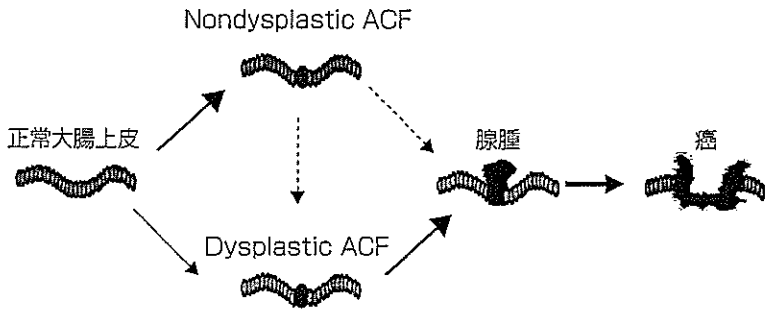

図3. ACFを介した発癌経路

性物質によりアポトーシスを受けて新陳代謝していると考えられる．われわれは，まず初めにACF組織を採取し，TUNEL染色という方法でアポトーシスを調べたところ，ACFでは正常上皮に比べてアポトーシス陽性細胞が少ないこと，つまり，腺腫と同様に細胞が死ににくくなっていることを見出した．一方，腺腫や癌ではcyclooxigenase-2 (COX-2) が発現し，アポトーシスからの逸脱に関与することが指摘されている．そこで，ACFにおけるCOX-2の発現を調べたが，ACFではCOX-2の発現は認められなかった．それでは，どのような機序でACFはアポトーシス抵抗性を獲得しているのであろうか？

6. ACFにおけるGST-πの発現とその意義

以前より，大腸腺腫や癌ではGlutathione S-transferase-π (GST-π) が発現増加していることが知られている．GST-πは，もともと種々の毒性物質をグルタチオン抱合する解毒酵素であるが，いろいろな毒性物質から細胞を保護し，アポトーシスを抑制することも知られている．そこで，GST-πに注目し，ACFにおけるGST-πの発現を調べたところ，高率にその発現を認めた．また，ACF組織をGST-π阻害剤で処理(胆汁酸存在下)すると，アポトーシスが引き起こされることも判明した．そこで，大腸発癌におけるGST-πの意義を検討するため，GST-πのノックアウトマウスに大腸発癌物質を投与したところ，コントロールマウスに比べて，ACFの数，癌の数ともに有意に減少することが確かめられた．つまり，大腸発癌において，GST-πは発癌を促進させる重要な因子の一つであることが明らかとなった．

7. 拡大内視鏡を用いてACFを観察することの臨床的意義

拡大内視鏡を用いてACFを観察することには，大きく2つの意義があると考えられる．一つは，下部直腸領域のACFを数えることにより，腺腫や癌の高危険群を絞り込めることである．例えば，前述の結果から，dysplastic ACFを有する者は無い者に比べて癌である危険性(オッズ比)は約10倍高く，large ACFを有するものは約24倍高いと計算される．従って，直腸を観察するだけで，癌の高危険群をある程度予測できることになる．ACFを観察することのもう一つの意義は，大腸癌の予防試験に応用できることである．

8. ACFを標的とした大腸癌の予防

大腸癌の多い欧米では，種々の薬剤により癌を予防しようとするケモプリベンション（化学予防）が積極的に試みられている．例えば，最近大腸ポリープを切除したヒトを対象にアスピリンを3年間投与すると，アスピリン投与群(17%) ではプラセボ群 (27%) に比べてポリープの発生率が有意に減少することが報告された．このように，これまでのケモプリベンションは

表．ACFに対するスリンダクの効果

症例	年齢	性	ACF数	
			投与前	投与後*
1	53	男性	3	0
2	72	女性	9	1
3	67	男性	7	0
4	71	男性	4	0
5	73	女性	10	1

*スリンダク投与2～3カ月後に行ったACF数の評価

主にポリープ（腺腫）を評価基準としてNSIADsやCOX-2阻害剤を投与するものであった．しかし，このような従来の方法では，1)効果判定までに長期間（数年）かかること，そのため2)副作用の問題，3)コンプライアンスの問題，が指摘されている．一方，ACFはポリープより早期の病変であり，遺伝子異常も単純であることから，ケモプリベンションの格好の標的病変と考えられる．われわれは，実際にACFを有するものを対象に，NSAIDsの一種であるスリンダクを投与すると，わずか2カ月間でACFの大部分が消失することを見出している（表）．このように，短期間の投与であれば副作用やコンプライアンスの問題も解決されると思われる．

スリンダクによるACF消失の機序としては，ACFにCOX-2は発現していないこと，またスリンダクを含むNSAIDsはGST-π活性を抑制することから，GST-π活性の抑制を介する機序を考えている．現在，ACFを有する者を対象に，スリンダク，COX-2選択的阻害剤であるエトドラク，プラセボを投与する大規模な無作為抽出二重盲検試験を行っており，近々詳細な結果が出る予定である．このようなACFを標的としたケモプリベンションは，最近米国のNIHでも取り入れられ，全米規模の臨床試験としても進行中である．

9. Colitic cancerとその前癌病変

潰瘍性大腸炎（UC）に合併する癌は，慢性炎症を有する大腸粘膜を発生母地とすることからcolitic cancerと呼ばれる．Colitic cancerは，通常の大腸癌と比較しびまん性に浸潤するものが多く，病理組織学的には低分化型腺癌や粘液産生癌が多く，発見が遅れることも重なり，予後不良である．Colitic cancerの周囲には高率にdysplasiaが存在すること，逆に生検組織にてdysplasiaが証明された腸切除標本には高率に癌が存在することなどから，dysplasiaはcolitic cancerの前病変と考えられている（dysplasia-carcinoma sequence）[4]．しかし，dysplasiaを内視鏡的に診断することは必ずしも容易ではなく，欧米ではUC患者の大腸から一定間隔でランダムに生検（ランダムバイオプシー）してdysplasiaの診断を試みている施設もある．

Dysplasiaの発生機序や癌に進展する機序の詳細は不明である．Dysplasiaやcolitic cancerでは，通常の腺腫や大腸癌と異なり，APCやK-rasの変異は認められない．一方，p53はdysplasiaとcolitic cancerのいずれにおいても高率に認められる．最近，dysplasiaではマイクロサテライト不安定性や，p16，estrogen receptorなどのメチル化が報告されており，これらの異常はdysplasiaのみならずUCの背景粘膜においても一定の頻度で認められる．従って，これらの遺伝子異常をもった粘膜上皮がdysplasiaの発生母地になっている可能性がある[5]．

10. UC患者におけるACFの観察

われわれは，UC患者においてもACFを観察しうることを見出している．15例のUC患者を調べたところ，いずれの症例にもACFが観察された．但し，UC患者のACFは，メチレンブルーに淡く染色され，大型のACFが多く，前述の非UC症例のACFとは質的に異なることが示唆された．実際に，病理組織学的にも軽度の核異型を有するものが多く，間質にはリンパ球浸潤が認められた．Dysplasiaや癌を合併したUC症例では，ACF

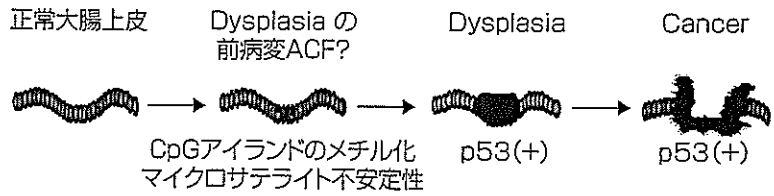

図4. 潰瘍性大腸炎における発癌

の数が明らかに多いことも判明した．さらに，これらのACFでは，p16などのメチル化も高率に認められたことから，ACFがdysplasiaの前病変である可能性が示唆される(図4)．UCでは，dysplasiaや癌の診断が難しいことから，ACFが癌の良いサーベイランスマーカーになる可能性がある．

おわりに

大腸癌の前病変として，われわれが研究しているACFを中心に概説した．本稿では紙面の都合上割愛したが，最近Hyperplasia（過形成）から癌になるhyperplasia-carcinoma sequenceが注目されている．ACFの一部（特にdysplastic ACF）は腺腫に進展すると考えられるが，他の一部は（特にhyperplastic ACF）hyperplasiaに進展し，やがて癌になる可能性がある．ACFがどのような経路から癌に至るのか，その詳細は近い将来明らかにされるものと思われる．

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Original Paper

Reduction in Salivary Cortisol Level by Music Therapy during Colonoscopic Examination

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ABSTRACT

Background/Aims: Premedication for endoscopy promotes patient cooperation and makes subsequent examinations more acceptable. Music therapy is widely used in the treatment of acute and chronic pain. Therefore, we investigated the effects of music therapy on pain and on salivary cortisol levels in patients undergoing screening colonoscopy.

Methodology: The subjects were 29 consecutive patients undergoing colonoscopy for various reasons. Patients were randomly assigned to undergo colonoscopy while listening to music (n=15) or while not listening to music (n=14). Cortisol levels were measured in samples of saliva obtained before and after colonoscopy. After colonoscopy, patients were asked to rate their maximum pain during colonoscopy.

Results: Patients who listened to music during colonoscopy tended to have lower pain scores. Salivary cortisol levels increased significantly less in the group receiving music.

Conclusions: Music therapy during colonoscopy markedly reduces fear-related stress, as indicated by changes in salivary cortisol levels.

KEY WORDS:
Music therapy;
Colonoscopy;
Salivary cortisol

INTRODUCTION

With instrumental advances in videoendoscopy and improvements in endoscopic techniques, colonoscopy is now less painful and better tolerated. However, premedication promotes patient's cooperation and makes subsequent endoscopies more acceptable (1-3)

Several studies have demonstrated that music can induce physiologic relaxation, as indicated by decreases in heart rate, blood pressure, respiratory rate, and galvanic skin response (4-10). In 1994, Palakanis *et al.* (11) reported that patients who listen to self-selected music tapes while undergoing flexible sigmoidoscopy have significantly less anxiety and lower heart rates and mean arterial pressure. In 1998, Lembo *et al.* (12) found that audio and visual stimulation reduces the abdominal discomfort associated with flexible sigmoidoscopy. Their results indicate that music is an effective anxiolytic for flexible sigmoidoscopy. However, few studies have examined changes in "stress hormones," such as cortisol (13), with music therapy. Therefore, we investigated the effects of music therapy on salivary cortisol levels in patients undergoing colonoscopy.

METHODOLOGY

Patients Selection

Subjects were recruited from among patients aged 40 to 69 years who were to undergo screening colonoscopy at the gastrointestinal endoscopy unit of the Osaka Medical Center for Cancer and Cardiovascular Diseases and were able to give informed consent for participation. Patients were excluded if they had endocrine disorders, chronic renal failure, or psychiatric disorders or were receiving glucocorticoids. The study protocol was approved by the Ethics Committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases, and written informed consent was obtained from all patients.

Randomization

Subjects were randomly assigned to undergo colonoscopy while listening to music (music-therapy group) or while not listening to music (control group). The music was of the "easy-listening" style and was played from the beginning of colonoscopy and continued throughout the examination. No patients were receiving anxiolytic medications, and no anticholinergic agents were administered to avoid antisecretory effects and the prick of a needle. All colonoscopic examinations were performed by one senior, experienced endoscopist (N.U.) with a standard technique and a video colonoscope (CF200I, Olympus, Tokyo, Japan). Care was taken to avoid creation of a sigmoid loop by application of clockwise torque, frequent deli-

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cate suction, and scope withdrawal. Biopsies were performed as indicated, but no polypectomies were done.

Grade of Pain

After the examination, patients were asked to rate their maximum pain on a scale from 0 to 3 (0 = none; 1 = mild; 2 = moderate; and 3 = severe) (14). The grades of maximum pain were compared between the two groups.

TABLE 1 Clinical Data for Patients undergoing Screening Colonoscopy With and Without Music

Therapy	Control	Music	*p*-value
Number	15	14	
Mean age (years old, ±SD)	54±8	54±6	0.927
Sex (male/female)	11/4	7/7	0.181
Mean examination time (minutes, ±SD)	36±19	31±10	0.484
History of abdominal surgery (yes/no)	3/12	3/11	0.639
History of colonoscopy (yes/no)	6/9	7/7	0.434
Mean initial cortisol level (μg/dL, ±SD)	0.20±0.15	0.23±0.20	0.919

TABLE 3 Response to EFS before Blockade of the Adrenergic Cholinergic Nerves

Grade of pain	Control	Music
None, mild	2	6*
Moderate	10	6
Severe	3	2

*: p=0.076 for Control *vs.* Music groups comparing none, mild with moderate and severe.

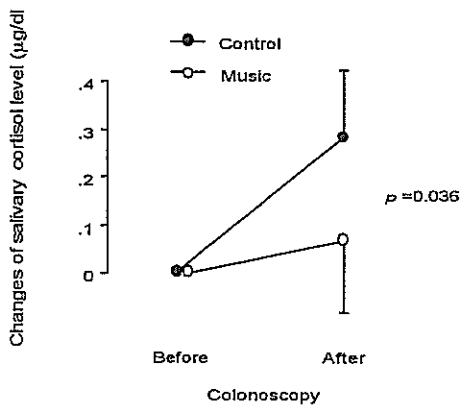

FIGURE 1
Salivary cortisol levels in the music-therapy group (●) and the control group (○). *p*-values were given by Fisher's exact probability test and Student's *t*-test.

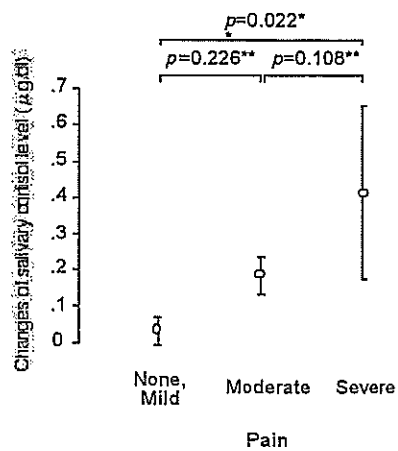

FIGURE 2
Salivary cortisol levels and patients reported levels of pain. *p*-values were given by one-way ANOVA.

Salivary Cortisol Levels

Saliva samples were collected just before and just after examinations. To collect a sufficient quantity of saliva, "Salivette" sampling devices (Sarstadt, Inc., Rommelsdorf, Germany) were used (15). The Salivette includes a small cotton swab and stimulates saliva flow to a rate that enables a sufficient amount to be collected within 1 minute. After centrifugation at 3000 rpm for 10 minutes, saliva was stored at -80°C until assay. Saliva cortisol levels were determined with a commercial enzyme immunoassay kit (CIRON, Tokyo, Japan) (16).

Statistical Analysis

Data are given as mean ±SD. The data were analyzed with a computer software program (StatView, version 5.0, SAS Institute Inc., North Carolina, USA). Fisher's exact probability test and the Student's *t*-test were used to compare clinical data of the groups. Repeated measured ANOVA was used to compare changes in salivary cortisol levels between the groups. Spearman's rank correlation was used to analyze correlation between cotisol level and grades of pain. One-way ANOVA was used to compare changes in salivary cortisol levels with grades of pain and Bonferroni/ Dunn test was performed to find which groups were significantly different each other after rejection of equality by the ANOVA. Calculated p values of less than 0.05 indicated statistical significance.

RESULTS

Effect of Music on Patient Pain

Thirty consecutive outpatients fulfilling the criteria were asked to participate; one patient declined. Therefore, 29 patients were enrolled. There were no significant differences between the control group (n=14) and the music-therapy group (n=15) in age, sex, starting time of colonoscopy, duration of endoscopy, or incidence of previous abdominal surgery or colonoscopy. Reaching the cecum was achieved in all patients. Mean levels of salivary cortisol before colonoscopy in each group were also similar **(Table 1)**.

Patients' perceptions of maximal pain during colonoscopy were reduced by a slight, but not significant degree, in the group receiving music (p=0.076, **Table 2**).

Effect of Music on Salivary Cortisol Levels

Changes in salivary cortisol levels immediately after colonoscopy was significantly lower in the music-therapy group than in the control group (p=0.039, **Figure 1**).

Cortisol levels in patients who reported severe pain were significantly higher than those in patients who reported no pain or mild pain (p=0.022, **Figure 2**).

DISCUSSION

Our results show that salivary cortisol levels increase significantly less in patients who listen to music during screening colonoscopy. We conclude that music therapy markedly reduces endoscopy-related stress, as reflected by changes in salivary cortisol levels.

Lembo *et al.* (12) report that audio and visual stimulation significantly reduces, principally through distraction, abdominal discomfort during flexible sigmoidoscopy. Distraction techniques are widely used to treat acute (17) and chronic pain (18). Distraction is thought to reduce pain by decreasing the amount of attention a person gives to painful stimuli (19). In our study, there was a trend toward lower pain scores during colonoscopy in the music therapy group, but this was not statistically significant. We suppose music is not so powerful that it could not reduce subjective pain during colonoscopy. Actually, half of the patients who listened to the music still had moderate to severe pain. To make colonoscopy less painful and better tolerated, intravenous administration of sedative agents is widely used. Sedation for colonoscopy is associated with a small but definite risk of cardiorespiratory complication (2). Although, music alone does not have enough effect on reducing subjective pain, it may lead to prevent complications of sedatives through reduction of administered dose.

Music therapy has been successfully used to help patients overcome anxiety and, thus, to reduce stress. However, few studies have examined changes in the "stress hormone" cortisol, because blood sampling itself might increase anxiety (13). Mckinney *et al.* (20) have found that music therapy reduces cortisol levels in healthy adults and have suggested that such changes in hormonal regulation may affect the health of persons feeling constant stress. Mockel *et al.* (21) found that cortisol levels in serum were lower after subjects had listened to a Strauss waltz. Escher *et al.* (22) reported that the increase in plasma levels of cortisol during gastroscopy were significantly less when patients listened to music. Cortisol levels can now be measured reliably and accurately in saliva (23); measuring cortisol in saliva provides a better index of adrenal function than does measuring cortisol levels in blood (24,25). Furthermore, we found that salivary cortisol levels were correlated with the pain levels during colonoscopy. It suggests that it may be a convenient and feasible biomarker for assessing patients' pain during colonoscopy.

In conclusion, music therapy is a noninvasive and inexpensive technique and an effective anxiolytic adjunct to colonoscopy.

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LETTER TO THE EDITOR

Re: *Helicobacter pylori* Infection and Gastric Cancer: Facing the Enigmas

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Dear Sir,

Lunet and Barros[1] reported the results of an international ecologic study on *Helicobacter pylori* infection and incidence and mortality rates of gastric cancer after adjustment for intake of vegetables and fruit, cigarette smoking and alcohol drinking. They found positive correlations between *H. pylori* seroprevalence and the incidence of and mortality from gastric cancer for most countries and concluded that *H. pylori* infection is a definite factor of stomach cancer. However, they found negative correlations in African and Asian countries, for which they proposed the term "enigmas."

Stomach cancer may be caused by chronic inflammation related to *H. pylori* infection after initiation by exogenous and endogenous carcinogens.[2–4] The former include pyrolysate chemicals and components of tobacco smoke, and the latter include nitrosamines generated in the stomach from nitrite and amine precursors. Vegetables and fruit are classified as convincing preventive factors associated with intake of vitamin C and other antioxidants. However, intake of salt and salted foods is another important factor,[3–5] regarded as having promoting or progressing effects. Thus, the authors are advised to examine salt consumption or salting as a confounding factor in future studies.

Lunet and Barros intensively collected *H. pylori* seroprevalence data based on several assay systems and amalgamated them. Commercial IgG kits react with specific *H. pylori* strains and thus may yield false-negative results. The urea breath test detects bacteria that possess urease activity and may provide false-positive data. Analysis procedures should be standardized or one method, *e.g.*, the urea breath test, needs to be chosen for international comparisons. In addition, prevalence rates of *H. pylori* infection appear to differ across age groups,[2] *e.g.*, of the EUROGAST study,[6] and age-adjusted rates should be adopted for comparison.

There are some different genotypes of *H. pylori* with discrepant pathogenicity and different outcomes with regard to persistent inflammation: indeed, there are Western, African and East Asian types.[7–9] Of these, the East Asian type appears to be particularly pathogenic for chronic inflammation. Atrophic gastritis markers in the blood, like pepsinogen I, pepsinogen II and the ratio of the two,[10] which correlate well with the Sydney System for diagnosing gastritis,[11] need to be analyzed. Host genetic factors related to cellular immunity against bacterial infection and persistent inflammation may differ with ethnicity and should be examined.[12]

It thus appears premature to label the phenomenon described by Lunet and Barros as "enigmas". Variation in diagnostic techniques may to some extent exist in African and Asian countries. We need to accumulate data for standardized *H. pylori* seropositivity with adjustment for age and salt consumption along with vegetable and fruit intake and smoking. Furthermore, we should add information on chronic atrophic gastritis, *H. pylori* strain/genetic type and host genetic polymorphisms for cellular immunity for bacterial infection and chronic inflammation.

Yours sincerely,

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REVIEW ARTICLE

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Chemoprevention of carcinogenesis in familial tumors

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Abstract Among familial cancers, chemoprevention has been studied for familial adenomatous polyposis, hereditary nonpolyposis colorectal cancers, and familial breast cancers. This report reviews the studies on chemoprevention in familial adenomatous polyposis. A large number of clinical trials have been performed using sulindac, a nonsteroidal anti-inflammatory drug (NSAID). Sulindac reduces the size and number of large-bowel polyps. However, as yet, it cannot be used for this indication in the clinical setting, because of the frequent occurrence of serious gastrointestinal side effects, and there are a number of patients in whom aggressive tumors developed despite a reduction in the size of polyps. Studies of cyclooxygenase-2 (COX-2) selective inhibitors, with minimal side effects on the digestive tract, are showing promising results. In addition to NSAIDs, clinical trials have been performed using vitamins and dietary components. These show minimal side effects, but their efficacy is still insufficient for clinical use, and further studies are anticipated.

Key words Familial adenomatous polyposis · Colorectal cancer prevention · Interventional trial

Introduction

Prophylactic resection of target organs is frequently performed for the treatment of familial tumors. However, it is desirable to prevent tumor occurrence, because of the significant dysfunction associated with the removal of diseased organs. Although cancer prevention has been aggressively studied, an effective method has not been established.

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Due to the higher occurrence of tumors in the families of afflicted persons compared to the general population, clinical trials in patients with familial tumors can be performed using a smaller number of subjects and a shorter period of time. It has also become clear that the knowledge obtained from studies of familial tumors can be applied to sporadic cancers of the large bowel, as the mechanisms of cancer development are becoming better understood. Thus, clinical trials have been frequently conducted on cancer prevention of familial tumors, with the objective of applying the results to the prevention of cancers in general.

Clinical trials on cancer prevention have been performed for familial adenomatous polyposis, hereditary nonpolyposis colorectal cancers, and familial breast cancers. This review is limited to studies of the prevention of familial adenomatous polyposis among these three cancers.

Chemoprevention of familial adenomatous polyposis

Among familial tumors, most studies on cancer intervention have been conducted on familial adenomatous polyposis. A large number of adenomatous polyps, regarded as precancerous lesions, are present in the large bowel of patients with familial adenomatous polyposis. Clinical studies can be carried out relatively easily, because these adenomatous polyps can be used as an intermediate surrogate marker of cancer development. Table 1 shows the clinical studies reported.[1–50] Sulindac, a nonsteroidal anti-inflammatory drug (NSAID), was frequently reported as a preventive candidate drug in these studies. Since Kudo et al.[51] reported in 1980 that the NSAID indomethacin prevented the chemically induced development of large-bowel cancers in rats, it has been reported in many studies that a variety of NSAIDs prevented the development of large-bowel cancers in rats and mice. In humans, the development of large-bowel cancers was reduced in persons who used aspirin for an extended period, as shown in case-control[52] and cohort studies.[53] Because NSAIDs may prevent the development of large-bowel cancers and because sulindac is a prodrug

Table 1. Study design and results of published intervention trials for familial adenomatous polyposis

Year	Authors	No. of patients	Study design	Treatment	Dose (/day)	Follow-up (months)	End-point	Results
1975	DeCosse et al.[1]	5	Case report	Ascorbic acid	3 g	4–13	Polyp	20% Disappeared, 20% regressed
1977	Watne et al.[2]	10	Case report	Ascorbic acid	3 g	3–11	Polyp	70% Regression
1982	Bussey et al.[3]	36	DB-RCT	Ascorbic acid	3 g	15–24	Polyp	Reduction in both number and area
1983	Waddell and Loughry[4]	4	Case report	Sulindac	150–300 mg	4–12	Polyp	Almost completely disappeared
1985	Gonzaga et al.[5]	1	Case report	Sulindac	?	12	Polyp	Regressed
1989	Lipkin et al.[6]	7	Case report	Calcium	1.3–1.5 g	3–4	CECP	Reduced
1989	Itoh et al.[7]	4	Case report	5-Fluorouracil (suppository)		2–4	Polyp	Decreased in 75%; severe rectal urgency
1989	Waddell et al.[8]	10	Case report	Sulindac	150–400 mg	12–85	Polyp	Decreased
1989	DeCosse et al.[9]	58	DB-RCT	Ascorbic acid α-tocopherol Wheat fiber	4 g 400 mg 22.5 g	48	Polyp	Decreased by wheat fiber
1990	Charneau et al.[10]	7	Case report	Sulindac	200–300 mg	1–8	Polyp	Decreased
1990	Friend[11]	3	Case report	Sulindac	150–300 mg	2–3	Polyp	Complete regression
1990	Stern et al.[12]	31	DB-RCT	Calcium	1.2 g	9	CECP	Reduced (6 months only)
1991	Rigau et al.[13]	7	Case report	Sulindac	400 mg	6–36	Polyp PGE_2 6-keto-$PGF_{1\alpha}$	Decreased Decreased Decreased
1991	Labayle et al.[14]	9	DB-RCT crossover	Sulindac	300 mg	4	Polyp CECP	Decreased No change
1993	Thomas et al.[15]	25	DB-RCT	Calcium	1.5 g	6	Polyp CECP	No change Reduced
1993	Schussheim et al.[16]	1	Case report	Sulindac	75 mg	12	Polyp	Decreased (7-year-old patient)
1993	Nugent et al.[17]	14	DB-RCT	Sulindac	400 mg	6	Polyp CECP	Decreased Reduced
1993	Giardiello et al.[18]	22	DB-RCT	Sulindac	300 mg	9	Polyp	Decreased
1993	Tonelli and Valanzano[19]	13	Case report	Sulindac	200 mg	6–107	Polyp	Decreased (6 months) reappeared (long-term therapy)
1993	Winde et al.[20]	15	Dose-finding	Sulindac (suppository)	25–300 mg	10	Polyp	Decreased
1994	Labayle et al.[21]	10	Case report	Sulindac	100–300 mg	12–84	Polyp	Decreased (300 mg→100 mg)
1994	Spagnesi et al.[22]	20	Case report	Sulindac	200 mg	2	Polyp CECP	Decreased No change
1994	Hirata et al.[23]	2	Case report	Indomethacin (suppository)	50–100 mg	24	Polyp	Decreased
1994	Niv and Fraser[24]	1	Case report	Sulindac	450 mg	28	Polyp	Complete regression (rectal cancer occurred)
1995	Lynch et al.[25]	1	Case report	Sulindac	300 mg	15	Polyp	Complete regression (rectal cancer occurred)
1995	Debinski et al.[26]	24	DB-RCT	Sulindac	400 mg	6	Polyp	Decreased
1995	Burn et al.[27]	–	DB-RCT (2 × 2)	Aspirin Resistant starch	600 mg 30 g	12–	-olyp CECP	Ongoing
1995	Pasricha et al.[28]	7	DB-RCT	Sulindac	300 mg	3	Flow cytometry	Apoptosis: increased cell cycle distribution: no change

Table 1. *Continued*

Year	Authors	No. of patients	Study design	Treatment	Dose (/day)	Follow-up (months)	End-point	Results
1995	Winde et al.[29]	25	Dose-finding	Sulindac (suppository)	66–300 mg	33	Polyp	Decreased
1996	Hirota et al.[30]	8	Case report	Indomethacin (suppository)	50–100 mg	1–2	Polyp CECP	Decreased No change
1996	Bertoni et al.[31]	1	Case report	Sulindac	300 mg	3	Ulcer	Rectal ulcer occurred
1996	Giardiello et al.[32]	22	Case report	Sulindac	300 mg	3	Polyp	Decreased (IRA performed)
1996	Nugent et al.[33]	20	DB-RCT	Sulindac	400 mg	6	PGE_2 $PGF_{2\alpha}$	Reduced Reduced
1997	Ishikawa et al.[34]	6	Case report	Sulindac	100–300 mg	4–24	Polyp	Decreased (perforation of gastric ulcer occurred)
1997	Winde et al.[35]	38	Dose-finding	Sulindac	25–300 mg	3–48	Polyp	Decreased (67–300 mg)
1997	Koizumi et al.[36]	2	Case report	Sulindac	200–300 mg	36–40	Polyp	Decreased (liver metastasis, J-pouch ulcer occurred)
1997	Kim et al.[37]	1	Case report	GTE	1 g	44	Polyp ODC activity	Decreased Reduced
1998	Ichikawa et al.[38]	7	Case report	5-Fluorouracil (suppository)	50–100 mg	48–96	Polyp	Decreased
1999	Ishikawa et al.[39]	10	RCT	Sulindac DHA	100–300 mg 2.2 g	24	Polyp	Sulindac: decreased DHA: no change
1999	Keller et al.[40,45]	21	DB-RCT	Sulindac	300 mg	3	Polyp Apoptotic ratio	Decreased Decreased
2000	Steinbach et al.[41]	77	DB-RCT	Celecoxib	200–400 mg	6	Polyp	Decreased
2001	Ishikawa et al.[42]	80	DB-RCT	GTE	1 g	24	Polyp	Ongoing
2002	Akasu et al.[43]	7	Case report	Indomethacin	75–100 mg	12	Polyp	Decreased (anemia occurred)
2002	Giardiello et al.[44,45,49]	41	DB-RCT	Sulindac	150–300 mg	48	Polyp PG Apoptotic index Prostanoids ODC activity Polyamines	Did not prevent development of adenomas Reduced No change Reduced No change No change
2002	Cruz-Correa et al.[46]	12	Cohort study	Sulindac	158 mg	14–98	Polyp	50% polyp-free (50% rectal mucosal erosions occurred; rectal cancer occurred)
2003	Sugihara et al.[47]	21	DB-RCT	Rofecoxib	25 mg	9	Polyp	Decreased
2003	Hallak et al.[48]	8	Case report	Rofecoxib	25 mg	16.4	Polyp	Decreased
2004	Lynch[50]	–	DB-RCT	Celecoxib + eflornithine Celecoxib + placebo		6	Polyp	Ongoing

DB, double-blind; RCT, randomized controlled trial; CECP, colonic epithelial cell proliferation; PG, prostaglandin; ODC, ornithine decarboxylase; IRA, colectomy and ileorectal anastomosis; DHA, docosahexaenoic acid; GTE, green tea extract

causing a relatively low level of side effects on the digestive tract compared to other NSAIDs, many studies on chemoprevention by sulindac have been performed. In 1983, Waddell and Loughry[4] reported that polyps in the rectum almost entirely disappeared after treatment with sulindac in four patients with familial adenomatous polyposis. Later, it was reported consistently from a large number of clinical studies that sulindac decreased polyps in patients with familial adenomatous polyposis. Although it was suggested in these studies that sulindac reduced colonic epithelial cell proliferation and induced apoptosis, these effects have not been confirmed in later studies.

Serious side effects, such as ulcers and perforations of the intestinal wall, have been reported after the administration of sulindac or other NSAIDs.[31,34,36] Generally, NSAIDs have been used as painkillers in patients with chronic rheumatism, and their long-term use has not been recommended.

Cyclooxygenase-2 (COX-2), which is not expressed in the normal mucous membrane, is expressed in cancerous tissue in the large bowel. Therefore, COX-2 has been suggested to be involved in cancer development in the large bowel. Because COX-2 inhibition will not significantly damage the mucous membrane of the digestive tract, due to the absence of COX-2 expression in normal tissue, clinical studies have been recently performed using selective COX-2 inhibitors, such as celecoxib and rofecoxib.[41,47,48] These studies showed that polyps in familial adenomatous polyposis were reduced by COX-2 inhibitors only at higher doses, but not significantly at the regular dose used for pain relief.

Furthermore, there are some reports of the development of aggressive cancers despite a reduction in polyps after administration of sulindac.[24,25,46] It was also reported that rectal cancers developed during sulindac administration in patients with sporadic adenomatous colonic polyps.[54]

In the United States, celecoxib has been approved for the treatment of familial adenomatous polyposis, by reducing the size of polyps. However, it remains to be carefully evaluated whether celecoxib indeed prevents the development of large-bowel cancer.

Clinical studies have been performed on suppository and oral administration of indomethacin as an NSAID other than sulindac. Indomethacin reduces colonic polyps, but because of anemia caused by its effect on the mucous membrane of the digestive tract, continuous administration for a long period of time remains problematic. There are reports of a reduction of colonic polyps by suppository administration of 5-fluorouracil, and also of associated serious side effects. Besides NSAIDs, there are reports on vitamins and dietary components, such as ascorbic acid, α-tocopherol, calcium, wheat bran, decosahexaenoic acid (DHA), and green tea extract. Although side effects are minimal with these compounds compared to NSAIDs, the efficacy obtained with sulindac has not been achieved. In Japan, a double-blind randomized control study (Japan Familial Adenomatous Polyposis Prevention Study [J-FAPP Study]), using green tea extract,[39] is currently being performed, and its efficacy will be made clear in 2005.

The National Cancer Institute (NCI) of the United States is currently enrolling subjects for a new clinical study[50] of combination treatment with celecoxib and an ornithine decarboxylase inhibitor, eflornithine (difluoromethylornithine: [DFMO]), or placebo.

Among members of the same family with familial adenomatous colonic polyposis, differences in the size of polyps and the time of occurrence are observed, suggesting that there are, besides genetic mutations, contributing environmental factors, such as exercise, diet, and smoking. Although the role of environmental factors in the development of familial adenomatous colonic polyposis has not yet been studied, dietary surveys may be productive for the development of preventive methods.

Best efforts should be given to the development of new drugs and recommendations on lifestyle, in order to postpone the time of surgical dissection, resection of the large bowel and, eventually, to avoid surgery in patients with familial adenomatous colonic polyposis.

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Rare *Helicobacter pylori* infection as a factor for the very low stomach cancer incidence in Yogyakarta, Indonesia

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Abstract

To elucidate factors associated with the very low risk of gastric neoplasia in Yogyakarta, Indonesia, approximately 1/50 of the level in Japan, we recruited 52 male and 39 female participants from the general populace in the city of Yogyakarta in October 2003. *Helicobacter pylori* IgG antibodies were found in only 5% (0–13) (95% confidence interval) and 4% (0–9) for Javanese males and females, respectively, and were statistically lower than the 62% (58–65) and 57% (53–60), respectively, in Japanese. Furthermore, positive findings of pepsinogen test were only 0 and 2% (0–6) for males and females, in Yogyakarta, and were again significantly lower than the 23% (22–25) and 22% (20–23), in Japan. The very low incidence of stomach cancer in Yogyakarta may be due to a low prevalence of *H. pylori* infection and chronic atrophic gastritis.

Keywords: *Helicobacter pylori*; Yogyakarta; Stomach cancer; Ecological study

1. Introduction

Since 2002, collaborative epidemiologic studies on host and environmental factors for stomach and colorectal cancer have been underway in a number of Southeast Asian countries. Ecological and case-control studies are now being performed in Hanoi,

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Viet Nam; Khon Kaen, Thailand; and Yogyakarta, Indonesia in order to take advantage of the major variation in incidence rates among these geographical locations and also with data for Japan. Such international comparisons clearly have potential for providing clues for epidemiology and prevention of neoplastic development. Stomach cancer incidences in Hanoi, Khon Kaen and Yogyakarta are approximately 1/2, 1/10 and 1/50 of the level in Japan, respectively: that is, those for Yogyakarta are $1.3/10^5$ for males and $0.7/10^5$ for females during 1994–1996, and for Japan $67/10^5$ for males and $27/10^5$ for females in 1995 [1–3].

We here report results of an ecological study of stomach cancer with reference to the prevalence of *Helicobacter pylori* (*H. pylori*) infection, a definite and necessary carcinogen for the stomach [4,5], and chronic atrophic gastritis (CAG) markers along with sodium and potassium excretions in Yogyakarta, compared with those intakes in Japan. Analysis of *H. pylori* in the feces is also underway, but results are not yet available for inclusion in this report.

2. Subjects and methods

In October 2003, we randomly recruited 52 male and 39 female participants from the general populace in the city of Yogyakarta. Mean ages were 48.0 ± 9.0 (SD) for males and 46.6 ± 8.5 for females. Written informed consent was obtained from the study participants. The protocol was submitted to the Internal Review Boards of Nagoya City University and Gadjah Mada University, and approved. The subjects were requested to respond to lifestyle and food frequency questionnaires, which had also been adopted for a case-control study, and were interviewed by health nurses at a local health center. Body weight and height were measured, and overnight-fasting blood, breath, second morning voiding urine (SMVU) and feces were sampled from each participant.

Serum antibodies for *H. pylori* were examined by enzyme immunoassay (EIA) (Kyowa Medics, Co., Tokyo, Japan) and values ≥ 2.3 were defined as positive. Serum pepsinogen (PG) I and PGII were measured by chemical luminescence enzyme immunoassay (CLEIA) (Eiken Chemicals Co., Tokyo, Japan) with cut-off points of PGI ≤ 70 ng/ml and PGI/PGII ≤ 3.0 [6]. For the urea breath test (UBT), UBiT-IR300 kits (Otsuka Pharmaceutical Co., Tokyo, Japan) were employed with $\geq 2.5‰$ as positive. Because the values differed by sex and age, age-adjustment was made for the rates, adopting the world population [1] as standard, for comparison with the figures for Japan. Using SMVU, excretions of sodium, as a marker of intake of salt and salty foods, and potassium, as a marker of consumption of vegetables and fruit, were analyzed by electrode assay and creatinine by an enzymatic method. Daily excretions of salt (sodium chloride) and potassium were then estimated with adjustment for creatinine [7], which were compared with those intakes in Japanese after adjustment for age.

3. Results

As shown in Table 1, age-adjusted *H. pylori* IgG antibodies were found in only 5% (0–13) and 4% (0–10) of males and females, respectively, in Yogyakarta, and were significantly lower than

Table 1
H. pylori-related markers in Javanese vs. Japanese

	Javanese		Japanese	
	Male ($n=52$)	Female ($n=39$)	Male	Female
Serum *H. pylori* IgG (+)	5% (0–13)[a]	4%(0–9)	62%(58–65)[b]	57%(53–60)
Urea breath test (+)	4%(0–10)	0%	NA[c]	NA
Pepsinogen test[d] (+)	0%	2%(0–6)	23% (22–25)[e]	22% (20–23)

[a] Age-adjusted prevalence (95% confidence interval).
[b] The values were cited from Ref. [8].
[c] Values of urea breath test by sex and age in the Japanese populace were not available.
[d] Positive test was defined as pgI $\leqq$ 70 ng/ml and pgI/pgII $\leqq$ 3.0.
[e] The values were cited from Ref. [9].

Table 2
Urinary excretions of salt and potassium in Javanese vs. consumption in Japanese

	Javanese		Japanese	
	Male	Female	Male	Female
Salt (g/day)	11.0 (10.0–12.1)[a]	9.4 (8.5–10.3)	12.9 (12.7–13.1)[b]	11.2 (11.1–11.4)
Potassium (g/day)	2.1 (1.9–2.2)	2.2 (2.0–2.3)	2.5 (2.5–2.5)[b]	2.4 (2.3–2.4)

[a] Age-adjusted mean (95% confidence interval).
[b] The values were cited from Ref. [10].

the 62% (58–65) for males and 57% (53–60) for females in Japan [8]. Positive rates for UBT were 4% (0–10) for Javanese males and 0% for females. Positive findings of the PG test were 0 and 2% (0–6) for Javanese males and females, respectively, and again were significantly lower than the 23% (22–25) and 22% (20–23) reported for Japan [9]. Salt excretions were calculated to be 11.0 g/day (10.0–12.1) for males and 9.4 g/day (8.5–10.3) for females in Yogyakarta, and were significantly/marginally lower than the consumption of 12.9 g/day (12.7–13.1) for males and 11.2 g/day (11.1–11.4) for females, Japan [10] (Table 2). Potassium excretions were 2.1 g/day (1.9–2.2) for males and 2.2 g/day (2.0–2.3) for females, and were again significantly lower than the consumption of 2.5 g/day (2.5–2.5) and 2.4 g/day (2.3–2.4) in Japan.

4. Discussion

This is the first report to assess the association between prevalence of *H. pylori* infection and risk of stomach cancer in the Javanese, in Yogyakarta. Prevalence of *H. pylori* IgG antibodies were only 5% (0–13) and 4% (0–9) for males and females, respectively, in Yogyakarta, and were statistically lower than the 62% (58–65) and 57% (53–60), respectively, in Japan. Positive rates for the urea breath test were 4% (0–10) for Javanese males and 0% for females. Furthermore, positive findings of pepsinogen testing were only 0 and 2% (0–6) for males and females, in Yogyakarta and were again significantly lower than the 23% (22–25) and 22% (20–23), in Japan. The very low incidence of stomach cancer in Yogyakarta seems to be ascribed not only to a low prevalence of *H. pylori* infection but also chronic atrophic gastritis.

Serum *H. pylori* IgG was assayed by EIA using HM-CAP, which may give rise to false negatives [11], but this was offset by use of the UBT, which detects all bacteria with urease activity and thus can yield false positives. *H. pylori* IgG seroprevalence is ordinarily lower than that of UBT, but this was here not the case. The precise reason remains, however, unclear. Whatever the case, it would appear that the *H. pylori* infection rate is very low in the Javanese, which is in line with the very low seropositivity of *H. pylori* reported for Malay people [12–14]. The findings, however, seem contradictory to the hypothesis of so-called 'African/Asian paradox/enigmas,' in which the prevalence rates of *H. pylori* are high but incidence rates of stomach cancer are low in certain African and Asian countries [14,15].

H. pylori is well established to be a major factor for causing CAG, a precursor of stomach cancer [4,16]. Because results of the PG test correlate well with the Sydney classification of CAG [6,17], it can be utilized as a non-invasive surrogate for histopathological evidence. The implied low prevalence of CAG in Yogyakarta is very plausible given the present findings for *H. pylori*, which is again compatible with the observations: that is, both prevalence of gastric ulcer and incidence of stomach cancer are low in Malay people [14,18]. Host genetic polymorphisms associated with cellular immunity for bacterial infection and chronic inflammation [19], along with differences of *H. pylori* DNA [11,20], may make a certain contribution.

While consumption of salt and salty foods is another factor for stomach cancer risk [21,22], a high-salt diet and *H. pylori* infection act synergistically on the development of stomach cancer in human [23] and in animal models [24]. But the differences between values for Javanese and Japanese would suggest that consumption of salt and salty foods as well as

vegetables and fruit is less important as an explanation for the very low incidence of gastric tumors in Indonesia, where the definite and necessary carcinogen, *H. pylori,* scarcely exists. Furthermore, compared with Japan, there may be reduced exposure to exogenous carcinogens, including pyrolysate chemicals and components of tobacco smoke, and sustained yield of endogenous carcinogens, including nitrosamines generated in the stomach from nitrite and amine precursors.

We should admit that ecological studies are generally regarded as providing low-rank evidence and the number of recruited subjects was not sufficiently large to be representative of the Yogyakarta populace. Furthermore, variation in diagnostic techniques and cancer registration could have a bearing since the data for the Javanese are hospital rather than population-based. However, it seems obvious that the incidence of stomach cancers is very low and the present observations for prevalence of *H. pylori* infection and CAG markers are very suggestive that *H. pylori* is a definite and necessary factor for stomach cancer, and we may conclude that the disease has an infection-dependent etiology.

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CLINICAL TRIAL NOTE

A MULTICENTER RANDOMIZED CONTROLLED TRIAL DESIGNED TO EVALUATE FOLLOW-UP SURVEILLANCE STRATEGIES FOR COLORECTAL CANCER: THE JAPAN POLYP STUDY

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Colorectal cancer is the third leading cause of cancer mortality, and the incidence of colorectal cancer in Japan is increasing gradually. To reduce colorectal cancer mortality, a higher compliance for colorectal cancer screening and follow-up programs is needed. Consequently, it is necessary to establish firm recommendations based on strong evidence from postpolypectomy colonoscopic surveillance. The Japan Polyp Study (JPS) began in 2000, and its objective is to evaluate follow-up surveillance strategies in patients who have undergone two complete colonoscopies for the control of colorectal cancer, with the removal of all detected polyps by high-resolution chromoendoscopy, including the removal of flat or superficial depressed (0-IIc) lesions. The JPS is scheduled to continue until the year 2010, and future data will help to develop recommendations for surveillance guidelines for such patients.

Key words: colorectal tumors, randomized controlled trial (RCT), study overview, the Japan Polyp Study (JPS).

INTRODUCTION

Colorectal cancer is the third most important cause of cancer mortality in Japan.[1] Since 1992, annual fecal occult blood test (FOBT) screening for colorectal cancer has been recommended for everyone over 40 years using a 2-day immunochemical test.[2] To reduce colorectal cancer mortality significantly, a higher compliance for colorectal cancer screening and follow-up programs is needed. Consequently, it is necessary to establish firm recommendations based on strong evidence from postpolypectomy colonoscopic surveillance, because the current intervals between colonoscopies after polypectomy are variable, often a year long, and not based on reliable data from randomized controlled trials.

The JPS Workgroup first convened in 2000.[3] The overall objective of the JPS is a multicenter randomized controlled trial designed to evaluate follow-up surveillance strategies in patients who have undergone two complete colonoscopies for the control of colorectal cancer, with the removal of all detected polyps by high-resolution chromoendoscopy, including the removal of flat or superficial depressed (0-IIc) lesions. Here, we present an overview of the study and participating centers. The Japan Polyp Study Workgroup is presented in Appendix I. The homepage of the Japan Polyp Study is at http://www.jps21.jp/index.html

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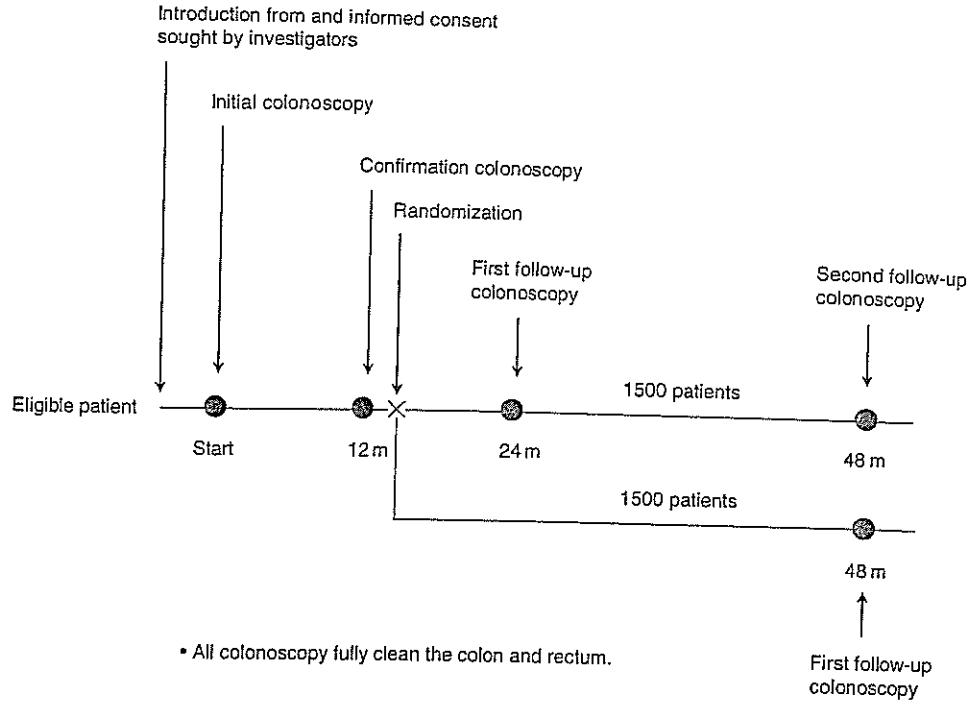

Fig. 1. Schematic overview of the Japan Polyp Study.

OVERVIEW OF THE JPS

The primary goal is to address the hypothesis that after two complete colonoscopies with the removal of all detected polyps, the incidence of clinically significant lesions would not be different between patients undergoing two further follow-up examinations and those undergoing just one (Fig. 1). Clinically significant lesions are defined as index lesions (IL) if they are larger than 10 mm, if they have high-grade dysplasia, or if they are invasive. All interventions excise not only newly diagnosed adenomatous polyps but also flat and superficial depressed (0-IIc) lesions.[4]

In the present study, all patients referred for colonoscopy at the 10 participating centers shown in the Appendix to this article, who are 40–69 years old, who do not have a family or personal history of familial polyposis, hereditary nonpolyposis colorectal cancer (HNPCC), inflammatory bowel disease, or a personal history of polypectomy with unknown histology, who have not had invasive colorectal cancer or colectomy have been considered for inclusion from February 2003. Patients are excluded if colonoscopy reveals invasive colorectal cancer invading beyond the muscularis mucosa or a sessile adenoma with a base longer than 3 cm. Patients are eligible for inclusion if they have had two complete colonoscopies to the cecum, with the removal of all detected polyps. Data collected from all patients in both arms of the trial include detailed demographics, medical history, procedure and individual polyp information. We are aiming to recruit 3000 eligible patients (1500 randomized to each treatment arm) by January 2006.

DISCUSSION

Although the incidence of colorectal cancer in Japan is increasing gradually, there has been a reduction in the incidence of and mortality from colorectal cancer in the USA as well as in some European countries.[5,6] This has been attributed to the effects of changing lifestyle, earlier diagnosis, screening, cancer-preventative polypectomy, and improved therapy. Colonoscopy is the only technique currently available that offers the potential to both find and remove premalignant lesions throughout the colon and rectum. The National Polyp Study (NPS) in the USA, which began in 1980, showed that the removal of all polyps by colonoscopy reduces the incidence of colorectal cancer, and is recommended at an interval of at least 3 years between colonoscopic removal of newly diagnosed adenomatous polyps and the follow-up examination.[7,8] However, there are no established recommendations based on the reliable evidence for postpolypectomy colonoscopic surveillance in Japan.

We described the overview of the JPS for future reference as results are reported. By virtue of its design, its multicenter character, and its uniform prospective pathological and endoscopic interpretation, we expect the JPS will contribute data to evaluate and clarify the objectives mentioned above and help to develop recommendations for surveillance guidelines for Japanese patients after they undergo the removal of neoplasms. However, as the study is scheduled to report in 2010, complete evidence to provide information for the development of colorectal cancer screening recommendations will not be available soon.

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