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Review Article: Strategy for Drug Discovery at Pharmaceutical Companies

Proposal for the Breakdown of Increased Cancer Healthcare Cost and Its Improvement

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Technological progress in the field of cancer treatment can be expected to accelerate in the future, giving hope to such patients. At the same time, there is concern that cancer care will become more expensive. It is indispensable to minimize the economic burden of patients to deliver technological advances in treatment. It is important for the physician engaged in cancer care to recognize the economic burden of patients and to reduce this burden as much as possible. The Cancer Control Act was enacted in 2007 to promote work on cancer control using all the resources of the nation, and this should surely entail financial support. In order to take advantage of innovations in cancer care, reform of the payment system to lighten the economic burden of the patient would be a pressing necessity.

Key words: economic burden – cancer economics – cost of cancer – molecular targeted drugs – healthcare reform

EXPANDING MEDICAL EXPENSES OF CANCER

The national medical care expenditure in fiscal year 2010 in Japan announced at the end of September 2012 was 37 420 200 million yen, an increase of 3.9% compared with the previous fiscal year. The national income ratio, which was 8.1% in 2000, became 10.7%. The medical expenditure tends to increase sequentially when a slump in economic growth is prolonged. As for the medical care expenditure by age group, it was 55.4% for those 65 years old and older, 45.1% for those 70 years old and older and 33.3% for those 75 years old and older. These were 48.3, 37.4 and 25.1%, respectively, in 2000. Rapid aging of the population was found to be the major factor in the increase in medical care expenditures.

The medical care expenditure per capita was 292 200 yen, a record high. This generally represents an increase in each age group, and it is thought that technological progress is a major factor in the increase. The medical care expenditure for cancer in 2010 was 3 031 200 million yen. In total, 498 800 million yen were spent for colorectal cancer, 381 100 million yen for cancer of the trachea, bronchus and lung, 323 900 million yen for stomach cancer, 252 900 million yen for breast cancer and so on. The ratio of the cancer expenditure to the total medical expenditure was 11.2%. The growth rate of expenditures for cancer was 45.7% from 2000 to 2010, while that of the national medical care expenditure was 24.1% (Fig. 1). The increase in the cancer care expenditure is really remarkable.

In order to tackle with the high price of new technology and new therapeutic drugs, Central Social Insurance Medical Council in Japan has begun to discuss the possibility to introduce technology assessment in the actual public health insurance system. The point at issue is how to reduce health-care cost and to improve the quality at the same time. Some indicators such as cost-effectiveness and quality-adjusted life years is taken up for the discussion.

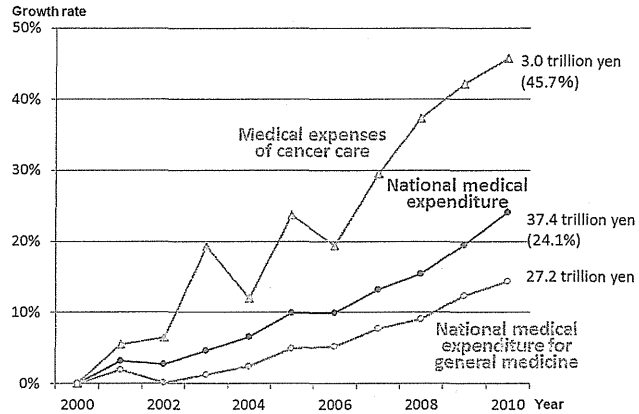

Figure 1. The trend of increase of cancer care expenses from the year 2000. The growth rate of expenditures for cancer was 45.7% from 2000 to 2010, while that of the national medical care expenditure was 24.1

INCREASING ECONOMIC BURDEN OF PATIENTS

Along with the increase in the national medical care expenditure, the economic burden of patients as well as the financial burden of the country became heavier. The co-payment for patients was raised from a fixed charge to 10% in 1984. The ratio of the patient's co-payment was raised from 10% to 20% in 1997 and from 20% to 30% in 2002. Thereafter, the co-payment of 30% (~15% for all ages) has continued. Since the medical care expenditure continued to increase and the co-payment ratio is always 30%, the actual economic burden for the patient increases constantly.

The increase in the cancer care expenditure largely resulted from the increase in the number of cancer patients along with the aging of the population. Simultaneously, rapid technical progress influences the increase in the cancer care expenditure to a great extent. Aging factor and other factors including technical progress have contributed in 46 and 54%, respectively, to the increase in the national medical care expenditure from fiscal year 2007–2008 according to the statistics of Ministry of Health, Labour and Welfare.

The cancer care expenditure per patient increased 9% for 5 years from 2002 through 2007, whereas the average annual salary has decreased 11% from 4.61 million yen in 2000 to 4.12 million yen in 2010 according to National Tax Agency 'Private salary investigation'. This means that the economic burden of patients has become heavier.

The actual situation of the economic burden of patients with cancer is not fully grasped. Therefore, we investigated 40 institutions such as university hospitals and cancer centers through the country (2010 through 2011). This was a self-completed survey asking patients with cancer to list the expenses related to cancer based on a household account book or on the receipts. Moreover, we got clinical information from physicians upon the approval of the patients and conducted a data linkage of the patient survey (1).

As a result, the average annual out-of-pocket expenses for cancer were 864 000 yen ($n = 2022$). The direct expenses of hospitalization, ambulatory care and transportation were 294 000 yen (applicable patients: 68.2%), 259 000 yen and 56 000 yen, respectively. For indirect expenses, the premium of private insurance and cost of alternative medicine were 380 000 yen (applicable patients: 55.0%) and 213 000 yen (32.3%), respectively (Fig. 2).

On the other hand, the refunds and benefits were 624 000 yen on average. The benefits from private insurance, medical refunds and tax refunds were 1 140 000 yen (applicable patients: 43.3%), 242 000 yen (48.2%), 62 000 yen (22.3%), respectively. The substantial economic burden when refunds and benefits were deducted from out-of-pocket expenses was 240 000 yen. Private insurance in Japan complements public insurance, and many patients are aided by this benefit.

For gastric cancer ($n = 158$), the out-of-pocket expenses and the refunds/benefits were 724 000 yen and 664 000 yen, respectively. These were 931 000 yen and 636 000 yen for colorectal cancer ($n = 244$), 1 102 000 yen and 681 000 yen for lung cancer ($n = 302$), 687 000 yen and 496 000 yen for breast cancer ($n = 773$), and 489 000 yen and 246 000 yen for prostate cancer ($n = 102$), respectively. The out-of-pocket expenses and the refunds/benefits differ considerably by types of cancer due to the large variety of treatments and prognosis and so forth.

The out-of-pocket expenses and the refunds/benefits were 1 217 000 yen and 652 000 yen for molecular targeted treatment ($n = 494$), and were 1 156 000 yen and 615 000 yen for the treatment of hematological malignancies, respectively. The out-of-pocket expenses (direct and indirect expenses) were 1 104 000 yen for chemotherapy using Trastuzumab ($n = 206$), 1 160 000 yen for Gefitinib ($n = 61$) 1 242 000 yen for Imatinib ($n = 213$), and 1 533 000 yen for Bevacizumab ($n = 160$), respectively.

DIFFERENCE IN BURDEN BY CLINICAL STAGE

The economic burden differs according to the clinical stage. The out-of-pocket expenses and the refunds/benefits were 610 000 yen and 509 000 yen in Stage I, 683 000 yen and 478 000 yen Stage II, 982 000 yen and 754 000 yen in Stage III, and 1 284 000 yen and 778 000 yen in Stage IV, respectively. The expenditures for alternative medicine and supplements tended to increase with the seriousness of the disease. The annual length of hospital stay was 20.6 days in Stage I, 23.3 days in Stage II, 37.1 days in Stage III and 44.3 days in Stage IV, respectively. The number of visits to hospital was 14.2 times in Stage I, 18.9 times in Stage II, 22.4 times in Stage III, and 24.9 times Stage IV, respectively. Looking at this according to the types of therapy, the length of stay was 27.8 days for surgery, 39.9 days for chemotherapy and 32.6 days for radiotherapy. The number of visits was 18.6 times for surgery, 24.6 times for chemotherapy and 29.3 times for radiotherapy.

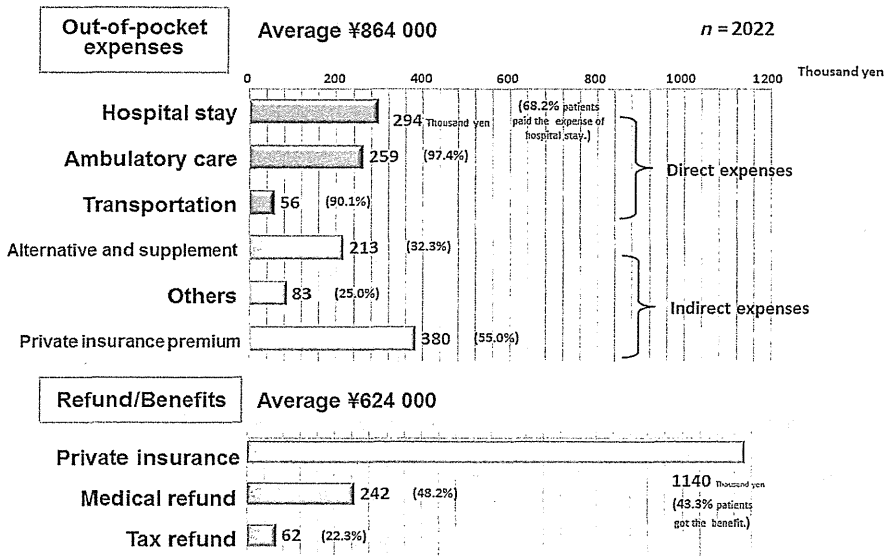

Figure 2. Annual economic burden of cancer patient. The average annual out-of-pocket expenses for cancer were 864 000 yen and the refunds and benefits were 624 000.

The economic burden also differed according to the ratio of the patient's co-payment. The out-of-pocket expenses and the refunds/benefits were 934 000 yen and 746 000 yen with a co-payment of 30% ($n = 1443$ average age 58.5 years old), respectively. In other words, the actual burden was 188 000 yen. However, these were 672 000 yen and 275 000 yen with a co-payment of 10% ($n = 554$, 75.4 years old). In this case, the balance was 397 000 yen, which was heavier than burden with a co-payment of 30%. In case of a co-payment of 10%, the average benefit from private insurance (683 000 yen on average for 32.4% of the patients) and the medical refund (86 000 yen for 54.8% of the patients) are much smaller than that of a co-payment of 30%.

Around 69% of the patients had economic worries ($n = 2037$). The mean out-of-pocket expense (752 000 yen) of the patients without economic worries was three-fourths that of the patients (987 000 yen) with economic worries (Fig. 3). In the viewpoint of promoting work, if the length of stay is shortened and the number of hospital visits is decreased, the patients with cancer would have more working opportunities. For example, in patients with breast cancer ($n = 774$), the average length of stay was 14.1 days and the number of visits was 20.4 times. If the hospitalization included Saturday and Sunday for 4 days and ended on a half day, the suspension of work due to treatments would be almost equal to annual paid holidays.

DECLINING THE TREATMENT DUE TO ECONOMIC REASONS

According to our survey, three-fourths of the patients with colorectal cancer felt that the medical expenses under public insurance were heavy ($n = 232$). Half of the above patients felt that the premium of private insurance and the costs of alternative medicine were also heavy. Many patients think that the indirect expenses are crucial. Sixty percent of patients with colorectal cancer were obliged to withdraw deposits and savings, and 10% managed to pay the medical costs by borrowing from a family member or relative ($n = 249$). In our survey, the average age of patients with colorectal cancer was 64.4 years and a pension was the sole regular income for many patients. For one-third of the above patients, the household income was between 1 million and 3 million yen. For 40% of the above patients, the household savings were less than 7 million yen.

Although medical treatment cannot be denied for economic reasons under Japanese universal health insurance system, patients who refused an expensive therapy have recently increased. According to our survey for physicians engaged in cancer care ($n = 1176$, clinical experience: 17.8 years), 1.6 inpatients and 1.5 outpatients per month gave up the most appropriate treatment due to some economic reason.

Sixteen percent of the above patients had to cancel the scheduled treatment, 56% could not avoid changing the treatment and 13% were obliged to interrupt the treatment. It is an extremely serious situation for patients, and also for their physicians, when patients must forego necessary treatments, especially considering that refunds are available expensive medical treatments. Since molecular-targeted drugs are expensive in general, it is not rare to modify or withdraw these drugs such as Bevacizumab or Sorafenib for the treatment of solid tumors and Rituximab or Imatinib for hematological malignancies. In the case of Bevacizumab, for instance, a planned regimen such as Bevacizmab + XELOX was modified to XELOX. In the same manner, some regimens were modified from Bevacizmab + mFOLFOX6 to mFOLFOX6, and from Bevacizmab + FOLFIRI to FOLFIRI.

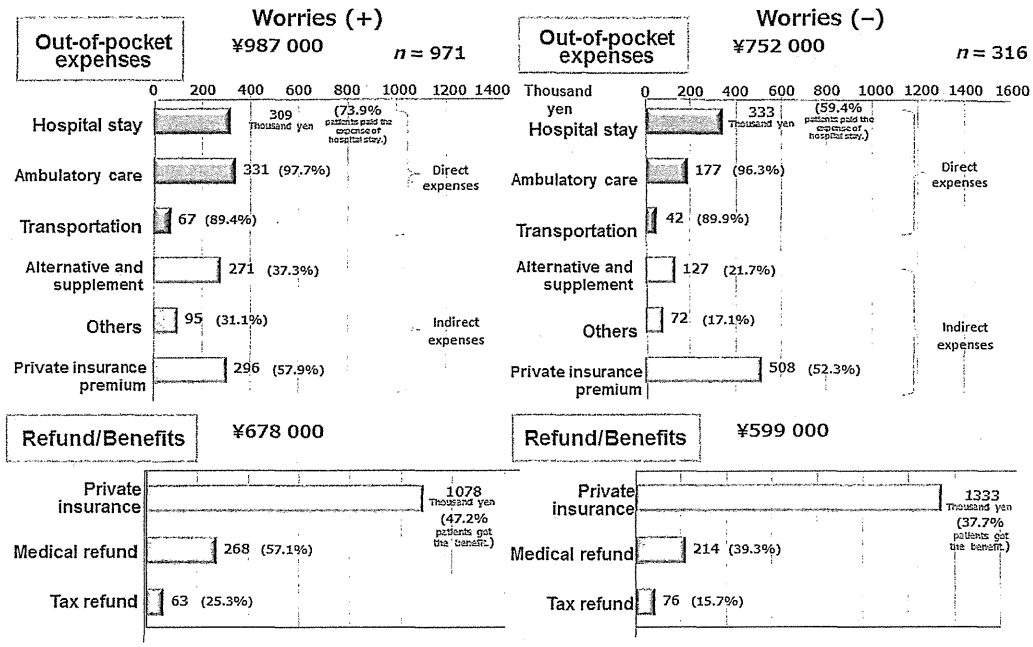

Figure 3. Annual economic burden of cancer patient by worries about economic problems. The mean out-of-pocket expense of patients without economic worries was three-fourths that of the patients with economic worries.

We calculated the change in drug costs on the basis of the payment system for medical services in 2011 (the standard treatment for a male patient of 60 kg and 165 cm) in the above three cases. Drug costs were decreased by 48.6%, from 468 000 yen to 228 000 yen, by 49.8%, from 299 000 yen to 149 000 yen, and by 35.4%, from 232 000 yen to 82 000 yen, respectively. Given the payment system, if one half of the current drug costs is supported by a second or third party, more patients would be able to undergo optimal treatment.

IMPORTANT ROLE OF MEDICAL REFUND SYSTEM

There are limits to the expenses patients must pay based on their income. The medical refund system is a safety net that complements the health insurance system (co-payment of 10–30% by the patient). The government expenditure for medical refunds has doubled during the 8 years from 2000 through 2008 (1713 billion yen), suggesting that the economic burden on patients has been increasing. The medical refund system was founded in 1973, and many regulations were introduced afterwards. User cannot easily understand this complicated system. However, the detailed rules of the system have come to be understood by patients, since this system is requested by the patients the number of users has increased. This system is explained in detail when required in the consultation support center of cancer center hospitals. Forty-eight percent of patients with cancer and 80% of patients administered molecular-targeted treatment applied for this system, which has recently become indispensable. We examined how the medical refund system reduces patients' payments using the survey data. We found that this system lightens the patients' burden by 32.5% on average ($n = 686$) (Fig. 4). These are 35.4% in patients with colorectal cancer and 36.6% in patients from 40 to 49 years old.

MEASURES AGAINST RISING COST OF CANCER TREATMENT

There are many requests for relief from the economic burden from patients with cancer, who want the cost of anticancer drugs to be reduced, the ceiling for reimbursement to be lowered, the percentage of co-payment to be lower than for other diseases and that more information about the economic burden should be given to patients and so on ($n = 236$). Measures corresponding to the patients' suffering from the economic burden of treatment are very urgent. The problem of so-called 'economic refugees with cancer' (patients who cannot undergo the adequate treatment for economic reasons) might be addressed along with the accelerating technological progress.

These measures could be broken down into three levels: physicians' consideration in the clinical setting, better operation of the actual system and drastic healthcare reform. The first level includes the promotion of ambulatory care as an alternative to hospitalization, shortening the duration of hospitalization, reducing excessive testing and medication, the use of cheaper generic drugs and adequate explanation about the costs. The second level includes reductions in the ceiling

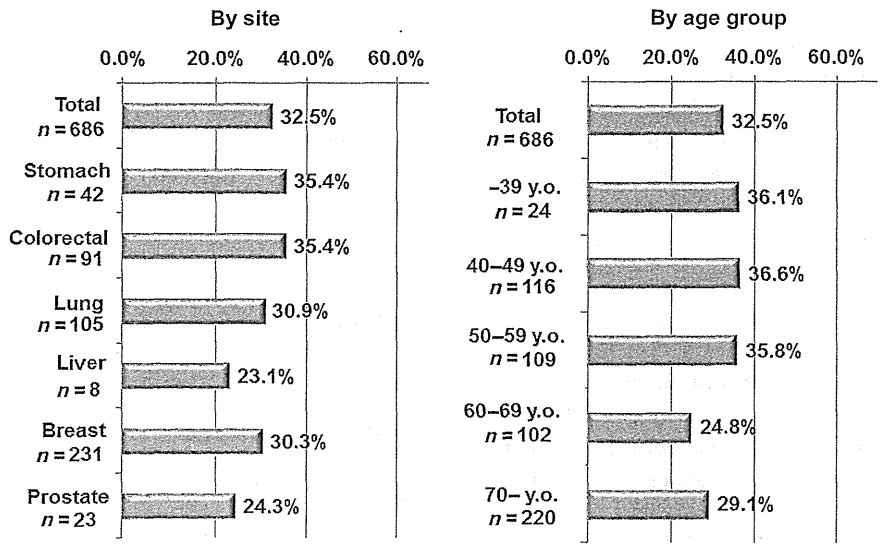

Figure 4. Percent reduce of the patients' payments with medical refund system. The medical refund system lightens the patients' burden by 32.5% on average. y.o., years old.

for reimbursement and improvement of the so-called 'drug lag' (shortening the approval process for new drugs) and 'device lag' (that of new technology). A few patients are obliged to the new drugs by way of the personal import on their own expense.

For the third level, it is necessary to review the proper percentage of co-payments depending not only on age but also on the seriousness or other characteristics of the disease to relieve the excessive economic burden of the patients. The national income has been decreasing while medical costs per person have been increasing for the past decade and there is surely a limit to the economic relief that can be provided by the medical refund system. This is because the payment of medical refunds has greatly expanded and the government will suffer from insufficient funds.

Information about patients' out-of-pocket expenses in other countries would be useful for our healthcare reform, although health insurance systems differ country by country and a simple comparison might lead to misunderstandings. Medical care is free of charge as a rule in such countries as the UK, Canada and Australia (excluding drug costs). The out-of-pocket expenses of a patient is 10 euros per day for hospitalization and 10 euros per quarter for ambulatory care (it is free of charge if there is a letter of introduction) in Germany. There is an upper limit of 80 krona per day (~9600 yen) for hospitalization and an upper limit of 900 krona per year for ambulatory care in Sweden. The economic burden of a patient is rather light in these countries.

The percentage of out-of-pocket payments is 20% for hospitalization and 30% for ambulatory care in France, whose system resembles that of Japan. However, some private insurance can bridge most of the payment gaps, and medical care for 30 diseases including cancer is free of charge. This is an important example of how the heavy economic burden of long-term and expensive treatments can be avoided by patients. That is, it turns out that the out-of-pocket payments in Japan act at a particularly high level for developed countries. It is extremely important to secure necessary healthcare resources from and to drastically rationalize the distribution of medical expenditures. Such reform of the current insurance system is inevitable because of the need to cope with constantly advancing innovation. Healthcare systems in some western countries have introduced the concept of priority (so-called 'triage' not only in emergency medicine but also in general medicine), which serve as a reference *for* Japan.

The total sum of out-of-pocket payments by patients with cancer in Japan comes to 461 billion yen per year based on the data of our survey. Therefore, making cancer treatment free of charge would be possible in Japan if an additional 500 billion yen in public spending were made available. There is little risk of moral hazard (increase of the number of patients and medical expenditures caused by the lack of fee) since the diagnosis of cancer is concrete. Financial support depending on the type of disease is more rational than that depending on the age group (such as charge-free medical care for the elderly ~40 years ago), because the elderly vary in health status significantly even at the same age.

The average age of patients with cancer exceeds 60 years old. The income is restricted to a pension in many cases and the out-of-pocket expenses for cancer treatment are often covered by drawing on savings. When looking at the annual household income (tax included), 31% of the patients earned 1~3 million yen or less and more than half is <5 million yen ($n = 2928$, average age 61.7 years old). As for the amount of household savings, in 40% it was <7 million yen and in half it was <10 million yen. Many senior citizens tend to reduce daily living expenses on the preparation for the high probability suffering from serious illness in the future. The domestic demand is reduced if those of middle

and advanced age, which occupy the majority of the population, refrain from consumption because of worries about future illness. It is essential to stabilize the pension system, but the solution to this problem will likely take time before anxiety about the future is alleviated. Relief from the economic burden of cancer care must be a reasonable certainly for the elderly, and it would be one of the most cost-effective measures to implement.

CONCLUSION

Technological progress in the field of cancer treatment can be expected to accelerate in the future giving hope to such patients. At the same time, there is concern that cancer care will become more expensive. It is indispensable to minimize the economic burden of patients to deliver technological advances in treatment. The economic burden of the patient might influence the outcome of treatment, and the costs would therefore be an important element in high-quality cancer care, as ASCO (American Society of Clinical Oncology) noted (2). It is important for the physician engaged in cancer care to recognize the economic burden of patients and to reduce this burden as much as possible. The Cancer Control Act was enacted in 2007 to promote work on cancer control using all the resources of the nation, and this should surely entail financial support. In order to take advantage of innovations in cancer care, reform of the payment system to lighten the economic burden of the patient would be a pressing necessity.

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Conflict of interest statement

None declared.

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Study Profile

Cohort Profile of the Japan Collaborative Cohort Study at Final Follow-up

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ABSTRACT

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) was established in the late 1980s to evaluate the risk impact of lifestyle factors and levels of serum components on human health. During the 20-year follow-up period, the results of the study have been published in almost 200 original articles in peer-reviewed English-language journals. However, continued follow-up of the study subjects became difficult because of the retirements of principal researchers, city mergers throughout Japan in the year 2000, and reduced funding. Thus, we decided to terminate the JACC Study follow-up at the end of 2009. As a final point of interest, we reviewed the population registry information of survivors. A total of 207 (0.19%) subjects were ineligible, leaving 110 585 eligible participants (46 395 men and 64 190 women). Moreover, errors in coding date of birth and sex were found in 356 (0.32%) and 59 (0.05%) cases, respectively, during routine follow-up and final review. Although such errors were unexpected, their impact is believed to be negligible because of the small numbers relative to the large total study population. Here, we describe the final cohort profile at the end of the JACC Study along with selected characteristics of the participants and their status at the final follow-up. Although follow-up of the JACC Study participants is finished, we will continue to analyze and publish study results.

Key words: JACC Study; cohort study; Japan; follow-up

INTRODUCTION

To evaluate the risk impact of lifestyle factors and levels of serum components on human health, in the late 1980s we established a large-scale cohort study, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). During a follow-up period of approximately 20 years, data on deaths from major causes such as stomach cancer, lung cancer, and cardiovascular diseases enabled examination of risk factors. We subsequently published results regarding associations between lifestyle factors and health status in almost 200 original research articles in peer-reviewed English-language journals. Additionally, we are currently developing a website to increase public awareness.[1]

The enthusiasm of researchers is always important in promoting a cohort study, but enthusiasm is not enough since such work takes many years to bear fruit. A substantial budget is also required. The JACC Study was started after receiving a promise of funds for 10 years; however, after the initial 10 years had passed, it became necessary to apply for small public grants to maintain and follow cohort participants. In addition, administrative mergers of cities, towns, and villages throughout Japan in the year 2000 sometimes caused further difficulties in following subjects in the study area, due to changes in partnerships between local governmental offices and researchers. Moreover, with the retirement of key researchers, it was not always easy to transfer their work to their successors. As a result of these challenges, we decided to

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terminate follow-up of participants in the JACC Study at the end of 2009.

As a final point of interest, we used population registers in the study area to review the list of survivors. Some subjects were found to be no longer living in the study area, although the overall number of such participants was small. Moreover, a small number of errors in the coding of date of birth and sex were identified during follow-up data collection. Here we describe the final cohort profile obtained upon completion of the JACC Study. Data on cancer incidence have not yet been compiled because of the time lag of the cancer registry system. This process is expected to continue until 2013, at which point incidence information until 2009 will be made available.

METHODS

Study subjects

Details of the study design and concept have been described elsewhere.[2–4] Briefly, the JACC Study was a multicenter collaborative study in which 24 institutions voluntarily participated. Recruitment of study subjects living in 45 areas was managed by individual investigators whose responsibility was to construct the cohort in that area. Data were collected from 1988 through 1990. However, although most baseline surveys were performed during this 3-year period, some subjects were recruited before and after this period because of the need for a preliminary study in 3 areas and later collaboration in 1 area. Individual informed consent before participation in the study was obtained in 36 of the 45 study areas (written consent in 35 areas and oral consent in 1 area); in the remaining 9 areas, group consent from the area leader was obtained. Participant eligibility was verified by individual investigators, who confirmed that (1) the participant was living within the study area and (2) was aged 40 to 79 years at baseline. In addition, date of birth and sex were further verified using official documents and/or a completed self-administered questionnaire.

Follow-up

As follow-up information, dates and causes of death were annually or biannually confirmed, with the permission of the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post and Telecommunications) and/or the Ministry of Health, Labor and Welfare, Japan. The date of move-out of cohort members from the study area was also annually or biannually verified by the investigator in cooperation with key members of the local governmental office. In 24 of the 45 areas, data on cancer incidence such as date of diagnosis and primary site were also collected through population-based cancer registers or by reviewing the records of local major hospitals. In most areas, follow-up was completed at the end of 2009; however, it was stopped at the end of 1999 in 4 areas, at the end of 2003 in another 4 areas, and at the end of 2008 in 2 areas.

Final data setup: correction of birth date and sex information, identification of decedents and subjects who had moved, and deletion of ineligible participants

To confirm if study participants had survived and were living in the study area at the end of follow-up, we conducted a systematic review of population registers of cohort members in 17 areas followed until 2009. In the remaining 18 areas followed until 2009, annual or biannual follow-up surveys were routinely performed using population registers; thus, no further reviews were conducted. If data from participants presumed to survive were found to be missing at the end of 2009, attempts were made to obtain information on their mortality status or current location, and relevant information was added to the follow-up data. A few participants were found to have never lived in the study area and were thus excluded from the baseline data.

This review process revealed some errors in coding of date of birth and sex. Moreover, during the merge of follow-up data with baseline identifiable data (name, date of birth, and sex), further errors in date of birth and sex were found. All such errors were corrected.

RESULTS

Of 110 792 participants aged 40 to 79 years at baseline, 207 (0.19%) were found to have never lived in the study area. As a result, 110 585 participants (46 395 men and 64 190 women) were ultimately deemed eligible as subjects for the JACC Study, with 707 136 and 1 025 703 person-years of follow-up for men and women, respectively. Errors in the coding of date of birth and sex were found in 356 (0.32%) and 59 (0.05%) cases, respectively, during routine follow-up and final review. Table 1 shows the age and sex distribution of study participants. There were no subjects from the Shikoku region. As compared with the overall distribution of the Japanese population in 1989, our cohort participants were slightly older and included a higher percentage of women.

Table 2 shows the follow-up results, and Table 3 shows the major causes of death up to 2009. These values include the follow-up information (death or move-out from the study area) that was reported in 10 of 17 areas for 516 subjects (0.5%) through a systematic review of population registers of cohort members. Finally, 27 410 deaths (24.8%; 15 401 men, 12 009 women) and 6402 move-outs (5.8%; 2343 men, 4059 women) were identified during the median 18.0-year follow-up. The first cause of death was cancer among men (37.6%) and circulatory disease among women (33.7%), and the second cause of death was circulatory disease (27.8%) and cancer (30.8%), respectively (Table 3). Among those who died of cancer, the first, second, and third leading causes of death were cancer of the lung (23.2%), stomach (18.4%), and liver (10.7%) among men and cancer of the stomach (15.4%), lung (11.2%), liver, and pancreas (9.2% for both)

Table 1. Age distribution of cohort members at baseline by region

	Age at baseline								Total	%
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79		
Men										
Japan general population 1989 (×1000)	5022	4562	3967	3706	3122	2049	1507	1169	25 104	
	20.0	18.2	15.8	14.8	12.4	8.2	6.0	4.7	100.0	
JACC Study participants	5991	5794	6309	7690	8415	5516	4021	2659	46 395	100.0
%	12.9	12.5	13.6	16.6	18.1	11.9	8.7	5.7	100.0	
Hokkaido	191	182	211	267	284	201	86	43	1465	3.2
Tohoku	809	625	797	1050	1270	894	494	293	6232	13.4
Kanto	1325	1231	1219	1320	1446	1115	707	447	8810	19.0
Chubu	1736	1646	1560	1763	1804	1167	916	691	11 283	24.3
Kinki	960	908	1148	1456	1419	996	651	459	7997	17.2
Chugoku	220	374	452	886	1251	589	770	509	5051	10.9
Kyushu	750	828	922	948	941	554	397	217	5557	12.0
Women										
Japan general population 1989 (×1000)	4989	4613	4052	3852	3426	2825	2141	1770	27 668	
	18.0	16.7	14.6	13.9	12.4	10.2	7.7	6.4	100.0	
JACC Study participants	7536	7912	9088	10 792	11 102	8589	5548	3623	64 190	100.0
%	11.7	12.3	14.2	16.8	17.3	13.4	8.6	5.6	100.0	
Hokkaido	310	310	433	436	382	257	93	37	2258	3.5
Tohoku	959	963	1412	1670	1670	1136	604	372	8786	13.7
Kanto	1428	1438	1442	1605	1744	1577	892	542	10 668	16.6
Chubu	1872	1669	1833	1933	2107	1613	1225	882	13 134	20.5
Kinki	1253	1219	1508	1784	1566	1300	876	623	10 129	15.8
Chugoku	300	796	828	1479	2194	1795	1289	844	9525	14.8
Kyushu	1414	1517	1632	1885	1439	911	569	323	9690	15.1

Table 2. Follow-up status until 2009 by sex and age

	Age at baseline								Total
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	
Men									
No. at baseline	5991	5794	6309	7690	8415	5516	4021	2659	46 395
No. of deaths	394	658	1113	2000	3252	3056	2782	2146	15 401
%	6.6	11.4	17.6	26.0	38.6	55.4	69.2	80.7	33.2
No. who left study area	539	377	303	298	292	242	180	112	2343
%	9.0	6.5	4.8	3.9	3.5	4.4	4.5	4.2	5.1
Person-years	107 048	102 338	108 465	124 421	123 896	74 267	43 689	23 012	707 136
Mortality rate (per 1000 person-years)	3.7	6.4	10.3	16.1	26.2	41.1	63.7	93.3	21.8
Women									
No. at baseline	7536	7912	9088	10 792	11 102	8589	5548	3623	64 190
No. of deaths	242	368	637	1218	1982	2544	2632	2386	12 009
%	3.2	4.7	7.0	11.3	17.9	29.6	47.4	65.9	18.7
No. who left study area	605	488	479	522	606	592	483	284	4059
%	8.0	6.2	5.3	4.8	5.5	6.9	8.7	7.8	6.3
Person-years	134 927	139 091	159 465	182 347	174 721	125 510	71 076	38 566	1 025 703
Mortality rate (per 1000 person-years)	1.8	2.6	4.0	6.7	11.3	20.3	37.0	61.9	11.7

among women. When cancers of the colon and rectum were grouped together, that category was the second leading cause of death (12.7%) among women.

DISCUSSION

This final profile of the JACC Study Group describes the number of participants and their follow-up status. During the median 18-year follow-up, we found errors in the coding of date of birth and sex data as well as incorrectly registered cases. Accordingly, we would advise future researchers planning a field study to thoroughly check participant eligibility and basic information such as date of birth and sex; this can be performed at least twice, by using a population register and a self-questionnaire.

Although follow-up information was annually or biannually confirmed, 516 subjects who had died or moved out of the study area were not identified during routine follow-up. The

Table 3. Mortality distribution according to cause of death during entire follow-up period

Cause of death		Men											Women										
		Age at baseline								Total	%	%[a]	Age at baseline								Total	%	%[a]
		40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79				40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79			
All causes		394	658	1113	2000	3252	3056	2782	2146	15401	100.0		242	368	637	1218	1982	2544	2632	2386	12009	100.0	
A00–B99	Certain infectious and parasitic diseases	6	10	18	38	56	62	44	33	267	1.7		4	4	18	31	62	50	43	36	248	2.1	
C00–D49	Neoplasms	160	312	542	927	1425	1073	792	561	5792	37.6	100.0	147	182	319	563	740	714	618	414	3697	30.8	100.0
C15	Esophagus	12	14	28	42	55	38	17	10	216		3.7	0	1	5	3	4	7	8	7	35		0.9
C16	Stomach	32	62	87	176	252	199	151	109	1068		18.4	19	26	33	93	91	127	104	76	569		15.4
C18	Colon	12	14	36	41	67	59	44	35	308		5.3	2	13	29	45	62	65	65	52	333		9.0
C19–C20	Rectum	8	17	26	52	39	30	27	22	221		3.8	9	8	12	18	35	16	26	11	135		3.7
C22	Liver and intrahepatic bile ducts	21	46	79	128	167	77	66	37	621		10.7	8	12	29	65	81	77	33	35	340		9.2
C23	Gall bladder	1	5	6	16	17	32	12	12	101		1.7	4	7	11	15	17	28	35	13	130		3.5
C24	Other and unspecified parts of biliary tract	5	11	11	34	41	42	28	16	188		3.2	3	8	11	22	31	37	37	23	172		4.7
C25	Pancreas	13	20	29	50	78	63	43	42	338		5.8	7	16	26	48	82	66	62	33	340		9.2
C33–C34	Lung	27	50	114	205	364	290	181	114	1345		23.2	18	20	39	54	96	78	70	40	415		11.2
C50	Breast	0	1	0	0	0	0	1	0	2		0.0	28	26	28	37	29	18	17	9	192		5.2
C53	Cervic uteri												6	2	10	5	9	5	7	5	49		1.3
C54	Corpus uteri												2	2	7	7	9	3	4	2	36		1.0
C55	Uterus, part unspecified												2	3	1	3	13	9	8	7	46		1.2
C56	Ovary												13	8	15	16	22	10	9	5	98		2.7
C61	Prostate	2	4	20	21	68	49	59	56	279		4.8											
C64	Kidney	0	4	7	12	14	9	12	4	62		1.1	0	0	1	5	3	11	5	1	26		0.7
C65–C67	Urothelial tract	2	7	13	11	40	31	34	17	155		2.7	1	0	6	6	21	14	16	14	78		2.1
C82–C85	Non-Hodgkin's lymphoma	0	8	17	29	44	20	15	15	148		2.6	5	6	10	25	23	17	12	7	105		2.8
C90	Multiple myeloma	2	7	4	12	18	12	9	5	69		1.2	4	4	9	12	15	15	11	10	80		2.2
C92	Myeloid leukemia	5	10	11	16	17	7	9	3	78		1.3	1	4	4	12	15	9	8	3	56		1.5
E00–E89	Endocrine, nutritional and metabolic diseases	8	10	17	29	38	35	27	28	192	1.2		2	4	7	10	36	49	48	43	199	1.7	
G00–G99	Diseases of the nervous system	4	7	17	19	50	39	18	10	164	1.1		1	4	12	23	44	27	29	13	153	1.3	
I00–I99	Diseases of the circulatory system	86	132	252	460	857	908	919	673	4287	27.8		52	70	138	306	585	913	1001	978	4043	33.7	
I20–I25	Ischemic heart disease	34	45	69	124	199	204	181	147	1003			11	8	34	51	105	188	176	185	758		
I48	Atrial fibrillation and flutter	0	0	4	10	19	25	24	15	97			1	0	1	3	16	21	29	26	97		
I50	Heart failure	7	19	26	56	121	151	178	153	711			8	5	22	44	101	180	200	239	799		
I60–I69	Cerebrovascular disease	30	44	113	194	362	389	408	285	1825			24	43	63	130	256	393	461	407	1777		
I71	Aortic aneurysm and dissection	4	4	12	21	44	40	38	15	178			2	3	2	17	22	29	28	13	116		
J00–J99	Diseases of the respiratory system	14	40	62	219	408	501	550	500	2294	14.9		3	18	23	67	182	281	357	354	1285	10.7	
J09–J18	Influenza and pneumonia	6	20	30	115	228	273	327	327	1326			2	11	15	39	110	173	247	245	842		
J43	Emphysema	0	1	6	19	58	58	64	44	250			0	0	0	2	2	4	4	4	16		
K00–K95	Diseases of the digestive system	28	35	53	78	82	109	80	46	511	3.3		1	12	13	54	54	106	91	82	413	3.4	
K74	Fibrosis and cirrhosis of liver	16	16	27	34	20	13	19	6	151			1	8	6	23	22	31	19	10	120		
N00–N99	Diseases of the genitourinary system	2	9	14	33	67	68	67	59	319	2.1		2	3	15	22	51	78	82	81	334	2.8	
N17–N19	Acute kidney failure and chronic kidney disease	2	7	12	22	50	52	52	53	250			1	2	12	17	38	50	63	60	243		
R00–R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	4	4	6	7	26	52	99	109	307	2.0		1	1	1	7	26	84	172	234	526	4.4	
R54	Age-related physical debility	0	0	0	4	19	37	87	99	246			0	0	1	2	18	71	150	224	466		
S00–T88	External causes	78	86	113	150	170	150	126	93	966	6.3		22	57	72	97	143	147	117	73	728	6.1	
	Others	4	13	19	40	73	59	60	34	302	2.0		7	13	19	38	59	95	74	78	383	3.2	

[a]Percentage of deaths per neoplasm.

use of population registers to verify that subjects are living in the study area is therefore necessary because it enables identification of deceased individuals and those who have moved out of the study area. Furthermore, 356 (0.32%) and 59 (0.05%) cases of incorrect coding of date of birth and sex, respectively, were found during routine follow-up and final review. Miscoding of data can occur by verification only once, and miscoding of date of birth and sex information may cause errors such as merging of the follow-up information of 1 participant with the baseline data of another participant. Thus, careful efforts such as independent double-entry are essential to reduce such miscoding.

The JACC Study is one of the largest cohort studies in Japan. Selected characteristics of study participants were similar to those of the Japanese general population, and thus, the JACC Study can be regarded as representative of the Japanese population, though it should be noted that no subjects were recruited from the Shikoku region. Almost 200 original articles on the risk factors for cancer, cardiovascular disease, and other diseases have been published using the results of the JACC Study. It was not an easy task to establish and maintain such a large collaborative cohort study with a limited budget; the voluntary efforts of the collaborators were essential. Although unexpected errors were found, we believe that the impact of these errors was negligible because the number of ineligible cases and amount of missing data were small relative to the large total study population.

Cohort studies need to continue over a long period if they are to yield fruitful results. Moreover, because all study participants must be followed up carefully and thoroughly, considerable funding is required. The JACC Study received systematic support for the first 10 years, at which point this funding ceased and maintenance and follow-up of cohort participants was accomplished by means of smaller grants. The retirements of principal researchers and city mergers throughout Japan made it difficult to continue follow-up. Thus, we decided to terminate the follow-up of participants in the JACC Study at the end of 2009. Our experience indicates that the development and maintenance of an appropriate long-term management system is essential when launching a cohort study and that adequate and steady support from funding bodies is also important.

We would like to express our sincere thanks to all participants and researchers related to the JACC Study, and to all the funding bodies that supported our study. Hereafter, we plan to use the final dataset and remaining sera to examine the risk impact of lifestyle factors and levels of serum components on human health.

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Conflicts of interest: None declared.

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Original Article

Obesity/Weight Gain and Breast Cancer Risk: Findings From the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk

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ABSTRACT

Background: We analyzed data from the Japan Collaborative Cohort Study (36 164 women aged 40–79 years at baseline in 1988–1990 with no previous diagnosis of breast cancer and available information on weight and height) to examine the association between baseline body mass index (BMI)/weight gain from age 20 years and breast cancer risk in a non-Western population.

Methods: The participants were followed prospectively from enrollment until 1999–2003 (median follow-up: 12.3 years). During follow-up, breast cancer incidence was mainly confirmed through record linkage to population-based cancer registries. A Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% CIs for the association between breast cancer risk and body size.

Results: In 397 644.1 person-years of follow-up, we identified 234 breast cancer cases. Among postmenopausal women, the adjusted HR increased with BMI, with a significant linear trend ($P < 0.0001$). Risk was significantly increased among women with a BMI of 24 or higher (HR: 1.50, 95% CI: 1.09–2.08 for BMI of 24–28.9, and 2.13, 1.09–4.16 for BMI $\geq$ 29) as compared with women with a BMI of 20 to 23.9. Weight gain after age 20 years and consequent overweight/obesity were combined risk factors for postmenopausal breast cancer risk. This combined effect was stronger among women aged 60 years or older. However, the HRs were not significant in premenopausal women.

Conclusions: Our findings support the hypothesis that weight gain and consequent overweight/obesity are combined risk factors for breast cancer among postmenopausal women, particularly those aged 60 years or older.

Key words: breast cancer; obesity; weight gain; cohort study

INTRODUCTION

Since the early 1990s, breast cancer has been the most frequently diagnosed cancer in Japanese women.[1] Among women, the mortality rate of breast cancer is second only to that of stomach cancer. The recent continuous increase in breast cancer incidence has been an important public health concern in Japan, and the attention devoted to obesity/weight gain as a risk factor for breast cancer has also increased.

Obesity is a well-known risk factor for postmenopausal breast cancer.[2–4] Numerous epidemiologic studies have reported positive associations between obesity and breast cancer risk among white,[5–10] African-American,[11–13] and East Asian women.[14–17] Furthermore, weight gain has been reported as an independent risk factor.[8,9,11,17–21] Several studies have reported an inverse association between body weight in early adulthood and breast cancer incidence.[17,19,20] However, the association has been somewhat inconsistent among

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premenopausal women. Obesity is associated with a decreased risk of breast cancer among white women,[4,10,22–24] although accumulating evidence suggests that the inverse association is limited to women with estrogen receptor- and progesterone receptor-positive tumors.[25–28] Studies of non-white racial/ethnic groups are more limited, and the results are mixed.

To assist in cancer prevention, we analyzed data from a large cohort study—the Japan Collaborative Cohort (JACC) Study—which included 64 327 Japanese women, to examine the association of baseline body mass index (BMI)/weight gain with breast cancer risk, considering menopausal status at baseline. We also investigated the interaction of age on this association.

METHODS

Study population

We analyzed data from the JACC Study, a prospective cohort study that evaluated cancer risk associated with lifestyle factors among the Japanese population. The study has been described in detail previously.[29,30] In brief, the JACC Study was initiated in 1988–1990 and included 110 792 individuals (46 465 men and 64 327 women) aged 40 to 79 years from 45 areas throughout Japan. All participants were subsequently followed for all-cause mortality. In addition, study participants living in 24 areas with cancer registry systems were followed for cancer incidence.

Of the 64 327 women in the baseline cohort, 38 720 lived in the 24 areas where data on cancer incidence were available. The present study excluded 248 women who reported a previous diagnosis of breast cancer and 2308 women who did not provide information on height or weight at baseline. Thus, 36 164 women were included in the present analysis.

Informed consent was obtained from the participants in the form of signatures on the cover pages of the questionnaires, with the exception of those in a few study areas where informed consent was provided at the group level after the aims and data confidentiality had been explained to community leaders. The Ethics Board of Sapporo Medical University approved our study.

Exposure assessment

As a relative indicator of body weight, BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Information regarding weight and height was obtained from the self-reported questionnaire. Change in weight from age 20 years to the baseline measurement was calculated as the difference in the reported values at baseline among 20 418 women whose information on weight at age 20 years was available. We did not use BMI for age 20 years because we did not have access to height information at that age.

Information on other potential breast cancer risk factors such as family history of breast cancer, tobacco and alcohol use, age at menarche, marital status, parity, age at first birth, menopausal status, hormone use, and physical activity was collected in the baseline questionnaire. We have no information after baseline, including information on body size or menopausal status.

Follow-up and identification of breast cancer cases

We followed the study participants from enrollment until 1999–2003. During this period, a population registry was used in each municipality to ascertain the residential status and vital status of the participants. In Japan, the Family Registration Law requires registration of all deaths, which theoretically provides complete mortality data. Breast cancer incidence was confirmed mainly through record linkage to population-based cancer registries in each area. To complete the incidence data, we also conducted a systematic review of death certificates and medical records at major local hospitals in some areas.

During the study period, 1799 (5.0%) participants were lost to follow-up due to moving out of their designated study areas. Among the 234 breast cancer cases, no information on diagnosis was available for 13 (5.6%), ie, they were identified with death certification only (DCO). The world standard for DCO in cancer registration is less than 10%. The mortality-to-incidence ratio for breast cancer was 0.262 (58/221) in the cohort covered by cancer registries, which was within the range calculated using available data from population-based cancer registries in Japan (0.20–0.30). We estimated that 36.5 cases of incident breast cancer were not included in the cancer registries.

Statistical analysis

For each cohort subject, person-years of follow-up were counted as time from enrollment to diagnosis of breast cancer, death from any cause, or end of follow-up (1999–2003), whichever occurred first. For breast cancer cases ascertained only by death certificates, person-years of follow-up were calculated from enrollment to death from breast cancer. Those who died from causes other than breast cancer or who moved out of the study areas were treated as censored cases. We used a Cox proportional hazards model to estimate hazard ratios (HRs) and 95% CIs for the association of breast cancer risk with baseline BMI/weight change. Women were divided into 5 categories, using baseline BMI (in accordance with the World Health Organization classification)[31]: less than 18.5, 18.5–19.9, 20–23.9, 24–28.9, and 29 kg/m^2 or higher. Furthermore, BMI was entered directly to evaluate the linear trend of relative weight. The effect of age on the association between BMI and breast cancer risk was examined by analyzing the relationship between age and BMI. Finally, to investigate the combined effect of baseline BMI and weight change from age 20 years, we recategorized the participants into 4 groups using the following cutoff points: baseline BMI less than 24 kg/m^2 and weight gain of less than 10 kg from age 20 years to the baseline measurement.

Table 1. Baseline characteristics associated with BMI in the JACC Study

Characteristics	BMI at baseline				
	<18.5	18.5–19.9	20–23.9	24–28.9	≥29
Number, *n* (row%)	2373 (6.6%)	3654 (10.1%)	18231 (50.4%)	10737 (29.7%)	1169 (3.2%)
Height (cm)	152.0 ± 7.0	151.0 ± 5.8	151.3 ± 5.5	150.7 ± 5.6	149.3 ± 6.4
BMI	17.4 ± 1.0	19.3 ± 0.4	22.0 ± 1.1	25.8 ± 1.3	31.0 ± 2.0
Weight at age 20 years (kg)	46.5 ± 6.1	47.8 ± 5.7	49.6 ± 6.2	51.0 ± 6.6	52.2 ± 6.8
Weight change[a] (kg)	−6.3 ± 5.9	−3.7 ± 5.4	1.1 ± 6.3	7.8 ± 7.0	17.1 ± 8.3
Age at inclusion (years)	61.3 ± 10.8	58.5 ± 10.7	57.1 ± 10.0	57.9 ± 9.3	58.3 ± 9.3
Age at menarche (years)	15.2 ± 1.8	15.0 ± 1.8	14.9 ± 1.8	14.8 ± 1.8	14.9 ± 1.9
Age at first birth (years)	25.4 ± 3.5	25.2 ± 3.3	25.0 ± 3.2	24.9 ± 3.2	25.0 ± 3.5
Age at menopause (years)	48.2 ± 4.9	48.5 ± 4.5	48.8 ± 4.6	48.7 ± 4.8	48.5 ± 5.1
Years of education	16.5 ± 2.2	16.6 ± 2.1	16.7 ± 2.1	16.3 ± 2.0	16.0 ± 2.1
Nulliparous, *n* (%)	144 (6.6%)	175 (5.2%)	700 (4.1%)	404 (4.0%)	53 (4.9%)
Not married, *n* (%)	69 (3.4%)	61 (1.9%)	227 (1.4%)	111 (1.2%)	20 (2.0%)
Exogenous female hormone use, *n* (%)	124 (6.2%)	160 (5.2%)	792 (5.1%)	471 (5.2%)	61 (6.1%)
Family history of breast cancer, *n* (%)	30 (1.3%)	42 (1.2%)	269 (1.5%)	167 (1.6%)	13 (1.1%)
Current smoker, *n* (%)	162 (7.6%)	201 (6.2%)	779 (4.7%)	470 (4.8%)	81 (7.7%)
Current drinker, *n* (%)	453 (20.4%)	790 (23.1%)	4250 (24.8%)	2444 (24.2%)	223 (20.5%)

BMI, body mass index.
Mean (SD) or %, calculated from subjects with no missing data for any variable.
[a]Difference in body weight at age 20 years and baseline.

We evaluated the association using age-adjusted and multivariable models with adjustment for age (using 10-year age groups), tobacco smoking (never, past, current, or unknown), alcohol consumption (never, past, current, or unknown), age at menarche (<15, 15–16, ≥17 years, or unknown), education level (attended school until age <16, 16–18, ≥19 years, or unknown), parity (nulliparous, 1, 2–3, ≥4 births, or unknown), age at first birth (<22, 22–23, 24–25, ≥26 years, or unknown), menopausal status (premenopausal at baseline, <45, 45–49, or ≥50 years), use of exogenous female hormone (yes, no, or unknown), first-degree family history of breast cancer (yes, no, or unknown), and physical activity categories[32] (4 groups using the following cutoff points of physical activity: daily walking <1 h and exercise time <1 h a week, or unknown). All analyses were performed with regard to menopausal status and stratified by 6 study areas (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu).

We repeated the analysis after excluding the first 2 years of follow-up, during which 38 cases of breast cancer were diagnosed. All *P* values were 2-sided, and a *P* value less than 0.05 was considered to indicate statistical significance. All regression analyses were performed using the PROC PHREG procedure of SAS Version 9.1 (SAS Institute, Cary, NC, USA). Study areas were not incorporated in the Cox model with other potential confounders but were adjusted for using the strata option in the PHREG procedure.

RESULTS

Average age and BMI (SD) at baseline of the 36164 women were 57.8 (10.0) years and 22.9 (3.1) kg/m^2, respectively. In 397644.1 person-years of follow-up (median follow-up time, 12.3 years), we identified 234 breast cancer cases. Table 1 shows the distribution of risk factors for breast cancer in association with BMI. Women with a BMI less than 18.5 were older and more likely to be nulliparous and unmarried. The 2 extreme BMI groups had higher percentages of smokers and lower percentages of drinkers. Groups with higher BMI at baseline had increased weights at age 20 years and greater weight gain from age 20 years to baseline. However, the difference in weight at age 20 years between the 2 extreme BMI groups was relatively small (46.5 kg vs 52.2 kg), and weight change from age 20 years (−6.3 kg vs 17.1 kg) was a stronger contributor to body size at baseline. The average (SD) overall change in weight during the period was 2.7 (8.2) kg.

Table 2 shows breast cancer risk associated with baseline BMI in relation to menopausal status. After adjustment for potential confounding factors, neither a significant HR nor a linear trend was observed among the 8131 premenopausal women. In contrast, among 28033 postmenopausal women, the adjusted HR increased with BMI and showed a significant linear trend ($P < 0.0001$). Furthermore, significantly increased risk was observed among women with a BMI of 24 or higher (HR: 1.50, 95% CI: 1.09–2.08 for BMI of 24–28.9; 2.13, 1.09–4.16 for BMI ≥29) as compared with those with a BMI of 20 to 23.9. The adjusted HRs per 5-kg/m^2 increment in BMI among pre- and postmenopausal women were 0.95 (95% CI: 0.60–1.50) and 1.68 (95% CI: 1.34–2.01), respectively.

To observe the effect of age on the association between BMI and breast cancer risk among postmenopausal women, we calculated the HR for a 5-kg/m^2 increment in BMI in younger (40–59 years) and older (60–79 years) age groups. The older group had a higher HR (2.00, 95% CI: 1.48–2.70) than the younger group (1.37, 95% CI: 0.96–1.96) for a

Table 2. Hazard ratios for breast cancer associated with BMI in the JACC Study

BMI	Cases	Person-years	Age-adjusted		Multivariate[a]	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Premenopausal women						
<18.5	3	4799	0.89	(0.28–2.89)	0.82	(0.25–2.68)
18.5–19.9	6	10327	0.83	(0.35–1.97)	0.78	(0.33–1.84)
20–23.9	39	55363	1.00	Reference	1.00	Reference
24–28.9	13	25975	0.71	(0.38–1.33)	0.76	(0.40–1.43)
≥29	1	2453	0.54	(0.07–3.97)	0.62	(0.08–4.58)
P for trend			0.97		0.82	
Postmenopausal women						
<18.5	7	19412	0.71	(0.33–1.55)	0.64	(0.30–1.40)
18.5–19.9	7	28831	0.47	(0.22–1.02)	0.46	(0.21–1.00)
20–23.9	77	146684	1.00	Reference	1.00	Reference
24–28.9	71	93372	1.47	(1.06–2.03)	1.50	(1.09–2.08)
≥29	10	10427	2.00	(1.03–3.89)	2.13	(1.09–4.16)
P for trend			<0.0001		<0.0001	

BMI, body mass index.
[a]Adjusted for age, height, age at menarche, age at menopause (among postmenopausal women only), years of education, parity, marital status, use of exogenous female hormone, first-degree family history of breast cancer, smoking status, alcohol drinking, physical activity, and study area.

Table 3. Multivariate hazard ratios for breast cancer associated with baseline BMI and weight change among postmenopausal women in the JACC Study

Weight change from age 20 years	Baseline BMI <24		Baseline BMI ≥24	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Premenopausal women				
Loss, unchanged, or gain of <10 kg	1.00	Reference	0.94	(0.35–2.55)
Gain of ≥10 kg	0.53	(0.07–3.96)	1.88	(0.85–4.16)
Postmenopausal women				
Loss, unchanged, or gain of <10 kg	1.00	Reference	1.34	(0.69–2.58)
Gain of ≥10 kg	0.99	(0.24–4.19)	2.55	(1.47–4.42)

BMI, body mass index.
Adjusted for age, height, age at menarche, years of education, parity, marital status, use of exogenous female hormone, first-degree family history of breast cancer, smoking status, alcohol drinking, physical activity, and study area.

5-kg/m^2 increment of BMI, after adjustment for potential confounders.

An effect of weight gain between age 20 years and baseline on breast cancer risk was observed only among postmenopausal women. The HR (95% CI) for 1 increment of weight gain was 1.04 (1.01–1.07). Among premenopausal women it was 0.99 (0.94–1.04) and not significant.

The combinatorial effect of baseline BMI and weight change between age 20 years and baseline was examined to evaluate the effect of these factors separately (Table 3). In premenopausal women, no significant HR or association was found. Conversely, in postmenopausal women, only those with a baseline BMI of 24 or higher and weight gain of at least 10 kg from age 20 years to baseline had a significant HR (2.55, 95% CI: 1.47–4.42), as compared with those with a baseline BMI of less than 24 and a weight gain of less than 10 kg from age 20 years to baseline. These findings indicate that weight gain after age 20 years and consequent overweight/obesity are combined risk factors for breast cancer among postmenopausal women. This combined effect was particularly strong in older women (HR: 4.08, 95% CI: 1.88–8.88). In addition, weight at age 20 years was not a significant predictor of breast cancer after adjustment for height at baseline and other potential confounders among premenopausal and postmenopausal women in this study. Furthermore, similar results were obtained after excluding the 33 breast cancer cases that occurred during the first 2 years of follow-up (data not shown).

DISCUSSION

To our knowledge, this is the first prospective report from Japan on the association between obesity/weight gain and breast cancer risk by age group. Our findings revealed a significant association between BMI/weight gain and postmenopausal breast cancer risk, particularly among older women. For postmenopausal women, especially those aged 60 years or older, weight gain after age 20 years and consequent

overweight/obesity were identified as combined risk factors for breast cancer, after adjusting for potential confounders. In other words, being overweight or obese at baseline was a much greater risk factor among women who were postmenopausal, were aged 60 years or older, and had gained at least 10 kg from age 20 years to baseline.

Our results for postmenopausal women are consistent with those obtained in a number of studies worldwide. The adjusted HR per 5-kg/m^2 increment in BMI in the present study (1.68) was slightly higher than the summary risk ratios from a meta-analysis[4] of studies conducted in the Asia-Pacific (1.31), North America (1.15), and Europe and Australia (1.09). Breast cancer prevention via weight control is expected to be more effective among postmenopausal women in the Asia-Pacific region. With regard to cancer pathogenesis, the increased risk in overweight/obese postmenopausal women is due to the fact that adipose tissue is the major source of estrogenic hormones after menopause.[33,34] Furthermore, our results conform with those of an earlier report showing that adult weight gain might be better than cross-sectional BMI as an adiposity index.[35]

In contrast, we did not observe any significant association between BMI/weight change and breast cancer risk among premenopausal women. In our cohort, age at baseline was 40 years or older; thus, follow-up did not completely cover the premenopausal period. A previous study reported an inverse association between BMI and breast cancer risk among white women. One hypothesis is that young overweight women are more likely to have anovulatory cycles with less cumulative exposure to endogenous estrogen.[36,37] Another hypothesis is that there is greater clearance of estrogen by the liver in young overweight women.[38] These hypotheses are strengthened by results from studies suggesting that the inverse associations are limited to women with tumors that are estrogen receptor- and progesterone receptor-positive.[25–28] Thus, the heterogeneity of pathologic types among premenopausal breast cancer weakens the association and possibly explains the inconsistent results among non-white racial/ethnic groups. This heterogeneity of cancer etiology in relation to BMI and receptor type makes cancer prevention in premenopausal women difficult and of less practical importance. Further investigations of cancer pathogenesis are needed among non-white racial/ethnic groups.

A major advantage of the present study was its prospective design, which may avoid the possibility of recall bias inherent to case-control studies. Moreover, information on other breast cancer risk factors was included, and potential confounding factors were controlled in analyses of the association.

This study has some limitations that should be considered when interpreting our results. First, because we did not have updated information on menopausal status, which would modify the association between BMI/weight change and breast cancer, the possibility of misclassification of menopausal status at breast cancer onset should be considered. Such misclassification would be problematic in premenopausal women, since recently menopausal women would be misclassified as premenopausal during the follow-up period. Such misclassification could partly explain the inconsistent results from several studies of the association between body size and breast cancer among premenopausal women. Studies of younger women with updated information on menopausal status should be initiated among premenopausal women. However, this limitation is a minor concern for postmenopausal women. Changes during follow-up, especially those related to lifestyle, might alter the results. However, many risk factors, such as marriage status, number of children, and family history of breast cancer, would be unlikely to change after age 40. To our knowledge, substantial changes in risk factors for breast cancer related to BMI have not been reported.

Second, because we used simple questionnaires at baseline only, we have data at only 2 time points, ie, age 20 years and baseline. We did not have data on the time period of weight gain, which would provide useful information for recommendations. Lack of information on weight gain around menopause would also weaken the association among premenopausal women. Furthermore, weight at age 20 years is retrospective information and may be systematically biased among women at extremes of body size. However, these data were obtained before breast cancer diagnosis, and therefore any misclassification is not likely to be differential.

The accuracy of cancer identification in the present study was not ideal. We estimated that 36.5 cases of incident breast cancer were not included in our follow-up, and this number is not inconsiderable. However, these cases would be independent of body size; thus, estimated HRs would tend toward the null.

In summary, our findings support the hypothesis that a weight gain of 10 kg or more and consequent overweight/obesity (BMI ≥24) are combined risk factors for breast cancer among Japanese postmenopausal women, particularly those aged 60 years or older. Thus, to prevent breast cancer, weight gain after age 20 years should be avoided and weight control should be increasingly emphasized with increasing age. The association between body size and premenopausal breast cancer was not clear in the present study and varies across studies; thus, optimal weight for breast cancer prevention cannot be specified at this time.

ONLINE ONLY MATERIALS

Abstract in Japanese.

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