer	0.12	16	25	33	41	48
Cerebral infarction	0.08	13	19	24	29	34
Subarachnoid hemorrhage	0.07	12	18	23	28	33
Artery thrombosis of lower limbs	0.07	12	18	23	28	33
Ovarian cancer	0.07	12	18	23	28	33
Myocardial infarction	0.05	11	15	19	22	26
Cerebral hemorrhage	0.03	9	12	15	17	19

Alpha = 0.05 (two-tailed), total sample size = 18,000, unexposed-exposed ratio = 4:1.

able to work, thus they had diseases with relatively favorable prognoses. It is possible that severe outcomes were excluded, which could have resulted in an underestimate of the prevalence of past diagnoses. Nevertheless, the prediction of an incidence rate might not be greatly influenced, because this underestimate may share similar tendencies between 5-yr age groups, and that non- severe outcomes occur more frequently than severe ones.

Few reliable statistical data are available regarding the incidence rate of diseases among Japanese women, except for an estimated incidence rate of cancer based on population-based cancer registries[12]. According to these cancer registries, the incidence rate of breast cancer is 0.170 (per 1,000 women per year) among women aged 30–34 yr, 0.419 among women aged 35–39 yr, 0.810 among women aged 40–44 yr, 1.264 among women aged 45–49 yr, 1.122 among women aged 50–54 yr, and 1.012 among women aged 55–59 yr. These incidence rates are consistent with the predicted incidence rates of breast cancer for corresponding age groups in Table 2. With regard to uterine cervical cancer, uterine cancer, ovarian cancer, stomach cancer, and colorectal cancer, there were marked variations in each incidence rate among the age groups due to sample size limitations. However, the predicted overall incidence rate from ages 30 to 59 was mostly comparable with that of the cancer registries. We believe that the predicted incidence rate can be a reference for the incidence rate of each disease investigated in our study population of the JNHS.

Based on the predicted overall incidence rate, the statistical power for each disease was examined. For diseases with high incidence rates, such as uterine myoma, hypercholesterolemia, and hypertension, the statistical power was able to assess an increase of 1.5 or more in relative risk for factors with an exposure prevalence of 20% within 4 yr. With regard to diseases with an overall incidence rate of ≥1.2 (per 1,000 women per year), such as thyroid disease, hepatitis, and gallstone disease, it was possible to investigate an increase of about 1.5 or more in relative risk within 10 yr. Furthermore, with an increase of about 2.5 or more in relative risk, it was possible to investigate diseases with an overall incidence rate of ≥0.25, such as endometriosis, diabetes mellitus, osteoporosis, stomach cancer, and uterine cervical cancer, within 10 yr.

The incidence rate of diseases was predicted in the present study when the age composition of the survey population was the same as that of the baseline survey. However, as the follow-up surveys continue, the age distribution of the survey population will gradually shift towards higher ages. Therefore, the overall incidence rate of the entire population group will be higher, even if it is assumed that the incidence rate for each age group does not change. It is expected that the JNHS will have greater statistical power to detect a risk factor for each disease. On the other hand, a loss of follow-up reduces statistical power. However, the U.S. Nurses' Health Study had maintained a high follow-up rate of >90% during more than 10 yr[1]. Maintenance strategies for our JNHS cohort are described in detail elsewhere[10].

Conclusion

Overall, we conclude that even with the current sample size, it is possible to achieve the stated goal of the JNHS; to clarify gynecological health problems in Japan and establish epidemiological evidence of health care at various life stages among Japanese women.

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