Fatherhood and Distal Adenomas of the Large Bowel: A Study of Male Self-Defense Officials in Japan

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Abstract
Parity has been studied extensively as a risk factor for colorectal cancer but has not been definitively shown to be associated with altered risk. In a few studies, risk of colorectal cancer in childless men has been compared to risk in men with children, but results have not been consistent. We analyzed the association of fatherhood with risk of colorectal adenomas in male self-defense officials (ages 49–55) in Japan. The study participants received a preretirement health examination including flexible sigmoidoscopic or colonoscopic examination of the rectum and sigmoid colon as a part of the examination. Multiple logistic regression analysis assessed the association of colorectal adenomas with these risk factors. The present study is the first to examine the association of colorectal adenomas with fatherhood in men.

Introduction
Reproductive and hormonal risk factors for colorectal cancer in women have been studied extensively over the past 25 years (1). Some studies have found parity protective as it appears to be protective against breast cancer (2–10); others have not (11–20). Breast cancer in women has been observed to resemble breast cancer in geographical distribution and time trends (21). Women with breast cancer also have been found to have decreased risk for both cancers than women in the general population (22).

A few studies of reproductive and hormonal risk factors for colorectal cancer have included male study participants (5–7, 26). Of these studies, three found parity protective in females (5–7). Of those three, two found having children protective in males as well (6, 7), one found being married protective in males (5), and one found early age at birth of the first child protective in males (7). A fourth, large-scale, prospective study, which found parity protective in females only at certain colonic subsites, did not find having children protective in males (26).

The geographical distribution of adenomas has been found to parallel that of cancer (22, 27), and colorectal cancers appear to arise from preexisting adenomatous polyps (28–30). Studies of risk factors for colorectal adenomas have generally focused on risk factors associated with colorectal cancer, such as diet (31), family history (32–33), and lifestyle variables such as smoking and drinking (34–35).

A continuing study of adenoma risk factors in male self-defense officials in Japan has reported findings on diet (36, 37), physical activity (36), obesity (38), and smoking and alcohol intake (34, 35). Study participants interviewed during 1991–1992 were asked to supply information on reproductive factors. The present study is the first to examine the association of colorectal adenomas with these risk factors in males.

Materials and Methods
The study population consisted of male self-defense officials admitted consecutively to Self-Defense Forces Fukuoka and Kumamoto hospitals between January 1991 and December 1992 and to the Self-Defense Forces Sapporo Hospital from April to December 1992 for a preretirement physical examination. Details of the health examination have been described elsewhere (36, 37, 38). The examination included flexible sigmoidoscopic or colonoscopic examination of the rectum and sigmoid colon as a part of the examination.
routine screening procedure; more proximal sites were studied among men at Fukuoka Hospital who tolerated the procedure and among men at Sapporo Hospital who had a positive fecal occult blood test or prior history of large bowel disease. Subjects were included as controls if they had been examined up to at least 60 cm from the anus, or if the intubation was explicitly reported to have reached the sigmoid-descending junction, and they were found to be free of pathological lesions.

In the total series of 2228 men, 104 refused colonoscopy. Results of the colonoscopic examinations were as follows: unsatisfactory study, 29; macroscopic carcinoma, 2; other nonpolypoid lesions, 37; normal colonoscopy, 1543; and at least one polyp, 513. Histological examination was done with 496 of the 513 men with colorectal polyps, and 321 men were found to have adenomatous polyps without cancer. Twenty-one subjects with adenomas and 59 with normal colonoscopy were excluded because of known colorectal polyps (n = 15); prior history of colorectal polypectomy (n = 36), colectomy (n = 7), or malignant neoplasm (n = 21); or newly diagnosed malignant neoplasm (n = 7). Some met more than one exclusion criterion. Thus, 300 men had incident colorectal adenomas. Of these, 265 were found to have adenomas of the rectum and/or sigmoid colon (defined as 11–60 cm from the anus). All the cases had been married at least once. Four of the 1484 controls had never been married. We excluded the 4 never-married controls and used 265 cases and 1480 controls for the present analysis.

Numbers of cases by diameter of the largest adenoma were: <5 mm, 132; ≥5 mm, 119; and unknown, 14. Sixteen of the 265 cases were found to have additional adenomas at more proximal sites. A separate analysis comparing the 228 cases who had sigmoid adenomas to all controls also was conducted.

All study participants responded to a self-administered questionnaire covering dietary habits, tobacco and alcohol use, recreational physical activity, marital status, number of children, and history of work assignment away from family. The questionnaire was distributed on the first day of a 5-day admission and collected on the second day; a nurse-interviewer conducted a supplementary face-to-face interview to make sure all questions were answered. Spearman’s rank correlation coefficients for serum levels of high density lipoprotein cholesterol and questionnaire data in the complete data set (n = 2228) were: cigarettes smoked currently/day, 0.14; current alcohol intake/day, 0.23; and recreational exercise (minutes/week), 0.12.

Multiple logistic regression was used for the analysis. Because of the narrow age range of the study participants, age was not included as a variable in the analysis. Cigarette smoking history, alcohol intake, body mass index, recreational physical activity, and rank were taken into account as potential confounders. In the analysis, smoking was categorized into 0, 1–399, 400–799, and ≥800 cigarette-years (number of cigarettes/day multiplied by years of smoking). Alcohol use was classified into five categories: never drinkers; past drinkers; and current drinkers consuming <30, 30–59, or ≥60 ml of alcohol/day. Body mass index categories were <22.5, 22.5–24.9, 25.0–27.4, and ≥27.5 kg/m². Recreational physical activity was categorized as 0, 1–89, 90–179, and ≥180 min/week. Rank in the Self-Defense Forces ranged from sergeant to lieutenant general, and study participants were categorized as having low (sergeant to warrant officer), middle, or high (major to lieutenant general) rank.

Odds ratios and 95% confidence intervals were derived from the regression coefficient and standard error for an indicator term corresponding to a category of each independent variable. All computations used the Statistical Analysis System (39).

Results

Table 1 shows the demographic characteristics of cases and controls. The age range of the participants in the study was 49–55, and more than 85% of both cases and controls were 51 or 52 years of age.

More than 98% of both cases and controls were currently married. About 35% of cases and controls had experienced a work assignment away from their families, usually as a result of conflict between the location of the work assignment and the requirements of schooling for the children.

Table 2 shows the extent of association of childlessness with selected confounding variables among controls. Men who had children tended to be of higher rank than childless men. Childless men tended to be heavier smokers, more obese, and less physically active in recreation than fathers. In this study population, cigarette smoking was strongly associated with an increased risk of distal adenomas, and alcohol intake tended to be associated with adenoma risk (detailed data will appear elsewhere). Body mass index but not recreational exercise was materially related to adenoma risk (38).

Table 3 shows the association of number of children and colorectal adenomas in terms of crude and adjusted odds ratios. The risk of an adenoma was significantly re-
duced in men with at least one child, although having more children was not more protective. No association of risk with marital status was found. Adenoma risk also was significantly increased in men with at least one child, although having more children, 1-2 children, and 3 children, were significantly associated with having children.

The current study has advantages over previous studies in that participants were relatively homogeneous with respect to age, ethnicity, and occupational history. A weakness of the study is the lack of consistent scrutiny of the large bowel proximal to the sigmoid. Some proportion of both cases and controls may have had undetected proximal adenomas. Detecting such adenomas would not change the status of previously identified cases but would shift some controls into the case group. If these previously misclassified cases had had large adenomas, the results of this analysis would be similar to those for all adenomas.

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Marital status</th>
<th>No. of children</th>
<th>Overall significance</th>
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<tbody>
<tr>
<td></td>
<td>Married</td>
<td>0</td>
<td>1-2</td>
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<td></td>
<td></td>
<td>0</td>
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<tr>
<th>Variable</th>
<th>Median alcohol intake (ml/day)</th>
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<tr>
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<td>33.0</td>
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<tr>
<td></td>
<td>31.0</td>
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<td>35.0</td>
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<tr>
<th>Variable</th>
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<td>75.0</td>
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<td></td>
<td>88.0</td>
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<td>90.0</td>
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<thead>
<tr>
<th>Variable</th>
<th>Median body mass index</th>
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<tr>
<td></td>
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<td></td>
<td>23.7</td>
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<td>23.7</td>
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- a P<0.001.
- b Brown-Mood test for median.
- c One-way analysis of variance.

Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
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- a Adjusted for rank, cigarette smoking, alcohol intake, body mass index, and recreational physical activity. Analysis of rank was adjusted only for the latter 4 variables.
The association of risk with rank found in the analysis of risk for all adenomas was substantially attenuated when the case group was limited to those with large adenomas alone. This shift is probably attributable to more diligent examination of high ranking officers; cases of high rank were more likely to be diagnosed with small adenomas than those of lower rank. The mean age of study participants of high rank was also slightly older than of middle and low rank and accounted for the small age difference between cases and controls. Controls of high rank were more likely to have three or more children than other controls; thus, adjusting for rank strengthened the association of childlessness with risk. No studies of socioeconomic status and health have dealt with adenomas, perhaps because colorectal screening is itself a marker of high socioeconomic status in most settings.

Our findings are somewhat similar to those of studies of reproductive risk factors for colorectal cancer in the United States (6) and Australia (5, 7). Like the study by Wu et al. (6), ours failed to find a correlation of risk with number of children.

Our findings are different from those of a prospective, population-based study of number of children and risk for colorectal cancer in Norway (26). However, the Norwegian cohort members were born in 1935–1969; our study participants were born in 1935–1943; several studies of female populations have found a protective effect of parity only in older age groups or increased risk with parity in younger age groups (8, 25). Fewer of our study participants were childless than in other studies in males (5, 7). In a Norwegian population sample in which childlessness may be more prevalent (the distribution of study participants by number of children was not shown), and in which the participants were predominantly younger and had a more varied occupational history, other exposures might easily have obscured risk due to childlessness.

A case-control study of male breast cancer also found increased risk associated with childlessness (40). However, males with colorectal cancer have not been found to be at increased risk for male breast cancer, nor vice versa, although they have been found to be at increased risk of prostate cancer (41).

Wu et al. have suggested that parenthood might be a marker for other lifestyle variables, such as physical activity, that could affect risk (6). In our study, adjustment for diet, smoking, alcohol intake, and recreational physical activity did not alter the effect of having children.

Potter and McMichael (5) used their analysis of risk of colorectal cancer in males to test the validity of a biological interpretation of the effect of parity on risk in women. In their data, married childless women, unlike married childless men, had higher risk than the unmarried childless or those with children. This observation seemed to point to a biological basis for risk in women but not in men. However, some evidence suggests that in the United States, men with impaired health are less likely to marry than are women with impaired health (42).

It is known that colorectal tumors in both males and females have sex steroid receptors (43, 44). Sex steroids also are known to affect cell proliferation in the colonic mucosa (45) and in colonic tumors in vitro (46) and in vivo (47). These findings suggest that a biological interpretation of risk associated with childlessness in males as well as females cannot be ruled out. However, the observed association of risk for colorectal adenomas with childlessness in men remains difficult to explain. One possibility is that in our study population, childlessness is a marker for an unidentified biological condition that is associated with increased risk for colorectal adenomas. Such causes of male infertility as chromosomal abnormalities, certain infectious diseases, radiation, and pesticide exposure also are associated with increased cancer risk.

Another possibility, not exclusive of the first, is that having children results in lifestyle changes that reduce risk over the long term. This interpretation also might be applied to the association of risk with reproductive and hormonal variables in women. Further studies in defined populations of males and females are needed to explore this association further. If confirmed, the importance of the observation that reproductive factors affect adenoma risk lies not in its implications for family planning but in its clinical implications; perhaps screening should have especially high priority among individuals who are childless at age 50 or beyond.

Acknowledgments

The authors gratefully acknowledge the assistance of the staffs of the participating hospitals.

References

4. Weiss, N. S., Daling, J. R., and Chow, W. H. Incidence of cancer of the rectum in the United States (6) and Australia (5, 7). Like the study by Wu et al. (6), ours failed to find a correlation of risk with number of children.
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