Characteristics and prognosis of Japanese colorectal cancer patients: The BioBank Japan Project

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Abstract
Background: Colorectal cancer is the third most common cancer worldwide, and in Japan, it is estimated that about 10% of men and 8% of women will be diagnosed with colorectal cancer during their lifetime.
Methods: We focused on 5864 participants (3699 men and 2165 women) who had colorectal cancer and were registered with BioBank Japan (BBJ) between April 2003 and March 2008. Characteristics of colon and rectal cancer patients were calculated separately. Among the enrolled patients registered in BBJ within 90 days after diagnosis, we also calculated the 5-year cumulative and relative survival rates, and estimated the effect of lifestyle factors on all-cause mortality.
Results: Our participants included younger men than those in the Patient Survey and the Cancer Registry Japan. In more than 95% of cases the histological type was adenocarcinoma both in colon and rectal cancer. Rectal cancer patients tended to eat more meat and less green leafy vegetables compared with colon cancer patients. The 5-year cumulative survival rate was 73.0% (95% CI; 70.1%–75.7%) and the 5-year relative survival rate was 80.6% (77.4%–83.6%), respectively, for colon cancer. For rectal cancer, the rates were 73.3% (69.1%–77.0%) and 80.9% (76.3%–85.0%), in the same order. Lifestyle factors such as consuming less green leafy vegetables, being underweight, smoking, not consuming alcoholic beverages and being physically inactive were found to be related to poor survival.
Conclusions: We described lifestyle characteristics of colorectal cancer patients in BBJ and examined the impacts on subsequent all-cause mortality.

Introduction
Colorectal cancer is the third most common cancer worldwide and the fourth most common cause of death. Its known risk factors
are westernized lifestyles\textsuperscript{2} such as alcohol consumption, obesity and eating red and processed meat. For this reason, the incidence and mortality rates of colorectal cancer in Japan have increased, with an especially large increase up until the 1990s. Nowadays, the upward trend has slowed and it is estimated that about 10% of men and 8% of women in Japan will be diagnosed with colorectal cancer during their lifetime.\textsuperscript{3}

With early detection by cancer screening and progress in its treatment, the 5-year survival rate of colon and rectal cancer is up to 71.6% and 70.1%, respectively, for those diagnosed between 2006 and 2008.\textsuperscript{2} Recently, modifiable lifestyle factors which contributed to the prognosis of colorectal cancer have been examined. Although the evidence from randomized controlled trials is limited, maintaining high levels of physical activity, avoiding high carbohydrate intake and limiting consumption of red and processed meats and sugar-sweetened beverages are recommended for patients diagnosed with colorectal cancer.\textsuperscript{1}

The BioBank Japan (BBJ) Project is a large-scale patient-based biobank which aims at the implementation of personalized medicine for common diseases such as cancer and cardiovascular disease.\textsuperscript{1} Because of the nationwide scope of patient recruitment and survival survey of BBJ, it might be necessary to describe the lifestyle and clinical characteristics of Japanese colorectal cancer patients in BBJ and to examine their prognoses. The increasing trend in colorectal cancer in Japan nowadays is mostly attributed to colon cancer, thus, we show the results of colon cancer and rectal cancer separately.

Participants and methods

Study design and population

The details of the BBJ Project are described elsewhere.\textsuperscript{5,6} In brief, the BBJ Project enrolled patients who had any of 47 targeted common diseases including colorectal cancer at 66 hospitals consisting of 12 cooperating medical institutions nationwide. Clinical information and biological samples of all patients were collected from April 2003 to March 2008 with written informed consent, under the diagnosis of diseases by each attending physician. The BBJ Project then followed up patients who had 32 of the 47 diseases registered to BBJ and to examine their prognoses. The study protocol of the BBJ Project was approved by the Research Ethics Committees of the Institute of Medical Science, the University of Tokyo, RIKEN Yokohama Institute and the 12 cooperating medical institutions.

Data collection

Data were collected through interviews and medical records.\textsuperscript{8} The data included age and year of entry, diagnosis, patients' own and family medical history, height, weight, lifestyle at entry such as consumption of meat and green leafy vegetables, smoking status, alcohol intake and physical exercise. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Presence of medical history of type 2 diabetes was evaluated from 2 data sources; disease name registered to BBJ and disease name checked on medical history. Stage of colorectal cancer was classified according to the Japanese Classification of Colorectal Cancer, Sixth edition, 1998. In this paper, histological type was based on the findings from biopsy or cytological sample.

Statistical analysis

In this paper, we focused on 5864 participants (3699 men and 2165 women) who had colorectal cancer with information on their sex, age and duration from diagnosis to registration and were registered to the BBJ Project. The characteristics were described for all colorectal cancer patients, and also for colon and rectal cancer patients separately. Colon cancer included cancers that occurred in the cecum, the ascending colon, the transverse colon, the descending colon and the sigmoid colon, and rectal cancer included cancers that occurred in the rectosigmoid colon, and the rectum. There were 3334 colon cancer patients, 1893 rectal cancer patients and 118 patients were classified to both. The patients with appendiceal or anal cancer were only included in the overall analysis. We also showed the characteristics of 1708 newly diagnosed participants (1018 men and 517 women) who were registered in BBJ within 90 days after their diagnosis. When examining the association between lifestyle factors and subsequent all-cause mortality, 1598 newly diagnosed participants (987 men and 611 women) who consented to the follow-up survey and whose follow-up information was successfully obtained were included in the analysis.

We calculated the 5-year cumulative survival rate using the Kaplan–Meier method. We also calculated the 5-year expected survival rate, using a survival-rate table of reference Japanese cohort from Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan,\textsuperscript{9} based on sex- and age-specific mortality rates and Gompertz-Makeham’s law in Abridged Life Tables, annually published by the Statistics and Information Department of Ministry of Health, Labour and Welfare, Japan.\textsuperscript{10} Relative survival rate was then obtained by dividing cumulative survival rate by sex- and age-adjusted expected survival rate.

To examine the impact of the obtained lifestyle factors on mortality, Cox proportional hazards model was used to estimate the hazard ratios and 95% confidence intervals (CIs) for all-cause mortality. All models were stratified by sex and institutions and adjusted for age and entry year. The statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All probability values were two-tailed, and the significance level was set at $p < 0.05$.

Results

Characteristics of the colorectal cancer patients in BBJ

The average age at entry of colon and rectal cancer patients was 67.4 years and 65.5 years, respectively. Fig. 1 shows the age distribution of overall colon and rectal cancer patients in BBJ and those of Patient Survey, Japan, 2005, which represented prevalent cases, separated by sex. The ratio of men to women was 1.6 for colon cancer and 2.0 for rectal cancer, while that of Patient Survey was 1.1 and 1.6, revealing that more men tended to be registered in BBJ than women. Also compared with Patient Survey, elderly patients were registered less often in BBJ, for both men and women and both colon and rectal cancer. When restricted to only patients registered within 90 days after diagnosis, the average age at entry was 65.7 for colon cancer and 63.4 for rectal cancer. The sex ratio was 1.4 for colon cancer and 2.2 for rectal cancer in BBJ, and the number was 1.2 and 1.7 in the Cancer Registry in 2005, which represented incident cases, respectively. As shown in Fig. 2, compared with age distribution of patients in the cancer registry, BBJ patients were younger, especially among the women.

Table 1 shows the characteristics of the all colon and rectal cancer patients and those of the newly diagnosed patients. Among all patients, about 20% were diagnosed before the year 2000. About half of the patients were registered within 1 year after diagnosis, and 17% were survivors longer than 5 years after their diagnosis. Information of stage and histology were mainly not registered.
Among 72% of participants with available information, in more than 95% the histological type was adenocarcinoma both in colon and rectal cancer. About 12% of colon and rectal cancer patients had a medical history of type 2 diabetes and over 13% had a family history of colorectal cancer, even under conditions such that we could not distinguish absence of family history from missing data. For lifestyle factors at entry, rectal cancer patients tended to consume more meat than colon cancer patients (10.8% vs. 9.0% of patients consumed meat almost everyday), while the opposite trend was found for consumption of green leafy vegetables (76.5% vs. 79.6% of patients consumed green leafy vegetables almost everyday). We did not find large differences in BMI distribution between colon and rectal cancer patients, though those registered within 90 days after diagnosis (i.e., newly diagnosed patients) were categorized more to the underweight (BMI < 18.5 kg/m²) group compared with all patients (14.8% vs. 12.2%).

Among 971 and 492 eligible colon and rectal cancer patients, 260 and 130 deceased cases were identified during 5 years of follow-up, respectively. Consequently, the 5-year cumulative survival rate was 73.0% (95% CI, 70.1%–75.7%) and the 5-year relative survival rate was 80.6% (77.4%–83.6%) for colon cancer. For rectal cancer patients (23.0% vs. 21.2% of patients exercised ≥3 times/week); however, all patients tended to engage in exercise compared with those registered within 90 days after diagnosis (22.8% vs. 19.2%).

When compared with the distributions of the National Health and Nutrition Survey, Japan, 2005,11 both colon and rectal cancer patients registered within 90 days tended to be underweight, current drinkers and not having physical exercise habits. They also tended to not be never-smokers except colon cancer patients aged 40–49 years old (Fig. 3, because of small numbers, we omitted to describe the distribution among patients under 40 years old (n = 12, 10, 9 and 3 for male colon and rectal cancer, and female colon and rectal cancer patients, respectively)).

**Prognosis of participants registered within 90 days after diagnosis**

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Table 1
Characteristics of colorectal cancer patients in BBJ.

| Year of diagnosis | Total 5864 | N (%) | N (%) | N (%) | N (%) | N (%) |
|-------------------|------------|-------|-------|-------|-------|-------|
| 2000              | 1287       | (21.9) | 691   | (20.7) | 436   | (23.0) |
| 2001              | 393        | (6.7)  | 225   | (6.7)  | 126   | (6.7)  |
| 2002              | 529        | (9.0)  | 300   | (9.0)  | 164   | (8.7)  |
| 2003              | 778        | (13.3) | 444   | (13.3) | 264   | (13.9) |
| 2004              | 852        | (14.5) | 508   | (15.2) | 261   | (13.8) |
| 2005              | 754        | (12.9) | 429   | (12.9) | 261   | (13.8) |
| 2006              | 657        | (11.2) | 387   | (11.6) | 204   | (10.8) |
| 2007              | 584        | (10.0) | 331   | (9.9)  | 170   | (9.0)  |
| 2008              | 30         | (0.5)  | 19    | (0.6)  | 7     | (0.4)  |

| Duration between diagnosis and registration | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
|---------------------------------------------|-------|-------|-------|-------|-------|-------|
| -90 days                                    | 1708  | (29.1) | 1018  | (30.5) | 517   | (27.3) |
| 0-5 years                                   | 631   | (10.8) | 347   | (10.4) | 226   | (11.9) |
| -1 year                                     | 616   | (10.5) | 359   | (10.8) | 193   | (10.2) |
| -2 years                                    | 801   | (13.7) | 449   | (13.5) | 270   | (14.3) |
| -3 years                                    | 489   | (8.3)  | 282   | (8.5)  | 158   | (8.3)  |
| -4 years                                    | 348   | (5.9)  | 194   | (5.8)  | 102   | (5.4)  |
| -5 years                                    | 268   | (4.6)  | 147   | (4.4)  | 91    | (4.8)  |
| Longer than 5 years                         | 1003  | (17.1) | 538   | (16.1) | 336   | (17.7) |

| Stage                                        | 71     | (5.1)  | 46    | (5.3)  | 46    | (5.3)  |
|----------------------------------------------|-------|-------|-------|-------|-------|-------|
| 0                                            | 256    | (18.5)| 140   | (16.2)| 140   | (16.2)|
| I                                            | 394    | (28.4)| 269   | (31.1)| 269   | (31.1)|
| II                                           | 345    | (24.9)| 209   | (24.2)| 209   | (24.2)|
| IIIb                                         | 108    | (7.8) | 67    | (7.8) | 67    | (7.8) |
| IV                                           | 213    | (15.4)| 133   | (15.4)| 133   | (15.4)|

| No information                               | 4477   | 2470  | 2470  |
|----------------------------------------------|-------|-------|-------|
| Age in years                                 | 1389   | 812   | 405   |

| Histology                                    | 4037   | 2355  | 1345  |
|----------------------------------------------|-------|-------|-------|
| Adenocarcinoma                               | 1212   | 742   | 385   |
| Adenosquamous carcinoma                      | 6      | 3      | 1     |
| Basaloid cell carcinoma                      | 132    | 656   | 419   |
| Squamous cell carcinoma                      | 405    | 238   | 238   |
| Carcinoid tumor                              | 422    | 220   | 128   |
| Malignant melanoma                           | 57     | 24    | 18    |
| Non-epithelial tumor                         | 77     | 43    | 25    |
| Unknown                                      | 132    | 656   | 419   |

| No information                               | 1626   | 861   | 482   |
|----------------------------------------------|-------|-------|-------|
| History of Type 2 diabetes                   | 1532   | 913   | 459   |

| Family history of colorectal cancer          | 5081   | 2849  | 1643  |
|----------------------------------------------|-------|-------|-------|
| Presence                                     | 1472   | 868   | 442   |

| Meat consumption                             | 1270   | 753   | 365   |
|----------------------------------------------|-------|-------|-------|
| Almost everyday                               | 1210   | 753   | 365   |
| 3-4 days/week                                 | 209    | 124   | 71    |
| 1-2 days/week                                 | 673    | 418   | 210   |
| Almost never                                  | 202    | 125   | 61    |

| No information                               | 131    | 49    | 24    |

| Green leafy vegetable consumption             | 4153   | 2483  | 1348  |
|----------------------------------------------|-------|-------|-------|
| Almost everyday                               | 1210   | 753   | 365   |
| 3-4 days/week                                 | 209    | 124   | 71    |
| 1-2 days/week                                 | 673    | 418   | 210   |
| Almost never                                  | 202    | 125   | 61    |

| No information                               | 131    | 49    | 24    |

| BMI                                          | 621    | 337   | 202   |
|----------------------------------------------|-------|-------|-------|
| <18.5                                        | 202    | 114   | 45    |
| 18.5-24.9                                    | 245    | 144   | 68    |
| 25-29.9                                      | 242    | 147   | 79    |
| ≥30                                          | 29     | 20    | 6     |
| No information                               | 75     | 41    | 14    |

(continued on next page)
cancer, they were 73.3% (69.1%–77.0%) and 80.9% (76.3%–85.0%), in the same order.

During 7.4 median years with 6333 and 3233 person-years of follow-up, 350 and 171 deaths occurred among colon and rectal cancer patients, respectively. **Table 2** shows the estimated hazard ratios for all-cause mortality. Patients with type 2 diabetes showed elevated risk (HR; 1.31, 95% CI; 1.02–1.67) in all colorectal patients, though we could not distinguish subgroup without information from patients without diabetes among the reference group. Consuming less green leafy vegetables was associated with an increased risk, and almost never-consumers showed 1.87 (1.22–2.88), 2.06 (1.10–3.86) and 1.40 (0.92–2.57) in all colorectal, colon and rectal cancer patients, respectively. Being underweight (BMI < 18.5) elevated the risk of all-cause mortality in all colorectal and colon cancer patients, with HRs of 1.40 (1.12–1.76) and 1.46 (1.09–1.95), respectively. Current smoking was also found to elevate the risk of all-cause mortality, showing HRs of 1.38 (1.06–1.81), 1.50 (1.07–2.11) and 1.54 (0.92–2.57) in all colorectal, colon and rectal cancer patients, respectively. In contrast, alcohol

**Table 1** (continued)

| Overall patients | Colorectal cancer | Colon cancer | Rectal cancer | Patients registered within 90 days after diagnosis | Colorectal cancer | Colon cancer | Rectal cancer |
|------------------|------------------|--------------|--------------|-----------------------------------------------|------------------|--------------|--------------|
|                  | N (%)            | N (%)        | N (%)        | N (%)                                        | N (%)            | N (%)        | N (%)        |
| **Smoking status** |                  |              |              |                                               |                  |              |              |
| Never-smoker     | 2509 (43.6)      | 1490 (45.5)  | 706 (38.1)   | 724 (42.7)                                   | 464 (46.0)       | 176 (34.4)   |              |
| Ex-smoker        | 2050 (36.3)      | 1201 (36.7)  | 749 (40.4)   | 638 (37.7)                                   | 367 (36.4)       | 226 (44.1)   |              |
| Current smoker   | 997 (17.3)       | 558 (17.1)   | 383 (20.6)   | 297 (17.5)                                   | 171 (16.9)       | 107 (20.9)   |              |
| Smoker with unknown status | 162 (2.8) | 23 (0.7) | 17 (0.9) | 35 (2.1) | 7 (0.7) | 3 (0.6) | |
| No information   | 106 –            | 62 –         | 38 –         | 14 –                                         | 9 –              | 5 –          |              |
| **Alcohol intake** |                  |              |              |                                               |                  |              |              |
| Never-drinker    | 2396 (41.7)      | 1390 (42.6)  | 729 (39.4)   | 705 (41.7)                                   | 439 (43.7)       | 199 (38.9)   |              |
| Ex-drinker       | 702 (12.2)       | 415 (12.7)   | 246 (13.3)   | 215 (12.7)                                   | 133 (13.2)       | 73 (14.3)    |              |
| Current drinker consuming 0–15 g alcohol/day | 999 (17.4) | 611 (18.7) | 339 (18.3) | 257 (15.2) | 157 (15.6) | 82 (16.0) | |
| Current drinker consuming 15–30 g alcohol/day | 523 (9.1) | 292 (9.0) | 176 (9.5) | 149 (8.8) | 85 (8.5) | 49 (9.6) | |
| Current drinker consuming ≥30 g alcohol/day | 903 (15.7) | 509 (15.6) | 324 (17.5) | 314 (18.6) | 182 (18.1) | 102 (19.9) | |
| Drinker with unknown status | 218 (3.8) | 45 (1.4) | 36 (1.9) | 50 (3.0) | 9 (0.9) | 7 (1.4) | |
| No information   | 123 –            | 72 –         | 43 –         | 18 –                                         | 13 –             | 5 –          |              |
| **Physical exercise** |                  |              |              |                                               |                  |              |              |
| ≥3 times/week    | 1183 (22.8)      | 704 (23.0)   | 366 (21.2)   | 298 (19.2)                                   | 182 (19.2)       | 85 (17.4)    |              |
| 1–2 times/week   | 229 (4.4)        | 137 (4.5)    | 74 (4.3)     | 54 (3.5)                                     | 33 (3.5)         | 19 (3.9)     |              |
| No habit          | 3776 (72.8)      | 2215 (72.5)  | 1283 (74.5)  | 1197 (77.3)                                  | 733 (77.3)       | 384 (78.7)   |              |
| No information   | 676 –            | 278 –        | 170 –        | 159 –                                        | 70 –             | 29 –         |              |

**Fig. 3.** Distributions of (A) BMI, (B) smoking status, (C) alcohol drinking status and (D) physical exercise status of the colon and rectal cancer patients in BBJ who were registered within 90 days after diagnosis and the general population in the National Health and Nutrition Survey, Japan 2005, according to sex and age group.
intake was found to reduce the risk, even in the highest category (30 g and more alcohol/day) compared with non-drinkers. Being physically inactive raised the all-cause mortality risk to 1.33 (1.05–1.68) and 1.52 (1.12–2.08) in all colorectal and colon cancer patients, respectively. Other characteristics showed no association with all-cause mortality in any sites.

### Discussion

In this paper, we have described the distribution of lifestyle characteristics of Japanese colorectal cancer patients registered in BBJ between April 2003 and March 2008 and the impact on subsequent mortality. Both the allowance patients registered in BBJ and patients who registered within 90 days after diagnosis were obviously younger than the patients of the Patient Survey and of the Cancer Registry, the former represented prevalent cases and the latter represented incident cases in Japan. Among the lifestyles previously reported as risk/preventive factors for development of colorectal cancer, being underweight, current or ex-smoker, current drinker and not having physical exercise habits were apparent among colorectal patients compared with the general public in the National Health and Nutrition Survey. Our rectal cancer patients tended to eat more meat and less green leafy vegetables compared with the colon cancer patients. Also smokers and drinkers were more evident in the rectal cancer patients than the colon cancer patients. We found that lifestyle practices such as consuming less green leafy vegetables, being underweight, smoking, not consuming alcoholic beverages, and being physically inactive increased the subsequent mortality risk.

According to the stage distribution at diagnosis reported by the Japanese Society for Cancer of the Colon and Rectum, the prevalence of 0, I, II, IIIa, IIIb and IV stage between 2000 and 2004 was 5.4%, 19.1%, 28.5%, 19.9%, 9.3% and 17.8% for colon cancer, and 4.9%, 25.3%, 22.4%, 22.2%, 11.9% and 13.2% for rectal cancer.\(^{11}\) Though most of our patients did not have information about the stage of their cancer, more patients registered within 90 days after diagnosis in our study tended to be in stage I (24.2% and 26.5%) for colon and rectal cancer, respectively) compared with the patients reported from the Japanese Society for Cancer of the Colon and Rectum.

From the same registry, the 5-year cumulative survival rate was reported to be 72.8% and 71.3% for colon and rectal cancer,\(^{12}\) and the values were almost equivalent to our patients. On the other hand, the Japanese Association of Clinical Cancer Centers reported the 5-year cumulative survival rate was 72.8% and 71.3% for colon and rectal cancer,\(^{12}\) and the values were almost equivalent to our patients. On the other hand, the Japanese Association of Clinical Cancer Centers reported the 5-year cumulative survival rate was 72.8% and 71.3% for colon and rectal cancer, respectively.

### Table 2

| History of Type 2 diabetes | Colorectal cancer | Colon cancer | Rectal cancer |
|---------------------------|------------------|--------------|--------------|
| Person-years | Death | Adjusted HR (95% CI) | Person-years | Death | Adjusted HR (95% CI) | Person-years | Death | Adjusted HR (95% CI) |
| Absence/No information | 9442.4 | 484 | 1.00 | 5754.1 | 304 | 1.00 | 2904.3 | 147 | 1.00 |
| Presence | 997.2 | 75 | 1.31 (1.02–1.67) | 587.4 | 46 | 1.32 (0.96–1.81) | 328.6 | 24 | 1.26 (0.81–1.97) |
| Family history of colorectal cancer | 8938.3 | 487 | 1.00 | 5388.4 | 308 | 1.00 | 2764.9 | 142 | 1.00 |
| Absence/No information | 15014.2 | 72 | 0.93 (0.72–1.19) | 944.2 | 42 | 0.84 (0.61–1.16) | 468 | 29 | 1.28 (0.86–1.92) |

The hazard ratios were calculated using a Cox proportional hazards regression model stratified by sex and institutions and adjusted for age and entry year.
and physically inactivity were all associated with all-cause mortality risk in line with the previous studies. Medical history of type 2 diabetes was also found to increase the risk of all-cause mortality, however the reference group which was mixed up with patients without diabetes and those without appropriate information made it difficult to interpret this result. In contrast, obesity, and consuming more meat were not associated with all-cause mortality in our study. Consuming green leafy vegetables and moderate alcohol consumption were known to be associated with lower risk of occurrence of colorectal cancer, our results showed that these two lifestyles would also be associated with higher probability of survival.

The strength of the present study is the large-scale enrollment and follow-up of colon and rectal cancer patients nationwide, and the comparison of their characteristics between colon and rectal cancer. The factors associated with disease progression were evaluated among the newly diagnosed participants. However, most of patients registered in BBJ were prevalent cases and the lifestyle information was collected at the registration. Thus, even though we restricted patients to those registered within 90 days after diagnosis to evaluate prognostic factors, there might be some misclassification occurred. Furthermore, we have to exercise caution in interpreting the results because data on some variables including disease stage were missing in the BBJ Project database.

**Conflicts of interest**

All authors declare no conflicts of interest.

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**Appendix**

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