Oncofertility in Breast Cancer Survivors - A Nationwide-Population Study in Taiwan

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Abstract

Cancer incidence has risen in a staggeringly high pace and is accompanied with extended life expectancy in the last decades globally as well. Amid them, breast cancer has become the top female malignancy worldwide. Taiwan's breast cancer trend is no exception of this and with an even younger presentation, treatment of breast cancer might lead to infertility for young female survivors. And so, what is the landscapes of the breast cancer survivors' oncofertility after their treatment in terms of demographics, intervals from the diagnosis of breast cancer to the time of newborn delivery, the tumor stages, and the tumor molecular portfolios in a population level? Taiwan is located in southeastern Pacific Asia, and has launched single payer national health insurance (NHI) since March 1st 1994 with the coverage rate of almost 99%, which is around 23 million now. The Bureau of NHI has released NHI research database (NHIRD) after anonymizations since 1996. In this study we aimed to investigate the above research questions by Taiwan's longitudinal NHIRD. The results showed that 627 breast cancer survivors, mean aged 33.1 years succeeded in newborns delivery with a mean interval of 1086 days after cancer treatments. Furthermore, the cancer stages of these survivors mostly belonged to the stage zero, one, two to three; and their tumor molecular portfolios were mostly estrogen receptor positive , progesterone receptor positive and human epidermal growth factor two negative; therefore, clinical stages and tumor molecular portfolios also reflected breast cancer landscapes, i.e. an epitome here.

Introduction

Oncofertility was first coined by Teresa Woodruff in 2006 [1]. It was because of enhanced survival of malignancies in young female as well as the advancement of fertility technology to make the young female cancer survivors possible to conceive and deliver babies after cancer treatment, not to mention the trend of longer life expectancy nowadays. According to World Health Organization's report, the young female cancer patients aged under 40 accounted for 5% in 14 million cancer survivors worldwide in 2015 [2]. Therefore, the issue of fertility preservation for these childbearing female cancer survivors should be addressed and tackled multi-disciplinarily, namely, surgical and medical oncologists, obstetricians and gynecologists, psychologists, nurses, as well as patients and the family before and after cancer treatments. Amid these cancers, breast cancers have caught the attention of the medical society and the public as the uprising incidence and younger trend is evident. Taiwan is no exception of this; actually, Taiwan's breast cancer has become the youngest in terms of age in presentation worldwide [3]. These trends could be resulted from the environmental hormones, high lipid diet and sedentary lifestyle [4], as well as stress. Treatments of breast cancers might vary based on different TNM (stands for tumor, nodes and metastasis) staging and cell types with molecular portfolios as well. The TNM staging has been correlated to the relevant treatment strategies consisting of surgery, neo-adjuvant therapies, and adjuvant therapies which include chemotherapy, radiation therapy and monoclonal antibody treatments. Among them, radiation of breast and monoclonal antibody treatment would not impact fertility capabilities; on the other hand, some chemotherapy might lead to infertility. The majority of breast cancer survival rates have been quite satisfactory; Liu's report [3] showed the overall five-year-mortalities in Taiwan were 4.5 % and 4.4% respectively in 1997 and 2012. But the incidence has gone up from 52.34 to 93.0 per 100,000-person year [3], it is the top female cancer in Taiwan right now. These aspects lead to oncofertility to be crucial as it is related to the quality of life and well-beings after treatments of young female breast cancer survivors. The imperative issues such as whether to delay cancer treatment after the procedure of frozen oocytes for single females, frozen embryos for married females, or the frozen ovary tissues should be raised and discussed with the patients and family after the diagnosis of breast cancer [5].

Yet, how many breast cancer survivors could go through this fertility preservation or "oncofetility" process after breast cancer treatment in a population level; what was the demographic and how long did it take from the time of diagnosis of breast cancer to the delivery of a newborn baby, and what proportions of genomic receptors did these survivors belong to as well as the stage landscapes remains unknown. These were the burning questions we want to investigate and ultimately to answer them accordingly. Hopefully, these insights of our exploring could help raise the awareness of oncofertility which is not limited to breast cancer survivors, the breast cancer survivors were just an exemplar of this approach and could apply it to the future better practice as well as promotion of further quality of life in child-bearing breast cancer and other cancer survivors.

Taiwan has launched single payer national health insurance (NHI) since March 1st 1994. The Bureau of NHI has started to release the Nation Health Insurance Research Database (NHIRD) since 1996 after anonymization of the data. The NHIRD encompass the diagnostic codes, procedure codes, medication codes, and expenditures of outpatient department, emergent department as well as inpatient services. And so, we could employ the Taiwan's NHIRD to probe the research questions as follows: 1. what were the exact number of breast cancer survivors successfully delivered their offspring after treatments? 2. how long did it take from the time of diagnosis to the newborn delivery? 3. what were their tumor genomics types? and 4. How many breast cancer survivors deceased after their oncofertility process? Moreover, the Ministry of Health and Welfare (MOHW) also has provided the cancer registry data for research, and so we could connect our NHIRD to cancer registry to further our research results through the identification number.

Materials and Methods

Database

Taiwan's NHIRD has been released for research purpose since 1996. These NHIRD had been anonymized before release. The coverage is more than 99% [6], and includes around 23 million nationals in January 2023. Moreover, the NHIRD could be connected to Cancer Registry through identification number. The study was approved by the institutional review board (IRB) of Taipei Medical University (TMU) (TMU-JIRB N202103047), which complies with Declaration of Helsinki. The informed consent was waived by TMU's IRB as this study only used retrospective administrative claims data and de-identified data as well.

Identification of Cases

In this study, we identified breast cancer cases as the diagnosis of breast cancer as ICD-9-CM 174.xx from NHIRD in Taiwan. Additionally, we connected these breast cancer patients to cancer registry by identification number for further validation and retrieval of important data such as tumor stage, molecular portfolios, and survival or deceased status. After the identification of breast cancer cases, we traced further for the cases with later successful newborn delivery, and investigate the interval between the time of breast cancer diagnosis and newborn delivery as well as their breast cancer molecular portfolios which included Estrogen Receptor, Progesterone Receptor, Human Epidermal Growth Factor 2 and tumor stages which were from stage zero, one, two, three to four.

Results

Table 1 showed that there were 627 breast cancer survivors with successful newborn delivery, among them 32 had deceased after delivery, while the other 595 breast cancer survivors has survived until 2020. The mean age of delivery for these breast cancer survivors was 33.1 years with a standard deviation of 4.25 years. Furthermore, the mean interval between the diagnosis of breast cancer to successful newborn delivery was 1086.67 days with a standard deviation of 778.89 days, which was around three years after breast cancer diagnosis. Moreover, the number of stages of breast cancer survivors were as follows: stage zero: 146, stage one: 214, stage two:184, stage three: 52, stage four: 14, unknown: 17; most were with the early stages which were stages zero to three. In terms of molecular portfolio data: ER+: 447; ER-: 136; unknown ER status: 44; PR+: 424; PR-: 149; unknown PR status: 54; HER2+: 191; HER2-: 336; unknown HER2 status: 100. (Table 2)

Discussions

In present study, there were 627 breast cancer survivors with the mean age of 33.1 years succeeded in delivering newborns around three years (1086.67 days) after the treatments. These figures demonstrated how young could a breast cancer patient be, and so it's not possible to over-emphasize the importance of oncofertility or fertility preservation for breast cancer survivors here. To raise the offspring, to be a mother is not just a biological evolution for a young female; it also denotes the femininity for female breast cancer survivors which is critical mentally, and ultimately might cast impacts on their physical health as well [5]. Our results reflected this need in our young female breast cancer survivors. It just took three years to make these young female survivors to become a mother aroused our thoughts that cancer experiences might expedite this process because of facing challenges of life and death issues would lead survivors to pursue for their life purposes in a way of restricted timeframe. Additionally, 32 breast cancer survivors had succeeded in breeding a newborn, yet succumbed to the cancer after delivery also implied that some females outweighed the meanings of their offspring than their own lives, which were both shocking and touching. And we should respect this vantage point, a recent book entitled as "when breath becomes air" [7], depicting a young outstanding physician couple facing the end of life, which was stage four lung cancer of Dr. Kalanithi, a winner of alpha award and a neurosurgeon-to-be, chose their in-vitro fertilization of their baby daughter, eventually, the patient held his baby daughter while he was passing away.

Through this and other narratives, oncofertility is not definitely confined to the females; just we must take this into consideration as the fertility might not be taken for granted in these cancer survivors.

As for the stages of breast cancers, most survivors belonged to the early stages, namely stage zero, one ,two and three here (accounted for around 80%), which were quite rational; as the late stage survivors, fertility preservation might not be their top concern or there's not enough time for these procedures to be achieved.

In terms of molecular portfolios, survivors found with the better prognostic indicators such as ER or PR positive revealed higher percentage of successful fertility, accounted for 71% and 67% respectively here; on the contrary, survivors with HER2 receptor positive, a less benign behavior indicator showed 30%, HER 2 negative trait survivors demonstrated 60%.

And so, the oncofertility is also an epitome of the breast cancer disease landscapes, in both the stages and molecular portfolios, factors influencing survivor's outcomes also cast the huge influence on the success rate on fertility preservation in these survivors as well.

Conclusion

Taiwan's NHIRD was implemented to probe Taiwan's breast cancer survivors oncofertility status in a population level, and the results revealed there're 632 female breast cancer survivors with the mean age of 33.1 years to succeed in offspring fertility after around three years of breast cancer diagnosis; sadly there're 32 survivors succumbed to the breast cancer after delivering their newborns. These brave breast cancer survivors' molecular portfolios belonged to the ER+, PR+, HER2- mostly and their TNM stages were in the majority of stage zero to stage three. Oncofertility was a crucial issue to address breast cancer childbearing females because it is about their well- beings and life quality after cancer treatments especially in the extended life expectancy era nowadays.

			Age		Days from Diagnosis to newborn delivery	
		n	mean	sd	mean	sd
	Breast	632	33.1	4.25	1,086.67	778.89

Table 1: Duration of Breast cancer survivors with successful oncofertility features

	0	1	2	3	4	unknown
Stage	146	214	184	52	14	17
ER	ER+	ER-	unknown			
	447	136	44			
PR	PR+	PR-	unknown			
	424	149	54			
HER2	HER2+	HER2-	unknown			
	191	336	100			
Survival	Yes	Deceased				
	595	32				
Mean age	33.1	Standard Deviation	4.25			
Mean Interval	1,086.67	Standard Deviation	778.89			

		N
stage		
	0	146
	1	214
	2	184
	3	52
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ER		
	ER+	447
	ER-	136
	unknown	44
PR		
	PR+	424
	PR-	149
	unknown	54
HER2		
	HER2+	191
	HER2-	336
	unknown	100
death		
	0	595
	1	32

Table 2: Features of Breast cancer survivors with successful newborn delivery

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