

- 1 Nationwide Survey on the Status of Fertility Preservation Therapy in Japan and Involvement of
- 2 Embryologists in the Practice of Fertility Preservation Therapy
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29

30 **Abstract**

31 **Purpose**

32 To investigate the actual status of fertility preservation techniques in oncofertility in Japan and

33 to clarify the involvement of embryologists in this field.

34 **Methods**

35 This survey was conducted online, targeting embryologists working at 622 facilities registered

36 with the Japan Society of Obstetrics and Gynecology for Assisted Reproductive Technology.

37 **Results**

38 The response rate was 56.6%. In total, 56.8% of facilities used some form of cryopreservation
39 as fertility preservation therapy for patients with cancer; patients' age range was widely defined
40 at each facility. The most common renewal frequency of cryopreserved specimens for patients
41 with cancer was at 1-year intervals. The most common renewal methods were during patient
42 visits to the hospital and contact by letter. Knowledge levels regarding fertility preservation
43 therapy was not high among many embryologists, but respondents recognized the important role
44 of embryologists in oncofertility.

45 **Conclusions**

46 This study is the first to clarify the importance of embryologists in oncofertility. Many
47 embryologists felt that their knowledge of fertility preservation was limited and considered it
48 necessary to improve their education, including public certification. Guidelines for long-term
49 storage systems, including methods for renewal of cryopreservation, need to be established.

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51 Key words: assisted reproductive technology; embryologist; fertility preservation; Japan;
52 oncofertility.

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56 **Introduction**

57 In recent years, cancer diagnostic methods and multidisciplinary treatment methods such as
58 chemotherapy, radiotherapy, and bone marrow transplantation have advanced, and with the
59 remarkable improvement in cancer treatment results, rates of complete remission among
60 pediatric, adolescent, and young adult (AYA) patients with cancer have improved substantially.
61 However, the antitumor effect of high-dose chemotherapy and radiation therapy has been
62 reported to significantly reduce fertility.¹⁻³ In 2004, efforts to preserve fertility to improve
63 quality of life among pediatric and AYA began to be discussed in Japan, and in 2012, the Japan
64 Society for Fertility Preservation was established as the first oncofertility association in Japan.⁴

65 In the field of oncofertility, cryopreservation technology for germ cells such as gametes
66 (oocytes/sperm), embryos (fertilized oocytes), and ovarian tissue is essential. Similar to other
67 health care providers, embryologists have a huge role in this field. Cryopreservation of embryos
68 (fertilized oocytes) has a long history, and it is a desirable method for fertility preservation from
69 the perspective of the long-term prognosis of offspring. The laboratory techniques in this field
70 are nearly the same as those in assisted reproductive technology (ART). Furthermore, more than
71 130 live births after transplantation of frozen–thawed ovarian tissue have been reported
72 worldwide.⁵ In 2019, the American Society for Reproductive Medicine (ASRM) stated that
73 “freezing of ovarian tissue has already passed the research stage,”⁶ making this a method with

74 great potential for the future. Because ovarian tissue freezing requires laparoscopic surgery for
75 patients with an unstable general condition, and because it is often targeted toward pediatric and
76 adolescent patients with cancer, only a few facilities in Japan can currently handle
77 cryopreservation of ovarian tissue. Few embryologists are speculated to have mastered the
78 techniques involved in cryopreservation of ovarian tissue. Regarding the cryopreservation of
79 unfertilized oocytes, guidelines of the ASRM⁷ and American Society of Clinical Oncology
80 (ASCO)⁸ recognize unfertilized oocyte freezing as a technology that can be applied clinically. In
81 2014, the Japan Society of Obstetrics and Gynecology (JSOG) approved the clinical application
82 of medically adapted oocyte freezing. Embryologists who have mastered embryo (fertilized
83 oocyte) cryopreservation techniques can easily carry out cryopreservation of unfertilized
84 oocytes.

85 Presently, no consensus exists on ART laboratory technology in oncofertility, such as when
86 and how to freeze germ cells and tissues or how to thaw and fertilize them. In fact, fertility
87 preservation therapy is performed in accordance with the concept in each ART facility, and
88 technical disparities in fertility preservation therapy are assumed to exist among regions and
89 facilities. To solve this problem, the present situation of ART laboratory technology related to
90 oncofertility in Japan should be understood and these issues need to be clarified. Thus, the
91 purpose of this study was to investigate the actual status of fertility preservation techniques in

92 oncofertility in Japan and to clarify the role of embryologists in this field.

93

94 **Materials and methods**

95 This survey was approved on January 7, 2021 (IRB approval no. 5093) by the Bioethics
96 Committee of St. Marianna University School of Medicine. Survey respondents were
97 embryologists working at 622 facilities registered with the JSOG for *in vitro* fertilization and
98 embryo transfer (ART registered facilities). The questionnaire was designed to investigate the
99 implementation of fertility preservation therapy and the involvement of embryologists (**Table 1**).
100 The questionnaire comprised 13 multiple-choice or open-ended questions. For multiple-choice
101 questions, if the response did not match any of the provided choices for an item, the respondent
102 was permitted to provide their own response. Of the 13 items in the questionnaire, five items
103 were related to respondent information and ART facilities and five items addressed information
104 on the status of fertility preservation therapy. The other three items pertained to embryologists
105 in oncofertility. This survey was conducted in an online format by sending a request letter to the
106 hospital director or clinical department director of each facility and enclosing the QR code for
107 the survey. The system design for the online survey was commissioned to an online research
108 company (Macromill, Inc., Tokyo, Japan). The response period was from February 26 to March
109 24, 2021. In this survey, consent was obtained at the beginning of the questionnaire for use of
110 the responses in the present research. Then, the questions were made available to respondents
111 who gave their consent to participate in this study. Additionally, it was possible to withdraw
112 consent at any time even after starting the survey. Regarding privacy protection, because
113 responses and tabulation were done in an online format, access restrictions were set and
114 managed by assigning individual IDs and passwords.

115

116 **Results**

117 **Survey response status and respondent/facility background**

118 Table 2 shows the responses obtained from embryologists at 352 out of 622 ART facilities
119 registered with the JSOG (response rate 56.6%). Consent was obtained from all respondents for
120 research use. In total, 65.1% of respondents were women and 34.9% were men. Respondents'
121 ages ranged from 24 to 82 years; 6.8% were under age 30 years, 36.9% were in their 30s, 41.8%
122 were in their 40s, 11.9% were in their 50s, and 2.6% were age 60 years or older. Embryologists
123 had a mean \pm standard deviation (SD), min–max) 14.8 \pm 6.8 (0–34) years of experience, with
124 77.0% having more than 10 years' experience. Additionally, the number of embryologists at
125 each respondent's facility varied from 0 to 59, with an average (\pm SD) of 4.7 \pm 4.9. We obtained
126 survey responses from facilities in all 47 prefectures (**Figure 1**).

127

128 **Status of fertility preservation therapy**

129 In total, 200 facilities (56.8%) were implementing some form of cryopreservation as
130 fertility-preserving therapy for patients with cancer (**Figure 2**). Of these, 151 (75.5%) were
131 certified by the JSOG as medically indicated (**Figure 3A**), 127 (63.5%) were registered for
132 unfertilized oocytes, and 149 (74.5%) for embryos (fertilized oocytes). Fewer facilities (41
133 facilities, 20.5%) were registered for ovarian tissue (**Figure 3B**). Regarding age restrictions for
134 patients with cancer who were eligible for cryopreservation, 55.4% (93/168) of facilities had
135 age restrictions for embryo (fertilized oocyte) cryopreservation, 62.8% (86/137) for unfertilized
136 oocyte cryopreservation, 73.3% (33/45) for ovarian tissue cryopreservation, 12.8% (24/187) for
137 sperm cryopreservation, and 13.0% (9/69) of facilities had age restrictions for testicular sperm
138 cryopreservation (**Figure 4A**). In those facilities with age restrictions, the median age restriction

139 was 16.0–45.0 years for embryos (fertilized oocytes), 16.0–44.0 years for unfertilized oocytes,
140 1.5–40.0 years for ovarian tissue, 14.0–57.5 years for sperm, and 8.5–57.5 years for testicular
141 sperm (**Figure 4B**). The frequency of extended renewal of cryopreserved specimens for fertility
142 preservation in patients with cancer was annual renewal at most facilities (**Figure 5A**). The most
143 common procedures for renewing the cryopreservation period in cancer reproductive medicine
144 were having the patient come to the facility (56.8%) and contacting the patient via a letter
145 (54.9%); 28.2% of respondents said that they contacted the patient by phone, 14.7% by e-mail,
146 and 4.1% by managing the procedure through an app (**Figure 5B**).

147

148 **Involvement of embryologists in the practice of fertility preservation therapy**

149 When embryologists were asked to self-assess their level of knowledge regarding fertility
150 preservation therapy (100% was defined as needing no supplemental knowledge), 128 (36.4%)
151 answered 50%, followed by 119 (33.8%) who answered 70% (**Figure 6**). In total, 62.8% of
152 embryologists reported a knowledge level of 50% or less.

153 Open-ended responses were received from 41 facilities regarding difficulties in the ART
154 laboratory when performing cryopreservation of germ cells and tissues for patients with cancer
155 (**Figure 7**). The most common response was that they could not contact the patient during the
156 cryopreservation renewal procedure (n=43.9%,18/41), followed by concerns about the
157 long-term storage and management of frozen germ cells and tissues (n=39.0%, 16/41).
158 Additionally, respondents had the following opinions: 9.8% (4/41) said they need more close
159 contact with cancer treatment facilities; 7.3% (3/41) reported difficulty in acquiring skills and
160 securing an embryologist; 4.9% (2/41) said they lacked the time to provide information on
161 reproductive medicine to patients with cancer; 4.9% (2/41) said they lacked knowledge about
162 oncofertility; and 4.9% (2/41) said there was insufficient time before oocyte retrieval and

163 cryopreservation.

164 When asked an open-ended question about the role of embryologists in oncofertility, many
165 respondents indicated that embryologists have a critical role to play in oncofertility. A keyword
166 search of the content of the free-text descriptions revealed many opinions regarding stress
167 owing to the weight of responsibility, the importance of specialized skills and knowledge, and
168 the need for public qualifications and a continuing education system (**Figure 8**).

169

170 **Discussion**

171 Although several studies have reported on the status of fertility preservation therapy in Japan,⁹⁻¹³
172 this was the first nationwide survey of Japanese embryologists on the status of fertility
173 preservation therapy and the involvement of embryologists in oncofertility. There is no mention
174 of fertility preservation therapy in Japanese guidelines for reproductive medicine; consequently,
175 there is no discussion regarding the relationship between laboratory work and oncofertility.¹⁴
176 Additionally, few studies have focused on fertility preservation therapy among embryologists
177 worldwide. In fact, the European Society of Human Reproduction and Embryology (ESHRE)
178 and ASRM guidelines clearly state the importance of being able to provide cryopreservation
179 techniques for fertility preservation therapy, but these guidelines do not specifically mention
180 embryologists' involvement in oncofertility.^{6,15,16} In our survey, we obtained responses from

181 experienced embryologists from 352 facilities in all 47 prefectures of Japan, with ART facilities
182 of varying size. We consider this survey to be of high quality and helpful in understanding the
183 actual state of embryology technology in oncofertility in Japan and clarifying the role of
184 embryologists as technicians in this field.

185 According to survey responses, in fertility preservation therapy for patients with cancer,
186 56.8% of responding facilities used some form of cryopreservation. Many facilities performed
187 cryopreservation of oocytes, sperm, and embryos, which is also routinely performed in ART. Of
188 these, 75.5% were certified by the JSOG as medically indicated, but we found that even
189 facilities without such certification were performing cryopreservation for fertility preservation.
190 In this regard, because subsidies for fertility preservation therapy among patients with cancer
191 were expanded in Japan from April 2021, the number of facilities that are medically approved
192 by the JSOG—a condition for receiving subsidies for egg and embryo cryopreservation—is
193 expected to increase in the future. However, we found that fewer facilities were performing
194 ovarian tissue cryopreservation compared with cryopreservation of oocytes, sperm, and embryos
195 as fertility preservation therapy for patients with cancer. This means that patients are referred to
196 higher-level medical institutions such as university hospitals when they are diagnosed with
197 cancer, but few ART facilities in Japan collaborate in the cryopreservation of ovarian tissue. The
198 reasons for this may include the need for specialized equipment and facilities for the collection

199 and transplantation of ovarian tissue under laparoscopic conditions and the need for higher-level
200 techniques for freezing and thawing. The situation in other countries is not well known, but in
201 Japan, the ASRM requires that facilities be able to provide cryopreservation of embryos and
202 oocytes as a condition for fertility preservation therapy. However, because the ASRM does not
203 necessarily require cryopreservation of ovarian tissue,⁶ we assume that not many facilities in the
204 United States can provide ovarian tissue cryopreservation for patients with cancer, at least as in
205 Japan.

206 Regarding age restrictions for eligible patients in oncofertility, many facilities had age
207 restrictions for embryo, unfertilized oocyte, and ovarian tissue cryopreservation, but many
208 facilities did not have age restrictions for sperm and testicular sperm cryopreservation. In
209 facilities with age restrictions, we inferred that pediatric patients with cancer were included
210 because the lower limit for testicular sperm and ovarian tissue cryopreservation was low
211 whereas the age limit for embryo, unfertilized oocyte, and sperm cryopreservation was set
212 mainly for AYA. In Japan, there are no national or organizational regulations regarding age
213 restrictions in oncofertility. The present survey revealed that age restrictions are widely set for
214 both germ cell and tissue cryopreservation at each facility. A survey of data collected from 30
215 European countries reported that some countries have age restrictions on the use of
216 cryopreserved specimens: 17 countries have age restrictions for oocyte cryopreservation, 13 for

217 embryo cryopreservation, and seven for ovarian tissue cryopreservation.¹⁶ European data on age
218 restrictions and the upper age limit for oocyte cryopreservation are 42–55 years, 45–55 years for
219 embryos, and 40–50 years for ovarian tissue; these values are higher than those in our survey in
220 Japan. Regarding the age restriction for cryopreservation, the special adoption system may be a
221 good reference for ethical discussions, such as consideration of the developmental environment
222 of the future born child. Many local governments in Japan limit the age difference between
223 parents and children to approximately 40–45 years from the perspective of parents being able to
224 support their children physically and financially until they reach adulthood. For the same reason,
225 further discussion on this point may be needed because few facilities in this survey set an age
226 restriction for sperm and testicular sperm cryopreservation, and even those that did set such
227 restrictions had a high upper age limit of 57.5 years.

228 The most common renewal frequency of extended cryopreservation for various germline cells
229 and tissues in patients with cancer was set at 1-year intervals. The advantage of a longer interval
230 is that patients can save time by not having to visit the hospital for procedures so they can
231 concentrate on treatment of their primary disease. However, if the interval is too long, there is
232 less opportunity to check on the patient's underlying disease status and their willingness to
233 continue germline cryopreservation. Patients with a certain frequency should be contacted not
234 only for cryopreservation renewal but also so that the attending reproductive physician can

235 ascertain the treatment status of the primary disease; most facilities set this interval to 1 year. As
236 for the method of renewal, 56.8% of facilities chose to have the patient visit the clinic in person.
237 However, some facilities have patients renew without a visit, such as by letter, phone call, or
238 e-mail. Although not included in the survey, many facilities in routine clinical practice likely
239 choose methods that do not require in-person visits for cryopreservation renewal of embryos
240 (fertilized oocytes) or gametes (oocytes and sperm) for general ART patients. In fertility
241 preservation among patients with cancer, establishing a system that allows patients to confirm
242 their survival, treatment status of the underlying disease, and whether they wish to continue
243 cryopreservation of their germ cells and tissues without having to visit the clinic in person
244 would reduce the burden on patients.

245 Our survey revealed that many embryologists have low levels of knowledge about fertility
246 preservation therapy. This may be owing to the fact that cryopreservation of embryos,
247 unfertilized oocytes, sperm, and testicular sperm is commonly performed in ART, and the
248 method is not very different for patients with cancer, as well as the fact that few facilities can
249 perform ovarian tissue cryopreservation, a technique that is unique to oncofertility. In other
250 words, embryologists are able to provide cryopreservation techniques in oncofertility without
251 having knowledge of fertility preservation therapy, which may explain the lack of interest in
252 fertility preservation therapy.

253 The survey revealed two main concerns among embryologists regarding oncofertility. One
254 was that it is sometimes impossible to contact patients with cancer during the cryopreservation
255 renewal process. The reasons for this are that, unlike patients undergoing infertility treatment,
256 patients with cancer concentrate on treatment of their primary disease and do not have a high
257 level of awareness about the cryopreservation procedures that they have undergone. Moreover,
258 embryologists do not know what level of care is needed for patients with cancer, making it
259 difficult to contact them for renewal procedures. The second concern was about the long-term
260 storage and management of cryopreserved specimens from patients with cancer. The reason for
261 this is thought to be that patients with cancer require a longer cryopreservation period than
262 infertile patients, and there are concerns about the ability of laboratories to store and manage
263 cryopreserved specimens until the date when they can be used by patients with cancer. This
264 includes concerns about whether staff fluctuations during that time would affect the
265 management of cryopreserved specimens and their related information. The Japanese Society
266 for Reproductive Medicine has established some institutional requirements for the management
267 of cryopreserved specimens in ART in Japan, but other detailed requirements have not been
268 established. Recently, Japanese guidelines for reproductive medicine have been published,
269 providing broad recommendations for the safe long-term management of cryopreserved
270 specimens by referring to the guidelines of overseas organizations.¹⁴ Even now, however,

271 detailed information such as the ASRM guidelines¹⁷ is not available in Japan, and this is
272 considered to be an issue for the future.

273 In this survey, many embryologists recognized that the role of embryologists in oncofertility
274 is very important, and many commented on the importance of specialized skills and knowledge.
275 The survey also clarified the need to establish a public qualification for embryologists and a
276 continuing education system to ensure the quality of embryologists' professional skills and
277 knowledge.

278 In conclusion, we clarified the implementation status of embryologists' techniques in
279 oncofertility. Although most respondents were experienced embryologists, many had a low level
280 of knowledge about fertility preservation therapy. To create a medical environment in which
281 reproductive medical technology can be uniformly provided as fertility preservation therapy to
282 patients with cancer in all 47 prefectures of Japan, education for embryologists regarding
283 fertility preservation therapy should be improved. We also revealed difficulty among
284 respondents in contacting patients with cancer during the renewal period of cryopreservation
285 and concerns about the long-term storage and management of cryopreserved specimens,
286 suggesting the need to develop guidelines and crisis management strategies to address these
287 issues. The results of this survey suggest that embryologists play an important role in
288 reproductive medicine in general, including oncofertility, and that an educational system should

289 be established in consideration of public certification of embryologists.

290

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295

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305 that included animal participants.

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359

360

361 **Figure legends**

362 Figure 1 Location of participating facilities.

363 The distribution of facilities is displayed as prefecture-level information.

364

365 Figure 2 Does your institution offer fertility preservation therapy for patients with cancer using
366 cryopreservation of germ cells and tissues?

367

368 Figure 3 Registration status of facilities registered as medically indicated by the Japanese
369 Society of Obstetrics and Gynecology that perform cryopreservation for fertility preservation.

370 (A) Percentage of facilities registered as medically indicated by the Japanese Society of
371 Obstetrics and Gynecology. (B) Registration details of facilities registered as medically
372 indicated.

373

374 Figure 4 Age restrictions for patients with cancer undergoing cryopreservation as fertility
375 preservation therapy.

376 (A) Presence of age restrictions for patients with cancer eligible for cryopreservation at the
377 responding facility. (B) Range of age restriction in facilities with age restrictions.

378

379 Figure 5 Extended renewal of cryopreserved specimens for fertility preservation in patients with
380 cancer.

381 (A) Frequency of extended renewal of cryopreserved specimens for fertility preservation in
382 patients with cancer. (B) Procedure for renewal of cryopreservation period.

383

384 Figure 6 Embryologists' level of knowledge about fertility preservation therapy.

385 Embryologists were asked to self-rate their level of knowledge about fertility preservation
386 therapy, with 100% indicating no supplemental knowledge was needed.

387

388 Figure 7 Difficulties in the laboratory when cryopreserving germ cells and tissues of patients
389 with cancer.

390

391 Figure 8 Main keywords in open-ended responses regarding the role of embryologists in
392 oncofertility.

393

- 1 National Survey on the Status of Embryo Freezing for Fertility Preservation in Japan
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