

Patients' Views on Residual Blood Use for Research Purposes

Nobuyuki Hamajima,^{1,5} Kazuo Tajima,¹ Haruji Oya,² Taketoshi Kato,² Katashi Okuma,² Hisae Kaneda,³ Shigeko Moritaka³ and Tomoyuki Kato⁴

¹Division of Epidemiology, Aichi Cancer Center Research Institute, ²Department of Clinical Laboratory, ³Department of Nursing and ⁴Department of Outpatient Clinic, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464

In order to document patients' views on residual blood use for research purposes, a questionnaire survey was conducted at Aichi Cancer Center Hospital in October 1997. Subjects were patients who had undergone blood tests at a central blood sampling room in the morning during the week of the study enrollment. The questionnaire was handed out and collected at a waiting area in front of the blood sampling room. Of the 583 patients to whom we tried to hand out the questionnaire, 558 participated (258 males, 294 females, and 6 of sex unknown) and 25 refused. Those who regarded research to improve health care as important were 76.7% of those sampled. Only 28 patients (5.0%) answered that they would not permit the use of their residual blood for research purposes. Although logistic analysis did not detect significant factors influencing the giving of permission, the percentage who would not permit the use of their residual blood for research purposes was significantly higher in cancer outpatients (6.7%) than in inpatients (1.0%). It seems desirable for hospitals to establish an open policy concerning residual blood use for research purposes.

Key words: Residual blood — Informed consent — Questionnaire survey — Cancer patients

Informed consent is an established concept both in medical care¹⁾ and medical research,^{2,3)} though the content of information to be provided and process of obtaining consent vary depending on the situation.^{4,5)} Consent is required before any medical intervention, which includes blood tests either for medical care or for research purposes. The ethical issues involved in gaining consent before blood tests have been highlighted, especially for HIV testing⁶⁾ and genetic testing for cancer susceptibility.⁷⁾

The problem of consent before testing extends to samples stored in medical facilities, for which research use was not necessarily approved by the patients.⁸⁾ In the United States, a consensus has been reached for genetic testing that "informed consent is required for all genetic research using linkable samples unless conditions for limitation or waiver are met" and "informed consent is not required for genetic research using anonymous samples but may be considered if identifiers are to be removed from currently linkable samples."⁹⁾ A guideline on genetic tests for familial cancer is also under discussion in Japan.¹⁰⁾ Concerning non-genetic tests for stored samples, there are no documented guidelines in Japan. The problem could be addressed by more general ethical codes protecting patients' rights.

In order to standardize the process of informed consent, the preparation of such guidelines would be very useful and important, but it is also important to survey how

patients and the public consider the use of stored samples for research purposes. Although there are many papers addressing health care professionals' views on residual sample use,⁸⁻¹²⁾ no papers have been found on patients' views in Japan and presumably only a few have been published in other countries. This study aims to document patients' views on residual blood use for research purposes at a cancer hospital in Japan.

MATERIALS AND METHODS

An anonymous questionnaire study was conducted at a waiting area in front of the central blood sampling room of Aichi Cancer Center Hospital during one business week from October 20 (Monday) to 24 (Friday), 1997. The questionnaire was handed out to patients, with care not to disturb the blood sampling procedure or to increase patients' waiting time. Perfect distribution and collection of the questionnaire were therefore not expected. The study subjects were patients who had undergone blood tests in the sampling room between 9 o'clock in the morning and around noon.

The questionnaire was very simple, comprising only six questions on: 1) age, 2) sex, 3) times of visit to Aichi Cancer Center Hospital (first visit, second visit, third to fifth visit, sixth visit or greater, or inpatients), 4) patient's disease (cancer, disease other than cancer, not yet diagnosed, no disease, or do not know), 5) opinion on research to improve hospital care (needless, important, or no comment), and 6) opinion on residual blood use for

⁵ To whom correspondence should be addressed.

research purposes (permission not given, don't care, or permission given). In order to exclude the residual blood samples of the patients who did not give permission, the corresponding patients were asked to identify themselves by writing their names in the place provided on the questionnaire where it clearly stated "You will not be treated disadvantageously if you write your name in this space."

The differences in response percentages among two patient groups were tested by use of the χ^2 test or Fisher's exact test. The odds ratios of background factors against residual blood use were calculated by means of an unconditional logistic model using the SAS Logistic Procedure.¹³⁾

RESULTS

In total, 1,033 patients underwent blood tests at the central blood sampling room during the five consecutive days from 9:00 AM to 5:00 PM. In the first two days, patients during the enrollment hours from 9:00 to around noon were not tallied, but in the last three days those during the enrollment hours were found to be 84% (501/593) of the patients who underwent blood tests from 9:00 AM to 5:00 PM. About 10 patients per day were not asked to participate because of their age, visual problems and/or exhaustion due to effects of disease and/or treatment. Dozens of patients presented themselves for testing more than once during the week. They were, however, asked to participate in this study only once. In addition, 20 to 30 inpatients presented themselves at the sampling room around 8:30 AM to take a card specifying the order of blood draw and showed up again after 9:00 AM. It was hard to find the time to ask for their participation. As a result, the questionnaire was handed out to 583 patients (Table I). Among them, 25 patients (4.3%) refused to participate; the reason was not asked, but the great majority refused to participate before understanding the purpose of

the questionnaire, saying "I am in a hurry" or "I hate questionnaire surveys." The respondents were 558 patients, whose sex and age distribution is shown in Table II. There were 98 inpatients (57 males, 40 females, and 1 of unknown sex), and 459 outpatients (201 males, 253 females, and 5 of unknown sex). One patient did not answer question 3, so it was not clear whether the person was an outpatient or inpatient. Those who answered as having cancer were 410 (73.5%); 192 (74.4%) males, 215 (73.1%) females, and 3 of unknown sex. All 98 inpatients should have been cancer patients, but 7 responded as having a disease other than cancer, 7 as not having been diagnosed, and 1 did not answer.

The patients who answered that research to improve hospital care was important, were 76.7% in total; 80.6% among males and 73.5% among females (significant difference, $\chi^2=3.945$, $P<0.05$). This broke down to 74.2% among non-cancer outpatients, 75.5% among cancer outpatients, and 83.7% among inpatients (Table III).

Only 28 patients (5.0%) out of 558 respondents answered that they would not permit the use of their residual blood for research purposes. All except two patients identified themselves by name. One patient explicitly refused to provide her name, but also did not permit the use of her residual blood for research purposes. The proportion of those against residual blood use was higher in cancer outpatients (6.7%) than in inpatients (1.0%). The difference was statistically significant (Fisher's exact test $P<0.05$).

Table IV shows the odds ratios of background factors of the patients, estimated for refusing residual blood use by means of a logistic model. Although there were no significant factors observed in univariate analysis and multivariate analysis including the four factors listed on Table IV, inpatients tended to permit the use, and cancer patients tended not to; comparable results to those obtained by the simple stratified calculation shown in Table III.

Table I. Enrollment of Participants into the Questionnaire Study

	Mon.	Tue.	Wed.	Thu.	Fri.	Total
Blood test examinees per day ^{a)}	255	185	208	164	221	1,033
Blood test examinees during enrollment time ^{a)}	n.c.	n.c.	169	145	187	
Questionnaire distributed	143	104	134	87	115	583
Respondents	136	99	131	84	108	558
Refusers	7	5	3	3	7	25

a) Repeat samplings were tallied.
n.c., not counted.

Table II. Sex and Age Distribution of Respondents

Age	Non-cancer outpatients			Cancer outpatients			Inpatients			All subjects		
	M	F	T	M	F	T	M	F	T	M	F	T
20–29	4	4	8	3	1	4	2	3	5	9	8	17
30–39	3	6	9	4	7	11	4	2	6	11	15	26
40–49	8	9	17	12	41	53	4	9	13	24	59	83
50–59	10	21	32	22	60	83	15	13	28	47	95	144
60–69	13	22	36	67	39	107	19	7	26	99	68	169
70–79	15	8	23	32	28	60	10	4	14	57	40	97
80–89	5	2	7	3	5	9	3	1	5	11	8	21
Total	58	72	132	143	181	327	42	40	98	258	294	558

M: male, F: female, T: total.

“Total”s include age- or sex-unknown individuals.

Table III. Views on Research at Hospitals and Use of Residual Blood

	Non-cancer outpatients			Cancer outpatients			Inpatients			All respondents		
	M	F	T	M	F	T	M	F	T	M	F	T
<i>n</i> =	58	72	132	143	181	327	57	40	98	258	294	558
What do you think of research at hospitals in order to assure the quality of care and to improve it?												
Needless	0	2	2	8	6	15	1	0	1	9	8	18
	(0)	(3)	(2)	(6)	(3)	(5)	(2)	(0)	(1)	(3)	(3)	(3)
Important	47	50	98	110	135	247	51	30	82	208	216	428
	(81)	(69)	(74)	(77)	(75)	(76)	(89)	(75)	(84)	(81)	(73)	(77)
Cannot answer	11	20	32	25	40	65	5	10	15	41	70	112
	(19)	(28)	(24)	(17)	(22)	(20)	(9)	(25)	(15)	(16)	(24)	(20)
Would you permit your residual blood use for research purposes?												
No	1	4	5	10	11	22	1	0	1	12	15	28
	(2)	(6)	(4)	(7)	(6)	(7)	(2)	(0)	(1)	(5)	(5)	(5)
Do not care	25	34	60	62	77	139	20	11	32	107	123	232
	(43)	(47)	(45)	(43)	(43)	(43)	(35)	(28)	(33)	(41)	(42)	(42)
Affirmative	32	34	67	71	93	166	36	29	65	139	156	298
	(55)	(47)	(51)	(43)	(56)	(51)	(63)	(73)	(66)	(54)	(53)	(53)

M: male, F: female, T: total.

“Total”s include age- or sex-unknown individuals.

% in parentheses.

Table IV. Odds Ratio and 95% Confidence Interval of Factors against Residual Blood Use by Logistic Analysis

Factor	Univariate analysis	Multivariate analysis ^{a)}
Males	1	1
Females	1.10 (0.51–2.40)	0.97 (0.44–2.16)
Age: 10 year increase	1.00 (0.75–1.33)	0.92 (0.68–1.24)
Non-cancer patients	1	1
Cancer patients	1.70 (0.63–4.56)	1.82 (0.67–4.94)
Outpatients	1	1
Inpatient	0.17 (0.02–1.23)	0.16 (0.02–1.19)

a) The four factors in the table were included in the analysis.

DISCUSSION

There are two modes of informed consent; “active consent” which occurs when relevant persons agree to take part, and “passive consent” which occurs when consent is presumed unless they explicitly decline to participate.¹⁴⁾ The latter is adopted in contracts in general when a great number of persons are involved in the contracts or when the contracts do not include serious rights and/or responsibilities.¹⁵⁾

In this study, the participants who would not permit the use of their residual blood for research purposes were asked to provide their name. We did not adopt the policy

that the patients who agreed to research purpose use be asked to provide their name. This is because we consider that the use of residual blood as approved by the Institutional Review Board (IRB) of Aichi Cancer Center is practiced on the basis of the passive consent process, for which the IRB requires before approval the applicants to make clear the substances to be measured, as well as the purpose of the study. Within this framework, patients who do not permit research purpose use, but do not write down their name, are not excluded. This policy will not be applied to analyses which would influence patients' medical care and/or social life, such as for HIV antibodies. For such residual blood tests, active consent should be obtained unless complete anonymity is certain. When an additional volume of blood is sampled for research purposes, patients' consent is mandatory. We have to distinguish clearly between the use of residual blood and extra blood sampling.

Shortly after this questionnaire study, the Department of Clinical Laboratory, Aichi Cancer Center Hospital announced that residual blood might be used for research purposes unless the patients expressed their intention not to allow the use of residual blood. As of November 21, four weeks after the study, there were no patients who had complained about or refused permission for residual blood use for research purposes.

This study shows that the patients who worried about residual blood use for research purposes were quite few (5.0%). Some of the patients who would not permit residual blood use misunderstood its purpose; they added orally "my blood is not clean because I am a hepatitis virus carrier. I was told not to donate my blood." Given the limited time for explanation, their responses were accepted without correcting their misunderstanding, which presumably caused an overestimation of the percentage of patients who did not permit the use. However, it is plausible that those who rejected participation in this study would have responded "not to permit the residual blood use," which may have caused an underestimation of the percentage. Taking these study limitations into account, the real percentage may not be far from the observed value.

In a study on reference to clinical data with a research purpose, which was conducted at Aichi Cancer Center

Hospital in 1995, a similar result was observed. It was found that only 20 respondents out of 293 (6.8%) expressed discomfort at the idea of reference to their own clinical data for research purposes to improve health care and treatment skills throughout Japan, under the condition that their personal details would remain confidential.¹⁶⁾ Both studies made it clear that although a small percentage of the patients did not wish for the information to be used for research purposes, the great majority of the patients regarded information use for research purposes as important. Needless to say, the views of the former group of patients should be respected, regardless of the number, so a possible process for meeting their wishes has to be considered.

The analysis of background factors of the respondents may give some insight into their true feelings. Inpatients are heavily dependent upon the medical staff of the hospital, so they may hesitate to express their views. Since the majority of cancer outpatients have had a relatively long history of treatment, they may have had an uncomfortable experience concerning blood sampling and/or clinical research in the past. The responses of patients with a different disease and/or different treatment experience may differ from those observed in this study. Studies of other groups are required to understand the views of patients or the public at large.

At present, many study groups in Japan are inclined to support the necessity of informed consent before the use of blood and/or tissue samples.¹⁷⁾ Hospitals now need to establish an open policy concerning use of stored samples for research purposes.

ACKNOWLEDGMENTS

The authors are grateful to Ms. Ryoko Takeshige, Ms. Fusako Taguchi, Ms. Hatsumi Shibata, and Ms. Yoshiko Harada for their technical assistance, and to Mr. Erick C. Ubels for assistance in preparing the English manuscript. This work was supported in part by a Grant-in-Aid for Cancer Research (8S-1) from the Ministry of Health and Welfare in Japan.

(Received November 28, 1997/Revised January 6, 1998/Accepted January 13, 1998)

REFERENCES

- 1) Committee on Informed Consent (Chairperson Kunio Yanagida), the Ministry of Health and Welfare in Japan. Report on informed consent. *Kousei Fukushi*, No. 4375, 10-15 (1995) (in Japanese).
- 2) The Council for International Organizations of Medical Sciences (CIOMS) in Collaboration with the World Health Organization. "International Ethical Guidelines for Biomedical Research Involving Human Subjects" (1993). Geneva.
- 3) The Council for International Organizations for Medical Sciences (CIOMS). "International Guidelines for Ethical Review of Epidemiological Studies" (1991). Geneva.
- 4) Williams, C. J. and Zwitter, M. Informed consent in European Multicentre Randomised Clinical Trials—Are patients really informed? *Eur. J. Cancer*, **30A**, 907-910 (1994).
- 5) Hamajima, N. A personal view on informed consent for clinical studies of cancer. *J. Jpn. Soc. Cancer Ther.*, **31**,

- 99–106 (1996).
- 6) Lewis, H. E. Acquired immunodeficiency syndrome: state legislative activity. *JAMA*, **258**, 2410–2414 (1987).
 - 7) American Society of Clinical Oncology. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility. *J. Clin. Oncol.*, **14**, 1730–1736 (1996).
 - 8) Therrell, B. L., Hannon, W. H., Pass, K. A., Lorey, F., Brokopp, C., Eckman, J., Glass, M., Heidenreich, R., Kinney, S., Kling, S., Landenburger, G., Meaney, F. J., McCabe, E. R., Panny, S., Schwartz, M. and Shapira, E. Guidelines for the retention, storage, and use of residual dried blood spot samples after newborn screening analysis: statement of the Council of Regional Networks for Genetic Services. *Biochem. Mol. Med.*, **57**, 116–124 (1996).
 - 9) Clayton, E. W., Steinberg, K. K., Khoury, M. J., Thomson, E., Andrews, L., Kahn, M. J. E., Kopelman, L. M. and Weiss, J. O. Informed consent for genetic research on stored tissue samples. *JAMA*, **274**, 1786–1792 (1995).
 - 10) The Japanese Society for Familial Tumor. Guideline for genetic tests of familial cancer (draft) (1997).
 - 11) Knoppers, B. M. and Laberge, C. M. Research and stored tissues: persons as sources, samples as persons? *JAMA*, **274**, 1806–1807 (1995).
 - 12) Stephenson, J. Pathologists enter debate on consent for genetic research on stored tissue. *JAMA*, **275**, 503–504 (1996).
 - 13) SAS Institute Inc. “SAS/STAT User’s Guide, version 6” (1990). SAS Institute Inc., Cary, North Carolina.
 - 14) Last, J. M. Guidelines on ethics for epidemiologists. *Int. J. Epidemiol.*, **19**, 226–229 (1990).
 - 15) Hamajima, N. Informed consent in randomized intervention trial for cancer prevention. *Jpn. J. Cancer Clin.*, **43**, 428–431 (1997) (in Japanese).
 - 16) Hamajima, N. and Tajima, K. Patients’ views on reference to clinical data. *J. Epidemiol.*, **7**, 17–19 (1997).
 - 17) Subcommittee of Ethical Issues. Ethics and epidemiology. What ethical issues are Japanese epidemiologists facing? Results of a questionnaire study for members of the Monbusho Research Committee on evaluation of risk factors for cancer by large-scale cohort study. *J. Epidemiol.*, **3**, S141–S146 (1996).